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Overview On: Oral Multiparticulate Enteric Coated Delayed Release System for Proton Pumps Inhibitors

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ABSTRACT

The aim of the present study is to put a overview on the oral multiparticulate enteric coated delayed release system. Pharmaceutical development, invention and research increasingly focusing on the delivery systems which enhances therapeutic activity and minimizes side effects. Nowadays recent trend shows that oral multiparticulate drug delivery systems (Pellets) are suitable to formulate delayed release dosage forms with minimum side effects and low risk of dose dumping. The multiparticulate governs the predictable, transportation and even distribution in gastrointestinal tract. The pelletization is novel advanced drug delivery system where fine powders are converted into pellets and this technology is most reliable, prominent and efficient for the formulation of the delayed release dosage forms as well. The proton pump inhibitors are most susceptible for the degradation when coming into the contact with acid. Therefore they need to be protected from such environment. The various enteric coated polymers such as HPMC P, PVAP, Eudragit L-30 D-55, and Eudragit S100 can be coated on to the surface of the drug coated pellets which ensures the protection of the drug from gastric environment and produces stabilized dosage form.

Keywords: Multiparticulate drug delivery system, pelletization, proton pump inhibitors, delayed release dosage forms, Enteric coated, etc.

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INTRODUCTION

The oral route of administration has wide acceptance in 50-60% of total drug formulation. Oral route of administration is the most preferred and convenient, the oral route is having precious advantage such as, ease of administration, ease of handling, dose accuracy, different kind of dosage release system and most important one is wide range of patient compliance. The oral route is most convenient route of administration for the most drugs and delivery systems. Oral solid dosage form can be made into either tablets or filled in capsules. But oral absorption of drugs is limited due to short gastro retention time.[1]

Oral drug delivery system is a strategic tool for expanding markets, extending product life cycles and developing opportunities. Oral drug delivery system made a significant contribution to global pharmaceutical market through market segmentation, and this drug delivery system is developing rapidly. Oral drug delivery systems are becoming increasingly sophisticated as pharmaceutical scientists acquire a better understanding of the physicochemical and biochemical parameters pertinent to their performance [2,3]. In recent years considerable attention has been focused on the development of new drug delivery systems. For the development of the ideal drug delivery system, the two facts should always be considered. First, the ideal formulation should deliver drug at a rate dictated by the needs of the body over the period of treatment and second it should transfer the active moiety solely to the desired site of action. The basic rationale for controlled drug delivery is to alter the pharmacokinetics and pharmacodynamics of pharmacologically active moieties by using novel drug delivery systems or by modifying the molecular structure and/or physiological parameters inherent in a selected route of administration. The primary objectives of the controlled drug delivery are to ensure safety and improve efficacy of drug as well as patient compliance.[4]

Delayed Release Dosage Form

Delayed release system is firstly reported in 1884 by Kendall. It is possibly the most established of all Modified release technology.[8] For the drugs which are destroyed in the gastric fluids or absorbed preferentially in the intestine or cause gastric irritation, delayed release dosage form is best formulation. This kind of preparation contains an alkaline core material which comprises of active substance, a separating layer (barrier coating) and enteric coating layer. [11, 12]

Delayed release dosage forms releases drug at delayed time instead of promptly after administration. The Delayed action in the delayed release formulation is either time based or based on the influence of the environmental conditions like gastrointestinal pH. This kind of release offers significant clinical benefits than single units such as reduced plasma fluctuations, Maximum

drug absorption, Minimizing potential side effects due to dose dumping and various advantages over conventional dosage forms.[5]

Enteric Coating [2, 11]

The word "enteric'' indicates the small intestine. The enteric coating is a barrier which protects the drug from acidic environment of stomach and releasing drug in the desired site of absorption. Enteric coating ensures that drug will not release before it reaches to the small intestine. The enteric coating is given by the enteric polymers such as HPMC P, CAP, PVAP, CAT, Acrylates and Methacrylate's. These enteric coating polymers having property that allow drug to remain in unionize form at low pH whereas as pH increases in GIT the acidic functional groups become responsible for swelling of polymers or solubilizing of polymers in intestinal fluid**.**

These are the following reasons for which enteric coating is to be implemented [2, 11]

1. To prevent gastric distress or nausea from drug due to gastric irritation (e.g. Sodium Salicylate).
2. To provide delayed component of repeat action.
3. For the delivery of drug that are optimally absorbed in the small intestine to their primary absorption site in their most concentrated form
4. To avoid the first pass metabolism.
5. To control the pH solubility profile of enteric coated dosage form it is very critical to select the polymer and proper thickness of coating layer.

Advantages [15, 16]

- Eliminating Stomach irritation. Enteric coating work by reducing or eliminating the vexation from such drugs which may create the nausea and vomiting.
- Some drugs get destroyed when getting directly exposed to the mucosa, gastric environment including aspirin and certain electrolytes such as Ammonium Hydrochloride.
- Delayed release formulation can protect acid labile drug which may be destroyed by gastric fluids.
- Enteric coating facilitates the Gastric transit for drugs that are better absorbed from intestine.

Disadvantages [16]

1. Process of coating is tedious and time consuming.
2. It requires highly skilled technician to handle the process.
3. It requires highly established equipment.

4. Requires relatively more cost.
5. It takes long coating time.

Limitations [11]

Due to presence of the different enzymes and different pH values in the GI tract which is encountered by the drug before reaching the target site, the reliability and delivery efficiency becomes doubtful.

Single unit or multiple unit's enteric coating

Delayed release enteric dosage forms can be made in two ways

1. Single Unit (Tablets)
2. Multiple units (Delayed release pellets filled in capsules)

The multiunit delayed release enteric coated dosage form is having more advantages than that of enteric coated tablets as given below.

The main difference between single unit (Delayed release tablets) and multi unit delayed release dosage form (pellets) is, delayed release tablets relatively have longer intestinal transit time than small multi unit particulate. Multi unit particulate empty readily from stomach into intestine thus provide rapid drug dissolution and absorption.

As delayed release multi-unit particles empty readily from intestine this enables the acid-labile drug better protection against gastric acid. Enteric coated tablets are having more residence time in the stomach pH this make dosage form more susceptible to coating damage and relatively require a thicker coating. Anyhow damage to coating leads to complete destruction of drug in acidic pH. Which is not in case of delayed release enteric coated small multi-unit particles.[2]

Proton pump inhibitors (ppi's) [13]

PPIs are anti-secretory agents used in the treatment of gastric and duodenal ulcers, Gastro esophageal reflux disease and Zollinger Ellinson Syndrome. H^+, K^+, ATPase are undoubtedly most effective suppressors of gastric acid secretion and widely used in the antiulcer therapy. PPI's are α-pyridylmethylsulfinyl benzimidazoles with different substitutions on the pyridine or the benzimidazole group. PPI's are act as prodrugs requiring activation in the acidic environment. These agents enter in the parietal cells from the blood, because of their weak basic nature; they accumulate in the acidic secretory canaliculi of the parietal cells where they are activated by the proton catalyzed process that results in the activation of the thiophilic sulfonamide or sulfonic acid.[13]

PPI's are acid labile require an enteric coating to protect them from degradation in the stomach when given orally. However it may lead to Delayed onset of action and absorption of PPI's.

This PPI's can formulate into enteric coated pellets and filled into gelatin shell or can formulate as delayed release tablets.

Pharmacology of proton pump inhibitors [3]

Proton pump inhibitors are undoubtedly have a huge success in clinical management of patients with acid related disorders, PPI's still have number of limitations because of their pharmacology. All currently available PPI's are substituted benzimidazoles including Rabeprazole, Lansoprazole, Dexlansoprazole, Pantoprazole, Esomeprazole and Omeprazole. These all are Prodrugs (figure 1).These agents are weakly basic in nature and get degraded in stomach, because of they are highly sensitive to the acid so before reaching the principle site of absorption in the proximal small intestine they need to be protected from gastric degradation by enteric coating. Enteric coating is very effective as it prevents the premature acid activation in the lumen of stomach but delay their absorption and therefore onset of their anti-secretory effect. PPI's enters the circulation following absorption and as they are weakly basic in nature they are concentrated in the secretory canaliculi of parietal cell.[3]

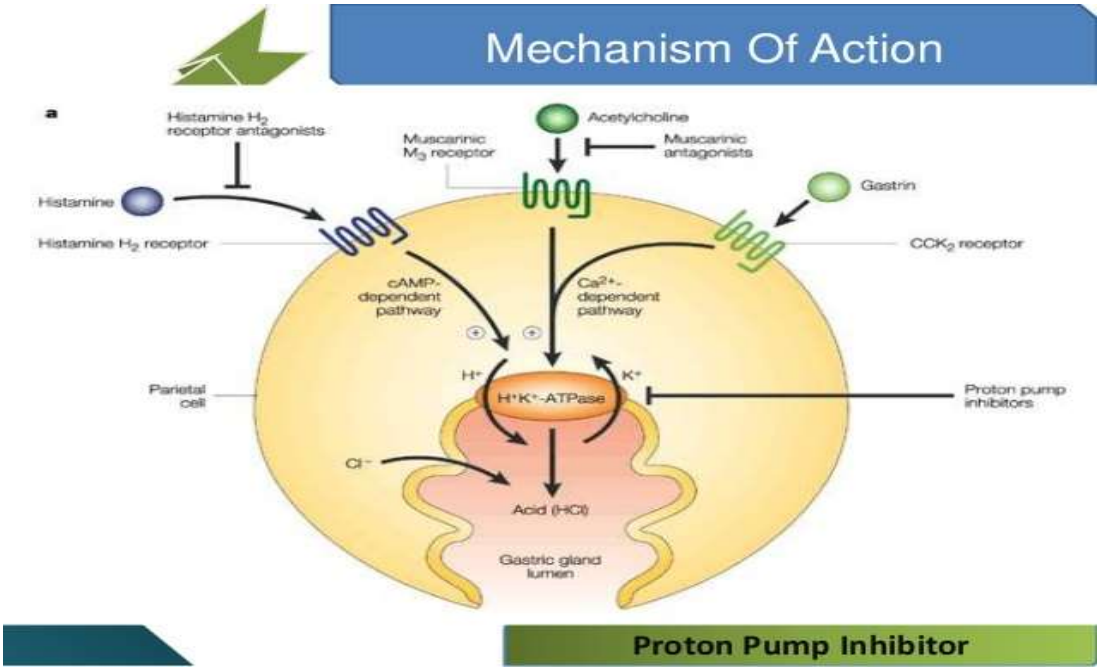

Figure 1: Mechanism of action of Proton pump inhibitor.

The inactive benzimidazole of the PPI's are converted to a cationic tetracycline sulfonamide which covalently binds to the cysteine on the alpha sub units of H^+, K^+ ATPase enzyme, inhibiting acid secretion of about 70% bound cell of active pumps.

Acid recovery is totally depends on the synthesis of new pumps, slow dissociation of the PPI from cysteine. Acid may be recovered because of the reduction of the disulfide bond from extracellular

glutathione. When new pumps are converted to their inactive form in the tubulovescicle to their active form at a canaliculi surface, the secretory capacity of the acid get restored, this occurs on average in 36-72 hrs.[10] The ant secretory effect of PPI's is depend on the time and its dose in relation with the meal, plasma half-life of PPI and state of activation of parietal cells. All PPI's have the similar plasma half-life between 1 to 2 hours and therefore PPI's are short acting drugs that cannot control the acid secretion over 24 hours period with a single dose. Whereas 30% of the patients require twice a daily dosing to obtain the effective control.[3]

Pharmacokinetics

All PPI's including Rabeprazole, Omeprazole, Lansoprazole, Esomeprazole, having short half- life typically 1-2 hrs. But may last up to 24 hrs. Because of necessity of new pump synthesis for acid secretion All PPI's are eliminated via hepatic P-450 cyp2c19 (table 1).

Table 1: Pharmacokinetic properties of PPI.

Parameters	Rabeprazole	Esomeprazole	Omeprazole	Lansoprazole	Pantoprazole
$t_{1/2}$	2-4	1-6	-	1-3.5	1.2-2.1
t_{max}	0.6-14	0.8-1.3	0.5-1.2	0.9-2.1	0.8-2.0
System clearance	-	160-330	400-620	400-650	90-225
Oral Bioavailability	55	50-80	25-40	80-90	77
Fraction of unbound drug in plasma	0.04	0.05	0.05	0.03	0.02
Apparent volume of distribution	-	0.22-0.26	0.13-0.35	0.4	0.15

Rabeprazole is most acid labile drug and therefore becomes the most potent candidate for the enteric coating. Whereas Lansoprazole, Dexlansoprazole and pantoprazole having greatest bioavailability, Pantoprazole is least reactive and least potent as well. Slower the PPI get cleared from the plasma cells, more of the drug will available to deliver the proton pump. All PPI's have same mechanism of action, but because of the nature of pyridine and benzimidazole substituent may make differences chemically and physically. Rabeprazole is having higher pKa, Rabeprazole activated in wide pH range than lansoprazole, Pantoprazole, and Omeprazole converts faster to sulfonamides than others.[10]

Clinical significance of ppi's

- To reduce the reflection of acid which may cause esophagitis and heartburn.
- In maintenance therapy to prevent esophagitis from the recurring after the esophagitis has healed.
- To treat zollinger-Ellinson syndrome.

- It is also used in the combination with the certain antibiotics for the complete destruction of Helicobacter pylori.
- Used for treatment of ulcers in the duodenum and stomach.
- Used in the treatment of the peptic ulcer and short term management of the GERD.[10].

Multiparticulate drug delivery systems

Despite of tremendous advancement in the various drug delivery systems Multiparticulate oral dosage form is the most prominent technology for getting delayed release formulation. It provides tremendous advantages in pharmaceutical development (figure 2).

Multiparticulate drug delivery systems are mostly used for an oral rout. It consists of the multiple distinct small units that exhibit different properties. These small units provide more surface area and it gives more scope for delayed release polymer to put a coat and it ultimately helps to achieve desired controlled release of dose.

Figure 2: multiparticulate drug delivery systems

These units are nothing but the subunits such as granules, beads, microspheres, pellets, spheroid, and Minitab. In MDDS drug substance is divided into number of subunits typically consist of thousands of spherical particulates having diameter of about 0.05-2.00 mm. These subunits are compressed into tablets or filled in capsules to administer the recommended dose.[19]

Multiparticulates provide many advantages over single unit systems because of their small size. This multiparticulates are less dependent on the gastric emptying this laid to the less inter and intra subject variability in gastrointestinal transit time. They are less likely to cause local irritation and get better distributed.

Recently multiunit particulates are being preferred more than that of the single unit systems because of their potential benefits such as reduced risk of local irritation, increased bioavailability, reduced risk of systemic toxicity and predictable gastric emptying.

Multiparticulates systems shows better reproducible pharmacokinetics than that of the single unit conventional dosage forms. The multiparticulate shows the greater inter and intra subject variability as their disintegration occurs within minute or often in minutes, the individual sub unit particles pass rapidly through the Gastrointestinal tract, if these subunit particles having diameter less than 2 mm, they are able to leave the stomach continuously no matters pylorus is open or closed. For modified release formulations the drug safety may also be increased. For e.g. if the film coat of the single unit enteric coated tablet is damaged, the complete dose is releases into the stomach where it may cause the ulceration or pain and even if there is damage in film coating of the sustained release formulation these can lead into dose dumping and result in the side effects whereas in multiparticulate formulation the every single unit is coated with the controlled release polymer and if any damage, that will affect only that particular subunit which is very small part of the total dose it ultimately governs the safety of product.[1, 19]

Methods for the preparation of the multiparticulates

- Pelletization
- Granulation
- Spray drying
- Spray congealing

Drug particles may be entrapped within the multipariculates or layered around them; these multiparticulates can be modified in many ways.

Pelletization by bottom spray technology [1, 10,18]

(Wurster Technology)

The Bottom spray technology (Wurster) is the most commonly known and implemented in the pharmaceutical industry. Developed in 1950 by Dr. Dale Wurster. This technique governs the excellent coating uniformity and efficacy. This equipment is featured with the air distribution plate and a partition that is responsible for the fluidization of particles through the coating zone. The nozzle is situated in the bottom of the container in the center at coating zone. It leads to high coating efficiency uniformity due to short distance between the coating materials and the particles during coating process which minimizes the spray drying (figure 3).

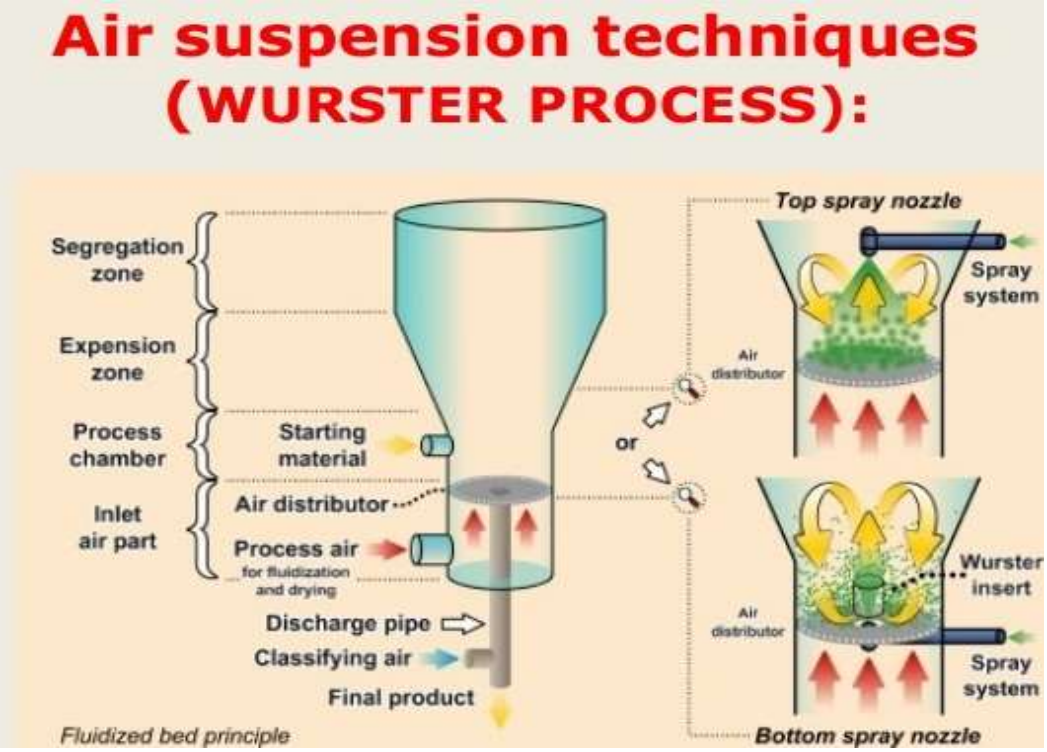

Figure 3: Fluidized bed drying (Wurster process)

Most of the process air is entered through the center via tube. It produces a venturi effect, which sucks the product from outside the partition past the nozzle. Velocity of the particles gets reduced when it leaves the cylindrical (figure 4). The solution or suspension is sprayed continuously with the help of automization air. The most common method use for the application of the coating on the multiparticulate is palletization (Air suspension technology).

Advantages of multiparticulates [18, 19, 30]

Multiparticulates are making huge impact in the global market. It acts as a vehicle for drug delivery, it releases drug at controlled rate. Multiparticulate provides various advantages as given below:

1. Gastric emptying is faster.
2. Avoidance of the dose dumping.
3. Reduced variability of gastric emptying.
4. Lower intra and inter subject variability in the dissolution of the drug substance.
5. Lower intra and inter subject variability in the absorption of the drug substance in the systemic circulation.
6. Lower dependency on the nutrition state.
7. Minimized risk of high local dose in the GI tract.
8. Increased residence time within the lower intestine with reduced risk of dose dumping.

9. Improved stability, patient compliance and the comfort.

Limitations of multiparticulates [18, 19]

1. Low drug loading.
2. Lack of manufacturing reproducibility and efficacy.
3. Large number of process variables.
4. Higher cost of production
5. Multiple formulation steps.
6. Required advanced technology.
7. Required skilled person for manufacturing.
8. Materials

Preparation of pellet [12, 14,17,29,31]

Pellets can be prepared in the fluid bed processor by the solution or suspension layering method. This is most reliable and efficient technology where drug substances and polymers can be deposited on to inert sugar spheres. The inert sugar sphere can be deposited with active drug substance along with the alkalizing agent as a stabilizer, binder such as HPMC, talc as an antistatic agent or glident). Mannitol, Pearlitol as a pore forming agent, Triethyl citrate as a plasticizer and enteric polymer (functional coating polymer) such as, HPMC phthalate, PVP, CAP and various grades of Eudragit (eudragit L-30 D-55, eudragit S100, L100) etc.

Experimental [9, 12, 13, 14, 30, 31, 32, 33, 34.]

Preformulation studies

Pre formulation studies must be carried out for appropriate selection of excipient in an extent to produce a stabilized enteric coated delayed release formulation.

Micromeritic properties of API

Angle of repose

The angle of repose of API powder can be determined by funnel method. The accurately weighed powder is to be taken in the funnel. The heights of funnel have to be adjusted in such way that the tip of funnel will just touch the apex of powder blend. Allow the powder blend to flow through the funnel freely on to the surface. Then measure the diameter of the powder cone and calculate the angle of repose using the following formula:

$\tan \Ø = h/r$

Where, h is height of powder cone

R is radius of powder cone

Bulk density (BD) and Tap density (TD)

Bulk density and Tap density can be determine by taking 2 gm of API powder (which have to shake in order to break any agglomerates formed) this have to add in 10ml of measuring cylinder. Then allow this cylinder to tap on the hard surface from the height of 2.5 cm at the second interval. Tapping is to be continued until and unless there will no further change in the volume.

The BD and TD can be calculated using following formula

BD=weight of powder/untapped volume of the powder in a measuring cylinder

TD= weight of powder/tapped volume of powder

Compressibility Index

The Compressibility Index can be determine by the Carr's index formula as given below

$$\text{Carr's index (\%)} = [(TD-BD)*100]/TD$$

Hausner's ratio

Hausner's ratio is nothing but the ratio of tapped density to bulk density of powder which calculates the flow ability of the powder. It can be calculated by following formulae:

Hausner's ratio (H) =TD/BD

Where TD is tapped density

BD is bulk density

Drug excipient compatibility study

The drug excipient study can be determined by mixing drug with various excipient in different proportion, stability study shall be carried out in ambered colored flint vials at accelerated conditions 40°C ± 2°C/75% RH ± 5%RH. The study should be conducted for 4 weeks and which is compared with the control at 2-8°C. The physical observation should be recorded at regular interval of one week. The DSC studies, FT-IR studies should carried out to determine the compatibility of excipient with the drug.

Estimation of API

The two different solution of API can be prepared in 0.1N HCL and 6.8 pH phosphate buffer respectively. Then UV spectra are to be taken using UV spectrophotometer.

Post formulation studies

Drug content

API content in pellet can be determined by UV spectrophotometer. The drug contents for different API's can be determined by their respective method. The crushed powder is to be taken equivalent to that of appropriate quantity of API, then transferred it to the 100ml volumetric flask. Then add buffer solution to the flask and volumes made up to 100ml further dilution are to be carried out and absorbance is to be measured it spectrophotometrically [31].

Weight Variation

The weight variation test is determined by USP specification. 20 capsule individually are to be weighed and then determine the average weight, none of the individual capsule should be less than 90% and more than 110% of the average weight.

Loss on drying

The moisture content of a product at each step can be determined by the LOD instrument. About 2 gm of sample is to be kept on an aluminum plate at 105°C for 5 min. % LOD is to be check.

In vitro dissolution

In vitro dissolution can be carried out using USFDA specification. In vitro dissolution study can be carried out using USP apparatus type 2 (paddle). It can be carried out in 0.1 N HCl for 2 hrs at 75 RPM followed by pH 6.8 0.05M Phosphate buffer. After acid stage add 250ml of 0.2mol/l trisodium phosphate and run the sample for 45min at 60 RPM. 5ml sampling is to be done for every 5min for buffer stage. The concentration measured using UV spectrophotometer at respective wavelength (USP).

Stability studies

The stability of drug in a dosage form at different environmental condition is crucial because it determines the expiry date. Where the optimized formulation is exposed to different conditions. Optimized formulation is to be subjected for accelerated stability study as per ICH guideline. The capsules are to be filled in HDPE container and sealed. This should be place in 40^0c and 75%RH for 30 days. Then evaluate the parameter like drug content, weight variation in vitro dissolution for every 7 days. The drug instability can be indicated by observing change in appearance, texture, color and odor of the formulation.

CONCLUSION

Multiparticulate drug delivery system provides the greater flexibility and adaptability which gives huge scope to optimize the therapy. This technology is popular and growing rapidly. The proton pump inhibitors are great candidate for degradation, as they are pretty much sensitive to the acid secreted in stomach. Therefore they need to be protected by giving enteric coating. As the multiparticulate drug delivery system is most efficient and reliable technology, the proton pump inhibitors can be formulated as delayed release multiparticulate. This can be done by the solution or suspension layering in fluid bed processor (Wurster process) with the help of enteric polymers. This helps to formulate a stabilized and more efficient formulation. Nowadays this type of

formulation has gained a lot of attention in global market and currently this are the frontier of future pharmaceutical development.

REFERENCES:

1. Saurabh S, Garima M. Fluid bed technology: Overview and parameters for process selection. Int J Pharma Sci Drug Res 2010; 2(4):36-245.
2. Pole S, Maurya S, Harnale P, Rathod N, Bendale S, Kutle N. A detail understanding of enteric coated tablet: Manufacturing and evaluation. Eur J Pharma Med Res 2016; 3(4):135-144.
3. Hunt RH. Review article: The unmet needs in proton pump inhibitor therapy in2005. Aliment Pharmacol Ther 2005; 22(3):10-19.
4. Horn JR, Howden CW. Review article: Similarities and differences among delayed release proton pump inhibitor Formulations. Aliment pharmacol Ther 2005; 22(3):20-24.
5. Poojan P, Tanwar YS, Jaimin M, Amit P. Orodispersible tablet of proton pump inhibitor drugs a review. J pharma sci Bioscientific res 2013; 3(2):68-76.
6. Bozdag S, Calis S and Sumnu. Formulation and stability evaluation of pharmaceutical technology, Faculty of pharmacy, Hacettepe University, Ankara, Turkey. S.R.P. pharm sciences; 9(4):321-327.
7. Rakesh NT, Puranik PK. Rabeprazole Sodium delayed release multiparticulates: Effect of enteric coating on product performance. J adv pharma tech res 2011; 2(3):184-191.
8. Kendall RA, Basit AW. The role of polymers in solid oral dosage form. In: Uchegbu IT, Schatzlein AG, editors. Polymers in drug delivery system. USA: Taylor and Francis 2006:35-40.
9. Robert A, Marcella N, Osvaldir PT. Enteric coating process of diclofenac sodium pellets in a fluid bed coater with a wurster insert: influence of process variables on coating performance and release profile. Elsevier Adva powder tech 2013; 659-666.
10. Mansuri NS, Parejiya PB, Soniwala M. Glimpse of of drug delivery systems for proton pump inhibitor. Inter J Pharma Sci Review Res 2016:36(1) Article No.14. 81-88.
11. Hussain DS, Roychowdhury, verma P, Bhandari V. A review on recent advances of enteric coating. IOSR J Pharmacy 2016:2(6); 05-11.
12. Sanjay RP, Priyal RP, Cintan NV. Formulation, Process parameters and evaluation of delayed release Tablets of Rabeprazole sodium. Inter J Pharm Pharma Sci 2011; 2(3); 144-156.

13. Petchimuthu S, Narayanan N. Formulation and characterization of Lansoprazole Delayed release pellets by fluid bed technique. Inter J Biological Pharma Res 2013:4(12); 977-986.
14. Tank NA, Shanthakumar GS. Formulation and Invitro evaluation of delayed release microspheres of Rabeprazole Sodium. Res J Pharma Biological Chemical Sci 2011:2(2); 780-789.
15. Deepak Y, Sachin S, Neeraj K. Dual coating of swellable rupturable polymers on Glipizide loaded MCC pellets for pulsatile delivery: Formulation, Design and In-vitro evaluation. Inter J Pharmacy 2011; 4(19):121-130.
16. Roobi S, Sharma PK, Dhakad PK. An overview on sustained release enteric coated pellets of Pantoprazole. J Drug Delivery Therapeutics. 2014; (4); 130-136.
17. Kavita B, Bhatt DC. Influence of plasticizer on concentration of physicochemical properties of antiulcer drug in enteric coated pellets. Scholars Res Library Der Pharma chem 2015:7(12); 405-410.
18. Ganndhi B, Baheti J. Multiparticulate drug delivery drug delivery system review. Inter J Pharma Innovations. 2012:2(5); 11-18.
19. Dey NS, Bajumdar S Rao MEB. Multiparticulate drug delivery system for controlled release. Tropical J Pharma Res 2008; 7 (3): 1067-1075.
20. Sellesic GI. A General review on Pharmaceutical pelletization Technology. New York: Marcel Decker 1989.
21. Dashvasky A, Kolter K, Bodmeir R. Compression of pellets coated with various aqueous polymer dispersions. Inter J Pharmacy 2004; 19-26.
22. Bankar SG. Film coating theory and practice. J Pharma Sci 1966: 81-90.
23. Sallassie GI, Gorden R, Rawzi MB, Nasbi HRU. Evaluation of a high speed pelletization process and equipment. Drug development and industrial pharmacy 1994; 20.
24. Pashupathi RT,Rao VT. Fluidized bed processing: A review. Indian J pharmacy Biotechnology. 2014; 2(4):1360-1365.
25. Kulakarni PA, Kulkarni AD, Gandhi AD, Shirolkar SV, kasture PV. Pelletization technique as a Pharmaceutical tool in Multiparticulate drug delivery system: A review. Inter J drug formul res 2010: 1; 89-118.
26. Pashupati RT, Vanketeswara Rao T. Fluidized bed processing: A Review. Indian J res pharmacy Biotech ISSN 2321-5674, 2320-3471.
27. Jyoti Y, Doniparthi J. Multiparticulate drug delivery system using natural polymer as release retardant materials. Inter J Pharmacy Pharma Sci 2014:6(1); 62-65.

28. Supriya P, Rajni B, Rona AC. Pelletization Techniques: A literature review. Inter res J pharmacy 2012:3(3); 45-47.
29. Kapadia J. Development and evaluation of novel pellets based tablet system of pantoprazole. World J Pharmacy Pharma Sci 2013;3(6):1734-1746.
30. B Gandhi and J Baheti. Multiparticulate Drug Delivery Systems. A review. Inter J Pharm chem sci ISSN: 2277-5005, 1620-1626.
31. K L Senthilkumar, M Muthukumaran and B Chenchuratnam. Formulation and evaluation of Rabeprazole sodium enteric coated pellets. Inter J Pharmacy, Biology Chemistry 2012; 1(1):7-14.
32. Venkateshwarlu P. Formulation and in –vitro evaluation of lansoprozole delayed released capsules. Inter J innovative pharma res 2013;4(3):328-336.
33. Naik NR, Pathi LR, Mogali RK, P Rao M, Sivasankar R, Beera V. Formulation and evaluation of esorepreprazole magnesium dehydrate multiple unit particulate system (pellets) as a delayed release dosage form. Inter J res develop pharmacy life sci 2014; 3(2):935-942.
34. Ramu S, Reddy P, DS Rao, Ramakrishna G. Formulation and evaluation of lansoprazole delayed release pellets. Int J Pharma, Chem. Biological Sci 2015; 5(4):860-878.]