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PRONIOSOMES: A VERSATILE DRUG DELIVERY SYSTEM

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ABSTRACT

In recent times nanotechnology is considered a technology that could revolutionize the field of life sciences including drug delivery. Further, one of the recent advancements in the field of nanotechnology is proniosomes. Proniosomes are a dry formulation of water-soluble carrier particles that are coated with surfactant and can be measured out as needed and dehydrated to form niosomal dispersion immediately before use on brief agitation in hot aqueous media within minutes. Prevesicular systems, such as proniosomes overcome the problems of vesicular systems such as aggregation, fusion, and leakage of drugs and provide additional convenience in transportation, distribution, storage, and dosing. Conventional vesicular systems such as liposomes and niosomes are particulate and face stability related problems. This new emerging concept has demonstrated the potential in improving the oral bioavailability, targeting drugs to the specific site and also permeation of drugs across the stratum corneum. It prolongs the existence of the drug in systemic circulation and reduces the toxicity. This review provides information regarding the formulation and evaluation of proniosomes including morphology, particle size, drug release, and their advantages over the niosomes.

KEYWORDS: Proniosomes; Niosomes; Permeation; Vesicular systems; Skin.

INTRODUCTION

Novel drug delivery systems have been delivered through various routes of administration, to attain the targeted and controlled drug delivery. Drug encapsulation in the vesicles will help to prolong the drug duration in systemic circulation and decreases the toxicity by selective uptake. Based on this technique, vesicular drug delivery systems such as liposomes, niosomes, and proniosomes have been developed. Liposomes are colloidal, vesicular

structures that are organized in one or several concentric phospholipidic bilayers with an aqueous core inside which encloses a wide variety of substances and drugs.[1] However, liposomes have limited success in terms of oral delivery and suffer from physicochemical stability problems such as sedimentation, aggregation, fusion, phospholipids hydrolysis, and/or oxidation. Further, to overcome the above-mentioned limitations in the early '80s niosomes have been developed as an alternative to liposomes as drug carriers and drug-targeting agents.[2,3] Niosomes can be considered as a potential alternative to liposomes as drug carriers with greater chemical stability, entrapment efficiency of both hydrophobic and hydrophilic drugs, and less toxic due to their non-ionic nature.[4] They overcome the disadvantages associated with liposomes such as phospholipids purity, difficulty in sterilization, and high cost.[5,6] However, niosomes possess some disadvantages like leakage, fusion, aggregation, and sedimentation which can be overcome by formulating proniosomes.[7]

Apart from that Proniosomes were studied as alternatives to liposomes and other carrier systems for entrapping both hydrophobic and hydrophilic drugs. The additional advantages with proniosomes are low toxicity owing to non-ionic nature, no requirement of special precautions and conditions for formulation and preparations. Besides, the method of formulation for both small and large scale batches can be done without using undesirable solvents. However, stability is the main concern in the advancement of any formulation and even proniosomes have advantages as drug carriers, such as cost productivity, chemically stability in comparison to liposomes and niosomes.[8] All these advantages of dry niosomes often termed as proniosomes have made them a promising industrial product. In the current review, an attempt has been made to understand the formulation and evaluation aspects of proniosomes.

Merits[9]

1. Both the non-ionic surfactants and phospholipids in proniosomes can act as penetration enhancers and help in the diffusion of the drug.
2. Proniosomes have higher advantages such as additional convenience of dosing, storage, transportation, and distribution.
3. They avoid the problems associated with either the aqueous noisome dispersion, such as problems of physical stability, aggregation, fusion, and leakage.

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ORAL DISPERSIBLE TABLETS: AN OVERVIEW

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ABSTRACT

Oral route is presently the gold standard in the pharmaceutical industry where it is regarded as the safest, most economical and most convenient method of drug delivery resulting in highest patient compliance. Recent advances in novel drug delivery (NDDS) aims to enhance safety and efficacy of drug molecule by formulating a convenient dosage form for ease of administration and to achieve better patient compliance. One such approach is orodispersible tablets (ODTs). ODTs are a solid unit dosage form, which disintegrates or dissolves rapidly in the mouth without the general requirement for swallowing, the chewing and water. Yet, dysphasia is the most common disadvantage of conventional tablets. To overcome such problems, certain innovative drug delivery systems, like 'Orodispersible Tablets' (ODT) have been developed. The aim of this article is to review the requirements, advantages, limitations, challenges in formulation, various technologies for preparation of ODTs, Evaluation tests of ODTs.

1. INTRODUCTION

For most therapeutic agents used to produce systemic effects, the oral route still represents the preferred way of administration owing to its several advantages and high patient compliance compared to many other routes. Orodispersible tablets are also called as orally disintegrating tablets, mouth-dissolving tablets, rapid dissolving tablets, fast-disintegrating tablets, fast-dissolving tablets. Recently, European Pharmacopoeia has used the term

orodispersible tablets. This may be defined as uncoated tablets intended to be placed in the mouth where they disperse readily within 3 min before swallowing.

Despite of tremendous advancements in drug delivery, the oral route remains the perfect route for the administration of therapeutic agents because of low cost of therapy, ease of administration, accurate dosage, self-medication, pain avoidance, versatility, leading to high levels of patient compliance. Tablets and capsules are the most popular dosage forms. But one important drawback of such dosage forms is 'Dysphasia' or difficulty in swallowing. This is seen to afflict nearly 35% of the general population. This disorder is also associated with a number of conditions like:

1. Parkinsonism
2. Motion sickness
3. Unconsciousness
4. Elderly patients
5. Children
6. Mentally disabled persons
7. Unavailability of water

The oral route remains the perfect route for the administration of therapeutic agents because the low cost of therapy, manufacturing and ease of administration lead to high levels of patient compliance. Many patients have difficulty swallowing tablets and hard gelatin capsules and consequently do not take medications as prescribed. It is estimated that 50% of the population is affected by this problem, which results in a high incidence of noncompliance and ineffective therapy. The demand for solid dosage forms that can be dissolved and suspended in water, chewed, or rapidly dissolved in the mouth is particularly strong in the pediatric and geriatricmarkets, with further application to other patients who prefer the convenience of a readily administered dosage form.

The oral route of administration is considered as the most widely accepted route because of its convenience of self administration, compactness and easy manufacturing. When put in the mouth, these dosage forms disintegrate instantly to release the drug, which dissolves or disperses in the saliva. Thereafter, the drug may get absorbed from the pharynx and oesophagus or from other sections of gastrointestinal tract as the saliva travels down. In such cases, bioavailability is significantly greater than that observed from conventional tablet dosage form.

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Review Article

A brief review on bubble baby disease

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ABSTRACT

Bubble baby disease is scientifically known as Adenosine deaminase - Severe combined immunodeficiency disease (ADA-SCIDS) which is a rarely occurring disease predominantly in infants (one in a lakh population). The disease is initiated by a complete deficiency of the immune system where the infants cannot tolerate even minor infections or allergies. Further, it is mainly caused due to the mutation in the gene IL2RG located on the X chromosome of the parents. To date, there is no particular test to diagnosis this disease, and delay in diagnosing this disease may lead to the death of a particular infant. Furthermore, in recent times researchers are concentrating on developing a test method to diagnose the disease rapidly. The treatment options include bone marrow transplantation, gene therapy, and pharmacotherapy (Calcarea phosp tablets) with reckeweg treatment (natural immunity booster drops). Though therapies very effective in improving the health of infants they possess few drawbacks like keeping the babies in sterile and isolated conditions which are done by placing the baby in a bubble made up of plastic. This short communication will cover about the disease and treatment options available in the present scenario.

Keywords: Bubble baby disease; Immunodeficiency; X chromosome; IL2RGgene; Infants

INTRODUCTION

Severe combined immunodeficiency (SCID) is a group of genetic diseases causing profound developmental and functional impairment of T cells, affecting cellular and humoral immunities. Under this classification when an infant is unable to synthesize adenosine which decreases levels of T&B lymphocytes leading to a complete shutdown of the immune system and making the baby live in a bubble made of plastic is termed as bubble baby disease as shown in Fig 1. [1]Further, among the various genes that cause this disorder IL-2 receptor gamma chain gene (IL2RG) which accounted for more than 19% of total 45 cases prior and post T-cell receptor excision circle (TREC) in the USA

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and a major cause factor for bubble baby disease. [3] Infants suffering from this disease will be very sensitive even for mild infections like a common cold, ringworm infections, etc. [3]

Fig 1. Boy in a bubble

SIGNS AND SYMPTOMS

Symptoms include rashes, diarrhoea, recurrent infections, and difficulty gaining weight, weakness, and/or growth delay.Organisms that would cause mild to moderate illnesses in healthy people may cause life-threatening infections in babies with this disease. And some of the infections observed are yeast (thrush or diaper rash), chickenpox, measles, herpes virus (cold sores), ear infections, meningitis (brain infections), or pneumonia that do not respond well to standard medical treatments. Children with SCID may also become infected with viruses (cytomegalovirus) from breastmilk, other live viruses (for example, the rotavirus or chickenpox) from vaccination or from common colds (viruses or bacteria) from siblings or surrounding children with healthy immune systems that can get rid of those infections.[4]

CAUSES

Bubble baby disease is a recessive genetic disorder where an infant will acquire two recessive genes (abnormal gene) from each parent. The parent with one normal gene and one recessive gene will acts as a carrier for future generations without showing any symptoms. The chance for a child to become a carrier of the disease is 50% if only one parent has the one recessive gene. The risk for two carrier parents to both pass the altered gene and have an affected child is 25% with each pregnancy. The risk to have a child who is a carrier like the parents is 50% with each pregnancy. The chance for a child to receive normal genes from both parents is 25%. The risk is the same for males and females.[5] Further, T-negative, B-positive, natural killer (NK)-negative (T-B+NK-) that occurs when T cells and NK cells cannot respond to growth factors (cytokines) needed to develop and survive in the body. The most common cause of T-B+NK- SCID, is X-linked recessive SCID (X-SCID) caused by an altered IL2RG gene found on the X chromosome which is the main cause for the occurrence of bubble baby disease. The *IL2RG* gene codes for the protein gamma subunit (γ_c) of the cytokine receptors for interleukin (IL-)2, IL-4, IL-7, IL-9, IL-15, and IL-21. The γ_c receptor is defective in boys with X-SCID and cannot send signals from the growth factors needed to make functional T cells and NK cells. The B cells in these patients are also non-functional without help from T cells.[6]

DIAGNOSIS[7]

A sequence of tests helps in the diagnosis of bubble baby disease in children. Most of these are blood tests. Here's a brief explanation of these screening techniques.

Complete Blood Count: The clusters of white blood cells are the main pillars in maintaining the immunity of an individual. Further, this complete blood count will reveal the total number of lymphocytes present in the body. Infants or kids suffering from this disease will have a low count of these white blood cells and they are extremely vulnerable to infections, even the mild ones.

T cell, B cell, and NK cell count: These cells are also part of the human immune system which will be absent for the infants suffering from bubble baby disease.

Immunoglobulin levels (IgG, IgM, IgA, IgE): These are antibodies produced by the body to fight the microbes. A child suffering from bubble baby disease will be low on the count of these antibodies.

Specific genetic testing: This is another effective way of screening for bubble baby disease because many known genetic factors are contributing to this disease.

A clinical study was performed by Yu Lung Lau with 147 patients of Asia and North-Africa origin and the results stated that performing an early lymphocyte subsets for any infant with one or more of the following clinical features: family history, persistent candidiasis, BCG infections and ALC less than $3x10^9$/L which would confirm the diagnosis of SCID. [8]

TREATMENT

Various approaches can be used to manage this bubble baby disease which includes gene therapy,

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FORMULATION AND EVALUATION OF ATORVASTATIN CALCIUM LIQUISOLID TABLETS & COMPARING THE DISSOLUTION DATA WITH MARKETED TABLET

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ABSTRACT

Objective: The objective of the present investigation was to improve dissolution and bioavailability of practically insoluble lipid lowering drug Atorvastatin calcium using liquisolid technique. **Method**: Liquisolid compacts were prepared by using various carriers and a mathematical model for calculating the required quantities of powder and liquid ingredient to produce an acceptably flow and a compressible admixture. Micro crystalline cellulose, Lactose monohydrate, Hydroxy propyl methyl cellulose, Dicalcium phosphate , Silicon dioxide, Crosscarmellulose were employed as carrier, coating material and super disintegrant respectively. The prepared liquisolid compacts were evaluated for their micromeritic properties and drug-excipient interactions by FTIR. The liquisolid tablets were prepared and evaluated for their tableting properties. **Results:** The liquisolid systems showed acceptable micromeritic properties, the FTIR studies states that there is no chemical interaction between the drug and the excipients. The tableting properties of the liquisolid compacts were within the accepted limits. The release rate of Atorvastatin calcium was higher when compared to the marketed Atorvastatin calcium. **Conclusion**: In the present research work, the potential of liquisolid systems to enhance the dissolution properties of Atorvastatin calcium was investigated. In case of Atorvastatin calcium liquisolid tablets thereby revealing enhanced dissolution rate than marketed tablets. Thus the objective of incorporating Atorvastatin calcium into liquisolid system to achieve faster dissolution rates was met with success.

INTRODUCTION

The oral route of administration is preferred route for drug administration because of its high patient compliance and drug development, the problem associated with oral route was plasma drug concentration may not be reached. The solubility of drug is the major concern, it is the major factor to achieve desired concentration of drug in systemic circulation. Most of the hydrophobic drugs are slightly soluble drugs, for such drugs dissolution is the rate limiting step. The major Challenge for poorly soluble drugs is to enhance to dissolution rate, because the therapeutic dose of the drug substance depends upon bioavailability which in turn depends on the solubility and dissolution rate[1]. Various techniques have been employed in order to formulate drug delivery system which enhances the dissolution rate were lyophilization, microencapsulation, solid dispersion, inclusion, co precipitation, of drug solution or liquid drugs into soft or hard gelatin capsules. all the above techniques having high production cost and technology demanding[2]. By using the

liquisolid technology, a liquid may transfer into a free-flowing, readily compressible & apparently dry powder by simple physical blending with various excipients like carrier and coating material. Liquisolid technique is the most promising & new technique for improving dissolution among the various novel techniques. It promotes the dissolution rate of water insoluble drugs to a greater extent & also enhances the drug flow property[3]. In the liquisolid system drug is already exist in solution form in liquid vehicle and it is carried by the powder materials. Then the wetting properties increased due to increased surface area of drug available for dissolution[4]. Atorvastatin calcium is a synthetic lipid lowering drug. Now days it is being highly used for cardiovascular disease, hypercholesterolemia and many other diseases. Atorvastatin is an inhibitor of 3- hydroxy-3-methylglutaryl-coenzyme-A-(HMG-CoA) reductase. It is used to lower cholesterol and triglyceride levels in the blood. According to biopharmaceutical classification system (BCS), the Atorvastatin calcium having poor solubility and high permeability and the dissolution properties can be improved by application of liquisolid technique. In the present work, liquisolid tablets of Atorvastatin calcium were formulated with different carrier materials and evaluated for their Precompression and post compression parameters. Finally the *in-vitro* dissolution rate compared with the marketed Atorvastatin calcium tablets.

MATERIALS:

Atorvastatin calcium Purchased from Yarrow Chem Products, Mumbai, Micro crystalline cellulose, Di calcium Phosphate, Lactose, HPMC and Crosscarmellulose sodium were obtained from S.D Fine Chem. Ltd, Mumbai and all the other chemicals were used as Analytical grade.

METHODS:

Determination of λmax: An accurately weighed 10 mg of Atorvastatin calcium was transferred in a 100ml volumetric flask. To flask phosphate buffer was added in small proportion so as to dissolve Atorvastatin calcium. The volume was made up to 100 ml with phosphate buffer pH 6.8 to get a concentration of 100 µg/ml. 20 µg/ml solution of Atorvastatin calcium was prepared in dilution. The resulting solution was scanned in UV-Vis spectrophotometer from 400-200 nm to determine the λmax.

Calibration Curve: 100 mg of Atorvastatin calcium transferred into 100 ml volumetric flask and makeup the final volume with pH 6.8 phosphate buffer. From this stock solution different concentration 5 – 40 µg/ml was made up with pH 6.8 phosphate buffer. From each concentration sample was taken & the absorption was measured at 242 nm by using UV spectrophotometer by using pH 6.8 phosphate buffer as a blank. The graph was plotted by taking concentration on X-axis and absorption on Y-axis.

Drug Excipients Compatibility Studies: Compatibility study was performed by the KBr pellet method using the Fourier transform infraredspectrophotometer[5]. A baseline correction was made using dried potassium bromide, and then the spectra of Atorvastatin calcium, carrier and coating materials were obtained[6].

Solubility Analysis: Saturated solution were prepared by adding excess amount of Atorvastatin calcium to appropriate solvents like propylene glycol, Tween-80, Tween-40 and Span-80, then shaking on orbital shaker for 48hrs at 25 rpm under constant vibrations. The solution were filtered through 0.45micron filter, diluted suitably and analyzed by UV-visible spectrophotometer at 242 nm[7].

Determination of Flowable Liquid-Retention Potential (Ø-value): The admixture containing nonvolatile solvent and carrier or coating material were mixed using motor and pestle. In constant weight of nonvolatile solvent (Tween-40), increasing carrier or coating material (MCC, HPMC, DCP, Lactose and collodial silicon dioxide) was incorporated and on each addition, an angle of repose was determined. The flowable liquid retention potentional (Ø-value) of each liquid/powder admixture was calculated using the following equation[8].

Ø value = weight of liquid/weight of solid

Determination of Liquid Load Factors (LF) &Carrier and Coating ratio(R Value): The maximum amount of liquid load on carrier/coating material, termed "load factor" (LF). Appropriate amounts carrier and coating materials used to procedure an acceptable

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RESEARCH ARTICLE

Formulation, Phytochemical, Physical, Biological Evaluation of Polyherbal Vanishing Cream, and Facewash

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ABSTRACT:

The present study aims at formulation of polyherbal vanishing cream and face wash, determination of total flavonoid content of herbs used, evaluation of formulations for various physical parameters followed by antibacterial and antifungal activities. The problems of premature ageing, damage due to irradiation, loss of pigmentation, moisture, nourishment, and acne can be solved by supplementation of health benefits provided by selected multiple herbs in the formulations. The use of polyherbal vanishing cream and face wash promotes skin health and beauty. The selected nine herbs in vanishing cream and eleven herbs in face wash formulations contain good amount of flavonoids capable of protecting skin against damage. The total flavonoid content of herbs used was determined, followed by evaluation of various physical parameters such as pH, viscosity, spreadability and compared with marketed formulations. Further, the formulations were tested against gram positive *S.aureus*, gram negative *E.coli*, and fungus *C.albicans* which are common associates of acne and cosmetic appliances. The results indicated that both the formulations displayed better antibacterial and antifungal activities than marketed formulations. Therefore, they can be tested further for their performance and quality control parameters.

KEYWORDS: Polyherbal vanishing cream, facewash, skin problems.

INTRODUCTION:

Skin, the largest human organ is the first line of defense for external exposure to UV radiations, dust, environmental bacteria, fungi *etc*., which cause ageing and other infections. Skin has been reported to reflect the general inner-health status and aging [1].

UV exposure is known to negatively affect immune system functions, cause erythema, changes in skin elasticity, structure (roughness, scaling, volume, and wrinkles), trans epidermal water loss, and skin cancers. The adverse effects of ultraviolet radiation on the skin, are caused by excessive generation of reactive oxygen

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species [2]. Prevention is the best and most effective way to work against skin aging effects [3,4]. The best prevention strategy against the harmful action of free radicals is a balanced nutritional diet containing rich anti-oxidative flavonoids [5]. *Acne vulgaris* is an extremely common disorder of skin which includes follicular hyper proliferation, increased sebum secretion and colonization of organism. Acne is not infectious disease, generally caused by various factors such as environmental pollution, harmful chemicals, bacteria, fungi and treated by different mechanisms such as controlling the sebum production, use of antibiotics against bacteria and fungi that are responsible and sometimes anti-inflammatory agents [6]. Natural or synthetic sponges used in daily hygiene and in removing make-up act as reservoirs and vehicles in the transmission of bacterial species such as *Staphylococcus epidermidis, Staphylococcus aureus and Escherichia coli* [7]. Some strains of *E. coli* are pathogenic, which means that they can cause infection that leads to illnesses, such as diarrhea, urinary tract infections, respiratory illness, and pneumonia [8]. *S. aureus* is the most dangerous of many common *staphylococcal* bacteria species. These gram-positive, sphere-shaped (Coccal) bacteria often cause skin infections but can also cause pneumonia, heart valve infections, and bone infections [9]. *Candida albicans*, a type of yeast fungus found in moist areas of human body such as mouth, skin and genitals. Yeast infections on the skin are called cutaneous candidiasis which may result due to lack of hygiene, excessive sweating, and use of harsh facial products, rough scrubbing, and facial tissue irritation. The skin rash due to candidiasis leads to itching, ulcers, dry skin patches, burning, and pimples [10]. Facial skin is delicate, regular use of ordinary soaps can cause loss of moisture in the skin. A low fat moisturizer that disperses into the skin is called as a vanishing cream [11]. The cream acts as a moisturizer, anti-bacterial, anti-fungal agent, and fairness expert, removes ageing signs, and provides required nutrients to the skin. A face wash is a mild cleanser that does the vital job of cleansing the skin, prevents acne, anti-wrinkle, anticancer, makes germ free, smooth, fresh, moisturizes the horny layer without causing any harshness to the skin, and makes to look younger [12].

Frequently researched antioxidants such as flavonoids, have been referred as agents capable of promoting skin health and beauty The use of flavonoids in cosmetic formulation provides both medicinal and cosmetic benefits [13]. They have been reported to possess potent anti-oxidant properties and have been widely used in the skin care industry either as topically applied agents or oral supplements in an attempt to prolong youthful skin appearance. Several thousand molecules having a polyphenol or flavonoid structure have been identified in plants being generally involved in defense against UV radiation, UV-induced skin inflammation, oxidative stress, DNA damage, and risk of skin cancers or aggression by pathogens [14]. These polyphenolic compounds or flavonoids have proven to improve skin microcirculation, protection of the blood vessels, [15] inhibit the synthesis of melanin [16], inhibit the release of inflammatory mediator - histamine [17], reduce erythema, inhibit the platelet aggregation [18] and thus produce beautifying effects on the skin surface. The contribution of the traditional preparations, which are normally polyherbal, is increasing day by day because of the general impression that these products are safe with multiple applications; while the single-molecule based modern drugs used in allopathic system can cause severe adverse effects [19]. Topical polyherbal formulations, containing flavonoids are used against acne, skin tan, and other skin problems due to their anti-microbial, anti-inflammatory and anti-oxidant activities. Skin, the organ of beauty has been an interesting research fields but also a common field of interest for humans throughout the years, from ancient times to nowadays. With this view the medicinal plants for the study were selected based on literature review. The current research has been planned to carryout *in vitro* flavonoid content of the selected plant species, formulate, and evaluate the polyherbal vanishing cream and face wash for pharmaceutical parameters followed by antibacterial and antifungal activities.

MATERIALS AND METHODS:

The plant materials were collected collected in the month of December during afternoon from local grounds of Prasadampadu and Enikepadu, Vijaya Institute of Pharmaceutical Sciences for Women, Enikepadu, coordinates 16°32'45"N 80°34'12"E of Vijayawada rural region, Krishna district, Andhra Pradesh, India. Dr. P. Satya Narayana Raju, Plant Taxonomist, Department of Botany and Microbiology, Acharya Nagarjuna University, Guntur, Andhra Pradesh, India, identified and authenticated the plant specimens namely jungle geranium *Ixora coccinea*, negundo *Vitex nigundo*, kalmegh *Andrographis paniculata*, pomegranate *Punica granatum*, bryophyllum *Millettia pinnata*, pongam *Kalanchoe pinnata*, lemon grass *Cymbopogon flexuosus* and kachnar *Bauhinea variegate* (Figure 1a-8b). The plant materials sandal wood, honey, seeds of mustard, green gram, fruits of myrobalan, amla, and lemon, were purchased from the local market. The liquorice root powder, camphor oil, lemon grass oil, and xanthan gum were collected from the department of Pharmacognosy, Vijaya Institute of Pharmaceutical Sciences for Women, Enikepadu, Vijayawada. Marketed formulations used were Himalaya kesar, alfalfa face cream and Patanjali neem, tulsi facewash. The collected plant materials used in the formulation of vanishing cream are jungle geranium (Figure 1a and 1b), kalanchoe (Figure 2a and 2b), and bryophyllum (Figure 3a and 3b).The collected plant materials used in the formulation of face wash are

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A REVIEW STUDY ON DETERMINATION OF ABACAVIR AND LAMIVUDINE BY USING DIFFERENT ANALYTICAL METHODS IN BULK AND TABLET DOSAGE FORMS

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ABSTRACT

Abacavir and lamivudine are well-established nucleoside reverse-transcriptase inhibitors available as a once-daily FDC. Hepatic function should be monitored closely in HIV/HBV co-infected patients who discontinue lamivudine-containing products as severe acute exacerbations of HBV have been reported. This is a different types of methods by using for the determination of abacavir and lamivudine accurately it shows the simple rapid, accurate, precise, and reproducible validated for the different analytical methods was developed for the determination of abacavir and lamivudine in bulk and tablet dosage forms. An analytical technique is a method that is used to determine the concentration of a chemical compound or chemical element. There are a wide variety of techniques used for analysis, from simple weighing (gravimetric analysis) to titrations (titrimetric) to very advanced techniques using highly specialized instrumentations. The most common techniques used in analytical methods are titrimetry, potentiometry and voltammetry, spectroscopy, chromatography.

KEYWORDS: abacavir and lamivudine, nucleoside reverse-transcriptase inhibitors, titrimetry, potentiometry, spectroscopy and chromatography.

INTRODUCTION

Abacavir

A sulfate salt form of abacavir, a nucleoside reverse transcriptase inhibitor analog of guanosine. This agent decreases HIV viral loads, retards or prevents the damage to the immune system, and reduces the risk of developing AIDS.[1] HIV infection is usually treated

with antiretroviral therapy regimens, which consist of three or more different drugs used in combination. Typical antiretrovirals used in these regimens include NRTIs, non-NRTIs, protease inhibitors, and integrase strand inhibitors.[2] Abacavir makes an ideal addition to these types of combination therapies because of its dosing flexibility. It can be administered either once or twice a day to match the dosing pattern of other drugs and can also be administered as tablets that contain other antiretroviral drugs such as lamivudine and zidovudine, allowing for a reduction in pill count. Abacavir is generally well tolerated, and common side effects include nausea, headache, and diarrhea.[3] The patients experience a hypersensitivity reaction (HSR) within the first 6 weeks of treatment. Symptoms of an HSR include at least two of the following: fever, rash, cough, gastrointestinal symptoms, dyspnea, and fatigue.[4]

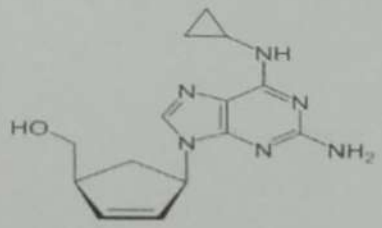

Fig: 1: Structure of abacavir.

Lamivudine

A synthetic nucleoside analogue with activity against hepatitis B virus (HBV) and HIV. Intracellularly, lamivudine is phosphorylated to its active metabolites, lamivudine triphosphate (L-TP) and lamivudine monophosphate (L-MP). In HIV, L-TP inhibits HIV-1 reverse transcriptase (RT) via DNA chain termination after incorporation of the nucleoside analogue into viral DNA. In HBV, incorporation of L-MP into viral DNA by HBV polymerase results in DNA chain termination. L-TP is a weak inhibitor of mammalian DNA polymerases alpha and beta, and mitochondrial DNA polymerase.[5] Lamivudine may be included as part of post- exposure prevention in those who have been potentially exposed to HIV. Common side effects include nausea, diarrhea, headaches, feeling tired, and cough. Serious side effects include liver disease, lactic acidosis, and worsening hepatitis B among those already infected.[6]

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IN-SITU GEL DRUG DELIVERY SYSTEMS FOR THE TREATMENT OF PERIODONTITIS

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ABSTRACT

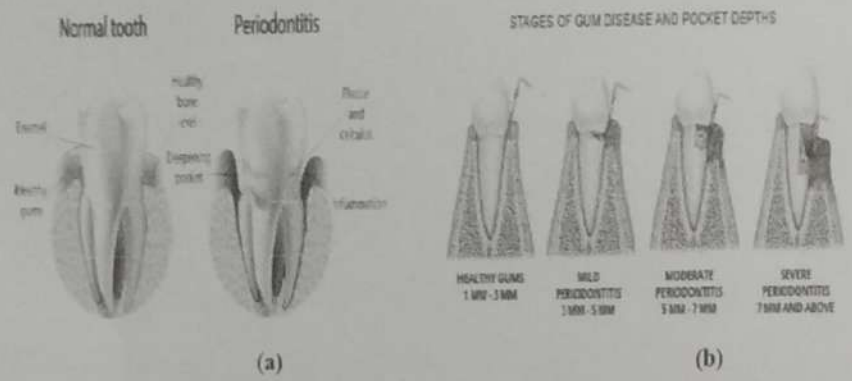
Periodontitis is an inflammatory disease characterized by progressive destruction of periodontal soft and hard plaque tissues leading to permanent tooth loss. The incidence of these diseases can be reduced by mechanical plaque removal or scaling and root planning (SRP) along with systemic and locally delivered antimicrobial agents or statins. *In-situ* gels are the drug delivery systems that are in solution form before administration in the body, but once administered in to the body undergoes gelation *in-situ* to form gel. Mechanisms involved in *in-situ* gel formation are solvent exchange, UV-irradiation, ionic cross-linkage, pH change, and temperature modulation. Polymers exhibit sol-gel phase transition and thus trigger drug release in response to external stimuli. The polymers used must be biocompatible, adhere properly to mucus, and exhibit pseudo plastic behavior. The main advantages of this route of drug administration is that it can deliver the active agents directly to the site of action at bactericidal concentration and it can facilitate prolong drug delivery.

KEYWORDS: *In situ* gel, Periodontitis, Thermo-sensitive modulation, pH change and Statins.

INTRODUCTION

Periodontitis (PD) is an immuno-inflammatory disease of tooth supporting tissues (the gingiva, bone and periodontal ligament), which results in progressive destruction of surrounding soft and hard tissues with eventual tooth mobility and exfoliation. PD starts as an

inflammatory reaction confined to the gingival tissue (gingivitis), but when left untreated it spreads to periodontal ligament, cementum and supporting alveolar bone, resulting in pocket formation which provides a favourable environment for the growth of pathogenic anaerobic microorganisms. Chronic periodontitis primarily affects adults, but aggressive periodontitis may intermittently occur in children. Perioceutics, involves the delivery of a right therapeutic agent via systemic and local means as an adjunct to mechanical therapy.[1,2]



(a) (b)

Fig.1: a) Signs of Gum Disease/Periodontitis b) Stages of Periodontitis.

Classification of Perioceutics

Based on the application

1) Personally applied (in patient home self-care)

a. Subgingival non-sustained drug delivery: Home oral irrigation jet tips, Traditional jet tips, Oral irrigation (water pick), Soft cone rubber tips (pick pocket).

b. Sustained subgingival drug delivery

2) Professionally applied (in dental office)

a. Nonsustained subgingival drug delivery - Professional pocket irrigation

b. Sustained subgingival drug delivery.[1,2]

Drugs used for the treatment of PD

1. Antimicrobial agents or Antibiotics: Tetracycline, Minocycline, Doxycycline, Chlorhexidine, Clarithromycin, Clindamycin, Ciprofloxacin, Ampicillin, Fluoroquinolones (Ciprofloxacin), Erythromycin, Azithromycin, Metronidazole.[12,15]
2. The pleiotropic effects of statins have been evaluated to assess their potential benefit in the treatment of various inflammatory and immune-mediated diseases including periodontitis.[4,7,25]

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(REVIEW ARTICLE)

Bilayer tablet technology: A novel approach

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Abstract

Bilayer tablet is new era for the successful development of controlled release formulation along with various features to provide a way of successful drug delivery system. Controlled release dosage forms have been extensively used to improve therapy with several important drugs. Use of bilayer tablet is a very different aspect for anti-inflammatory and analgesic. Bilayer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances and also for sustained release tablet in which one Layer is immediate release as initial dose and second layer is maintenance dose. Bilayer tablet is improved beneficial technology to overcome the shortcoming of the single layered tablet. This article provides an overview of the bilayer tablet technology, highlighting the main benefits of this type of oral dosage forms while providing a description of current challenges and advances toward improving manufacturing practices and product quality.

Keywords: Bilayer tablet; Sustained release; Immediate release; Incompatible

1. Introduction

Over the past 30 years greater attention has been focused on development of sustained or controlled release drug delivery systems. The development of combination of two or more active pharmaceutical ingredients (API) in a single dosage form has increased in the pharmaceutical industry, promoting patient convenience and compliance [1]. Bilayer tablet is new era for the successful development of controlled release formulation along with various features to provide a way of successful drug delivery system. Bilayer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances and also for sustained release tablet in which one layer is immediate release as initial dose and second layer is maintenance dose [2].

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Figure 1 Bilayer tablet [14]

Need of bilayer tablets

1. Controlling the delivery rate of single or two different active pharmaceutical ingredients.
2. To modify the surface area available for API by swellable/erodible barriers for modified release.
3. To separate incompatible Active pharmaceutical ingredient (APIs) from each other.
4. To control the release of API from one layer by utilizing the functional property of the other layer.
5. For the administration of fixed dose combinations of different APIs.

Advantages

1. Cost is subordinate compared to all other oral dosage form.
2. Maximum chemical and microbial stability over all oral dosage form.
3. Offensive odor and bitter taste can be masked by coating technique.
4. Flexible Concept.
5. They offer greatest dose accuracy and least content variability.
6. Easy to swallowing with least tendency for hang up.
7. Suitable for large scale production

Disadvantages

1. Some drugs resist compression into dense compacts due to low density character.
2. Bitter tasting drugs or drugs that are sensitive to oxygen may require coating.
3. Difficult to swallow in case of children and unconscious patients.
4. Drugs with poor wetting, slow dissolution properties may be difficult to formulate.

Ideal characteristics of bilayer tablets

1. It should be free from defects like chips, cracks, discoloration and contamination.
2. It should have sufficient strength during its production, packaging, shipping and dispensing.
3. It should have the chemical and physical stability overtime.
4. It releases the agents in a predictable and reproducible manner.
5. It must have a chemical stability and shelf-life.

2. Challenges in bilayer tablet manufacturing

Conceptually, bilayer tablets can be seen as two single-layer tablets compressed into one. In Practice, there are some manufacturing challenges [3].

Delamination: Tablet falls apart when the two halves of the tablet do not bond completely.

Cross-Contamination: When the granulation of the first layer intermingles with the granulation of the second layer results cross contamination occurs. Proper dust collection goes a long way toward preventing cross contamination.

Production yields: To prevent cross contamination, dust collection is required which leads to losses. Thus, bilayer tablets have lower yields than single layer tablets.

Cost: Bilayer tableting is more expensive than single layer tableting for several reasons. First, the tablet press costs more. Second, the press generally runs more slowly in bilayer mode. Third, development of two compatible granulations is must, which means more time spent on formulation development, analysis and validation [4].

3. Types of bilayer tablet press

3.1. Single sided tablet press

The simplest design is a single sided press with both chambers of the doublet feeder separated from each other. Each chamber is gravity or forced fed with different power, producing the two individual layers of tablets. When die passes under the feeder, it is first loaded with the first layer powder followed by the second layer powder. Then the entire tablet is compressed in one or two steps [5].

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LIQUISOLID TECHNOLOGY: A REVIEW

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ABSTRACT
The liquisolid (LS) technique is a novel approach for delivery of drugs through the oral route. This technique is suitable for poorly soluble or water insoluble drugs, highly permeable drugs (BCS Class II drugs) and also for immediate or sustained release formulations. The design of liquisolid systems are mainly intended for enhancement of solubility, dissolution rate and bioavailability of poorly water-soluble and highly lipophilic drugs. Improvement in bioavailability may be due to increased surface area, increased aqueous solubility and increased the wettability of the drug. Liquisolid technique also has the potential to be optimized for the reduction of drug dissolution rate and thereby production of sustained release systems. Overall, liquisolid technique is a most promising and novel technique for enhancing the dissolution and bioavailability of poorly water soluble drugs and sustaining drug release from tablet matrices. The current review mainly focuses on different carriers, solvents and coating materials employed in liquisolid technique. Literature reports on the applicability of liquisolid compact techniques over a wide range of pharmaceutical formulations are also explicated.

KEYWORDS: Bioavailability, Wettability, Carrier and Sustained Release.

INTRODUCTION
Solubility is one of the important parameters to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown. Poorly water soluble drugs will be inherently released at a slow rate owing to their limited dissolution rate within the gastrointestinal tract (GIT) contents. One challenge for poorly water soluble drugs is to enhance the rate of dissolution. Various techniques have been employed to formulate oral drug delivery system that would enhance the dissolution profile.[1] Solid dispersions, micronization, use of mesoporous silica carriers, ball milling technique, use of complexing agents, crystal engineering, solubilization by surfactants and liquisolid (LS) technique developed. These techniques take advantage of the increased dissolution rate resulting from the addition of a solubilizing agent, particle size reduction or the drug being in an already dissolved or amorphous state.

LS technique has been identified as a promising technique to improve the dissolution rate of poorly water soluble drugs.[2] When properly formulated, LS powder blends possess acceptable flowability and compressibility properties. They are prepared by simple blending with selected powder excipients referred to as the carriers and the coating materials. This technique was successfully applied for low dose poorly water soluble drugs. Drug can be present in a completely or partially dissolved state in the LS formulation. The LS formulation can then facilitate the release of this drug by two mechanisms: (1) Already dissolved drug only need to diffuse out of the formulation and (2) the liquid component of the formulation act as a solubilizing aid to facilitate the wetting and dissolution of undissolved particles. Since dissolution of a non polar drug is often the rate limiting step in gastrointestinal absorption, better bioavailability of an orally administered poorly water soluble drug is achieved when the drug is formulated using a LS system.

Advantages
1. Poor water soluble or water insoluble drugs can be formulated into LS systems.
2. Better availability of an orally administered poorly water soluble drugs.
3. LS tablets or capsules of poorly water soluble drugs exhibit enhanced *in vitro* and *in vivo* drug release.
4. Can be applied to formulate liquid medications such as oily liquid drugs.
5. Enhanced bioavailability can be obtained as compared to conventional tablets.

6. Drug release can be modified using suitable formulation ingredients.
7. Can be used in controlled drug delivery and zero-order release can be obtained.
8. Capability of industrial production is also possible.
9. Production cost is lower than that of soft gelatine capsules.

Limitations

1. This technique is only for slightly / very slightly water soluble and practically water insoluble drugs.
2. In LS formulation, high levels of carrier and coating materials should be added. This will increase the weight of tablets to above one gram which makes them difficult to swallow.
3. The LS systems have drug loading capacities and they require high solubility of drug in non-volatile liquid vehicles.

Classification of Ls Systems

The term LS systems refers to the powdered forms of liquid medications formulated by converting liquid lipophilic drugs or drug suspensions or solutions of water insoluble solid drugs in suitable non-volatile solvent systems, into dry, non-adherent, free flowing and readily compressible powder admixtures by blending with the selected carrier and coating materials. Based on the type of liquid medication encapsulated, LS systems may be classified into three subgroups: (1) Powdered drug solutions, (2) powdered drug suspensions and (3) powdered liquid drugs. Simultaneously, based on the formulation technique used, LS systems may be classified into two categories namely: (1) LS compacts and (2) LS microsystems.

The term **LS compacts** refers to immediate or sustained release tablets or capsules prepared, combined with the inclusion of appropriate excipients required for tableting or encapsulation, such as lubricants and for rapid or sustained release action, such as disintegrants or binders, respectively.

The term **LS microsystems** refers to capsules prepared by combining the drug with the carrier and the coating materials with inclusion of an additive in the liquid medication wherein the resulting unit size may be as much as five times that of LS compacts.[3]

EXCIPIENTS USED IN PREPARATION OF LS SYSTEMS

Non-volatile Solvents

With the LS technology as described by Spireas, a liquid may be transformed into free flowing, readily compressible and apparently dry powder by simple blending with selected excipients such as the carriers and coating materials. The liquid portion, which can be a liquid drug, a drug suspension or a drug solution in suitable non-volatile solvents is incorporated into the porous carrier material. Inert, preferably water-miscible, not highly viscous, non-toxic organic solvents with high boiling point such as propylene glycol (PG), liquid polyethylene glycols (PEG), glycerine and polysorbates are best suitable as liquid vehicles.[4] Once the carrier is saturated with liquid, a liquid layer is formed on the particle surface which is instantly adsorbed by the fine coating particles. Thus, an apparently dry, free flowing and compressible powder is obtained.

Non-volatile solvents enhance the solubility of poorly water soluble drugs by formation of micelles and act as dispersants. For immediate release LS compacts, the selection of solvent is based on high drug solubility and for sustained release, solvents with least solubilizing capacity is selected. Since there are no specific non-volatile liquid vehicles used in the preparation of LS compacts, different non-aqueous solvents have been used as non-volatile liquid vehicles in the preparation of immediate release and sustained release LS formulations with different drugs. So, selection of non-volatile solvent in LS technique is important to obtain immediate or sustained release formulation.[5]

Propylene glycol (PG), an inert solvent miscible with water is a suitable liquid vehicle for LS systems. It is not highly viscous (dynamic viscosity: 58.1 cp at 20 °C) and has a high boiling point (188 °C). PG is used in a wide variety of pharmaceutical formulations and is generally regarded as a relatively non-toxic material.[5] PG was successfully used as non-volatile solvent in LS preparation of drugs such as bromhexine hydrochloride, pioglitazone hydrochloride[6], to name a few.

Carrier materials

In LS approach, the carrier material plays as a major role in obtaining the dry form of the powder from the liquid medication. Each carrier has its unique property. Selection of the carrier will depend upon its liquid holding capacity, the flowability of the powder and which carrier requires less compression force.[7] The particles of the carrier materials are compression enhancing, relatively large, preferably porous particles possessing sufficient absorption property which contributes in liquid absorption, *e.g.* various grades of microcrystalline cellulose (MCC), starch, lactose, sorbitol, dibasic calcium phosphate (DCP), etc.

Microcrystalline cellulose (MCC) is a purified, partially depolymerized cellulose that occurs as a white, odorless, tasteless, crystalline powder composed of porous particles. It is commercially available in different particle sizes and moisture grades that have different properties and applications. The specific surface areas and particle sizes of carrier materials are important parameters for the optimization of LS systems.

MCC is widely used in pharmaceuticals, primarily as a binder/diluent in oral tablet and capsule formulations where it is used in both wet granulation and direct compression processes. In addition to its use as a carrier

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Review Article

Nanoparticles: A smart drug delivery

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ABSTRACT

In recent years, there has been an exponential interest in the development of novel drug delivery systems using nanoparticles. Nanoparticles are defined as particulate dispersions or solid particles with size in the range of 10-1000nm. There has been a considerable research interest in the area of drug delivery using particulate delivery systems as carriers for small and large molecules. Particulate systems like nanoparticles have been used as a physical approach to alter and improve the pharmacokinetic and pharmacodynamic properties of various types of drug molecules. Nanoparticles have been extensively studied as particulate carriers in the pharmaceutical and medical fields, because they show promise as drug delivery systems as a result of their sustained and targeting release properties, subcellular size, biocompatibility with tissue and cells. Various polymers have been used in the formulation of nanoparticles for targeting drug delivery research to increase therapeutic benefit, while minimizing side effects. Polymeric nanoparticls with a size in the nanometer range protect drugs against *in vitro* and *in vivo* degradation. The use of nanoparticle drug delivery is a universal approach to increase the therapeutic performance of poorly soluble drugs in any route of administration. In this review focused various aspects of nanoparticle formulation, characterization and their applications in targeting delivery.

Keywords: Nanoparticles, Drug Targeting and Controlled Release.

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INTRODUCTION

The control drug delivery alters the pharmacokinetics and pharmacodynamics of drug substance in order to improve the therapeutic efficacy and safety. Besides more traditional matrix or reservoir drug delivery systems, colloidal drug delivery system has gained in more popularity[1]. Colloidal drug delivery systems offer a number of advantages over conventional dosage forms. Due to their small particle size, colloidal preparations lend themselves to parenteral preparations and may be useful as sustain release injections for the delivery to a specific organ or target site. The major colloidal drug delivery systems include liposome and nanoparticles[2].

Nanoparticles in pharmaceutical applications have gained plenty of research attention during recent decades. Although the research concerning formulation of nanoparticles into drug delivery devices has been extensive, only a few polymeric nanoparticulate products have reached the market. Among the drugs used in nanoparticle formulations, particularly cancer therapeutics is widely studied because the formulation might reduce toxicity of the drug while improving efficacy of the treatment[3]. In addition to drug molecules, other candidates to be encapsulated in or coupled with nanoparticles include macromolecules like proteins, peptides and genes (nucleic acids). These kinds of molecules tend to be inactivated in the body by enzymatic degradation. In terms of controlled release, nanoparticles provide protection against the body conditions resulting in sustained release and maintenance of bioactivity before the drug reaches the target[4].

Nanoparticles are colloidal polymeric particles of size below 1μm with a therapeutic agent either dispersed in polymeric matrix or encapsulated in polymer. The term polymeric nanoparticle encompasses nanospheres and nanocapsules. Nanospheres are defined as a polymeric matrix in which the drug is uniformly dispersed and nanocapsules are described as a polymeric membrane that surrounds the drug in the matrix[5].

Advantages: These advantages include

1. Targeted delivery of drugs to the specific site to minimize toxicity
2. Improved bioavailability by reducing fluctuations in therapeutic ranges

3. Improved stability of drugs against enzymatic degradation
4. Controlled release reduces dosing frequency with improved patience compliance.
5. The small particle size also reduces potential irritant reactions at the injection site.

MATERIALS USED FOR PREPARATION OF NANOPARTICLES

A broad range of synthetic and natural polymers available for nanoparticle formation, but their biocompatibility and biodegradability are the major limiting factors for their use in the drug delivery area. Synthetic polymers, on the other hand, offer better reproducibility of the chemical characteristics of the synthesized nanoparticles as compared to the natural polymers

Natural Polymers

Various polymers have been used in the formulation of nanoparticles for drug delivery research to increase therapeutic benefit, while minimizing side effects. Natural polymers have been classified into polysaccharides and proteins. Proteins are gelatin, albumin, lecithin, legunin and vicillin. Polysaccharides are alginate, dextran, chitosan and pollulan[8].

A. Chitosan

Chitosan is a modified natural carbohydrate polymer prepared by the partial N-deacetylation of chitin, a natural biopolymer derived from crustacean shells such as crabs, shrimps and lobsters. Chitosan is also found in some microorganisms, yeast and fungi. After cellulose chitin is the second most abundant polysaccharide in nature. It is physically protected, non poisonous, biocatalyst and eco-friendly polysaccharide[7]. Although chitin is insoluble in most solvents, chitosan is soluble in most organic acidic solutions at pH less than 6.5 including formic, acetic, tartaric, and citric acid.

B. Gelatin

Gelatin is one of the protein materials that can be used for the production of nanoparticles. It is obtained by controlled hydrolysis of the fibrous, insoluble protein, collagen, which is widely found as the major component of skin, bones and connective tissue. The interest was based on the facts that gelatin is biodegradable, non-toxic, easy to crosslink and to modify chemically and has therefore an immense potential to be used for the preparation of colloidal drug delivery systems such as microspheres and nanoparticles[7].

C. Albumin

Albumin is an good-looking macromolecular shipper and extensively use to arrange nanospheres and nanocapsules, due to its availability in pure form and its biodegradability, nontoxicity and nonimmunogenicity. On the other hand, albumin nanoparticles are biodegradable, easy to prepare in defined sizes, and carry reactive groups on their surfaces and also offer the advantage that ligands can easily be attached by covalent linkage[8].

D. Alginate

Alginate, a naturally occurring copolymer of glucuronic acid and manuronic acid, is widely used for pharmaceutical applications. Specifically, the simple aqueous-based gel formation of sodium alginate in the presence of divalent cations such as Ca^{2+} has been used for drug delivery[9]. Alginate is anionic polysaccharide that it has been widely used in drug delivery High drug encapsulation efficiency was achieved in alginate nanoparticles, ranging from 70%-90%.

Synthetic Polymers

Synthetic polymers offer better reproducibility of the chemical characteristics as compared to the natural polymers. Common classes of polymers used to encapsulate drugs in colloidal systems include polyamides, poly (amino acids), polyesters, polyorthoesters and polyanhydrides.

A. Lactide and Glycolide copolymers

Most popular biodegradable polymers used in drug delivery are polyester copolymers based on lactic and glycolic acids. Poly (d,l-lacticco-glycolic acid) (PLGA) is used for the manufacture of implants and internal sutures and is known to be biocompatible, degrading to produce the natural products lactic acid and glycolic acid[4].

B. Poly (ε-Caprolactones)

PCL is a water permeable polymer with hydrophobic and high crystalline properties. It undergoes bulk erosion by random hydrolytic chain cleavage in the first phase, resulting in a decrease in the molecular weight of the polymer[10].

C. Polyanhydrides

The hydrophobic and crystalline materials have been shown to undergo erosion by surface hydrolysis, minimizing water diffusion into the bulk of the delivery device. The monomeric anhydride bonds have extreme reactivity toward water and undergo hydrolysis to generate the dicarboxylic acids[10]. Although hydrolysis is catalyzed by both acid and base, an increase in pH enhances the rate of hydrolytic degradation.

PREPARATION OF NANOPARTICLES

The nanoparticles prepared by using following methods:

Emulsification–solvent diffusion

It is widely used method for preparing nanoparticles[3]. The drug and polymer dissolved in a partially water soluble solvent. Commonly used solvents are propylene carbonate, benzyl alcohol, ethyl acetate, isopropyl acetate, methyl acetate, methyl ethyl ketone, butyl lactate or isovaleric acid. The organic phase is saturated with water and is then diluted with an extensive amount of pure water to facilitate diffusion of the organic solvent from the organic phase droplets leading to the precipitation of the polymer as presented in Figure: 1. The aqueous phase may contain surfactants such as Pluronic, PVA and sodium taurocholate. Finally, the solvent is eliminated by evaporation.

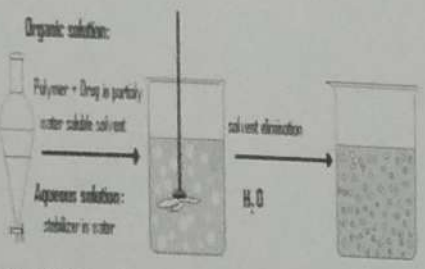

Figure 1: Schematic representation of the emulsification-solvent diffusion method

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ACID NEUTRALIZATION CAPACITY AND COST EFFECTIVENESS OF ANTACID SUSPENSIONS SOLD ACROSS VARIOUS RETAIL PHARMACIES IN VIJAYAWADA

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Keywords:

Antacids, Acid neutralizing capacity, Cost effectiveness and Titrimetric method

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ABSTRACT: Antacids are the commonly prescribed drugs for treating gastroesophageal reflux disease (GERD). As these are manufactured and marketed by various multinational and local companies there is a need for evaluating the cost effectiveness and efficacy of these antacids as a matter of public concern. In the present study an attempt has been made to determine and compare the acid neutralization capacity of antacid preparations sold across various retail pharmacies in Vijayawada, Andhra Pradesh, India to find out unit cost and effectiveness of antacid with respect to its composition and manufacturer. Six different antacid suspensions manufactured by different companies were evaluated for the oraganoleptic properties, viscosity, pH and particle size and were compared with each other. Acid neutralizing capacity was determined by titrimetric method. Cost effectiveness was done by calculating the cost per ml of antacid and efficacy was evaluated based on acid neutralizing capacity of antacid preparation. Suspension Medicaine® having higher acid neutralization capacity (30.22 mEq) with unit cost Rs.0.52/ml was found to be the most effective brand as this product exhibited the highest neutralization capacity with the lowest dose and price. Good acid neutralization capacity and the cost effectiveness of antacid medicaine® suspension have beneficial parameters in improving the prescribing pattern. It benefits both doctor as well as patient.

INTRODUCTION: Antacids are widely used to neutralize excess acid and relieve the condition of heartburn or acidity in many patients. A wide spectrum of antacids is now available in the world pharmaceutical market as over the counter (OTC) drugs. These one or multiple component drugs contain medical ingredients suitable for treating symptoms such as heartburn and dyspepsia, which are associated with hyperacidity in the stomach.

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The principal characteristics of the antacids are their rapid action and effective neutralization of acid. The potency of an antacid is generally expressed in terms of its Acid neutralizing capacity (ANC). ANC is defined as the number of milli equivalents (mEq) of 1N HCl that is brought to a pH of 3.5 in 1 hour by a unit dose of an antacid preparation [1].

Commonly, antacids are available as solid dosage forms and as suspensions. In comparison to solid dosage forms liquid antacids are generally preferred as they possess a higher neutralization capacity due to their smaller particle size and greater surface area. The ANC and price of the product are two important attributes for an ideal antacid product in addition to the safety and

palatability. Hence there is a need to study the marketed antacid formulations on regular basis for their safety and efficacy along with economic considerations [2]. Several countries have conducted several comparative studies on ANC, palatability, sodium content and cost aspects of different marketed antacid formulations. However, there is no single study till now to assess the available antacid preparations in the Vijayawada market.

The present work was aimed to study and compare the ANC and other physicochemical properties of different generic antacid suspensions sold in the Vijayawada market. All the selected formulations containing aluminum hydroxide and magnesium hydroxide as main active ingredients except Medicaine suspension, which contained the drug in the form of aluminium hydroxide gel.

MATERIALS AND METHODS:

Materials: Antacid Suspensions were purchased from local market at Vijayawada. NaOH from S.D. Fine Chem. Ltd, Mumbai, HCl was obtained from Qualigens Fine Chem, Mumbai and all other ingredients used were of analytical grade.

Methods: In all suspensions the minimum dose was 5 ml where as for Gel MPS was 10 ml. The strength of aluminium hydroxide, magnesium hydroxide and other ingredients were given in **Table 1**. The quantities were different in different preparations.

TABLE 1: COMPOSITION OF ANTACID SUSPENSIONS

Brand Name	$Al(OH)_3$ (mg)	$Mg(OH)_2$ (mg)	Others (mg)	Batch no.	Mfg - Exp Date
Alcid	200	200	Dimethicone 25	ALCL6041SK	2016-2018
Gel MPS	250	250	Activated polydimethylsiloxane 50	INS15L11	2015-2017
Medicaine	291	98	Oxetacaine 10	AL15185	2015-2017
Oxecaine	291	98	Oxetacaine suspension 10	GS5R17	2015-2017
Omee	200	200	Dimethicone 25	OME16019SK	2016-2018
Dynacid	200	200	Activated Dimethicone 25	AK1L6125	2015-2017

***In-vitro* Evaluation:** *In-vitro* analysis was carried out on antacid suspension formulations as per USP32/NF27 methodology at 37±3 °C [3].

Organoleptic Properties: The organoleptic tests were explained about the products before the test procedure. During the study, all the formulations were evaluated by human volunteer with one hour interval for each formulation testing. The colour was visually identified and the odour was inspected by nasal inhalation by healthy human volunteers and the average qualitative values were noted. The taste of the formulations were inspected by placing the required dose of the formulation on the tongue, allowing to stay in the mouth for 30 seconds and the taste was perceived and the qualitative value was reported [4, 9].

Particle Size: Particle size was measured by using Olympus optical microscope. The microscope was calibrated using the objective micrometer, Tokyo. Two hundred particles were considered for the measurement and the average particle size was reported [5, 6].

Specific Gravity: Specific gravity was determined by using specific gravity bottle [6, 7].

Measurement of pH: The pH meter was calibrated using buffer solutions 4 and 7. The pH of each generic suspension was read from the monitor of the pH meter [6].

Viscosity: 100 ml of the antacid was taken in a beaker and the viscosity determination in triplicate was carried out by Brookfield viscometer LVDV-I Prime fitted with spindle 62 and at an angular velocity of 60 rpm at room temperature (28 °C) [7, 8].

***In-vitro* Acid Neutralizing Capacity:** Preparation and standardization of NaOH: 4 gm of NaOH was weighed and dissolved in 1000 ml distilled water to obtain 0.1 N NaOH. Further it was standardized against Potassium hydrogen phthalate (KHPh). For standardization, 0.004 gm KHPh was dissolved in 50 ml distilled water and 2-3 drops phenolphthalein was added to it. NaOH solution was added drop-wise to the above solution till light pink colour appears. The volume of NaOH used was noted down and the molarity of NaOH solution was calculated by equation [7, 8].

Preparation and Standardization of HCl: 8.8 ml of conc. HCl was taken and 1000 ml of distilled water was added to obtain 0.1 N HCl. This solution

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FORMULATION AND EVALUATION OF FAST DISSOLVING ORAL FILM OF LEVOCITRAZINE DI HYDROCHLORIDE BY SOLVENT CASTING TECHNIQUE

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Antihistaminic Agent, Film forming Polymers, Disintegrating Agent, Solvent Casting Method and *In-vitro* drug release.

ABSTRACT

Levocetirizine dihydrochloride is a class of third generation antihistaminic agent. It is an active enantiomer of cetirizine; its principal effects are mediated via selective inhibition of H1 receptor. Fast dissolving films have been played an important role in the current pharmaceutical research. They have convenience and ease of use over other dosage forms such as orally disintegrating tablets and immediate release tablets. In the present research, rapidly dissolving films of Levocetirizine dihydrochloride were developed using low viscosity grades of HPMC E-5LV & HPMC E-15LV as film forming polymers. To decrease the disintegration time of formulations crosspovidone was used as disintegratmg agent. Levocetirizine dihydrochloride is moderately bitter drug, taste masking was achieved by use of sweeteners and flavours. The films of Levocetirizine dihydrochloride were prepared by solvent casting method using dichloromethane and methanol as solvents. The prepared films (F1 – F6) were evaluated for weight variation, thickness, drug content, folding endurance, surface pH, *in vitro* disintegration time and *in-vitro* drug release. Formulation F1 was considered optimum which contained drug and HPMC E5 in 1: 3 ratios. The *in vitro* disintegration time of the optimized formulation was found to be below 25 seconds respectively. The prepared films exhibited good integrity and thickness. *In vitro* dissolution studies were performed as per the FDA dissolution guidelines for about 10 minutes, the optimum formulation released complete drug within 10 minutes. FTIR studies showed no drug polymer interaction.

INTRODUCTION:

Oral route is the most preferred route for the delivery of the drugs till date as it bears various advantages over the other route of drug administration, but It is estimated that 25 % of the population finds it difficult to swallow tablets and capsules and therefore do not take their medication as prescribed by their doctors resulting in high incidence of non-compliance and ineffective therapy. Furthermore, 90% of the drugs administered through oral route are subjected to extensive first pass metabolism before reaching to the systemic circulation. In spite of all the cones, the oral route of administration still remains to be the most popular means of drug administration due to its ease of administration, virtually pain free and patient compliance. A new oral dosage form is the oral thin films prepared using hydrophilic polymers which rapidly disintegrates and dissolves on tongue or the buccal cavity. The drug administered via oral mucosa gain access to the systemic circulation through a network of arteries and capillaries. The major artery supplying the blood to the oral cavity is the external

carotid artery. The venous backflow goes through branches of capillaries and veins and finally taken up by the jugular vein. This novel approach is in great demand for the paediatric and geriatric patients.

Oral thin film is a dosage form containing medicinal substances which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue[1]. It employs water dissolving polymer which allows the dosage form to quickly hydrate, adhere and dissolve when placed on the tongue or the oral cavity to provide rapid local and systemic drug delivery[2]. Due to rapid dissolving of the film, the term soluble film is preferred by FDA, where as the European Medicines Agency is using the term orodispersible film[3]. A distinctive composition of the film contains 1-30 % w/w of the active pharmaceutical ingredient. Always low dose active pharmaceutical ingredients are used because high doses of drugs are difficult to incorporate in fast dissolving films. Micronized APIs are used because they enhance the texture of film, provide improved dissolution and uniformity in the fast dissolving film.

The advantage of oral films are large surface area, enhanced safety compared to liquid forms, high level of patient compliance, high precision during dose administration and quick relief. Oral thin film provides instant onset of action through the extensive supply of blood capillaries in the buccal cavity and also skips the first pass metabolism by the liver. Unlike the tablet dosage forms the disintegration and dissolution are not the rate limiting step for oral thin films to be absorbed. They disintegrate and release the drug instantly for quick onset of action. Thus, such a kind of formulations can be used to treat conditions like pains, sleep disturbances, anxiety, gastric problems and allergies which requires quick onset of action. A number of drugs such as anti-emetics, serotonin inhibitors, $5HT_3$ antagonists, anti-epileptics, dopamine D_1 and D_2 antagonists, newtropics, statins, anti-migraines and anti allergic drugs etc., can be formulated as fast dissolving oral films.

Levocetirizinedihydrochloride is a class of third generation antihistaminic agent. It is an active enantiomer of cetirizine; its principal effects are mediated via selective inhibition of H1 receptor. It does not prevent actual release of the histamine from the mast cells, but prevents its binding to its receptor. The daily dose of levocetirizine is 10mg per day. Many researchers developed and reported the oral films of levocetirizine using different film forming polymers like HPMC E-15LV, HPMC E-5LV, HPMC E-3, PVP and PVA.

In present research work aim to prepare and evaluate an oral fast dissolving film of levocetirizinedihydrochloride with different concentration of HPMC E-5 and HPMC E-15 as a film forming polymer and PEG-400 as plasticizer for the fast dissolution of the films and quick relief in different allergic conditions.

MATERIALS:

Levocetirizinedihydrochloride was given gift sample by Lee Pharma, Hyderabad, HPMC E-5, HPMC E-15, Methanol, Potassium dihydrogen phosphateare obtained by S.D. Fine Chem. Ltd, Mumbai. PEG – 400, Dichloromethane are supplied by Qualigens Fine chem. Ltd, Mumbai and all other ingredients used were of analytical grade.

METHODS:

ANALYTICAL TESTS FOR API:

Solubility Analysis: Pre-formulation solubility analysis was done, which included the selection of suitable solvent system to dissolve the drug as well as various excipients.

Melting Point Determination: Melting point determination of the obtained drug sample was done; as it is a first indication of purity of the sample. The presence of relatively small amount of impurity can be detected by lowering as well as widening in the melting point range[4].

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COMPARATIVE IN VITRO STUDIES AND BIOEQUIVALENCE ASSESSMENT OF SOME COMMERCIALLY AVAILABLE METFORMIN HYDROCHLORIDE TABLETS IN VIJAYAWADA

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ABSTRACT

Metformin Hydrocloride tablets prescribed for treatment of non-insulin dependent diabetes mellitus (NIDDM). The aim of the study is to compare the differences in dissolution behavior and asses bioequivalence of some commercially available Metformin Hydrocloride tablets in Vijayawada. The objective is to find out potent generic brand and reduce the cost of treatment for diabetes mellitus with respect to its composition and manufacturer. Eight generic brands manufactured by different companies were evaluated for physicochemical properties, drug content, *in vitro* dissolution studies and compared with each other. The *in vitro* dissolution studies were performed in USP Dissolution Apparatus II using pH 6.8 phosphate buffer solution for 1 hr. The bioequivalence was assessed based on *In vitro* dissolution profile and f1 & f2 factors. *In vitro* dissolution of all the brands was satisfactory and the brand Obimet[$] shown highest dissolution of 94.49% within 1 hr. The f1 and f2 values were in the range of 2 – 8 and 74 – 93 respectively. It is evident that test products were bioequivalent to the reference product and the brand Obimet[$] could be used as a best generic substitute which reduce the dose and cost of treatment for diabetes mellitus.

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INTRODUCTION

Nowadays drug's cost increases due to the expensive branded drug and the cost can reduced by substituting cheaper generic drugs. The increase in production and consumption of generic drugs need bioequivalence for therapeutically equivalent to the branded drug. In order to find this, bioequivalent studies are conducted according to the Food and Drug Administration (FDA). Two different formulations of a same drug are bioequivalent when their rate of dissolution and absorption is same. Bioequivalence studies focus on the drug release from the formulation and subsequent absorption into the systemic circulation, which consist of both *in vivo* and *in vitro* studies (Demirturk E, 2006). According to US Pharmacopeia, necessary *in vitro* tests are assay, content uniformity and dissolution studies. The *in vitro* dissolution used to predict the *in vivo* bioequivalence.

Therefore, *in vitro* tests can used to determine bioequivalence of products. The dissolution profile comparison is more precise than others to characterize the drug product. To compare dissolution profiles, two model independent fit factors, the difference factor (f1) and the similarity factor (f2) introduced by Moore and Flanner (1996) as mathematical indices, were used in this study. Metformin Hydrocloride is a biguanide, which used orally in hyperglycemic patients. Nowadays it is widely used in the management and control of non-insulin dependent diabetes mellitus (NIDDM). The oral bioavailability of metformin is 50 – 60% and biological half-life is 1.5 – 1.6 hr (http://www.rxlist.com/glumetza-drug.htm). It is freely soluble in water and has low permeability to cell membranes. Despite of widespread of NIDDM and extensive use of metformin (World Health Organization, 1998), there are no reports on the bioavailability and bioequivalence of the various brands of metformin Hydrocloride tablets in

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Vijayawada. Hence, the present study was carried out to investigate *In-vitro* study and bioequivalence of metformin Hydrocloride tablets in Vijayawada market.

MATERIALS

Metformin Hydrochloride tablets were purchased from local market at Vijayawada. Metformin was purchased from Yarrow chem Products, Mumbai. NaOH from S.D. Fine Chem. Ltd, Mumbai. HCl and Potassium Dihydrogen Phosphate were obtained from Qualigens Fine chem. Mumbai and all other ingredients used were of analytical grade.

METHODS

Eight brands of antidiabetic tablets containing Metformin hydrochloride as main active ingredient was selected and procured from the local market in Vijayawada. All the brands contained label strength of 500 mg Metformin hydrochlorid. The physicochemical equivalence of eight brands of Metformin hydrochloride tablets was determined through the evaluation of both official and non-official standards. All tests were performed within product expiration dates. The strength of Metformin hydrochloride and other details were given in Table 1.

ANALYTICAL TESTS FOR API

Melting Point Determination: Melting point determination of pure drug Metformin hydrochloride was done; as it is a first indication of purity of the sample. The presence of small amount of impurity can be detected by lowering as well as widening in the melting point range.

Identification of Pure Drug: FTIR spectroscopy was used for identification of pure drug Metformin hydrochloride.

Determination of λ_{max}: An accurately weighed 10 mg of Metformin hydrochloride was transferred in a 100ml volumetric flask. To the flask phosphate buffer was added in small proportion so as to dissolve Metformin hydrochloride. The volume was made up to 100ml with phosphate buffer pH 6.8 to get a concentration of 100µg/ml ((Imad H and Ahmed BJ., 2010). 20µg/ml solution of Metformin hydrochloride was prepared in dilution. The resulting solution was scanned in UV-Vis spectrophotometer from 400- 200nm to determine the λ_{max}.

Calibration of Standard Curve: Accurately weighed 100 mg of Metformin hydrochloride was dissolved in 100 ml of pH 6.8 phosphate buffer solution. The resultant solutions were having concentration of 1000 µg/ml (1 mg/ml). 1 ml of this solution was further diluted up to 100 ml with 6.8 pH phosphate buffer to give a solution of Concentrations 10 µg/ml. Appropriate aliquots were pipetted out from the stock solution in to a series of 10 ml volumetric flasks. The volume was made up to the mark with 6.8 pH phosphate buffer to get a set of solutions having the concentration range of 0, 2, 4, 6, 8 and 10 µg/ml for Metformin hydrochloride. Absorbance of the above solutions was measured at 232 nm ((Imad H and Ahmed BJ., 2010), a calibration curve of absorbance against concentration was plotted, and the regression equation and correlation coefficient was determined.

IN VITRO EVALUATION OF TABLETS

The physicochemical equivalence of eight brands of Metformin hydrochloride tablets were determined through the evaluation of both official and non-official standards according to the USP pharmacopoeia including uniformity of weight, friability, hardness, disintegration, dissolution rate and drug content (Osadebe PO and Akabogu A., 2004).

Visual Inspection: The shape and color of the different brands of tablets were examined visually.

Thickness & Diameter: Three tablets from each brand were used for thickness determination. Thickness & diameter of each tablet was measured in mm using Vernier Calipers (Mitutoyo Dial, Mitutoyo, Japan). The mean and standard deviation values were calculated and reported.

Hardness Test: The crushing strength of the tablets was determined using hardness tester (Lab India). Sample tablets (10) of each brand were taken, a tablet was placed between the spindle of the Lab India hardness tester machine until the tablet breaks and the pressure required to break the tablet was then read off the machine and recorded (Arcot RC, Chan J, *et.al*., 2011).

Friability Test: Twenty tablets of each brand were weighed and subjected to abrasion using a Roche friabilator at 100 revolutions for 4 min (Aulton ME., 2002). The tablets were dedusted and weighed again then percent of weight loss was recorded. The friability of the tablets were then calculated using the following expression.

% Friability = [(Initial weight – Final weight)/Initial weight]×100

Weight Uniformity: Total20 tablets from each brand were weighed individually using a digital analytical balance. The average weight was determined and the percentage (%) deviation of the individual tablets from the mean was determined (Aulton ME., 2002).

$$\% \text{ Weight variation} = \frac{(\text{Average weight} - \text{Individual Weight})}{\text{Individual Weight}} \times 100$$

Disintegration Test: Tablet disintegration was determined at 37 °C using (Lab India) disintegration apparatus. The disintegration time of randomly selected six tablets of each brand was determined in distilled water (Aulton ME., 2002). The disintegration time was taken to be the time no granule of any tablet was left on the mesh.

Drug content estimation: Ten tablets from each brand was finely powdered and powder equivalent to 100 mg of Metformin was accurately weighed and transferred to 100 ml volumetric flasks containing 50 ml of phosphate buffer (pH 6.8). The flasks were shaken thoroughly to get uniform solution. The volume made up to the mark with phosphate buffer solution and filtered. One ml of the filtrate after suitable dilution was subjected for the estimation Metformin content at 232 nm using a double beam UV-visible spectrophotometer (Pamila RB, Surender G, *et.al*., 2010).

INDO AMERICAN JOURNAL OF PHARMACEUTICAL RESEARCH

A REVIEW OF ANALYTICAL PERSPECTIVES OF LINAGLIPTIN

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ABSTRACT

Linagliptin is an oral anti-diabetic drug belong to the class of dipeptidyl peptidase -4 (DPP-4 inhibitors).It is widely used in the treatment of type –II diabetes mellitus which is characterized by insulin resistance in pheripheral tissue and insulin secretory defect of the β – cells.Linagliptin is been approved by the US food & Drug administration for the management of type –II diabetes. This work aims to compiling the published analytical methods referred so far in the literature in the determination of linagliptin in the biological samples and pharmaceutical formulations. Techniques like HPLC, UV & MASS spectroscopy, EI – Tandem Mass spectrometry, pharmacokinetic studies & spectrophotometric methods have been utilized so far in the analysis, from which we can seen HPLC methods have been operated most extensively in various analytical perspectives. Based on the findings of the present review, linagliptin is widely used as an treatment adjunctive to a regimen of an insulin secretagogue.

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INTRODUCTION

Linagliptin { 1 H – (Purine-2,6 dione, 8- (3R) – 3- amino -1- Piperdinyl) -7 -(2- butyn -1-yl) -3,7 dihydro – 3-methyl – 1 – (4 methyl -2- quinazolinyl) Methyl} is a DPP-4 inhibitors in the treatment of type –II diabetes. DPP-4 (Dipeptidyl pepitadase -4) is an enzyme that degrades the hormones, glucagon like peptides -1 (GLP-1) and glucose dependent insulin tropic polypeptide (GIP).Both GLP-1 & GIP increases the insulin biosynthesis and secretion from pancreatic α –Cells resulting in the reduction of hepatic glucose output [1].Linagliptin is indictaed as adjuvant to diet and exercise to improve glycemic control in patients with diabetes –II [2]. Various techniques have been reported in the determination of linagliptin in the pharmaceutical dosage forms.The objective of review article is to understand the various simple accurate RP-HPLC methods with short retention time (migration time) and various methods to validate the newly developed method as per the ICH guidelines[3].In the present review, we have compiled the published analytical methods reported so far in the determination of linagliptin in pharmaceutical and biological samples.Techniques like spectrophotometry,HPLC,LCMS,LC-ESI-MS where have been used for analysis, from which HPLC methods were been extensively adopted.

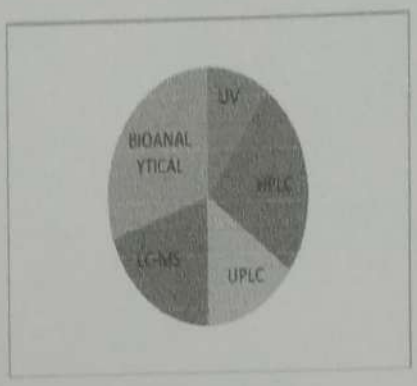

Fig.1 Structure of linagliptin.

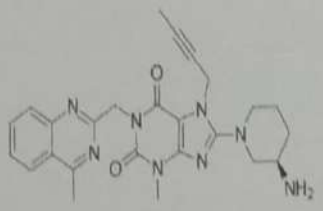

Fig.2 Overview of analytical methods for estimation of a linagliptin in pharmaceutical and biological samples

Sample preparation strategies

Sample preparation is an integral part of analytical methodology and it was reported that approximately 30 % error is contributed from sample analysis was due to sample preparation [6]. The various diluents utilized for analysis of linagliptin are 0.02M phosphate buffer (p^H 5.5), acetonitrile, methanol. In major cases, methanol was used as a diluent. The sample preparation techniques for the extraction of linagliptin from biological matrices like serum, plasma and urine include liquid –liquid extraction with diethyl ether, N-butyl ether & ethyl acetate and protein precipitated with methanol.

Analytical methods

Spectrophotometry:

In the literature, twenty simple, accurate, zero order, first derivative spectrophotometric methods have been developed [7] out of which four methods were for determination of linagliptin alone, where as remaining are quantifying linagliptin in combination with other drug substances.

Table :1 Representative spectroscopical method analysis of linagliptin.

S.NO	Compound	Method	λmax	Solvent	LOD	Reference
1.	Linagliptin	Spectrophotometric	299	Methanol	0.247	[8]
2.	Linagliptin	Spectrophotometric	294	Methanol & Water	0.246	[9]

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RESEARCH ARTICLE

FORMULATION DEVELOPMENT AND *IN VITRO* EVALUATION OF GASTRORETENTIVE EFFERVESCENT FLOATING TABLETS OF DILTIAZEM USING VARIOUS POLYMERS

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ABSTRACT

In the present research work sustained release floating matrix formulation of diltiazem HCL by using various concentrations of polymer were developed. The formulation blend was subjected to various preformulation studies, flow properties and all the formulations were found to be good indicating that the powder blend has good flow properties. Among all the formulations F8 formulation was retarded the drug release up to desired time period i.e., 12 hours in the concentration of 60 mg. The dissolution data of optimized formulation was subjected to release kinetics; from the release kinetics data it was evident that the formulation followed higuchi release kinetics.

INTRODUCTION

Oral route of drug delivery was most utilized route of various pharmaceutical dosage forms, due to its ease of administration and patient compliance (Nayak, 2010 and Singh, 2011). The oral controlled drug delivery system was developed to allow a controlled rate of drug release over an extended period of time. This system, however, has a disadvantage of short gastric retention time, resulting in the incomplete release of drugs with narrow absorption window in the upper part of the gastrointestinal tract (Singh, 2011 and Singh, 2000). To overcome this drawback, gastroretentive drug delivery systems (GRDDS) were introduced (Singh, 2000). GRDDS are designed to retained in the stomach for a prolonged time and release their active ingredients and there by enable sustained and prolonged input of the drug to the upper part of the GIT (Singh, 2010; Singh, 2011; Singh, 2000; Arora, 2005 and Mayavanshi, 2008). To formulate a successful GRDDS, several techniques are currently used such as floating drug delivery system, low density system, raft systems incorporating alginate gel, bioadhesive or Mucoadhesive systems, high density systems, superporous hydrogel and magnetic system (Dehghan, 2009).

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The floating system is the most used system as it is a simple and practical approach to increase the gastric retention time and to control the drug release (Nayak, 2010 and Singh, 2011). Floating drug delivery systems have a bulk density less than gastric fluid and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After the release of drug, the residual system is emptied from the stomach. Thus, results in an increased gastric retention time and control of the fluctuation in plasma drug concentration (Mathur, 2010 and Shah, 2009). Diltiazem hydrochloride is a calcium channel blocker. It is widely prescribed for the treatment of hypertension and angina. Diltiazem hydrochloride undergoes extensive biotransformation results in bioavailability of 30% to 40% only. It has an elimination half-life of 3 to 4.5 h and has an absorption zone from the upper intestinal tract. Efficacy of the administered dose may get reduced due to incomplete drug release from the device above the absorption zone. The dosage is 30 mg, 4 times a day and increased as necessary up to 360 mg/day in divided doses (http://www.drugbank.ca and Hudson, 2014). Due to short half-life diltiazem hydrochloride require frequent administration. These disadvantages can

overcome by developing a floating dosage form to be remained buoyant in the stomach. The gastroretentive drug delivery systems can be retained in the stomach and assist in improving the oral sustained delivery of drugs that have an absorption window in a particular region of the gastrointestinal tract. These systems help in continuously releasing the drug before it reaches the absorption window and thus ensuring optimal bioavailability. Therefore, although studies have been carried out using diltiazem hydrochloride as the model drug, there is yet a study on the development of floating tablets of diltiazem hydrochloride. This study was conducted with the aim of formulating gastroretentive floating tablets of diltiazem hydrochloride that floats and releases the drug content in a controlled manner over the period of 12 hours.

MATERIALS AND METHODS

Diltiazem HCl purchased from Yarrow drugs pvt.ltd. Eudragit RL100, Eudragit RS100, ethyl cellulose were gift samples from Merck specialities pvt. Ltd. Mumbai and lactose, talc and magnesium stearate were procured from Central Drug House, New Delhi. All other solvents and reagents used were of analytical grade.

All the formulations were prepared by direct compression. The tablets were prepared as per the procedure given below and aim is to prolong the release of diltiazem HCL. Total weight of the tablet was considered as 300mg. Sodium bicarbonate was employed as effervescent gas generating agent. It helps the formulation to float. Various concentrations of sodium bicarbonate were employed; floating lag time and floating duration were observed. Based on the floating lag time and floating duration the concentration of sodium bicarbonate was optimized. The compressions of different batch formulations are given in Table 1. Diltiazem HCL and all other ingredients were individually passed through sieve no ≠ 60. All the ingredients were mixed thoroughly by triturating up to 15 min. The powder mixture was lubricated with talc. The tablets were prepared by using direct compression method.

Evaluation parameters

Pre Compression parameters

Bulk density (D_B): An accurately weighed quantity of granules (w) (which was previously passed through sieve No: 40) was carefully transferred into 250 ml measuring cylinder

Table 1. Composition of different batches of diltiazem floating tablets

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Diltiazem HCL (mg)	60	60	60	60	60	60	60	60	60
Ethyl cellulose (mg)	30	60	90	-	-	-	-	-	-
Eudragit S-100 (mg)	-	-	-	30	60	90	-	-	-
Eudragit L-100 (mg)	-	-	-	-	-	-	30	60	90
$NaHCO_3$ (mg)	45	45	45	45	45	45	45	45	45
Mag. Stearate (mg)	3	3	3	3	3	3	3	3	3
Talc (mg)	3	3	3	3	3	3	3	3	3
MCC pH102 (mg)	QS	QS	QS	QS	QS	QS	QS	QS	QS
Total weight (mg)	300	300	300	300	300	300	300	300	300

Preparation calibration curve

Diltiazem HCL pure drug (100mg) was dissolved in 100ml of 0.1NHCl (stock solution). Above solution (10ml) was taken and make up with100ml of 0.1N HCL (100µg/ml). This solution was subsequently diluted with 0.1N HCL to obtain series of dilutions Containing 5, 10, 15, 20 and 25 µg/ml of diltiazem HCL per ml of solution. The absorbance of the above dilutions was measured at 236 nm by using UV-Spectrophotometer taking 0.1N HCL as blank. Then a graph was plotted by taking Concentration on X-Axis and Absorbance on Y-Axis which gives a straight line linearity of standard curve was assessed from the square of correlation coefficient (R^2) which determined by least-square linear regression analysis.

Fourier Transform Infrared (FTIR) spectroscopy

The physical properties of the physical mixture were compared with those of plain drug. Samples was mixed thoroughly with 100mg potassium bromide IR powder and compacted under vacuum at a pressure of about 12 psi for 3 minutes. The resultant disc was mounted in a suitable holder in Perkin Elmer IR spectrophotometer and the IR spectrum was recorded from 3500 cm^{-1} to 500 cm^{-1}. The resultant spectrum was compared for any spectral changes.

Formulation development of Tablets

and measure the bulk volume. Bulk density is the ratio between a given mass of the powder and its bulk volume.

Bulk density = Mass of Powder / Bulk volume of the powder

Bulk density (D_B) = W / V_0

Tapped Density (D_T)

An accurately weighed quantity of granules (w) (which was previously passed through sieve No: 40) was carefully transferred into 250 ml measuring cylinder and the cylinder was tapped on a wooden surface from the height of 2.5 cm at two second intervals. The tapping was continued until no further change in volume (until a constant volume) was obtained (V_f). The tapped density was calculated by using the formula. Tapped density [11] is the ratio between a given mass of powder (or) granules and the constant (or) fixed volume of powder or granules after tapping.

Tapped density = mass of the powder/ tapped volume

Tapped density (D_T) = W/V_f

Hausner's ratio: Hausner's ratio [12] is an indirect index of ease of powder flow and was calculated by the formula,

Hausner's ratio = D_T/D_B

Where, D_T is the tapped density

D_B is the bulk density

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PHYTOCHEMICAL CONSTITUENTS OF *GOMPHRENA SERRATA L*

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ABSTRACT

The aim of the study was to screen the phytoconstituents present in the flower extracts of *Gomphrena serrata L.* and their further analysis by GC-MS. The flowers of the plant were extracted using solvents hydroalcoholic mixture (50:50) and acetone. Preliminary phytochemical screening showed the presence of alkaloids, glycosides, tannins, flavonoids, steroids, amino acids and proteins. Column chromatography was carried out on the acetone extract of the plant. GC-MS analysis of chloroform fraction showed the presence of 30 bioactive compounds. The study forms a basis for the biological characterization and importance of the compounds identified.

Keywords: *Gomphrena serrata*, GC-MS, bioactive compounds

1. INTRODUCTION

Plants are the rich source of bioactive constituents with diverse pharmacological properties. The extraction and characterization of phytochemicals from plants have resulted in the discovery of novel drug entities with high therapeutic value (Reische DL, 1998). The plants of the genus *Gomphrena* belonging to family *Amaranthaceae* are employed in the treatment of various ailments like asthma, diarrhea, gastric disturbances (Vieira et al., 1994; Reische DL, 1998). The plant has been studied to possess antimalarial, carminative and diuretic properties (Gessler et al., 1994; Dhawan et al., 1977). Oleuropein has been isolated from the plant (Babu et al., 2012). The plant extracts have been studied to possess anticholinergic and antihistaminic properties (Vani et al., 2016). The present study has been undertaken to explore the phytoconstituents of the plant by GC-MS.

2. MATERIALS AND METHODS

Collection of plant material

The plant material was collected from local grounds of Prasadampadu and Enikepadu coordinates 16°32'45"N 80°34'12"E of Vijayawada rural region, Krishna district, Andhra Pradesh, India. The plant specimen was identified and authenticated by Dr. P. Satya Narayana Raju, plant taxonomist, Dept. of Botany & Microbiology, Acharya Nagarjuna University (ANU), Guntur (Dt), Andhra Pradesh, India. A voucher specimen 001/VIPW was deposited in the department of Pharmacognosy, Nirmala college of Pharmacy, Atmakur, Mangalagiri, A.P., India for future reference.

Preparation of powder and extract

The flowers were dried under shade, powdered, coarsely using a mechanical grinder. Then the powder was extracted with 50:50 methanol, water and acetone alone using soxhlet apparatus. The extracts obtained were dried under vacuum, preserved in refrigerator for future use. The yield of extracts was found to be 25.0% w/w for hydroalcoholic mixture and 24.2% w/w for acetone solvent respectively (Evans et al., 2000).

Preliminary Phytochemical screening

The plant extracts were tested for the presence of various phytochemicals by using standard methods (Evans et al., 2000).

Isolation by column chromatography

Column chromatography was performed on a classic 20 cm long × 2 cm diameter glass column packed with silica gel (Merck, Germany). Acetone extract of the plant (20 ml) was applied to the column by use of a pipette. It was eluted sequentially with

The Great Indian Novel: A Postcolonial Artifact of Cultural Significance

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Culture is a description of a particular way of life, which expresses certain meanings and values, not only in art and learning, but also in institutions and ordinary behavior. --- Richard Johnson

Novels are cultural forms, and present a discursive formation of ideas, images and practices. In Cultural Studies, the text is considered for its various representations and meanings. The focal point of Cultural Studies is related to power and hegemony among the various institutions in the society. Power relations are observed as governing aspects among the social relationships too. Power acts as a restricting force as well as a constructive phenomenon. Class, race, gender and nation are some of its important subjects. The critical theory of cultural studies and the powerful power play is intended to be applied to the famous text of Shashi Tharoor, The Great Indian Novel. The paper tries to bring about the social implications on which the text is based upon and the various cultural identities it tries to construct. The Great Indian Novel, the retelling of the Mahabharata, tries to re-describe, re-establish and re-enforce the cultural heritage of the country. The text enquires the inequalities observed during the Mahabharata time and the oppression of the Indians by the British. The Great Indian Novel is a cultural critique of the power struggle among parties and people, of the legendary characters portrayed as ordinary human beings with their own strengths and weaknesses.

A postcolonial text clearly or allegorically tries to represent several elements of colonial oppression, which traces the readers can notice in The Great Indian Novel. Problems of cultural dissolution and enquiry of some challenging views happen in postcolonial criticism. It also tries to create awareness through philosophic enquiry.

Post-colonialism tries to interpret the texts with a healthy degree of self-consciousness and suspicion. Terry Eagleton (1994) was of the opinion that postcolonial criticism observes the issues of power, economics, politics, religion and culture in association with colonial hegemony.

Culture, according to Stuart Hall was a tool used to have control over the society politically and socially. Tharoor leaves no stone unturned to depict the culture of the changing, newly born India in the garb of the mythological India. But, yet, the re-creation of the history and the historical characters authenticates the statement that history is the presentness of the past and the pastness of the present. Subjectivity was a social and political creation and identity was always in negotiation with the changing society and henceforth, not permanent. Identity of various characters and events in the novel help the readers to notice the significance of the same and the challenges and opportunities the characters faced. Bhim is looked upon as the identification of the Indian army, Arjuna as the press and Draupadi as democracy. The challenges open to the government as well to the public of India during the emergency period are paralleled to the disrobing of Draupadi in the epic.

The paper studies about how culture is organized or observed during pre-independence and early post-independent India; and how the postcolonial studies facilitates to get back to the colonial history of India to observe the oppression and marginalization of the natives.

Globalization has a profound influence on local cultures. With globalization, modernization took place. Along with modernization, there was also resistance towards European power in the postcolonial period. In India, globalization and post colonialism go hand in hand, globalization focuses on free-market

capitalism and individualist consumerism, whereas postcolonialism interrogates the inequalities and exploitation of people in the society. It also focuses on the diminishing value system, resultant of globalization. It is observed as a history of the nation in relation with the contemporary socio-economic system. A country's development is a distinct and independent mission, where India also is no exception. This is a systematic step by step process of evolvement according to Walt Rostow in his commendable work, The Stages of Economic Growth: A Non-Communist Manifesto. Shashi Tharoor's novel demonstrates that the texts of the colonized nations wrestle with the colonial power in newer modes of representation.

Cultural Studies is a theoretical practice, wherein in the creation of that theory, there is an intervention of politics. Therefore, such knowledge can never be objective, but is posited. It is speaking about something to someone, from a definite place and with a definite purpose. The Great Indian Novel has been written with a motive to speak about the colonial atrocities and the typical nature of the actions of the heroes of independence struggle, making them equivalent to the legendary characters of the epic. The writer's intention in politicizing the motives of the characters is to make the readers comprehend the weaknesses of the characters.

Shashi Tharoor's The Great Indian Novel, is a fascinating blend of the Indian epic and contemporary political scenario, before and after Independence. Characters from the Mahabharata are paralleled to the characters of Indian Independence struggle and the narration continues on a satirical vein. The elderly personae of the epic, the historical personalities of India and their actions reverberate with the mocking tone of the author throughout the novel.

Mr. Tharoor says he chose Mahabharat for a retelling because it's an epic that still resonates with great relevance in contemporary India. Unlike the other Hindu epic Ramayana, Mahabharat is a secular story. – (the Hindu god) Krishna being the only divine presence in the book. And it had some very interesting characters – they had feet of clay, they made compromises, they struck shady deals and they had base motives. And there was enmity and jealousy; there was greed and treachery.

Some characteristic features of postcolonial Cultural Studies is associated with the global perspective of colonialism. As it is observed, the Europeans enforced their culture and at the same time, they tried to acclimatize themselves to the local cultures too. This phenomenon of acculturation is about the process of cultural change and psychological change that occurs as a result of the intersection of the two cultures. These changes can be observed at several levels in both the associated cultures.

Education and language are the two prime aspects where there is an interchange of cultures. While the language of the Britishers and the system of education was implemented by them in India, at the same time, they had to learn the native language to run the administration. In the novel, Sir Richard, the representative and Heaslop, the equerry have a conversation, it becomes quite humorous and satirical, as they discuss the basic structure of Hindi language and Sir Richard's knowledge of the language lands him in a funny and confusing situation.

Postcolonialism tries to emphasize the aspects of cultural variations and commemorates 'cultural polyvalency', wherein in a society people at the same time belong to the cultures of the colonized and the colonizer. This criticism brings forth an outlook of remarkable change in the aspects regarding marginality, plurality and otherness which form the basis of its study.

The Great Indian Novel is a novel written about India, during and after independence. It brings out the actions and reactions of the colonizer and the colonized. British political supremacy over the Indian sub-continent began as early as 1757 and continued till 1947. But, some of the Indian states were not under the direct control of the British; there were still some native states which had the benefit of their own rule and administration.

Hastinapur of The Great Indian Novel was one such state. The British Resident had to keep himself away from Hastinapur due to the powerful kings of the kingdom, Shantanu and Gangadatta. During 1848 – 1856, when Lord Dalhousie was the Governor- General of India, the British govern-

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REVIEW ARTICLE

A Review on Prospects of Zoo Therapy

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ABSTRACT:
The traditional medical knowledge of indigenous people throughout the world has played an important role in identifying biological resources worthy of commercial exploitation. Indeed, the search for new pharmaceuticals from naturally occurring biological material has been guided by ethno biological data. Animal-based medicines continue to play an important role in diverse systems of traditional medicine worldwide, as well as in modern pharmaceuticals. The various types of zoo therapy and therapy using animal derived rugs has been presented in the article.

KEYWORDS: Zoo therapy, animal derived drugs.

1. INTRODUCTION

Chemicals from nature have been a part of human civilization ever since our early ancestors began exploiting natural compounds to improve and enrich their own lives[1]. A major part of these chemicals come from animals. Indeed, animals are therapeutic arsenals that have been playing significant roles in the healing processes, magic rituals, and religious practices of peoples from the five continents. The healing of human ailments by using therapeutics that are obtained from animals or ultimately are derived from them is known as zoo therapy. Animal-based medicines have been elaborated from parts of the animal body, from products of its metabolism (corporal secretions and excrements), or from non-animal materials (nests and cocoons)[2,3].

The traditional medical knowledge of indigenous peoples throughout the world has played an important role in identifying biological resources worthy of commercial exploitation. Indeed, the search for new pharmaceuticals from naturally occurring biological material has been guided by ethno biological data. For example, Alexiades (unpublished data) recorded the medicinal use of 50 animals by the Ese Eja people from Peru. The blood of the black caiman *Melanosuchus Niger* is used to treat epilepsy and stroke; ants of the genus *Pseudomyrmex* are smashed and put in toothache, poisonous the animal, the more potent its ant poison". In India nearly 15-20 percent of the Ayurvedic medicine is based on animal-derived substances. In the area of Sierra Madre people use to say "The more or are left to bite painful joints[4].

2. HISTORY:

Records of zoo therapeutic practices have been identified in the surviving texts of ancient cultures, beginning with the earliest written records. For example, historical documents of ancient Egypt such as the Embers Papyrus (1550 B.C.) include medicinal descriptions of animal

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substances such as honey, lizard blood, sperm whale ambergris, and musk deer glands, among others [5,8,7]. Animals have clearly played a central role in the medical pharmacopeias of mankind for at least the past 3,000–4,000 years. Today, animal-based medicines continue to play an important role in diverse systems of traditional medicine worldwide, as well as in modern pharmaceuticals. Two good examples of this include ACE (angiotensin converting enzyme) inhibitors from pit viper snake, *Bothrop's jararacus* venom [8] and dietary supplements of Omega-3 PUFAs (polyunsaturated fatty acids) from certain fish oils [9]. The continued use of zoo therapeutics from ancient times to present day suggests that their use may be associated with some medical efficacy.

Table 1: Zoo therapy using various animals by ancestors[10]

Bees wax	Liquefied and arranged on the top of a small piece of cloth which is inserted (still warm) in the ear	To treat earache
Blood	The blood gathered after having cut the ear of the animal is put in the mouth of the same animal	to treat fever in animals
Cheese (fresh)	Applied extremely eaten raw or cooked with flour and eaten hot	To heal wounds, "to strengthen the stomach", anti-diarrheic
Cobweb	Applied externally	Hemostatic
Cow feces	Used fresh and applied	To heal burns
Cow milk	Drunk	To treat intestinal pains and poisonings (especially in Children, and also in animals)
	Drunk very hot	to treat mumps
Dog hair	applied externally	to treat wounds from dog bites
Donkey milk	Drunk fresh	to heal coughs in the elderly
Egg	eaten raw	Antidote against poisoning
		Also used for cattle and sheep
	The raw egg is put on a piece of raw wool which is adhered to the body with the help of oil (ritual)	To treat pains)the egg moves on the wool and where the yolk stops, the yolk "takes the pain away" and comes out of the membrane, the whole treatment last at least 1 h!)
	Cooked	Anti-diarrheic
	Eaten	To treat stomach ache
Fish	Left alive in a small amount of water	Diagnostic means to establish the length of hepatitis. While the fish is still alive, the affected person will remain ill (ritual
Goat fat	Heated and drunk (one spoonful)	To treat asthma
Hen muscular stomach	The membrane of the muscular stomach is extracted and dried, the ground and made into a decoction	To treat kidney stones
Honey	Applied externally under the ears	Mumps
	Applied on the mucosa	To treat mouth inflammations

There are several excellent studies that describe the state of medical pharmacopeias in different eras ranging from the tenth to nineteenth centuries in the Mediterranean basin. This includes studies on Medieval zoo therapy in the Levant, zoo therapy using various animals was given in table 1. People who are allergic to certain substances, or who want to avoid certain animal products for religious or cultural reasons may need to know about the origin/source of drugs and excipients contained within their medicines. This document provides information to assist clinicians in dealing with these types of situations. A number of medicines (including tablets, injections, capsules, creams, mixtures and vaccines) contain animal products or are animal derived. For example, gelatin is a partially hydrolyzed collagen which is usually bovine (beef) or porcine (pig) in origin. Gelatin is used in making capsule shells and is one of many types of stabilizers added to pharmaceutical products such as vaccines. Heparin, an injectable anticoagulant, is prepared from a porcine source[11]. Egypt[12].

3. TYPES OF ZOO THERAPY:

3.1 PET THERAPY AND MENTAL HEALTH:

Interactions with animals are considered to patients suffering from post-traumatic stress disorder and psychiatric disorders. Animal therapy is used to treat depression, (Figure 1) (www.dogtime.com) and decrease BP (Blood pressure). Alzheimer patients who have pets in their home are less likely to suffer of anxiety[13,14].

Fig. 1 Pet therapy and mental health

REVIEW ARTICLE

Nanoparticles for Herbal Extracts

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Abstract

Herbal medicines have been widely used all over the world since ancient times and have been recognized by physicians and patients for their better therapeutic value as they have fewer adverse effects as compared with modern medicines. Phytotherapeutics need a scientific approach to delivering the components in a sustained manner to increase patient compliance and avoid repeated administration. This can be achieved by designing novel drug delivery systems (NDDSs) for herbal constituents. NDDSs not only reduce the repeated administration to overcome non-compliance but also help to increase the therapeutic value by reducing toxicity and increasing the bioavailability. One such novel approach is nanotechnology. Nano-sized drug delivery systems of herbal drugs have a potential future for enhancing the activity and overcoming problems associated with plant medicines. Hence, integration of the nanocarriers as an NDDS in the traditional medicine system is essential to conflict more chronic diseases such as asthma, diabetes, cancer, and others. The article describes nano drug delivery systems, properties, advantages, disadvantages, types of nanoparticles, their method of preparation, different nano herbal medicines, and nano herbal cosmetics available in the market.

Key words: Herbal drugs, nanotechnology, novel drug delivery systems

INTRODUCTION

Importance of herbal medicine

Since ancient time, herbal remedies and natural products (NPs) are being used to cure the diseases.[1] NPs that are isolated from the plants are known as "herbal remedies." Practically, herbal remedies have the date back long history to the existence of the human civilization. New medicines are being developed and will be developed gradually by the scientists through the different ways. However, always ancient or herbal remedies and NPs have been the roots of these medicines. In the ancient time, before the arrival of high throughput screening concerned to drug discovery, 90–95% drug materials were NPs.[2] Information on the source of new drugs nearby 1981–2007 specifies that approximately half of the drugs are based on the NPs.[3,4] It has been proved that NPs are more voluntarily absorbed than synthetic drugs. Although the herbal formulations are not expected to treat diseases properly, they can help in better management of diseases by the patient himself. It can improve the quality of life by giving nutritional supplement as well. Silver nanoparticles have been synthesized for *Cardiospermum helicobacum* leaf extract.[5]

The pharmaceutical companies were laid when techniques were developed to produce a synthetic replacement for many of the medicines that had been derived from the forests. Now, the pharmaceutical efforts are cracking to developing the new pioneering or indigenous therapies and development the uniqueness of plant-based drugs or herbal remedies.[6]

Novel drug delivery system

The aim of novel drug delivery system (NDDS) is to provide a therapeutic amount of drug to the appropriate site in the body to accomplish promptly and then maintain the desired drug concentration. The drug delivery system should deliver drug at a rate control by the necessarily of the body over a specified term of treatment. The prime areas of research and development for NDDS are liposomes, noisome, nanoparticles, transdermal drug delivery, implants, oral

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system, microencapsulation/microcapsules, and polymer in drug delivery.

Nano drug delivery systems for herbal extracts

Phytotherapeutics need a scientific approach to deliver the components in a sustained manner to increase patient compliance and avoid repeated administration. This can be achieved by designing NDDSs for herbal constituents NDDSs not only reduce the repeated administration to overcome non-compliance but also help to increase the therapeutic value by reducing toxicity and increasing the bioavailability.[7] The novel carriers should ideally fulfill two prerequisites. First, it should deliver the drug at a rate directed by the needs of the body over the period of treatment. Second, it should channel the active entity of herbal drug to the site of action. Conventional dosage forms including prolonged-release dosage forms are unable to meet none of these. It has a number of advantages for herbal drugs including enhancement of solubility and bioavailability, protection from toxicity, enhancement of pharmacological activity, enhancement of stability, improving tissue macrophages distribution, sustained delivery, and protection from physical and chemical degradation. Thus, the nano-sized NDDSs of herbal drugs have a potential future for enhancing the activity and overcoming problems associated with plant medicines. Nanocarriers applying to herbal remedies will carry the optimum amount of the drug to their site of action bypassing all the barriers such as acidic pH of stomach, liver metabolism, and increase the prolonged circulation of the drug in the blood due to their small size.[1,8] Hence, use of herbal remedies in an NDDS will enhance the improvement in the use of herbal remedies that will come forth to treat the various chronological diseases.[9]

Nanotechnology is approaching new paradigm for drug delivery system by their unique small size and controlled release of the drug. Hence, using "herbal remedy" in the nanocarriers will increase its potential for the treatment of various chronic diseases and health benefits. This field of pharmaceutical technology has grown and diversified rapidly in recent years and emerged tremendously from macro level to micro level and currently growing at molecular level, i.e., nano level. The importance of technology in the field of pharmaceutics and medicine has been ever growing due to the changing trends of developing drugs and drug delivery systems.[10] Nanotechnology in some NDDSs like ocular drug delivery has been used to enhance the bioavailability by overcoming the drawbacks of the conventional dosage forms. This is possible due the capacity of the nanocarriers to protect the encapsulated drug molecule and transport it to various areas of the eyes[11-13] [Figure 1].

Nanoparticles

Nanoparticles are particles between 1 and 100 nanometers in size. In nanotechnology, a particle is defined as a small object that behaves as a whole unit with respect to its transport and properties. Particles are further classified according to diameter [Figure 2].[14]

Properties of nanoparticles[15-17]

- They are effectively a bridge between bulk materials and atomic or molecular structures
- The high surface area to volume ratio of nanoparticles provides a tremendous driving force for diffusion, especially at elevated temperatures. Sintering can take place at lower temperatures, over shorter time scales than for larger particles
- Suspensions of nanoparticles are possible since the interaction of the particle surface with the solvent is strong enough to overcome density differences, which otherwise usually result in a material either sinking or floating in a liquid
- Nanoparticles also often possess unexpected optical properties as they are small enough to confine their electrons and produce quantum effects. For example, gold nanoparticles appear deep red to black in solution
- Nanoparticles with one-half hydrophilic and the other half hydrophobic are termed Janus particles and are particularly effective for stabilizing emulsions. They

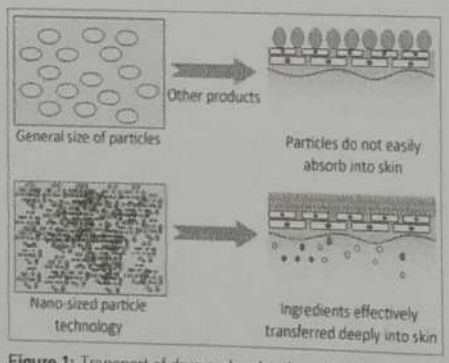

Figure 1: Transport of drug molecules through skin

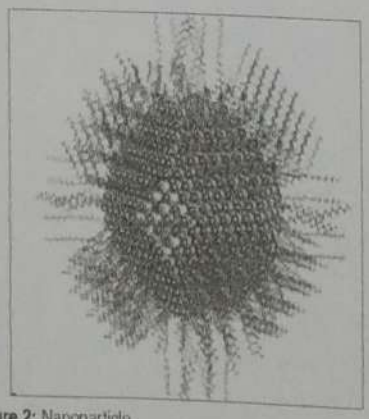

Figure 2: Nanoparticle

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RESEARCH ARTICLE

Anti-microbial Activity of Aqueous Extract of Natural Preservatives - Cumin, Cinnamon, Coriander and Mint

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ABSTRACT:

This study was aimed to overcome the problems of artificial preservatives used in food preservation with natural preservatives. In this aspect, four different plants was selected such as black cumin, cinnamon, coriander and mint for anti-microbial activity against some food borne pathogens such as three gram negative microorganisms *E. coli*, *P. aeruginosa*, *S. marcescens* and three gram positive microorganisms such as *Bacillus subtilis*, *S. aureus* and *B. cereus*. A selected plant material was extracted by the soxhlet apparatus with water. Aqueous extract and in combination of extracts (1:1) ratio was prepared and antimicrobial activity was analyzed by agar disc diffusion method. According to the: results obtained individual extract of mint against *E. coli* has produced the highest zone of inhibition 18 mm. The extract of mint with coriander showed 19 mm of zone of inhibition against *E. coli*. Overall all the plant extract and their combination showed very good antibacterial activity. The Plant extract are most probably used for food preservation than the chemical preservatives because the chemical preservative which leaves the chemical residue on the food which can cause harm to the life. Further studies may be carried out to screen the valuable antimicrobial constituents present in the plant materials.

KEYWORDS: Antimicrobial, Natural preservative, Plant extracts, Agar Disc Diffusion, Zone of inhibition.

INTRODUCTION:

Food preservation is a technique to fight against microorganisms otherwise they spoil the food. Worldwide use of food preservatives is increasing 4.1 % every year[1]. The artificial food preservatives reduce the moisture level of the food and prevent the microorganism growth.

It acts as antioxidants, preventing chemical reactions that cause the oxidation of food, those results in its spoilage[2] and it can be harmful because of chemical residue retain in foods and increased potential risk for cancer. The natural preservatives are substances that slow down the decomposition of biological products. It can add nutrients lost in processing and safe and effective tool for protecting the food from microorganisms. Plant-based antimicrobials have more therapeutic effect with lesser side effects[3].

Artificial preservatives may lead to toxic effect. So, the natural preservatives like cinnamon, coriander, mint, black cumin were selected to reduce the effect of toxicity produced by artificial preservatives.

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Cinnamon belongs to the family Lauraceae. Cinnamon bark is used as a spice and popular flavoring in numerous alcoholic beverages. It has good antidiabetic, anti-inflammatory, anti-oxidant and anti-microbial activity[4, 5].

Coriander belongs to family Apiaceae. All parts of the plant are edible, but the fresh leaves and the dried seeds are traditionally used in cooking. Both the leaves and seed contain antioxidant activity[6]. This is found to cure indigestion as well as induce appetite within minutes[7]. They are rich in vitamin A, vitamin C and vitamin K[8].

Mint belongs to the family Lamiaceae. Mint was originally used as a medicinal herb to treat stomach ache and chest pains. It contains essential oil and menthol is particularly used as flavorings in breath fresheners, drinks, antiseptic mouth rinses, calming anxiety, and promoting restful sleep[9].

Black Cumin belongs to the family Ranunculaceae. Black cumin is useful in cancers whose growth depends on angiogenesis. The seeds are used as a spice[10].

The present study was having main accurate goal to avoid the risk of artificial preservatives in food preservation with the natural preservatives like cinnamon, coriander, mint and black cumin.

MATERIAL AND METHODS:

1. Plant Materials

Mint (*Mentha spicata*), Black cumin (*Nigella sativa*), Coriander (*Coriandrum sativum L*), Cinnamon (*Cinnamonum verum*) used in the present study were procured from local shops of Vijayawada, Andhra Pradesh.

2 Standard Drugs

Tetracycine (Broad spectrum antibiotics) and streptomycin (Aminoglycosidic antibiotics) were used as standard drugs.

3 Microorganisms

E. coli (NCIM 2256), *P. aeruginosa* (NCIM 2037), *Serratia marcescens* (NCIM 2078) and three gram positive microorganisms such as *Micrococcus luteus* (NCIM 2871), *Bacillus subtilis* (NCIM 2710) and *Staphylococcus aureus* (NCIM 2794) were used in these studies.

4. Extraction of Plant Material

Freshly collected plant materials such as Mint, Black cumin, Coriander and Cinnamon were powdered and stored at a room temperature. The extraction was carried out with water by soxhlet apparatus. 15 g of dried Mint powder was extracted with 125 ml of water by soxhlet apparatus for 4 hrs[11, 12]. Aqueous extract of mint powder was prepared and stored in the refrigerator at 2-5 °C until it was used for the antimicrobial studies. Similarly, 15 g of dried black cumin, coriander and cinnamon powder was extracted with 125 ml of water separately by soxhlet apparatus for 4 hrs.

5. Screening of Antimicrobial Activity

5.1 Preparation of Inoculum

A loopful of organism was taken from a culture of *E. coli* and inoculated into 10 ml of Mueller-Hinton broth. A similar procedure was followed to prepare the inoculum of other bacterial species i.e., *S. aureus*, *S. marcescens*, *P. aeruginosa*, *B. cereus*, *B. subtilis*. The broth suspension was then incubated at 37 °C for 3 hr. and utilized for antibacterial assays.

5.2 Media for Test Organisms

Mueller-Hinton agar medium (19 gm) was dissolved in 250 ml of distilled water and autoclaved at 121 °C for 15 min at 15 lbs. Then, it was inoculated with gram positive and gram negative microorganism and poured into sterile plates and set aside until to get solidified.

5.3 Agar Disc Diffusion Techniques

Paper discs were dipped aseptically in four distinct aqueous extracts such as Mint, Black cumin, Coriander and Cinnamon. As well as the combination of all these four extracts in 1:1 ratio and placed over Mueller-Hinton Agar plates seeded with respective pathogens[13, 14]. The plates were incubated in an upright position at 37 °C for 24 hrs. The diameter of inhibition zone was measured in mm and the results were recorded.

RESULTS AND DISCUSSION

Antimicrobial activity of natural preservatives such as mint, coriander, black cumin and cinnamon aqueous extracts were evaluated and reported in the following Tables 1-4 and Figs 1-4.

Table 1 Antimicrobial activity of Natural Preservatives against Gram negative Microorganisms

S.NO.	PLANT EXTRACT	ZONE OF INHIBITION (mm)		
		E. coli	*P. aeruginosa*	*S. marcescens*
1	MINT	18	7	8
2	BLACK CUMIN	11	8	7
3	CORIANDER	9	6	8
4	CINNAMON	7	9	6
5	STREPTOMYCIN(Standard Drug)	16	12	21

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Formulation and evaluation of mucoadhesive microspheres of cimetidine

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ABSTRACT

The intention of the present study is to formulate mucoadhesive microspheres containing cimetidine by employing xanthan gum & gum kondagogu as mucoadhesive agent and by adapting ionotropic gelation technique. Response Surface Composite design was employed to study the effect of independent variables, polymer concentration (X1) and sodium alginate concentration (X2) on dependent variables mucoadhesion time. The best batch exhibited a high drug entrapment efficiency of 97.12% and a swelling index of 96.98%; percentage mucoadhesion after 10 h was 98%. The drug release was also sustained for 12 h. The prepared mucoadhesive microspheres were characterized for various properties like preformulation, flow properties, *in vitro* mucoadhesion, *in vitro* drug release, entrapment efficiency and surface properties. The external and internal surface morphological characteristics of mucoadhesive microspheres were investigated using Scanning Electron Microscope (SEM). The formulation which showed better flow properties, *in vitro* drug release and entrapment efficiency was selected as optimized formulation i.e., formulation MGK5. The *in vitro* release profiles from optimized formulations were applied on various release kinetic models of drug and suggested that the drug release from microspheres followed non-fickian diffusion. The optimized formulations MGK5 was subjected to stability studies for six months at $40^0 \pm 2^0$C & 75±5%RH as per ICH guidelines and result showed that there were no changes in physical parameters, formulation parameters and *in vitro* release studies.

Keywords: Mucoadhesive Microspheres, Cimetidine, Factorial Design, *In vitro* study.

INTRODUCTION

Microsphere carrier systems made from the naturally occurring biodegradable polymers have attracted considerable attention for several years in sustained drug delivery. Recently, dosage forms that can precisely control the release rates and target drugs to a specific body site have made an enormous impact in the formulation and development of novel drug delivery systems. Microspheres form an important part of such novel

drug delivery systems [1-3]. They have varied applications and are prepared using assorted polymers. However, the success of these microspheres is limited owing to their short residence time at the site of absorption. It would, therefore, be advantageous to have means for providing an intimate contact of the drug delivery system with the absorbing membranes [4]. This can be achieved by coupling bioadhesion characteristics to microspheres and developing bioadhesive microspheres. Bioadhesive microspheres have advantages such as efficient absorption and enhanced bioavailability of drugs owing to a high surface-to-volume ratio, a much more intimate contact with the mucus layer and specific targeting of drugs to the absorption site. [5]

Cimetidine is a histamine H2 receptor antagonist, which is widely prescribed in gastric ulcers, duodenal ulcers and gastroesophageal reflux disease. It is poorly absorbed from the lower gastrointestinal tract and has a short elimination half-life (~ 2 h) [6]. The purpose of the work was to prepare cimetidine (CM) microspheres in order to achieve an extended retention in the upper GIT, which may result in enhanced absorption and thereby improved bioavailability.

MATERIALS AND METHODS

Materials

Cimetidine was obtained as a gift sample from Aurobindo Pharma Limited, Hyderabad, India. Sodium alginate was obtained from Pruthvi Chemicals, Mumbai. Sodium Carboxy Methyl Cellulose, Xanthan gum and Gum Kondagogu were obtained from MSN Labs Ltd., Hyderabad. All other chemicals were of Pharmaceutical grade.

Method

Cimetidine mucoadhesive microspheres were prepared using polymers sodium alginate, chitosan, sodium CMC by ionotropic gelation method. A 3^2 full factorial design was employed to study the effect of independent variables, polymer-to-drug ratio (X1) and stirring speed (X2) on dependent variables percentage mucoadhesion, drug entrapment efficiency and swelling index. Different formulations were prepared by using different concentrations of polymers and mucoadhesive agent showed in **Table 1 & 2.** Cimetidine mucoadhesive microspheres were prepared using polymers sodium alginate & xanthan gum and gum kondagogu were used in different concentrations by ionotropic gelation method. In this method, weighed quantity of cimetidine was added to 100 ml sodium alginate, xanthan gum and gum kondagogu solution were thoroughly mixed at 500 rpm. Resultant solution was extruded drop wise with the help of syringe and needle into 100 ml aqueous calcium chloride solution and stirred at 100 rpm. After stirring for 30 min, the obtained microspheres were washed with water and dried at 60^0C for 4 h in a hot air oven and stored in desiccators [7].

Table 1 (a): Optimization of Cimetidine Mucoadhesive Microspheres containing Xanthan gum

Factor	Name	Minimum	Maximum	-1 Actual	+1 Actual	Mean	Std. Dev.
A	Sodium Alginate (%)	3.00	4.00	3.00	4.00	3.50	0.41
B	Xanthan Gum (%)	15.00	20.00	15.00	20.00	17.50	2.04

Table 1 (b): Composition of Cimetidine Mucoadhesive Microspheres containing Xanthan gum

Formulation Code	Cimetidine (g)	Sodium Alginate (%)	Calcium Chloride (%)	Xanthan Gum (%)
MX1	2	3.5	10	17.5
MX2	2	4.0	10	20.0
MX3	2	3.5	10	20.0
MX4	2	3.0	10	17.5
MX5	2	3.0	10	15.0
MX6	2	4.0	10	15.0

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Original Research Article

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In Vitro and *In Vivo* Evaluation of Cimetidine loaded mucoadhesive microspheres

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Abstract

In the present research work mucoadhesive microspheres of cimetidine was prepared using ionotropic gelation technique. All the microspheres were characterized for particle size, scanning electron microscopy, FT-IR study, DSC, percentage yield, drug entrapment, stability studies and for in vitro release kinetics and found to be within the limits. Among all the formulations M12 was selected as optimized formulation based on the physicochemical and release studies. In vitro drug release study of optimized formulation M12 showed 99.12% after 12 h in a controlled manner, which is essential for anti ulcer therapy. The innovator cimetine conventional tablet showed the drug release of 96.15% within 1 h. The drug release of cimetidine optimized formulation M12 followed zero order and Higuchi kinetics indicating diffusion controlled drug release. *In vivo* studies revealed that the optimized formulation M12 gave the highest AUC and T_{max}. The results are indicative of cimetidine as mucoadhesive microspheres for improving the oral bioavailability with controlled drug release.

Keywords: Cimetidine, mucoadhesion, chitosan, ionotropic gelation, bioavailability.

Introduction

Oral route is most sought-after for administration of drug molecules to the systemic circulation due to low cost therapy, ease of administration, patient compliance [1]. New drug delivery technologies are revolutionizing the drug discovery, development and creating R&D focused pharmaceutical industries to increase the momentum of global advancements. In this regard novel drug delivery systems (NDDS) have many benefits, which includes improved therapy by increasing the efficacy and duration of drug activity, increased patient compliance through decreased dosing frequency and convenient routes of administration and improved site specific delivery to reduce unwanted adverse effects [2].

Despite the problem frequently encountered with controlled release dosage forms is the inability to increase the residence time of the dosage form in the stomach and proximal portion of the small intestine, due to the rapid gastrointestinal transit phenomenon of the stomach which may consequently reduce the extent of absorption of many drugs since almost most of the drug entities are mostly absorbed from the upper part of the intestine, therefore it would be beneficial to develop a sustained release formulation which remain at the absorption site for an extended period of time so that maximum of dose is absorbed in systemic circulation. Several approaches have been immersed to prolong the residence time of the dosage forms at the absorption site and one of these is the development of oral controlled release mucoadhesive system. Various gastrointestinal mucoadhesive dosage forms, such as microspheres and tablets, have been thoroughly prepared and reported by several research groups [3,4].

Mucoadhesion is the relatively new and emerging concept in drug delivery. Mucoadhesion keeps the delivery system adhering to the mucous membrane [5].

Peptic ulcer disease is a break in the lining of the stomach, first part of the small intestine or occasionally the lower esophagus [6].

Cimetidine is histamine H_2-receptor antagonists, which is used to reduce the risk of stomach ulcers in patients treated with nonsteroidal anti-inflammatory drugs, which has less bioavailability (60%) and lesser half life of 2 h [7]. The aim of present work is to design and evaluate mucoadhesive microspheres of cimetidine *in vitro and in vivo* to enhance its bioavailability and prolong residence time in stomach.

Materials and Methods

Materials

Cimetidine pure drug was generous gift from Aurobindo Pharma Limited, Hyderabad, India. Sodium alginate was obtained from Pruthvi Chemicals, Mumbai. Sodium alginate, chitosan, xanthan gum, kondagogu gum and sodium CMC were gifted from MSN Labs Ltd., Hyderabad. All other chemicals used were of analytical grade.

Formulation of Cimetidine mucoadhesive microspheres

Cimetidine mucoadhesive microspheres were prepared using different polymers like sodium alginate, chitosan, sodium CMC, xanthan gum and gum kondagogu by ionotropic gelation method. Different formulation trials of cimetidine were prepared using different concentrations of polymer and cross linking agent. Total 14 formulations were developed using different polymers in different concentrations. In this method, weighed quantity of cimetidine was added to 100 ml sodium alginate solution and thoroughly mixed at 500 rpm. Resultant solution was extruded drop wise with the help of syringe and needle into 100 ml aqueous calcium chloride solution and stirred at 100 rpm. After stirring for 10 min the obtained microspheres were washed with water and dried at 60°C – 2 h in a hot air oven and stored in desiccator [8].

Table 1: Formulation trials for Cimetidine mucoadhesive microspheres

FORMULATION CODE	CIMETIDINE (g)	SODIUM ALGINATE	SODIUM CMC(mg)	CALCIUM CHLORIDE	XANTHAN GUM	GUM KONDAGOGU
M1	2	1 %	100	7%	1%	0.5%
M2	2	1.2 %	150	7%	1.2%	0.5%
M3	2	1.4%	200	7%	1.4%	0.5%
M4	2	1.6%	250	7%	1.6%	0.5%
M5	2	1.8%	300	7%	1.8%	0.5%
M6	2	2%	350	7%	2%	0.5%
M7	2	2.2%	400	7%	2.2%	0.5%
FORMULATIN CODE	CIMETIDINE (g)	SODIUM ALGINATE	CHITOSAN (mg)	CALCIUM CHLORIDE	XANTHAN GUM	GUM KONDAGOGU
M8	2	1%	10	10%	1%	0.5%
M9	2	1.2%	15	10%	1.2%	0.5%
M10	2	1.4%	20	10%	1.4%	0.5%
M11	2	1.6%	25	10%	1.6%	0.5%
M12	2	1.8%	30	10%	1.8%	0.5%
M13	2	2%	35	10%	2%	0.5%
M14	2	2.2%	40	10%	2.2%	0.5%

Evaluation studies of Cimetidine mucoadhesive microspheres

Micromeretic parameters like particle size[9], angle of repose, bulk density, tapped density, compressibility index, Hausner's ratio [10], swelling index [11], drug entrapment efficiency and % yield [12].

Mucoadhesiveness

The *in vitro* mucoadhesive test was carried out using small intestine from chicken. The small intestinal tissue was excised and flushed with saline. Five centimeter segments of jejunum were averted using a glass rod. Ligature was placed at both ends of the segment. 100 microspheres were scattered uniformly on the averted sac from the position of 2 cm above. Then the sac was suspended in a 50 ml tube containing 40 ml of saline by the wire, to immerse in the saline completely. The sacs were incubated at 37°C and agitated horizontally. The sacs were taken out of the medium after immersion for 1, 2, 3, 4, 5, 6, 7 and 8 h, immediately repositioned as before in a similar tube containing 40 ml of fresh saline and unbound microspheres were counted. The adhering percent was presented by the following equation [13].

Mucoadhesion= (No. of microspheres adhered/ No. of microspheres applied) x 100

In vitro drug release studies

In vitro drug release studies for developed cimetidine microspheres were carried out by using dissolution apparatus II paddle type (Electrolab TDL-08L). The drug release profile was studied in 900 ml of 0.1 N HCl at 37±0.5°C temperature at 100 rpm. The amount of drug release was determined at different time intervals of 0, 1, 2, 3, 4, 6, 8, 10 & 12 h by UV-visible spectrophotometer (Shimadzu UV 1800) at 218 nm [14].

Drug excipient compatibility studies

The drug excipient compatibility studies were carried out by Fourier transmission infrared spectroscopy (FTIR) method. Differential

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PHYTOCHEMICAL & *IN VITRO* ANTIUROLITHIATIC STUDIES ON THE LEAF EXTRACTS OF *BAUHINIA VARIEGATA* LINN.

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Keywords:

Fluorescence, Quantitative Determination, *In vitro*, Antiurolithiatic Study

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ABSTRACT: The aim of the present study is to carry out fluorescence analysis, phytochemical extraction, preliminary phytochemical screening, estimation of total flavonoids, tannins, alkaloids, steroids saponins and *in vitro* antiurolithiatic studies on the leaf aqueous and ethanolic extracts of *Bauhinia variegata*. The results of fluorescence analysis indicate that the powder on treatment with 50% H_2SO_4 shows dark brown colour under UV. The results of preliminary phytochemical screening indicated the presence of saponin glycosides, tropane alkaloids and acidic compounds. The results of quantitative determination indicated that the aqueous extract contains highest amount of flavonoids expressed as 54.6 mg/gm equivalents of quercetin, maximum amount of tannins in ethanolic exract as 56.30 mg/gm equivalents of quercetin, equal amounts of alkaloids are present in both extracts as 25mg/gm equivalents of atropine sulphate, steroids and saponins in lowest amount. The *in vitro* antiurolithiatic activity was studied as percentage inhibition of stones by nucleation, growth and aggregation assays for aqueous and ethanolic extracts at 200-1000 µg/ml taking cystone tablets as standard. The results indicated that the inhibition of growth of crystals increased with increase in concentration of the extract. Therefore, the plant claimed to possess antiurolithiatic activity and further *in vivo* studies as well as isolation of individual compounds responsible for the activity are necessary.

INTRODUCTION World Health Organization manifests that approximately 75% of the global population, of the developing world, depends on botanical medicines for their basic healthcare needs. [1] Exact identification and quality of the starting materials is an essential prerequisite to ensure reproductive quality of herbal medicine which will contribute to its safety and efficacy. [2]

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Deposition or formation of stones in any part of the urinary system i.e the kidney, the ureters or the urinary bladder is called Urolithiasis. Stone formation is the culmination of a series of physiochemical events *i.e.* super saturation and nucleation, growth of the crystal and aggregation that occurs as the glomerular filtrate traverses through the tubules of nephron.

Urine remains supersaturated with most stone forming salt components as well as chemicals that prevent or inhibit the crystals from urinary tract. These crystals remain tiny enough. [3] They will travel through the urinary tract and pass out of the body in the urine without being noticed. [4] Calcium oxalate stones represent upto 80% of analyzed stones. [5] It is considered as the third most common

affliction of the urinary tract. [6] However, the presence of certain molecules raise the level of supersaturation of salts needed to initiate crystal nucleation or reduce the rate of crystal growth or aggregation and prevents stone formation. [7]

Though technological advancements have made dramatic improvement, still some of the drawbacks of the methods exist which includes their being too costly and recurrence of stone formation along with number of other side effects [8]. The problem of urinary stones is an ancient one, and still remains a common problem worldwide.

Some medicinal plants contain chemical compounds like Glycosaminoglycans (GAGs) which themselves possess an inhibitory effect in the crystallization of calcium oxalate. Antioxidant constituents of the plants also help in ameliorating the crystal/oxalate induced renal cell injury. Thus, antiurolithiatic activity of plants or herbal formulation may be due to synergism of their diuretic activity, crystallization inhibition along with antioxidant activity [9]. The activity of the extracts was evaluated by measuring the ability of the extracts to inhibit the formation of calcium and phosphate precipitates [10]. In order to find new potential antiurolithiatics the plant selected was *Bauhinea variegata* belonging to the family *Leguminosae* as there were no scientific reports published on the leaves of the plant for antiurolithiatic activity.

The plant *Bauhinea variegata* has been used traditionally, the root is carminative, used in dyspepsia, flatulence and as an antidote to snake poison. [11] The bark, flower juice are used as astringent, tonic, anthelmintic, scrofula and skin diseases [12].

The leaves of the plant were evaluated for the pharmacognostic, powder microscopy and physiochemical studies [13]. The non woody aerial parts contain 6 flavonoids, namely kaempferol, ombuin, kaempferol 7,4'-dimethylether-3-o-β-D-glucopyranoside, kaempferol – 3 – o - β-D-gluco pyranoside, isorhamnetin-3-o-β-D-glucopyranoside & hesperidin together with one triterpene caffeate, 3β trans-(3,4 dihydroxycinnamoyloxy) olean-12-en-28-oic acid. The root contains novel flavonol glycosides [14].

The root bark possesses a new flavonone (2S) -5, 7-dimethoxy-3, methylenedioxy flavonone and new dihydrodibenzoxepin 5, 6 dihydro -1, 7-dihydro-1, 7-dihydroxy-3, 4-dimethoxy-2-methyldibenzoxepin, together with three known flavonoids [15]. The Stem contains an unknown compound naringenin 5, 7 dimethyl ether 4 – rhamnoglucoside, a new phenanthraquinone named Bauhinione has been isolated from *B. variegata* L. [16]. The leaves contain two new long chain compounds heptatriacontane- 12, 13-diol 7 dotetracont-15-en-9-ol. Anti cancer activity was studied on the ethanolic extract of stem [17]. Antimicrobial activity was studied on the ethanolic extract of leaf and bark. [18] Antiinflammatory avtivity for the flavonoid compounds isolated from the non woody aerial parts. [19] Hepatoprotective activity was studied on the ethanolic extract of stem.[20] Antiulcer activity was studied on the ethanolic extract of stem of *Bauhinea variegata*. [21] The aimof the present study was to carry out UV-Fluoresence analysis of the powder, preliminary phytochemical screening, to determine total amount of flavonoids, tannins, alkaloids, steroids and saponins and to evaluate *in vitro* antiurolithiatic studies by nucleation, growth and aggregation assays for the aqueous and ethanolic extracts of leaves of *Bauhinea variegata*.

MATERIALS AND METHODS:

Materials: The Plant material *Bauhinia variegata* was collected in the month of December during afternoon from the grounds of Vijaya institute of Pharmaceutical Sciences for Women, Enikepadu, Vijayawada. Herbarium was prepared and the sample was authenticated by Dr. D.T. P. Satyanarayana Raju, plant taxonomist, department of Botany and Microbiology, Acharya Nagarjuna University, Guntur. The photographs of the plant and leaves were depicted in **Fig. 1** and **Fig. 2** The authentication letter was also enclosed. The Chemicals used were purchased from Finar chemicals. The dried leaves were coarsely powdered and depicted in **Fig. 3 and Fig. 4.**

Powder Analysis:

Powder Analysis using Chemical Reagents with naked Eye: The leaf powder was studied with naked eyeby using the chemicals and the results were noted and given in **Table 1** [22].

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BIO COMPATIBLE MATERIALS USED IN MEDICAL PRACTICE

Review Article

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ABSTRACT

Medical implants are products that have to satisfy functionality demands defined by the human body as working environment. The choice of material used for designing a medical implant is governed by biocompatibility. The development of this area attracts commercial utility. Focus of this contribution is on metallic, ceramic and polymeric biomaterials and laws regulating their use in modern medical applications. Further studies relating to long-term effects of materials on biological tissues are necessary, and are likely to lead to an increased understanding of the biocompatibility of materials in the future.

KEY WORDS:

Medical implants,

biocompatible,

biomaterials

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I. INTRODUCTION

The development of medical implants utilizing new materials continues to attract considerable academic and commercial interest. The development of new biomaterials involves a complicated mix of materials science and cell biology. Collaboration of various experienced specialists such as material scientists, metallurgists, traumatologists, orthopedists, chemists, mechanical engineers, pharmacists and others in order to achieve better results in research, development and implementation of the extracted knowledge into the practice is of essential importance. Biomaterials are nonviable materials used in a medical devices intended to interact with biological systems (Ratner et al., 2004) and cover several classes of materials, such as metallic, ceramic, and polymeric materials. Medical implants are products that have to satisfy functionality demands defined by the human body as working environment. Ideally, they should have biomechanical properties

comparable to those of autogenous tissues without any adverse effects and are regulated in order to ensure safety and effectiveness. The choice of material used for designing a medical implant is governed by biocompatibility, bioadhesion, bio functionality corrosion resistance etc. To better understand implant material-biological organism interaction most of the studies are directed into the releases of particles from the material and offer screens for genotoxicity, carcinogenicity, cytotoxicity, irritation, sensitivity and sterilization agent residues (Balazic et al., 2007) Focus of this contribution is on metallic, ceramic and polymeric biomaterials and laws regulating their use in modern medical applications.

1.1 TYPES OF BIOMATERIALS:

Biomaterials are divided into following subgroups (Fig. 1).

1.1.1 Metallic biomaterials: Stainless steel, Cobalt alloys, Titanium alloys
1.1.2 Ceramic biomaterials: Aluminium oxide, Zirconia, Calcium phosphates
1.1.3 Polymeric biomaterials:

- Synthetic polymers- Silicones, polyethylene, polyvinyl chloride, polyurethanes.
- Natural polymers- Collagen, gelatin, elastin, silk, polysaccharide.

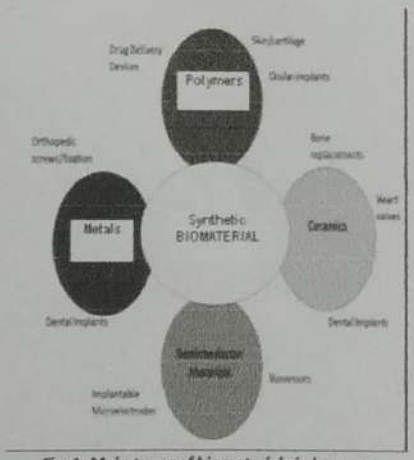

Fig. 1: Main types of biomaterials in humans

1.1.1 METALLIC BIOMATERIALS

Metallic biomaterials are often used to support and/or replace components of the skeleton. They are used e.g. as artificial joints, bone plates, screws, intramedullary nails, spinal fixations, spinal spacers, external fixators, pace maker cases, artificial heart valves, wires, stents, and dental implants. They possess greater tensile strength, fatigue strength, and fracture toughness when compared to polymeric and ceramic materials. Most widely used metallic biomaterials for implants devices are 316L stainless steels, cobalt alloys, commercially pure titanium, and Ti-6Al-4V alloys (Sumita M et al., 2004; Annual book of ASTM standards 1999; Williams 1993; Breme et al., 1998). Originally, these materials were developed for industrial purposes.

Table 1: Mechanical characteristics of metal alloys used in medicine

Characteristics	Stainless steel	Cobalt alloys	Titanium alloys
Stiffness	High	Medium	Low
Strength	Medium	Medium	High
Corrosion Resistance	Low	Medium	High
Biocompatibility	Low	Medium	High

The corrosion resistance, which results in very small release of harmful toxins when exposed to bodily fluids, is the main reasons for these materials can be left inside the body for a longer period of time and are therefore appropriate for medical uses. In Table 1 some mechanical and biological characteristics of stainless steel, cobalt and titanium alloys are presented. As additional information let us mention that production of metallic-based medical devices in general involves cutting operations (turning, milling, drilling etc.); forming operations (pressing, hydroforming, forging etc.) and other alternative machining operations (laser and waterjet cutting, different layer-by-layer sintering techniques such as direct metal laser sintering, selective laser melting, selective laser sintering, electron beam melting and laser engineered net shaping) (Bombac et al 200).

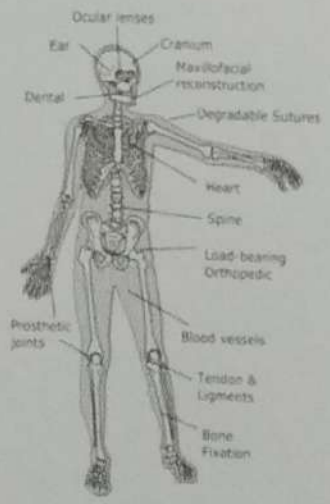

Fig. 2: Biocompatible materials in the human body

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Formulation and Evaluation of Fast Dissolving Tablets of An Anti Ulcer Drug by Sublimation Method

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ABSTRACT

The purpose of present research was to formulate and develop the patient friendly pantoprazole sodium fast dissolving tablets using sublimation method to achieve rapid dissolution. In this study, an attempt was made to fasten the drug release from the oral tablets by incorporating the superdisintegrants and camphor/ammonium bicarbonate as subliming agents. The prepared fast dissolving tablets were subjected to pre-compression analysis and evaluated for hardness, weight variation, friability, wetting time, water absorption ratio and disintegration time. From the results of *in vitro* drug release studies, the formulation F9 exhibited fast release profile of about 95.21% in 14 min and disintegration time 90 sec when compared with other formulations. For the optimized formulation F9, the initial dissolution rate was 38.82% / 2 min. Fourier transform infrared spectroscopy studies revealed that there was no possibility of interactions between drug and excipients. The present study demonstrated potential for rapid absorption, improved bioavailability, effective therapy and patient compliance.

Keywords: Fast dissolving tablet, pantoprazole sodium, subliming agent, superdisintegrant, proton pump inhibitor.

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INTRODUCTION

Oral route of drug administration offers wide acceptance up to 50-60% of total dosage forms. Solid dosage forms have gained popularity because of ease of administration, accuracy of dosage, possibility of self-medication and avoidance of pain as well as the patient compliance. Among the solid dosage forms, tablets and capsules are most popular; one major drawback of this dosage forms for some patients, is the difficulty to swallow. Drinking water plays a vital role in the swallowing of oral dosage forms. People experience inconvenience in swallowing conventional dosage forms such as tablet when there is unavailability of water, in case of motion sickness (kinetosis) and sudden episodes of coughing during the common cold, allergic condition and bronchitis[1]. For these reasons, tablets that can dissolve or disintegrate at a faster rate in the oral cavity have attracted a great deal of attention. Such tablets are also suitable for active people. Fast dissolving tablets are also known as mouth-dissolving tablets, melt-in mouth tablets, orodispersible tablets, quick dissolving tablets etc[2].

Pantoprazole sodium is a proton pump inhibitor that suppresses gastric acid secretion by specific inhibition of the enzyme system of hydrogen/ potassium adenosine triphosphatase (H^+/K^+ ATPase) at the secretory surface of the gastric parietal cell. It is used for the treatment or symptomatic relief of gastric disorders such as gastric and duodenal ulcers, gastroesophageal reflux disease and Zollinger - Ellison syndrome. It is freely soluble in water, pH 6.8 and 7.4 phosphate buffer, practically insoluble in n-hexane and chloroform. The systemic bioavailability of pantoprazole sodium is 77%, biological half life is 1 h; short duration of action. Its absorption is dose dependent and upon oral administration undergoes extensive first pass metabolism, thereby making it suitable candidate for fast dissolving tablet dosage forms[3].

There are various approaches to formulate rapidly disintegrating or dissolving tablets. Sublimation is one of these approaches in which a subliming agent and superdisintegrant are included into the formulation to achieve fast disintegration of tablets. Extremely fast disintegration of tablets would be required to increase the release of pantoprazole sodium from tablets for rapid absorption by the oral mucosal blood vessels. Therefore, an attempt to formulate pantoprazole sodium into fast disintegrating tablets for oral administration would have potential for emergency treatment of peptic ulcers. This could be achieved by selecting the suitable pharmaceutical excipients in the correct proportion, in combination with optimal manufacturing techniques[4].

The present research was mainly focused on the development and evaluation of fast dissolving tablets of an antiulcer drug, pantoprazole sodium. Various batches of pantoprazole sodium fast

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Silver(I)-catalysed domino alkyne-annulation/Diels–Alder reaction: a mild synthetic approach to tetrahydrospiro[carbazole-4,3′-indoline] scaffolds†

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A mild and efficient AgOTf catalyzed alkyne-annulation/Diels–Alder cascade for the construction of tetrahydrospiro[carbazole-4,3′-indoline] derivatives has been established from *N*-tosyl-2-(but-3-en-1-yn-1-yl) aniline in the presence of methyleneindolinones. This strategy provides access to the one-pot synthesis of a new class of various novel and structurally complex spirooxindole molecules with high diastereoselectivity.

Spirooxindoles represent an abundant core of privileged heterocyclic molecules which are known to be present in a number of natural products[1] (Fig. 1) that exhibit a diverse range of biological properties such as anticancer,[1b–f] antimalarial[1m] *etc.* On the other hand, a tetrahydrocarbazole nucleus is also found in a diverse array of naturally occurring alkaloids as well as in pharmacologically active agents.[2] For example, (*R*)-ramatroban is used for coronary artery disease[2d] and WAY-253752 is utilized as a dual-acting SSRI/5HT$_{1A}$ antagonist.[2e] Hence, the development of novel and efficient methods for the synthesis of this class of heterocyclic molecules is of great importance as far as synthetic and medicinal aspects are concerned.

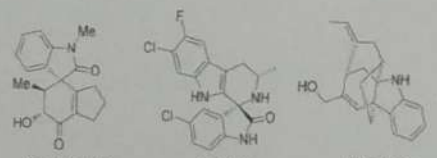

Fig. 1 Pharmaceutically important natural products/derivatives containing a spirooxindole and tetrahydrocarbazole core.

During the past few decades, transition metal-catalyzed cyclisation,[3] Diels–Alder (DA) cyclizations,[4] allenylanilines cyclisation[5] and enantioselective hydroarylation of allenes with indoles[6] have been intensively explored for the synthesis of tetrahydrocarbazoles. Later, organocatalytic asymmetric versions of DA reactions using enamine,[7,8] bifunctional acid–base catalysis[9] and hydrogen-bonding catalysis[10] have also been well reported in the literature. Bernardi and co-workers[10a] reported a catalytic asymmetric DA reaction of 3-vinylindoles with different dienophiles, whereas, Barbas and co-workers[10d] presented an elegant approach to the carbazolespirooxindole skeleton from 3-vinylindoles and methyleneindolinones. However, both the reactions were catalyzed by a C2-symmetric bis-thiourea organocatalyst in the cycloaddition reaction.

Next, Melchiorre and co-workers[11] developed an asymmetric amino catalyzed DA reaction of *ortho*-quinodimethanes (oQDMs) which were generated *in situ* from β-indolyl unsaturated aldehydes with methyleneindolinones for the construction of the spiro[tetrahydrocarbazole-3,3′-oxindole] framework. Recently, Shi *et al.*[12] reported a chiral phosphoric acid catalyzed stereoselective construction of a spiro[tetrahydrocarbazole-3,3′-oxindole] architecture from 2-vinylindoles with methyleneindolinones. Considering the medicinal significance of carbazolespirooxindole and limitations in establishing the challenging spiro-quaternary centre from previous methods, the development of catalytic methods for the synthesis of this class of spirooxindole either by transition metal catalysis or asymmetric organocatalysis is of prime synthetic value.

On the other hand, domino reactions[13] wherein, at least two or more steps are pooled into one synthetic operation, have attracted considerable attention for the synthesis of complex scaffolds due to their step economy. Intramolecular alkyne-annulations provide access to various substituted

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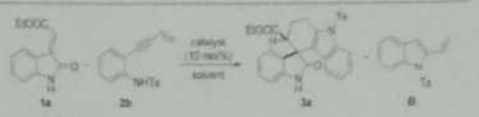
indoles from *o*-alkynylanilines by Lewis acid catalysis.[14] Inspired by the pioneering work of annulations on *o*-alkynylanilines and our earlier efforts in the design and synthesis of medicinally important oxindoles,[8–13,15] we then envisioned a domino reaction between *N*-tosyl-2-(but-3-en-1-yn-1-yl) aniline and methyleneindolinones for the synthesis of spiro[tetrahydrocarbazole-3,3′-oxindole] scaffolds by employing suitable Lewis acids. Thus, we sought an *in situ* generation of 1-tosyl-2-vinyl-1*H*-indole from *N*-tosyl-2-(but-3-en-1-yn-1-yl) aniline, which then concomitantly reacts with different methyleneindolinones *via* the [4 + 2] cycloaddition reaction that allows a rapid and direct access to structurally complex tetrahydrospiro[carbazole-4,3′-indoline] in a one pot manner. Moreover, to the best of our knowledge these scaffolds are new and have not yet been reported in the literature (Scheme 1).

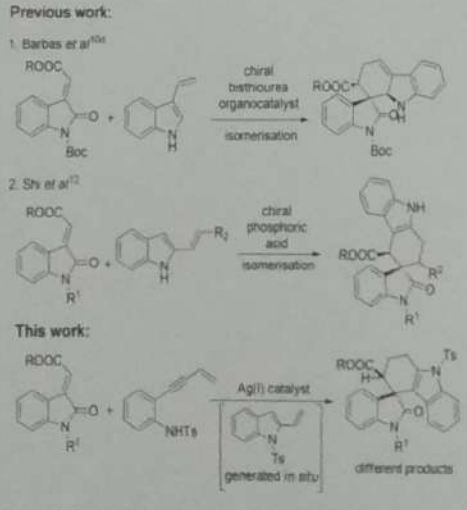
In order to explore a suitable Lewis acid to probe the feasibility of this reaction, methyleneindolinone **1a** was reacted with *N*-tosyl-2-(but-3-en-1-yn-1-yl) aniline (**2b**) under different reaction conditions (Table 1). The frequently used Lewis acids were not effective for this transformation (entries 2–8, Table 1). Usage of copper triflate and silver acetate resulted in aza annulation to form the intermediate 1-tosyl-2-vinyl-1*H*-indole (entries 4 and 9, Table 1, which has been isolated and characterized by spectroscopic studies) but did not show any influence on the cycloaddition reaction. Among different transition metal catalysts, it was noted that only silver based Lewis acids were effective for this transformation. However, among the screened silver catalysts, AgOAc and $AgNO_3$ were not effective in catalysing this reaction (entries 9 and 10, Table 1). Delightfully, usage of $AgSbF_6$ (10 mol%) resulted in 71% yield of the product **3a** in DCE solvent with >99 dr (entry 11, Table 1). Switching the catalyst to AgOTf (10 mol%) delivered the product **3a**, albeit with a little improvement in the yield (73%) without changing dr (entry 12, Table 1). Further investigations by screening various gold catalysts such as gold chloride (10 mol%) and triphenylphosphine gold chloride (10 mol%) revealed the fact that these catalysts are ineffective for this transformation (entries 13 and 14, Table 1). Next, we subsequently moved to examine the effect of the solvents on the reaction outcome in terms of yield (entries 15–17, Table 1). Solvents such as toluene and dichloromethane were shown to decrease the yield without affecting the diastereomeric ratio of the product (entries 15 and 16, Table 1), whereas in THF, the reaction did not result in the formation of the required product (entry 17, Table 1). Increasing the reaction temperature to 60 °C resulted in a decrease in the yield (entry 18, Table 1). Decreasing the load of the catalyst from 10 mol% to 5 mol% led to the decrease in the yield (entry 19, Table 1). Moreover, no improvement in the yield was observed on increasing the catalyst load from 10 mol% to 20 mol% (entry 20, Table 1).

Table 1 Optimization of the reaction conditions for the synthesis of **3a**[a]



Entry	Catalyst (10 mol%)	Solvent	dr[b]	Yield[c]
1	—	DCE	—	—
2	$In(OTf)_3$	DCE	—	—
3	$Yb(OTf)_3$	DCE	—	—
4	$Cu(OTf)_2$	DCE	—	28[d]
5	$Al(OTf)_3$	DCE	—	—
6	$Sc(OTf)_3$	DCE	—	—
7	$In(OTf)_3$	DCE	—	—
8	$IoCl_3$	DCE	—	—
9	AgOAc	DCE	—	42[d]
10	$AgNO_3$	DCE	—	—
11	$AgSbF_6$	DCE	>99	71
12	**AgOTf**	**DCE**	**>99**	**73**[e]
13	$AuCl_3$	DCE	—	—
14	Ph_3PAuCl	DCE	—	—
15	AgOTf	toluene	>99	54
16	AgOTf	CH_2Cl_2	>99	51
17	AgOTf	THF	—	—
18	AgOTf	DCE	>99	65[f]
19	AgOTf	DCE	>99	62[g]
20	AgOTf	DCE	>99	74[h]

[a] Reaction conditions: **1a** (0.230 mmol), **2b** (0.299 mmol), Lewis acid, solvent (DCE, 5 mL), 72 h. [b] Determined by ^{1}H NMR. [c] Isolated yields. [d] 1-Tosyl-2-vinyl-1*H*-indole was isolated. [e] Other than **3a**, 12% of 1-tosyl-2-vinyl-1*H*-indole (**B**) was isolated. [f] Heating at 60 °C for 12 h. [g] 5 mol% catalyst. [h] 20 mol% catalyst.



Scheme 1 Synthetic strategy comparison with previous approaches to construct spirooxindoles from methyleneindolinones.

It was quite interesting to observe that the product obtained from the present domino strategy was different from that of the earlier report.[12] ^{1}H NMR studies revealed that the characteristic peaks of earlier reported products[12] were not present in the obtained product **3a** (singlet proton of CH– attached to ester functionality). The regiochemistry of the obtained spiro product was further confirmed by 2D-^{1}H–^{1}H DQFCOSY

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Design & *In Vitro* Evaluation of Floating Microspheres Using Roxatidine Acetate HCl

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ABSTRACT

The purpose of the research was to prepare and evaluate Roxatidine acetate HCl floating microspheres by ionotropic gelation method. Fourteen formulations were prepared, among all the formulations F13 was selected as optimized formulation based on the micromeretic and evaluation parameters including drug release studies. In the *in vitro* release study of formulation, F13 showed 95.65% drug release after 12 h in a controlled manner, which is desired for disease like peptic ulcer. *In vitro* release profiles from optimized formulation F13 were applied on various kinetic models. The best fit with the highest correlation coefficient was observed in zero order and Higuchi model, indicating diffusion controlled principle. The innovator Rotane 150 mg conventional tablet showed the drug release of 96.45% within 1 h. FT-IR and DSC analyses confirmed the absence of drug-polymer interaction. The results obtained from evaluation and performance study of different types of Roxatidine microspheres showed that system may be useful to achieve a controlled drug release profile, reduce the dose of drug, dosing frequency and improve patient compliance when compared with marketed product.

Key words: Roxatidine, buoyancy, HPMC, gum olibanum, microspheres.

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INTRODUCTION

Since the last three decades many drug molecules formulated as Gastroretentive Drug Delivery System (GRDDS) have been patented keeping in view its commercial success. Oral controlled release (CR) dosage forms have been extensively used to improve therapy of many important medications. The bioavailability of drugs with an absorption window in the upper small intestine is generally limited with conventional pharmaceutical dosage forms. The residence time of such systems and thus, of their drug release into the stomach and upper intestine is often short. To overcome this restriction and to increase the bioavailability of these drugs, controlled drug delivery systems with a prolonged residence time in the stomach can be used[1].

Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control the emptying time is a valuable asset for dosage forms, which reside in the stomach for a longer period of time than conventional dosage forms[2]. Several approaches are currently used to prolong gastric retention time. These include floating drug delivery systems, also known as hydrodynamically balanced systems, swelling and expanding systems, polymeric bioadhesive systems, modified-shape systems, high-density systems and other delayed gastric emptying devices[3].

Floating microspheres are gastro-retentive drug delivery systems based on non-effervescent approach[4].Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control the emptying time is a valuable asset for dosage forms, which reside in the stomach for a longer period of time than conventional dosage forms[5].

Floating drug delivery system (FDDS) promises to be a potential approach for gastric retention. Floating microspheres are gastro-retentive drug delivery systems based on non-effervescent approach[6]. Floating microspheres have emerged as an efficient means of enhancing the bioavailability and controlled delivery of many drugs. The increasing sophistication of delivery technology will ensure the development of increasing number of gastro-retentive drug delivery systems to optimize the delivery of molecules that exhibit absorption window, low bioavailability, and extensive first pass metabolism[7].

Peptic ulcer disease, also known as a peptic ulcer or stomach ulcer, is a break in the lining of the stomach, first part of the small intestine, or occasionally the lower esophagus[8].

Roxatidine acetate is a specific and competitive histamine H_2 receptor antagonist, which is used to treat gastric ulcers, Zollinger–Ellison syndrome, erosive esophagitis, gastro-oesophageal reflux disease and gastritis. Roxatidine has less bioavailability (80%) and lesser half life of 5 hrs[9]. The

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RESEARCH ARTICLE

Analytical UV Spectroscopic Method Development and Validation for the Estimation of Mycophenolate Mofetil

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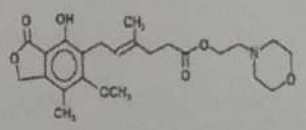
ABSTRACT:
A simple, precise, accurate UV-spectroscopic method was developed and validated for the determination of Mycophenolate Mofetil in bulk and dosage form using solvents like methanol for dissolving the drug and acetate buffer of pH-3.5 for dilutions. At the λ_{max} of 250nm, it was proved linear in the range 10- 50 µg/ml, and exhibit good correlation coefficient (R^2 =0.995) and excellent mean recovery (99.990-100.014). The developed method was validated for accuracy, precision, robustness, ruggedness according to ICH guidelines. All these parameters showed adaptability of the method for the quality control analysis of Mycophenolate Mofetil in bulk and in marketed formulation.

KEYWORDS: Mycophenolate Mofetil, UV-Spectroscopy, Acetate buffer, Validation.

INTRODUCTION:

UV-Visible Spectrophotometry is one of the most frequently used techniques in pharmaceutical analysis. It involves measuring the amount of ultraviolet or visible radiation absorbed by a substance in solution[1,2,3]. Mycophenolate Mofetil is chemically supported as 2-morpholinoethyl (E)-6-(1, 3 dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-4hexenoate. The structural formula is $C_{23}H_{31}NO_7$ and molecular weight of 433.50. Mycophenolate Mofetil is the 2-morpholinoethyl ester of mycophenolic acid (MPA), an immunosuppressive agent; inosine monophosphate dehydrogenase (IMPDH) inhibitor[4]. The chemical structure of Mycophenolate Mofetil is:



It is slightly soluble in water; the solubility increases in acidic medium (4.27 mg/mL at pH 3.6). It is freely soluble in acetone, soluble in methanol and sparingly soluble in ethanol. Since there are very few methods are available, there is a need a of more appropriate selective and specific method for measurements of content of Mycophenolate Mofetil in the presence of interference[5,6].

MATERIALS AND METHOD:[7,8]

Instruments:
UV-Visible Spectrophotometer (PG instruments T60), UV-Visible Spectrophotometer (lab India, 3000+), Ultra sonicator, pH meter, Weighing balance.

Chemicals:
API Mycophenolate Mofetil (gift sample provided by Murli Krishna Pharma Private Ltd, Pune), Tablet Cellmune by Cipla limited.

Reagents:
Methanol, Hydrochloric acid, Ammonium acetate, Ammonia, glacial acetic acid, Sodium acetate, Distilled water.

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Procedure for preparation of reagents:
Acetate buffer pH-3.5: Dissolve 2.5gm of ammonium acetate in 25ml of water and add 38ml of 7M HCl. adjust the pH to 3.5 with either 2M HCl or 6M ammonia and dilute with water to 100ml.

Acetate buffer pH-4.4: Dissolve 13.6gm of sodium acetate, 7.7gm of ammonium acetate in 25ml of water and add 25ml of glacial acetic acid and mix. Adjust the pH to 4.4 with either 2M HCl or 6M ammonia and dilute with water to 100ml. 7M HCl: Dissolve 5.95ml of conc. HCl in 10 ml of water. 0.1M HCl: Dissolve 0.85ml of conc. HCl in water and makeup the volume to 100ml with water.

Optimization of analytical method:
Several trails were made using water, 0.1N HCl, Acetate buffer of pH3.5, Acetate buffer of pH 4.5.

Table no 1: Optimization of analytical method

Solvent	Concentration	λ_{max}	Absorbance
Water	20 µg/mL	215 nm	1.522
0.1N HCl	20 µg/mL	215nm	1.477
Acetate buffer pH-3.5	20 µg/mL	250nm	0.3117
Acetate buffer pH-4.5	20 µg/mL	250nm	0.172

From all the above trails, it was found that the solvent acetate buffer of pH-3.5 gives optimum results. Hence Acetate buffer of pH 3.5 was selected as solvent for dilutions in the method developed.

Procedure for the preparation of standard solution:
Accurately weigh 100mg of Mycophenolate Mofetil and dissolve in 50ml of methanol and sonicate it for 5min. At that point pipette out 10ml of the above solution into another volumetric jar and make upto 100ml with Acetate buffer of pH 3.5. At that point from this make serial dilutions of 10 µg/mL, 20 µg/mL, 30 µg/mL, 40 µg/mL, 50 µg/ml.

Procedure for Calibration Curve:
The standard arrangements were prepared by the best possible dilutions of the essential stock arrangement with acetate buffer of pH 3.5 to get working standard. Every one of the estimations were performed at room temperature. The absorbance of the arrangements containing Mycophenolate Mofetil was measured in the UV range 200-800nm utilizing a fitting clear. The λ_{max} was observed to be 250um as appeared in figure-1 below. For linearity study, dilutions were made for Mycophenolate Mofetil in the range of 10 to 50 µg/ml, prepared by diluting the stock arrangement with acetate buffer of pH 3.5. The calibration curve was built up at this wavelength by plotting chart in the middle of absorbance and concentration figure-2.

No. P/V	Wavelength (nm)	Abs
1 Peak	305.00	0.207
2 Peak	250.00	0.430
1 Valley	275.00	0.058
2 Valley	235.00	0.277

Procedure for preparation of sample solution:
Accurately weigh and powder 20 tablets. Weigh accurately a quantity of powder containing about 0.1gm of Mycophenolate Mofetil, add 50ml of methanol and sonicate of 15 minutes make up to volume 100ml with acetate buffer pH 3.5. To 2.5 ml of the resulting solution add 50 ml of acetate buffer pH 3.5, mix properly and make up the volume to 100ml with acetate buffer of pH3.5.Measure the absorbance of the resulting solution at the maximum at about 250nm. Calculate the content of Mycophenolate Mofetil from the data derived from calibration curve.

Validation of Method Parameters:[9]
Specificity:
The Specificity was the ability of an analytical procedure to measure accurately an analyte in presence of components that may be expected to present in sample matrix. Standard solution, sample solution, placebo solution, and standard solution spiked with placebo were prepared and the absorbance was found at 250nm.

Precision:
Precision of the analytical method is established by carrying out the analysis as per the procedure and as per normal weight taken for analysis. Repeat the analysis six times. Calculate the % assay, mean assay, % Deviation and % relative standard deviation. The developed method was found to be precise as the %RSD values for the repeatability and intermediate precision studies were < 2%.

Accuracy:
Accuracy of the method is ascertained by standard addition method at 3 levels. Standard quantity equivalent to 50%, 100% and 125% is to be added in sample. The result shown that best recoveries (98-102%) of the spiked drug were obtained at each added concentration, indicating that the method was accurate.