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REVIEW ARTICLE

AN OVERVIEW ON SUSTAINED RELEASE ENTERIC COATED TABLET OF PANTOPRAZOLE

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ABSTRACT

Enset (Ensete Ventricosum, Family Musaceae) is a plant indigenous to Ethiopia, it is often called 'false banana" for its close resemblance to banana plant. The plant is the most important staple food for millions of people in the south and southwestern parts of Ethiopia. Enset plant contains starch as its major contents. The starch has been investigated for its physico-chemical properties including granule size, X-ray diffraction pattern, amylose content, gelatinization behavior, stability and various rhelogical properties of the gel. Based on its physico-chemical properties the starch was evaluated for various pharmaceutical applications such as in tablet binder and disintegrant. Several modifications were also attempted on the native enset starch so as to improve and modulate its physiochemical properties. Hence, this review aims to summarize the knowledge on the properties of enset starch and its pharmaceutical applications.
Key words: Enset Starch, Physico-Chemical Properties, Pharmaceutical Application

ABSTRACT

Pantoprazole drug is utilized for treatment of gastric and duodenum ulcer, utilized as proton pump inhibitor, belongs to group of Benzimidazole. Pantoprazole drug undergoes through acidic medium of the stomach, can be coated with enteric coating polymer after that they will safely distribute the drug in the musculin intestine, for the degradation. Pantoprazole has been prepared by direct compression method utilizing variant excipient on different concentration like crosscarmellose sodium as disintegrating agent, dicalcium phosphate as diluents and mannitol. Direct compression is economic since it requires fewer unit operations, compare to wet granulation method. This direct compression method require less equipment, need low power consumption, less space, short duration, leading to low cost of tablets dosage form. The prepared tablets has been evaluated by different evaluation parameter like hardness, surface morphology, weight variation, friability, percentage yield, and it was found that the results comply with official standards. The *in-vitro* release has been evaluated utilizing pH 1.2 acidic buffer and pH 6.8 phosphate buffer. The *in-vitro* release study showed that the prepared and evaluated pantoprazole tablets are capable to sustain release drug in the intestine.

Keyword: - Pantoprazole sodium, enteric coated, ulcer,*in-vitro* release.

INTRODUCTION

Tablets are utilized as solid dosage forms containing medicinal substances or excipient with or without diluents. Solid dosage forms are the most widely used form of medication both by pharmaceutical company as well as medicos and patients. They provide safe and facile ways of active pharmaceutical ingredients (API) administration with great physicochemical stability in comparison to some other different dosage forms, and also gives designates of precise dosing [1]. An enteric coating is an opportune barrier applied to oral medication (solid dosage form) that controls the targeted location in the digestive system where it is absorbed. Enteric coating refers to theminuscule intestine, therefore enteric coatings reduces release of medication before it reaches the minuscule intestine. Maximum enteric coatings perform by presenting a surface that is stable at the highly acidic pH found in the stomach, but rapidly breaks down at a low acidic mediapH[2]. Pantoprazole drugs with short half-lives are ideal dosage form for sustained drug distribution. Pantoprazole sodium is a white to off-white crystalline powder, racemic and has weakly basic and acidic properties. It is liberatingly soluble in dihydrogen monoxide, very slightly soluble in phosphate buffer at pH 7.4, and virtually insoluble in n-hexane. The stability of the compound in aqueous solution is pH-dependent. Different drugs have been marketed as sustained release tablets according to their cost efficacy and excellent patient compliance. Now present study, we made an endeavor to distribute pantoprazole in a sustained manner utilizing enteric coated release tablets and studied their efficacy for treating ulcer[3]. Several types of studies are published regarding pantoprazole pharmacokinetics, veryless studies of them have fixated on the proof of bioequivalence between two formulations. For such types of drugs, enteric coating mixed to the formulation inclines to avoid the stomach's acidic exposure, distributing them instead to a fundamental pH environment (intestines pH 5.5) where they do not degrade, and give their desired therapeutic effect.

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The aim of this study is to prepare and formulae of enteric coated pantoprazole tablet. Proton pump inhibitors (PPIs) reduced gastric acid secretion by concrete inhibition of the H+/K+- ATPase in the gastric parietal cell. This process follows with absorption of the Proton pump inhibitors in the parietal cell. Proton pump inhibitors are related to bases, so protonation takes place in the acidic region of the secretory canaliculus of the parietal cell. The main aim of an oral tablet is to provide a certain and agreeable amount of drug to the human body through GI system. Studies on bioavailability of drugs from a given study showed that in many situations tablets with same drug and drug amount did not give the same therapeutic effect. Formulation excipient in the tablet, physical which is responsible for variation in the quantified dissolution profile and therapeutic replication[4].Drugs such as pantoprazole which have an irritant effect on the stomach and must be absorbed in the gastrointestinal tract and because it is unstable under acidic conditions, enteric coated distribution systems are required. Similarly, certain groups of Azoles are acid-unstable. For such types of drugs, enteric coating integrated to the formulation inclines to eschew the stomach's acidic exposure, distributing them instead to a fundamental pH environment (intestines pH 5.5 and above)where they do not degrade, and give their desired action[2].The different release characteristics of the enteric polymers have profound impact upon the pharmacokinetic parameters of the drug [5, 6]. An Ideal enteric polymer should possess a hydrophilic and hydrophobic monomeric unit. Methacrylic acid and methyl methacrylate could make an ideal hydrophilic and hydrophobic unit respectively. Such compositions of polymer are essentially insoluble in gastric fluids and may avail conveyance of drugs across the proximal alimentary tract without degradation [7]. Pantoprazole is highly selective to acid secretive gastric parietal cells and its action is irrespective of the type of stimuli. Despite its several therapeutic benefits including maximal efficacy-safety ratio [8].

Ideal properties of enteric coating material[9, 10, 11].

- Resistance to gastric fluids
- Susceptible/permeable to intestinal fluid
- Compatibility with most coating solution components and the drug substrate
- Formation of continuous film
- Nontoxic, cheap and ease of application
- Ability to be readily printed

Advantage of enteric coated tablet[12]

1. Enteric coating is employed for a number of therapeutic, safety, and medical reasons. Some drugs are procure when directly exposed to the mucosa, gastric, including aspirin and vigorous electrolytes such as NH_4Cl.
2. Enteric coating is one method of reducing or eliminating vexation from such drugs. There are other drug that if abandonment in the stomach may create nausea and vomiting.
3. The low pH of the stomach destroy other drug, and hence enteric coating may be the desire to abandon the drug undiluted and in the highest concentration possible within the intestine.
4. In case of repeat action and other controlled release dosage form, the influence of altering the profile of the drug on total drug bioavailability, distribution, and pharmacokinetics must be investigated.

Disadvantages of tablet coating

1. Limitations of sugar coating such as relatively high cost, long coating time and high bulk had led to the use of other coating materials.
2. However the process of coating is tedious and time-consuming and it requires the expertise of highly skilled technician.

Coating equipment

A modern tablet coating system combines several component –

- A coating pan
- A spraying system
- An air handling unit
- A dust collector

Different types of polymer used in enteric coating tablets[13]**–**

Polymers	Dissolution pH
Shellac (esters of aleurtic acid)	7.0
Cellulose acetate phthalate (CAP)	6.2
Poly(methacrylic acid-co-methyl methacrylate)	5.5-7.0
Cellulose acetate trimellitate (CAT)	5.0
Poly(vinyl acetate phthalate) (PVAP)	5.0
Hydroxypropyl methylcellulose phthalate (HPMCP)	4.5-5.5

New materials used for tablet coating

- Zein
- Aqua-Zein, which is an aqueous zein formulation containing no alcohol.
- Amylose starch and starch derivatives
- Dextrin.

Patents:-

Patent No.	Title	Result
20090214602	Oral Dosage Forms Including An Antiplatelet Agent And An Enterically Coated Acid Inhibitor	Provides oral dosage forms comprising an antiplatelet agent and an enterically coated acid inhibitor [14].
7217429	Tableted oral a compound of benzimidazole labile in an pharmaceutical dosage form, with enteric coating, containing acid medium	The pharmaceutical dosage form consists of a plurality of units containing a benzimidazole compound labile in an acid medium as the active principle, each unit being comprised of an inert core, a layer containing the active principle and an intermediate layer. These units, commixed with compression excipients, compressed and coated with an enteric coating, provide a tableted pharmaceutical dosage form opportune for oral administration for averting and treating disorders cognate to eccentric secretion of gastric acid [15].
20070269509	Enteric Coated Pharmaceutical Oral Formulations Comprising Acid-Labile Active Substances, and a Method Thereof	This invention relates to an oral pharmaceutical formulation composed by a direct coating of an enteric layer containing polyethylene glycol as a plasticizer on a core containing an acid-labile pantoprazole [16].
20070042033	Pantoprazole multiparticulate formulations	Pantoprazole sodium multiparticulates are described which eschew sticking to nasogastric and gastronomy tubes [17].
20080003281	Modified Release Tablet Formulations for Proton Pump Inhibitors	An oral solid pharmaceutical dosage form comprising an acid sensitive proton pump inhibitor (PPI) as single active drug, relinquishing the PPI in two separate pulses, one immediate and one delayed[18].
20050042277	Pharmaceutical compositions having a swellable coating	A pharmaceutical dosage form containing a pharmaceutical active that is not stable in the presence of acid comprises a core containing the active and a disintegrant, a swellable coating circumventing the core, and an enteric coating circumventing the swellable coating [19].
7431942	Orally disintegrable tablets	An orally disintegrable tablet of the present invention, which comprises fine granules having an average particle diameter of 400 μm or less, which fine granules comprise a composition coatedby an enteric coating layer [20].
20090280175	Multilayer Proton Pump Inhibitor Tablets	Multilayer tablets of a proton pump inhibitor essentially bioequivalent in terms of plasma Cmax and AUC to capsules and/or tablets consisting of multiple unit pellets of the protonpump inhibitor are provided [21].
20120064159	Multilayer Oral Tablets Containing a Non-Steroidal Anti-Inflammatory Drug and/or Acetaminophen	Multilayer tablets of a non-steroidal anti-inflammatory drug (NSAID) and/or acetaminophen for oral administration containing an immediate release layer or layers containing a NSAID and/or acetaminophen and/or a second therapeutic agent and an elongated release layer containing a NSAID and/or acetaminophen are provided [22].
8574625	Tablet dosage form	The present invention relates to novel tablet dosage forms and methods of preparing these forms, which can be used for different classes of pharmaceutical active ingredients posing stability issues in a single unit system[23].
20090220621	Pharmaceutical compositions of a non-enteric coated proton pump inhibitor with a carbonate salt and bicarbonate salt combination	A method for treating gastric acid disorders with a non-enteric coated proton pump inhibitor in a pharmaceutically acceptable carrier including a bicarbonate salt of a Group IA metal and a carbonate salt of a Group IA metal; and a pharmaceutical composition of a non-enteric coated proton pump inhibitor in a pharmaceutically acceptable carrier including a bicarbonate salt of a Group IA metal and a carbonate salt of a Group IA metal are disclosed[24].
7785650	Method for dip coating dosage forms	Water soluble, gelatin-free dip coatings for pharmaceutical solid dosage forms such as tablets comprising HPMC and xanthan gum, carrageenan, and mixtures thereof, or HPMC and castor oil or maltodextrin[25].
6953808	Method for treating gastric disorders using optically pure (−) pantoprazole	Methods and compositions are disclosed utilizing optically pure (−) pantoprazole for the treatment of ulcers in humans while substantially reducing the concomitant liability of adverse effects associated with the racemic mixture of pantoprazole [26].
7387792	Pharmaceutical composition for compressed annular tablet with molded triturate tablet for both intraoral and oral administration	New pharmaceutical compositions in unit dosage form are disclosed for both intraoral and oral administration to a patient[27].

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MECHANISM OF ENTERIC COATED TIME-RELEASE PRESS COATED (ETP) TABLETS-

ETP tablets are consist of three layers, first drug containing core tablet (rapid release function), the press coated swellable hydrophobic polymer layer (Hydroxy propyl cellulose layer (HPC), time release function) and an enteric coating layer (acid resistance function).The tablet does not relinquish the drug in the stomach due to the acid resistance of the outer enteric coating layer. The enteric coating layer rapidly dissolves after gastric vacating and the intestinal fluid commences to gradually wear away the press coated polymer (HPC) layer. Efficient drug release occurs when the erosion front reaches the core tablet since the erosion process takes a long time as there is no drug release period (lag phase) after gastric emptying. The duration of lag phase (drug release period) is controlled either by the weight or composition of the polymer (HPC) layer [28, 29].

METHODS:

For developing and evaluating a pharmaceutical dosage form, it is very much paramount to quantify the physico-chemical properties of the drug molecule & the other derived properties of the drug powder. This first phase of the studies is known as pre-formulation studies which provide variants of information about the formulation development.

Preparation of sustained release tablet of pantoprazole by wet granulation method - Pantoprazole tablets has been prepared by the wet granulation method. Required quantity of pantoprazole, and variants of polymer hydroxypropylmethylcellulose, cassava starch and polyvinyl pyrrolidone and Avicel PH 102 are weighed according to the formula and transferred into a mortar with pestle and integrated exhaustively. The powder mass is commixed with a 5 % starch paste to found a sluggy mass, which is passed by a sieve with opening pore of 1.4 mm to found granules. The prepared granules are dried at 40 °C for 4 h. The dried granules are screened by sieves of 0.71 mm and 0.355 mm and stored for further studies. Designated quantities of magnesium stearate and talc are determinately integrated and commixed exhaustively. The mixture is directly punched into tablets weighing about 200 mg (containing 40 mg of pantoprazole), by utilizing a rotary tablet compression machine, and 8-mm diameter Concave punches. The different batches of pantoprazole tablets has been accumulated and stored in airtight containers [30].

Preparation of enteric coated tablet by spray coatingtechnique[31]

Preparation of core tablets-Granules has been prepared using wet granulation method. Drug and other excipients were passed through # 80 and add sufficient quantity of binding agent slowly to get dough mass. The mass is sieved through # 8 and dried at 45ºC for about 1 hrs. and then these granules are passed through # 20 and lubricated with magnesium stearate. Mixed blend is compressed into tablets on single punch tablet compression machine to a weight of 250 mg each with thickness of 4.46 ± 0.21 mm and diameter of 7.9 mm using shallow concave plain/plain punch.

Preparation of enteric coating solution-Weighed amount of pectin is dissolved in 50 ml of water and ethyl cellulose is dissolved in 50 ml of isopropyl alcohol. The two solutions are then mixed well to form a homogeneous solution and PEG-6000 was added as a plasticizer.

Coating of core tablets-Enteric coating of the compressed tablets is achieved by standard coating pan technique. Tablets are taken and are coated in a pan coater at 50 rpm at a temperature of 50ºC and at a flow rate of 10 ml/min. Coating is carried out with spraying method and dried. These solutions are applied over tablets using spray gun at appropriate pressure. The coated tablets are primarily dried using heat blower and secondarily dried in tray drier.

Coating methodology- The coating is executed in a 12 inch conventional coating pan, charged with 1 kg of core tablets. The tablet bed is pre-warmed to 40 ºC. Coating solution is applied through utilizing external spray gun with low pressure air atomized liquid spray system. The temperature of the system is maintained at 55 ºC utilizing external drying system, throughout the coating process. The pan speed is maintained at 12 rpm. The seal coating solution is first applied to build up a 2% weight gain of the tablets. Upon completion of the seal coating, the tablets are approvalto rotate in the pan at a more gradual rate, after that drying of the tablets. The seal coat is followed by Acryl-EZE coating. The coating material deposit has beenmeasured to obtain different weight gains such as 8%, 10% and 16% from its weight. The tablets are checked for the weight gain before and after the application of designated time of coating in order to verify the procurement of desired [32].

Coating of compressed pantoprazole sodium tablets

The enteric coating solution has been prepared by simple solution method utilizing 6 % w/w and 8% W /W of Eudragit L100 (E1 and E2) or cellulose acetate phthalate (C1 and C2) as an enteric polymer. The PEG is utilized as plasticizer and acetone and isopropyl acetone is utilized as solvent. This mixture is perpetually stirred for 1h with paddle mechanical stirrer and the stirred coating solution is again filtered through muslin cloth to obtain coating solution.

Enteric Coating of Pantoprazole Sodium Sesquihydrate Compressed Tablets by Dipping Method

The compressed tablets have been coated with enteric coating polymer (Eudragit L100 or cellulose acetate phthalate or Drug coat L100) solution by dipping method. Desired coating tablet is performed for the dipping and weight gain is achieved. The coated tablets are studied for its weight variation, thickness, uniformity of drug content and in vitro dissolution study [33].

Analytical method

This method involves the identification of the active pharmaceutical ingredient, evaluation of pharmacopoeial compliance and development of analytical procedure [34].

EVALUATION OF THE TABLET:

Hardness test:

The hardness is carried for 5 tablets utilizing Monsanto hardness tester.The average hardness of the tablets are obtained[35].

Weight variation test:

Tablets has been discarded arbitrarily and weighed individually. The average weight has been calculated and individual weight compared to the average weight. The tablet passes the test if not more than two of the individual weights deviate from the average weight by more than ± 7.5% and none deviated by twice ± 7.5% [35].

Size Analysis by Optical Microscopy

Dry granules are uniformly spread on a glass slide. Granule particle size are quantified along the longest and the shortest axes (cross shaped quantification) utilizing an optical microscope after calibration. Average of these two readings is given as the mean diameter of particles. The diameter of at least 50 granules in each batch has been determined [36].

Disintegration time

The disintegration time of the coated tablets is determined by utilizing the USP model disintegration apparatus. Six tablets are placed in the basket rack assembly, and is run for 2 hours in 0.1 N Hcl media with the discs. The tablets are abstracted from the solution, gently dried by bloating. The test is then continued by placing the tablets in phosphate buffer pH 6.8, for 1 h, maintaining the temperature at 37±2 ^{o}C[37, 38].

Stability studies

A study is carried out to assess the stability of the pantoprazole sodium sesquihydrate cellulose acetate phthalate coated tablet formulation. Generally, the observation of the rate at which the product degrades under mundane room temperature requires a long time. To achieve, this undesirable delay, the principles of expedited stability studies are adopted. The tablets are packed in glass container. Stability studies are carried out at 40°C and 75% RH over a period of 1 month. Samples are evaluated at 10th, 20th and 30th days for different parameters such as physical appearance, hardness, weight variation, drug content and dissolution[39].

Angle of repose

The frictional forces in a loose powder can be quantified by the angle of repose. This is the maximum angle possible between the surface of a pile of powder and the horizontal plane. Sufficient quantities of pantoprazole it composed a heap, which physically contacted the tip of the funnel. The height and radius of the heap are quantified. The angle of repose is calculated utilizing the formula [40, 41].

$$\text{Angle of repose } (\theta) = \tan^{-1}(h/r)$$

Where, h – Height of the pile in cm

r – Radius of the pile

Bulk density

Accurately weighed granules are conscientiously transferred in to graduated quantifying cylinder. The granules bed is then made uniform and the volume occupied by the granules is noted as per the graduation marks on the cylinder as mL. It is expressed in gm/mL and is calculated utilizing the following formula[42].

Dissolution Test

The dissolution test is conducted utilizing simulated gastric fluid (0.1N HCl) and intestinal fluid (phosphate buffer, pH-6.8) as dissolution medium. Utilizing simulated gastric fluid, 900 ml of 0.1N HCl is placed in the vessel and sanctioned to come to 37 ± 0.5°C. Then, pantoprazole tablets are placed in six baskets, one in each basket and stirrer is rotated at 100 rpm for 2 hrs. After 2 hrs. The medium is thrown to observe the integrity of coating layer of tablets. The coating layer is found to remain intact. Immediately, same tablets are placed in phosphate buffer (pH-6.8) at same rotation speed and temperature as mentioned above for 1 hr. After 15, 30 and 45 min, sample of 5 ml is pipetted out and same volume of fresh phosphate buffer is integrated to keep volume of the dissolution medium constant. The sample is diluted to 15 ml and the absorbance isquantified and calculation is done utilizing Lambert beer's law. Similarly, the absorbance of known concentration of standard solution of pantoprazole is quantified and percent drug release has been calculated [43].

Release kinetics.

The in vitro release data obtained from CAP coated tablets, Eudragit L100 coated tablets and drug coat L100 coated tablets are fitted to various kinetic models such as zero-order, first-order, Higuchi and Korsmeyer-Peppas models. The abandonment of pantoprazole from the tablets is first-order diffusion controlled, as designated by highest R2 values [44].

Accelerated stability studies

Stability of a drug in a dosage form at different environmental conditions is consequential as it determines the expiry date of that particular formulation. Transmutations in the physical appearance, color, odor, taste or texture of the formulation denote the drug instability. The stability studies are carried out at 40 ± 2 °C with 75 ± 5%% RH WH. There are no consequential variation in their physical appearance, average weight of tablets and hardness. It is observed that the initial drug content and the drug contents of the samples analyzed after 1, 2, 3 month of storage are closed. The abandonment profile additionally not showed any paramount changes denoting that there are no consequential changes in the physical as well as chemical characteristics of the formulation. Hence, it can be concluded from the results that the developed tablets are stable and retain their pharmaceutical properties over a period of 3 month [45].

Drugs Polymer Interaction Study by FTIR spectrophotometer:

FT-IR spectroscopy study is carried out discretely to ascertain, the compatibility between the drug pantoprazole and the different polymer hydroxypropyl methylcellulose, Cassava starch, polyvinyl pyrrolidone utilized for the preparation of tablets. The FT-IR is performed for drug, polymer and the physical mixture of drug polymer [46].

Friability test

The friability is tenacious utilizing Roche friabilator and expressed in percentage. 20 tablets from each batch are weighed discretely (Winitial) and placed in the friabilator, which is then operated for 100 revolutions at 25 rpm. The tablets were reweighed (Wfinal) and the percentage friability (F) is calculated for each batch by utilizing the formula [47].

***In-Vitro* Release Studies**

The in vitro dissolution studies 8 for all the formulations are carried out in two steeps, utilizing USP apparatus type II at 100 rpm. The dissolution medium consisted of Hydrochloric acid buffer solution pH - 1.2 (900 ml), and Phosphate buffer, maintained at 37 0C ± 0.5 0C. The drug release at different time intervals is quantified by UV-visible spectrophotometer (Phosphate buffer pH – 6.8). The abandonment studies are conducted in triplicate [48].

Physicochemical evaluations of coating films

The same polymer solution is adjusted to prepare the polymeric films and is subjected for the thickness of the dried films is tenacious by digital micrometer. The film solubility is studied with phosphate buffer (pH 1.2 and 6.8). The 1×1 cm2 coating film is discarded, weighed and transferred in a beaker containing 20 mL of designated phosphate buffer (pH 1.2 and 6.8) medium, which is in a magnetic stirrer for 1 h at 37 °C and determinately film solubility is examined [49].

CONCLUSION

Ulcers are crater-like sores which form in the lining of the stomach, just below the stomach at the commencement of the minuscule intestine in the duodenum. An ulcer is the result of an imbalance between truculent and defensive factors. Pantoprazole is a superseded benzimidazole derivative that targets gastric acid proton pumps, the final ordinary pathway for gastric acid secretion. The drug covalently binding to the proton pumps, causing perpetuated inhibition of gastric acid secretion. The stability of pantoprazole is a function of pH and it rapidly degrades in acid medium of the stomach, but has acceptable stability in alkaline conditions. Therefore, pantoprazole should be distributed into the intestine. Hence, an endeavor is made to formulate a sustained release drug distribution system for pantoprazole by utilizing sundry enteric coating polymers. Various percentage of the excipient are withal used to get best formulations with high bioavailability. Evaluation experiments such as friability, hardness, content uniformity, thickness, weight variation, disintegration time are carried out and found that the results are complete satisfactory.

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