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Lansoprazole (PPI) As Delayed-Release Pellets: A Review

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ABSTRACT

When compared to single unit dosage forms, multi-particulate drug delivery systems (MDDS) are innovative pharmaceutical dosage forms that have gained increasing appeal in recent years. Small pellets are usually used to make tablets because they are easier to work with. This review consists of an extensive survey of literature from Scopus, Elsevier, PubMed, Springer Nature, and other international reputed sources. This review was designed to emphasize delayed pellets preparation incorporating pantoprazole. The compression process has a lesser impact. Delayed-release drugs are intended to deliver a medicine to the distal human intestine in a specific location or at a specific time. Proton-pump inhibitors (PPIs) like pantoprazole are commonly utilized in hospitals and outpatient settings. Pantoprazole has been approved by the Food and Drug Administration (FDA) for the treatment of a variety of diseases, including erosive esophagitis caused by gastroesophageal reflux disease and pathological hypersecretory illnesses such as Zollinger-Ellison syndrome. The H+/K+ATP pumps are irreversibly inhibited by pantoprazole. Pantoprazole is likewise metabolized mostly in the liver by CYP2C19 demethylation and sulfation. A loading dosage of 80 mg followed by an 8 mg per-hourly infusion is advised for preventing peptic ulcer rebleeding. Two types of solid oral dosage forms were developed using enteric-coated pellets carrying the model drug: hard gelatin capsules and compressed tablets. Dual coating with two different enteric polymers-an inner acrylic coating followed by an outer cellulosic coating—yields the optimal product with all of the necessary features. It has become future-oriented research in drug (dosage) design to produce delayed pellets incorporating pantoprazole (PPI) and to give better patient benefits and compliance.

INTRODUCTION

When compared to single unit dosage forms, multi-particulate drug delivery systems (MDDS) are innovative pharmaceutical dosage forms that have gained increasing appeal in recent years. These multiple unit dosage forms (MUDF) are made up of several separate subunits (microparticles), each of which acts as an independent drug reservoir and releases the drug in a controlled manner, independent of the other subunits (Al-Hashimi et al. 2018; Ghebre-Selassie, 1989). Multi-particulates are particularly well suited to the manufacture of modified-release solid oral dosage forms (delayed/sustained) which provide advantages such as less variable gastrointestinal transit and a lower risk of dose dumping (Zaman et al. 2016). The size of pellets has been widely reported that is a very significant consideration during compaction (Haslam et al. 1998). Small pellets are usually used to make tablets because they are easier to work with. The compression process has a lesser impact. This is primarily owing to the increased smaller beads' mechanical strength concerning their size, as well as decreased contact force on each pellet, resulting in a considerable reduction in lowered transformation degree (Johansson et al. 1998).

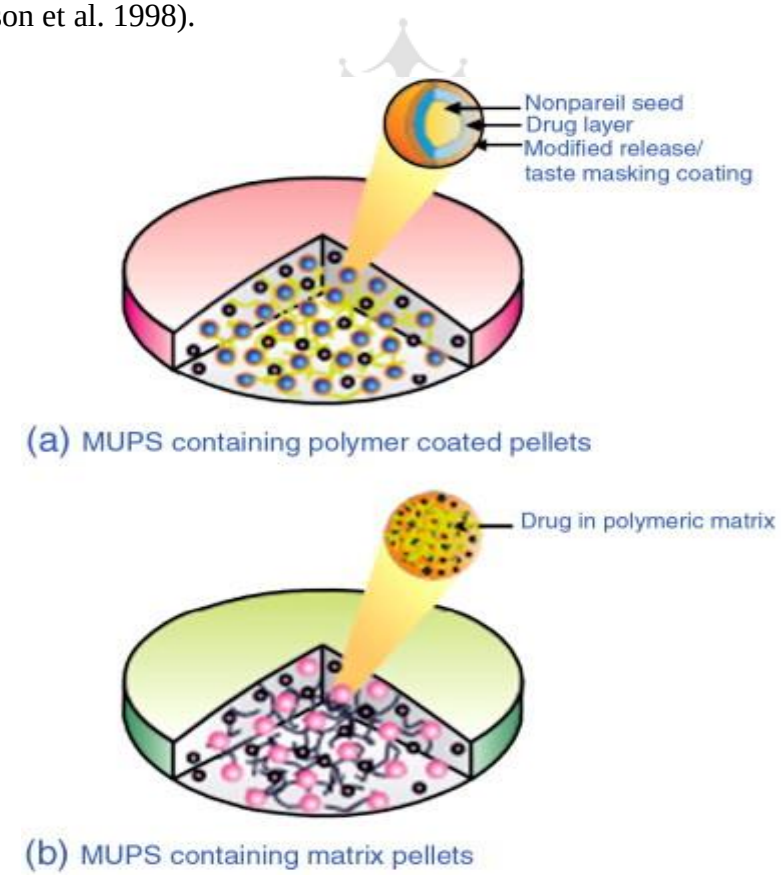

Figure No. 1: Multiple Unit Pellet System (MUPS)

Delayed-release drugs are intended to deliver a medicine to the distal human intestine in a specific location or at a specific time. Temporal delivery refers to the desired pace of medication release to target tissue throughout a given duration of treatment, whereas spatial placement refers to delivering medicine to a specific organ or tissue. The major goal of employing delayed-release medications is to shield the drug from gastric fluids, lessen gastric discomfort produced by pharmaceuticals that are particularly irritating to the stomach, or make gastrointestinal transit easier for drugs that are better absorbed from the intestine (Bauer et al. 1998).

Pantoprazole

Proton-pump inhibitors (PPIs) like pantoprazole are commonly utilized in hospitals and outpatient settings. Pantoprazole has been approved by the Food and Drug Administration (FDA) for the treatment of a variety of diseases, including erosive esophagitis caused by gastroesophageal reflux disease and pathological hypersecretory illnesses such as Zollinger-Ellison syndrome (Escourrou et al. 1999). It's also FDA-approved for erosive esophagitis healing maintenance. Off-label uses for pantoprazole include eliminating Helicobacter pylori bacteria and avoiding peptic ulcer rebleeding and/or NSAID-induced ulcers. [2] Pantoprazole may be used to prevent stress ulcers in critically ill patients. [3] This drug is safe to use in both adult and pediatric populations (Jensen et al. 2017).

Mode of action

The H+/K+ATP pumps are irreversibly inhibited by pantoprazole. When the pH of the environment drops, the rate of pantoprazole breakdown increases. As a result, it's not surprising that this drug works best in the stomach, where the H+/K+ ATP pumps are found (specifically within the parietal cells of the stomach lining). This is the final stage in the formation of stomach acid. As a result, pantoprazole binding to these pumps stops acid output for up to 24 hours. After 24 hours, additional pumps have formed, necessitating a second dosage of pantoprazole to prevent them from acting. The medicine takes effect quickly, with the maximum effect occurring between 2 and 6 hours after delivery. Pantoprazole is likewise metabolized mostly in the liver by CYP2C19 demethylation and sulfation.

Indications

Because varied delivery regimens are depending on the ailment being treated, accurate diagnosis is required to properly dose pantoprazole. Pantoprazole is used to treat several different diseases (Barkun et al. 2010).

- Pantoprazole can be taken orally or intravenously to treat erosive esophagitis caused by gastroesophageal reflux disease. Treatment is commonly 40 mg daily for oral administration, or 20 mg for milder cases, for a total of 8 weeks (Dettmer et al. 1998).
- The same dose can be continued for up to 12 months during the optional maintenance phase. 40 mg of pantoprazole is given intravenously every day for 7 to 10 days.
- Pantoprazole can be taken orally or intravenously to treat Zollinger-Ellison syndrome. Treatment for oral administration is usually 40 mg twice daily.
- The recommended dose of pantoprazole intravenously is 80 mg every 12 hours. Pantoprazole has a variety of off-label uses, as previously discussed (Bianchi et al. 2000).
- Pantoprazole can be included in medication regimens that include a variety of antibiotics to treat Helicobacter pylori bacterial infections (Mansour-Ghanaei et al. 2017). The recommended dose of pantoprazole is 40 mg twice daily for all of these regimens.
- A loading dosage of 80 mg followed by an 8 mg per-hourly infusion is advised for preventing peptic ulcer rebleeding (Zargar et al. 2006).
- For NSAID-induced ulcers, a daily dose of 20 to 40 mg is advised (Regula et al. 2006).
- Pantoprazole can be taken with or without food, but it is recommended that it be taken 30 minutes before a meal.

Adverse effects

Pantoprazole produces below mentioned adverse effects (Linder et al. 2017; Ozalas et al. 2017; Staines et al. 2021) -

- Diarrhea
- Headache
- upper respiratory tract infection
- abdominal pain
- infection to Clostridium difficile
- Small intestinal bacterial overgrowth
- vitamin B-12 deficiency
- iron deficiency
- calcium deficiency
- magnesium deficiency
- bone demineralization
- interstitial nephritis

Anhydrous dibasic calcium phosphate (DCPA)-based water-insoluble pellets have just been introduced to the market. These pellets include 80 percent DCPA and 20 percent MCC by weight. They are an appealing alternative to the other commercial goods available thus far due to their high density of over 1000 g/l, the very low water content of less than 1%, and reduced hygroscopicity. Another article compares the functional qualities of calcium phosphate-based pellets to those of other commercially available inert cores (Zakowiecki et al. 2019).

Method of preparation of multi-particulate dosage forms

Two types of solid oral dosage forms were developed using enteric-coated pellets carrying the model drug: hard gelatin capsules and compressed tablets. The medication API was 50.0 percent by weight, 44.5 percent by weight of MCC type 200, 5.0 percent by weight of L-HPC, and 0.5 percent by weight of magnesium stearate in the developed MUPS formulations. The pellets were manually filled into capsule shells of size "0" to make hard gelatin capsules. Compression forces of 18–20 kN are applied to tablets on a Korsch EK0 eccentric tablet press with concave punches (R 25 mm) of 12 mm diameter (Daniel et al. 2020).

Preparation of Enteric coating dispersion

A stainless-steel vessel was used to collect purified water. The filtered water was gently added to the methacrylic acid copolymer, and the contents were stirred continuously for 30 minutes. Purified water was added to TEC in a beaker, and the mixture was stirred for 5 minutes. Under constant stirring, Polysorbate 80 was added to the solution. To achieve uniform dispersion, talc was added to the aforementioned solution and agitated. The above-mentioned solution was slowly added to the first step, stirring constantly, and combined for about 30 minutes. The dispersion was collected in a stainless-steel tank after being sifted through mesh no. 100 (Ramu et al. 2015).

Evaluation parameters

In-Vitro drug release

The USP-22 dissolving apparatus-2, paddle-type is used to conduct drug release tests at a rotational speed of 50 rpm at 370.5°. For the first two hours, 900 ml of 0.1 mol/l HCl was employed, followed by 12 hours of pH 6.8 phosphate buffer solution. Throughout the experiment, the sink condition was maintained. At regular intervals, samples (10 ml) were extracted and replaced with the same volume of pre-warmed (370.5°C) fresh dissolving media to keep the volume constant. The withdrawn samples were filtered using a 0.45 membrane filter and the drug concentration in each sample was determined using a UV spectrophotometer at 233 nm after appropriate dilution (Basak et al. 2007).

Scanning electron microscopy

A scanning electron microscope is used to examine the surface properties of the drug-loaded DR pellets alone as well as when crushed into tablets. A standard sample holder and carbon tape were utilised to secure the sample, and a 5–10 kV acceleration voltage was used to capture images at a magnification of 300x.

Dissolution test

In vitro dissolution experiments of the enteric-coated tablets were conducted for about 2 hours in 0.1 N HCl, after which the tablets were moved to a pH 7.5 phosphate buffer and dissolution studies were conducted for about 10 hours. Three tests were conducted (Nagaraju et al. 2010).

Hardness

The hardness of the tablet was determined using a Monsanto hardness tester. It is expressed in kg/cm.

Friability

The capacity of the to endure abrasion is assessed by the formula in this test, which is closely related to tablet hardness.

(W1-W2) / W1 100 = percent friability

Mechanical strength

The volume of phase separation of the formulation was measured after centrifugation (Remi centrifuge) at 2000 rpm for various time intervals.

Content Uniformity

To determine the actual value of the active medication in experimental Microemulsions, a content uniformity test was performed. Microemulsions were chosen at random from all batches for testing. The drug content was determined with the help of a standard calibration curve. The average values obtained from three determinations were used to establish the mean percent drug content. Using an instrument UV Visible spectrophotometer, the samples were examined at 275nm for cumulative drug release.

Stability studies

The optimized RAB pellets are charged for the accelerated stability studies according to ICH recommendations (40±2°C & 75%RH) in stability chambers for 3 months. They are sealed with rubber plugs and aluminum caps and placed in flint vials. At 30, 60, and 90 days, samples are obtained and analyzed for various physicochemical parameters (Guideline IHT, 2003).

Weight variation

The contents of each capsule were extracted and weighed individually. The net weight of the contents was computed by subtracting the emptied capsules' weights, and the percent weight variation was calculated using the formula (Mansuri et al. 2016) below.

Weight variation = (Wt of Capsule − Average weight) / Average wt of capsule × 100

Biorelevant dissolution (Physio-grad device)

The Physio-grad gadget utilized in this investigation consisted of a microcomputer that controlled each measurement channel separately as well as a valve island. pH probes ensured accurate pH readings in each vessel and prompted pH adjustments where necessary. The addition of a titrant, in this case, CO2 and compressed air, was used to modify the pH levels. The dissolution was done in a paddle apparatus with a paddle rotational speed of 50 rpm. There were two steps to the dissolution test. For the first stage, tablets or pellets are immersed in 250 mL of 0.01 M HCl for 30 minutes. The test was then performed for 60 minutes with the addition of 750 mL of Hank's buffer concentrate. The pH of the hydrogen carbonate medium was regulated with a Physio-grad device after the addition of buffer and set at 6.8. The amount of dissolved drug was evaluated using quartz cuvettes with a 1 cm path length and an Agilent 8453 UV/VIS Spectrophotometer at a detection wavelength of 276 nm (Daniel et al. 2020).

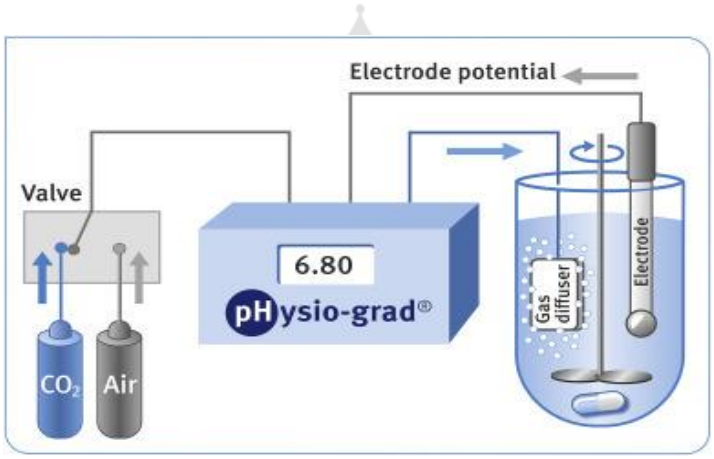

Figure No. 2: Physio-grad device

Advantages of delayed pellets Lachman et al. 1991)

- Reduce the frequency of dose to avoid patient compliance issues.
- Because a more equal blood level is maintained, the blood level oscillation characteristics of multiple dosing of the conventional dosage form are decreased.
- Use a lower overall medicine dosage.
- Minimize or eliminate systemic or local side effects.

- Reduce medication buildup by using persistent dosing.
- With prolonged use, there was less opportunity for drug activity reduction.
- Cure or control the condition faster.
- Improved condition control (lower drug level fluctuation) and improved bioavailability of some medicines
- Cost-effective
- administrations of sustained-release form provide greater therapy dependability.

Disadvantages (Shankar et al. 2012)

- As dose forms, decrease systemic availability in comparison to instant release convention.
- In the event of toxicity, poisoning, or a hypersensitive reaction, retrieving the medicine is challenging.
- Reduced ability to modify the dosage of medicine that is routinely given in different strengths.

Significance of pellets

Pellets have a wide range of uses in a variety of industries, and creative use could optimize profits. The following are a few examples of where smooth surface homogeneous pellets have been successfully used (Ramu et al. 2015). -

- Controlled release rate thanks to polymer coating; pellets with a larger surface area allow for improved distribution, dissolution, and absorption.
- Encapsulation allows chemically incompatible items to be administered in a single dosage form.
- Product aesthetics have been improved.
- In chemical industries, avoid powder dusting; several applications, such as sustained-release detergent powder and milkshake pellets, are feasible.
- Ensures enhanced flow characteristics and manufacturing flexibility in formulation development.

- Colored coating material distinguishes different thicknesses of beads, making it easier to combine in desired proportions.

CONCLUSION

The development of pantoprazole delayed-release pellets with the requisite physicochemical and stability properties was successful. To impart delayed-release features to the core drug pellets, pH-dependent, enteric acrylic, and cellulosic polymers were utilized alone, in combination, or one over the other. Designing a delayed-release pellet product of a PPI, especially one that is highly water-soluble, such as pantoprazole, has always been difficult. However, it can be concluded from the current study and the methodologies used that, in the case of pantoprazole, dual coating with two different enteric polymers-an inner acrylic coating followed by an outer cellulosic coating—yields the optimal product with all of the necessary features (Tirpude et al. 2011).

It has become future-oriented research in drug (dosage) design to produce delayed pellets incorporating pantoprazole (PPI) and to give better patient benefits and compliance.

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Nil.

CONFLICT OF INTEREST

The authors have confirmed no conflict of interest.

REFERENCES

1. Al-Hashimi N, N. Begg, R.G. Alany, H. Hassanin, A. Elshaer. Oral modified release multiple-unit particulate systems: compressed pellets, microparticles and nanoparticles Pharmaceutics (2018).
2. Ghebre-Selassie I., Pellets: a general overview I, in: Pharmaceutical Pelletization Technology, Marcel Dekker, 1989.
3. Zaman M., S. Saeed-Ul-Hassan, R.M. Sarfraz, N. Batool, M.J. Qureshi, M.A. Akram, S. Munir, Z. Danish, Pellets and pelletization: emerging trends in the pharma industry, Acta Pol. Pharm. - Drug Res. 73 (3) (2016) 1415–1425.
4. Haslam J L, A.E. Forbes, G.S. Rork, T.L. Pipkin, D.A. Slade, D. Khossravi, Tableting of controlled release multiparticulates, the effect of millisphere size and protective overcoating, Int. J. Pharm. (1998).
5. Zargar SA, Javid G, Khan BA, Yattoo GN, Shah AH, Gulzar GM, Sodhi JS, Mujeeb SA, Khan MA, Shah NA, Shafi HM. Pantoprazole infusion as adjuvant therapy to endoscopic treatment in patients with peptic ulcer bleeding: prospective randomized controlled trial. J Gastroenterol Hepatol. 2006 Apr;21(4):716-21.
6. Michelle A. Bernshteyn; Umair Masood. Pantoprazole, Treasure Island (FL): StatPearls Publishing; 2022.
7. Ozalas SM, Huang V, Brunetti L, Reilly T. Comparison of Two Versions of the Beers Criteria and Adverse Outcomes in Older Hospitalized Patients. Consult Pharm. 2017 Dec 01;32(12):752-763.

8. Staines KA, Myers K, Little K, Ralston SH, Farquharson C. Proton Pump Inhibitors Inhibit PHOSPHO1 Activity and Matrix Mineralisation In Vitro. Calcif Tissue Int. 2021 Dec;109(6):696-705.
9. Linder L, Tamboue C, Clements JN. Drug-Induced Vitamin B_{12} Deficiency: A Focus on Proton Pump Inhibitors and Histamine-2 Antagonists. J Pharm Pract. 2017 Dec;30(6):639-642.
10. Regula J, Butruk E, Dekkers CP, de Boer SY, Raps D, Simon L, Terjung A, Thomas KB, Lühmann R, Fischer R. Prevention of NSAID-associated gastrointestinal lesions: a comparison study pantoprazole versus omeprazole. Am J Gastroenterol. 2006 Aug;101(8):1747-55.
11. Escourrou J, Deprez P, Saggioro A, Geldof H, Fischer R, Maier C. Maintenance therapy with pantoprazole 20 mg prevents relapse of reflux oesophagitis. Aliment Pharmacol Ther. 1999 Nov;13(11):1481-91.
12. Mansour-Ghanaei F, Pedarpour Z, Shafaghi A, Joukar F. Clarithromycin versus Gemifloxacin in Quadruple Therapeutic Regimens for *Helicobacter Pylori* Infection Eradication. Middle East J Dig Dis. 2017 Apr;9(2):100-106.
13. Bianchi Porro G, Lazzaroni M, Imbesi V, Montrone F, Santagada T. Efficacy of pantoprazole in the prevention of peptic ulcers, induced by non-steroidal anti-inflammatory drugs: a prospective, placebo-controlled, double-blind, parallel-group study. Dig Liver Dis. 2000 Apr;32(3):201-8
14. Dettmer A, Vogt R, Sielaff F, Lühmann R, Schneider A, Fischer R. Pantoprazole 20 mg is effective for relief of symptoms and healing of lesions in mild reflux oesophagitis. Aliment Pharmacol Ther. 1998 Sep;12(9):865-72.
15. Barkun AN, Bardou M, Kuipers EJ, Sung J, Hunt RH, Martel M, Sinclair P., International Consensus Upper Gastrointestinal Bleeding Conference Group. International consensus recommendations on the management of patients with nonvariceal upper gastrointestinal bleeding. Ann Intern Med. 2010 Jan 19;152(2):101-13.
16. Jensen BES, Hansen JM, Larsen KS, Junker AB, Lassen JF, Jensen SE, Schaffalitzky de Muckadell OB. Randomized clinical trial: the impact of gastrointestinal risk factor screening and prophylactic proton pump inhibitor therapy in patients receiving dual antiplatelet therapy. Eur J Gastroenterol Hepatol. 2017 Oct;29(10):1118-1125
17. Johansson B, F. Nicklasson, G. Alderborn, Effect of pellet size on degree of deformation and densification during compression and on compactability of microcrystalline cellulose pellets, Int. J. Pharm. (1998).
18. Zakowiecki D, M. Lachmann, V. Schaum, T. Hess, Novel starter pellets based on dibasic calcium phosphate anhydrous: properties and application, Express Pharma 15 (1) (2019) 34–36.
19. Daniel Zakowiecki, Maja Szczepanska, Tobias Hess, Krzysztof Cal, Barbara Mikolaszek, Jadwiga Paszkowska, Marcela Wiater, Dagmara Hoc , Grzegorz Garbacz. Preparation of delayed-release multiparticulate formulations of diclofenac sodium and evaluation of their dissolution characteristics using biorelevant dissolution methods. Journal of Drug Delivery Science and Technology, 2020; 60:101986.
20. Basak SC, Rahman J, Ramlingam M. Design and in vitro testing of a floatable gastroretentive tablet of metformin hydrochloride. *Pharmazie.* 2007;62:145–8.
21. Nagaraju R, Y. Swapna, R. Hari Babu, Rajesh Kaza. Design and Evaluation of Delayed and Extended Release Tablets of Mesalamine. Journal of Pharmaceutical Science and Technology Vol. 2 (1), 2010, 103-110.
22. Lachman L, Liberman HA and Kanig JL: the theory and practice of industrial pharmacy. Varghese Publishing House Bombay, Fourth Indian Reprint 1991: 430.
23. Shankar KR, Madhan K and Swetha G: Formulation and evaluation of sustained release matrix tablets of Baclofen. Int J Pharm Sci & Res 2018; 9(10): 4402-09. doi: 10.13040/IJPSR.0975-8232.9(10).4402-09.
24. Guideline IHT, Stability testing of new drug substances andproducts, Q1A (R2), Current Step, 4, 2003.
25. Mansuri Niyaz S., Punit B. Parejiya, Moinuddin M Soniwala. evelopment of Delayed Release Rabeprazole Pellets EmployingQuality by Design (QbD) Principles. Int. J. Pharm. Sci. Rev. Res., 36(1), January – February 2016; Article No. 50, Pages: 281-287.
26. Bauer K. H., Lehmann K., Osterwald H. P., Rothgang G. (1998). Equipment for sugar coating and film coating processes Coated pharmaceutical dosage forms. Med pharm Scientiphic Publishers, Stuttgart.
27. Ramu S, P. Chandra Gopal Reddy, D. Srinivasa Rao and G. Ramakrishna. Formulation And Evaluation Of Lansoprazole Delayed Release Pellets. IJPCBS 2015, 5(4), 860-878.
28. Tirpude Rakesh N. and Prashant K. Puranik. Rabeprazole sodium delayed-release multiparticulates: Effect of enteric coating layers on product performance. J Adv Pharm Technol Res. 2011; 2(3): 184–191.