ORIGINAL ARTICLE

Rabeprazole sodium delayed-release multiparticulates: Effect of enteric coating layers on product performance

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ABSTRACT

Rabeprazole sodium is one of the most effective proton pump inhibitors (PPIs) used in antiulcer therapy. Like most other PPIs, owing to its acid-labile nature, the drug is formulated as enteric-coated dosage form. Conventional means of producing delayed release multiparticulate dosage forms of PPIs require large quantities of enteric polymer coatings. In the present study, in order to better evaluate the effect of polymeric coating on product performance, the pellet core structure and composition was kept constant. Four different enteric-coating formulations and designs were evaluated. Enteric-coated drug multiparticulates prepared with single polymeric coatings (acrylic or cellulosic) were compared with two different polymeric layer coatings to evaluate the effectiveness of latter coatings in more effectively producing a better rabeprazole sodium delayed-release pellet product. The pH-dependent, enteric acrylic, and cellulosic polymers were used either alone, in combination, or applied one over the other to impart delayed-release properties to the core drug pellets. It was demonstrated that dual delayed-release coating with two different enteric polymers—an inner acrylic coating followed by an outer cellulosic coating—yields the best product that provides all the desired physicochemical and drug dissolution characteristics.

Key words: Enteric, delayed-release, multiparticulates, proton pump inhibitors, rabeprazole sodium

INTRODUCTION

Enteric dosage forms are of two types—single unit, e.g., tablet, and multiple unit, e.g., pellets.[1] Besides offering the usual advantages of a multiunit dosage form, a delayed-release multiparticulate formulation is desirable in comparison with enteric-coated tablets for following reasons:

1. Small, delayed-release multi-units enable them to empty readily from the stomach into small intestine, thus facilitating rapid drug dissolution, absorption, and onset of action. Enteric-coated tablets take longer time to empty into the intestine.
2. Rapid emptying of delayed-release units into the intestine enables the acid-labile drugs, better protection against gastric acid. Longer residence of dosage form in the stomach pH, such as the case with enteric-coated tablets, make the dosage form more susceptible to coating damage or require thicker coating protection. Furthermore, failure of coating leads to complete drug destruction in acidic pH which is not the case with delayed-release polymer-coated microparticles.

However, challenges abound in the development and production of coated multiparticulates—need for application of larger amount of coating owing to small pellet size and thus larger surface area, difficulty in processing small particles, longer processing time, etc.[2] Since the amount of enteric coating to be applied to obtain the desired enteric property is too large for pellet products, there often is need to consider approaches by which one can reduce the coating applied without compromising the product performance and attributes. The challenge is more specific when the drug product to be designed contains proton pump inhibitors

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(PPIs), which are acid-labile drugs. Criticality of coating further increases when the issue is design of delayed-release multiparticulate product of a highly water-soluble PPI such as rabeprazole sodium, the most water-soluble and thus most labile (moisture, light, and pH sensitive) among all PPIs.[3] Reddy *et al*. identified and characterized the various impurities of rabeprazole sodium.[4] Excipients that are critical to stability of rabeprazole sodium in solution has been studied by Ren *et al*.[5]

First reported in 1884 by Kendall,[6] enteric- or delayed-release coating is possibly the most established of all modified-release technologies. The two primary aspects in the successful development of a delayed release multiparticulate formulation of a PPI are stability of formulation and performance of the drug product after oral administration. Building these essential attributes in the multiparticulate formulation is possible but quite often the amount of delayed-release coating that needs to be applied on the pellets is pretty large, thus making the amount of polymer ingested in daily dose of the drug product beyond the permitted levels as proposed in limits for inactive ingredients guide (IIG limits).[7]

The objective of the present study was thus to design a stable and effective delayed-release drug product of rabeprazole sodium that utilizes lesser amount of enteric polymer of particular kind which is well within the IIG limits as well as easy to process and manufacture owing to lesser use of coating polymer and thus lesser processing time. In particular, the study was aimed at using alternate layers of different enteric polymers *viz*. acrylic and cellulosic, to achieve the desired end result.

MATERIALS AND METHODS

Materials

The various materials used in the present study and their purpose are indicated in Table 1.

Equipments

The various equipments used in the present study with their purpose are indicated in Table 2.

Design of delayed-release rabeprazole sodium pellets involved the following three steps:

1. Design, composition, and preparation of rabeprazole sodium core pellets.
2. Design, composition, and preparation of seal-coated rabeprazole sodium pellets.
3. Design, composition, and preparation of delayed-release rabeprazole sodium pellets.

Schematic illustration of the delayed-release rabeprazole sodium pellet design is represented in Figure 1.

Table 1: Excipients used for the preparation of delayed-release rabeprazole sodium pellets

Excipients	Make/Grade	Function in formulation
Active and excipients used for preparing drug pellets by solution layering		
Rabeprazole sodium	Dr. Reddy's	Active
Sugar spheres (18-20 mesh)	Nitika Chemicals	Core or substrate pellets
Hypromellose E15	Dow Chemicals	Binder (pH-independent water soluble polymer)
Sodium hydroxide	Merck	Base (for providing alkaline microenvironment)
Purified water	-	Vehicle for drug and binder
Excipients used for seal coating of drug pellets		
Hypromellose E5	Dow Chemicals	Seal coating pH-independent water soluble polymer
Magnesium oxide, light	Nitika Chemicals	Base (for providing alkaline microenvironment)
Red oxide of iron	Nitika Chemicals	Colorant
Purified water	Dow Chemicals	Release modifier (hydrophilic polymer)
Excipients used for enteric coating of seal-coated drug pellets		
Eudragit L30D55	Evonik	Enteric polymeric dispersion
Eudragit NE30D	Evonik	Sustained-release dispersion
Hypromellose phthalate HP55	Shin et su	Enteric polymer
Triethyl citrate	Morflex	Water soluble plasticizer
Dibutyl sebacate	Morflex	Hydrophobic plasticizer
Purified talc	Nitika Chemicals	Lubricant
Acetone	Merck	Solvent for HP55

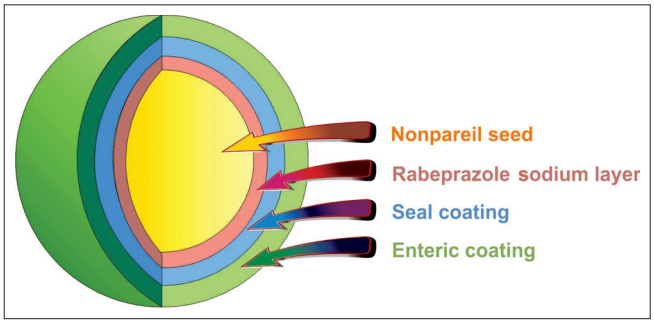

Figure 1: Schematic representation of structure of delayed-release rabeprazole sodium pellets

Since the present study was designed to evaluate and compare the efficacy of enteric polymeric-coating

composition in imparting the requisite delayed-release properties to the drug, the composition of pellets up to the seal-coating stage was common for all experiments. Process parameters for preparing delayed-release polymer-coated drug pellets using enteric polymers were also kept constant.

Rabeprazole Sodium Core Pellets—Design, Composition, and Preparation

Rabeprazole sodium core pellets were prepared by drug solution layering onto nonpareil seeds in bottom spray fluid-bed processor. Detailed composition of drug pellets is given in Table 3.

The steps involved in the preparation of core drug pellets are enlisted below:

1. Aqueous solution of hypromellose E15 was prepared by dissolving it in purified water with stirring.
2. Sodium hydroxide was added to solution of step 1 with stirring and the solution stirred continuously until it dissolved completely.
3. Rabeprazole sodium was dissolved in solution of step 2 with stirring to get a clear solution.
4. Nonpareil seeds were charged in a bottom spray fluid-bed processor and drug solution was continuously sprayed over them under an optimized set of process variables to obtain drug pellets.
5. After the completion of drug layering, the pellets were dried in the fluid-bed processor until loss on drying (LOD) of less than 2% w/w was attained.
6. The dried drug pellets were sifted to collect 16 to 20 mesh fraction. Undersize and oversize drug pellets were discarded.

Process parameters used for drug solution layering are indicated in Table 4.

Two such lots of core drug pellets were produced for further processing.

Rabeprazole Sodium Seal-Coated Pellets—Design, Composition, and Preparation

The primary objective of applying seal coat on rabeprazole sodium pellets was to separate the drug layer from the outermost enteric layer which is acidic in nature. Direct contact of acidic enteric layer with the drug would otherwise result in destabilization of drug and generation of impurities. Since the study was designed to evaluate the performance of different compositions of enteric coating, the quantum and composition of seal coat for all the proposed enteric-coated pellet prototypes were kept identical. The % w/w seal coating applied on core drug pellets for all the four prototypes was 10% w/w of core. Detailed composition of seal coating is given in Table 5.

The steps involved in the preparation of seal-coated drug pellets (in two equal lot sizes) are enlisted below:

1. Hypromellose E5 (80% by weight of total seal coating) was dispersed and dissolved with stirring in purified water.
2. Light magnesium oxide (20% by weight of total seal coating) and red iron oxide, previously sifted through 200 meshes, were dispersed in the hypromellose solution with stirring to produce the seal coating dispersion.

Table 2: Equipments used in the preparation of delayed-release rabeprazole sodium pellets

Equipment	Purpose
Mechanical stirrer (Remi)	Drug-binder and polymer solution/dispersion preparation
Vibratory sifter and sieves of various sizes (openings)	Sieving and grading of pellets
Wurster coater (bottom spray fluid-bed processor) Glatt, Germany, product chamber capacity 1 L	Preparation of drug pellets, seal coating and enteric coating of pellets and drying of pellets at all stages
Capsule filling machine	Encapsulation of pellets
Alu-alu blister packaging machine	Packaging of capsules

Table 3: Composition of rabeprazole sodium core pellets

Ingredients	Quantity
Sugar spheres (18-20 mesh)	400 g
Rabeprazole sodium	50 g
Hypromellose E15	5 g
Sodium hydroxide	5 g
Purified water*	200 g
Total	460 g**

*Removed during processing; **On anhydrous basis

Table 4: Process parameters for preparing rabeprazole sodium core pellets

Process parameters	Settings/specifications
Equipment make	Wurster coater, Glatt, Germany
Product chamber capacity	1 l
Total batch size	460 g
Nonpareil seeds (substrate)	400 g
Drug-polymer solution quantity	260 g
Inlet air temperature	60°C
Outlet air temperature	30-35°C
Humidity of inlet air	40%
Spray gun type	Pneumatic
Atomizing air (bar)	1.0
Spray rate	4-6 g/min
Atomizing nozzle diameter	0.8 mm
Pump for delivering drug dispersion	Peristaltic
Process time	3-4 hours (approximately)
Drying temperature	40°C
Drying time	1 hour
LOD of dried product (determined at 105°C)	NMT 2% w/w

NMT - Not more than

Application of seal coating composition on the core drug pellets was carried out in the Wurster coater by employing processing conditions given in Table 6. After completion of seal coating process, the coated pellets were subjected to drying at 40°C for 1 hour to obtain LOD of less than 2% w/w. LOD value is critical to stability of drug since higher level of moisture content may lead to destabilization of drug. The dried seal-coated drug pellets were sifted to collect 16 to 20 mesh fractions.

Two such lots of seal-coated pellets were produced for further processing.

Enteric-Coated Rabeprazole Sodium Pellets—Design, Composition, and Preparation

The seal-coated rabeprazole sodium pellets were divided into four lots, each lot comprising of approximately 300 g, for the application of enteric coating. Four different enteric-coating compositions were designed. Each of the four compositions was intended to be applied on seal-coated core drug pellets to obtain weight gain of about 25% w/w of enteric coat (in relation to seal-coated pellets).

The qualitative and quantitative compositions of four different enteric polymer formulations [Table 7] were as under—

1. *Prototype A* – Eudragit L30D55 alone with triethyl citrate (20% w/w of dry polymer) as plasticizer, wherein the said polymer possesses only enteric property and dissolves at pH ≥5.5.
2. *Prototype B* – Eudragit L30D55 and Eudragit NE30D (in ratio 90: 10) containing triethyl citrate (20% w/w of dry polymer) as the plasticizer, wherein the former polymer, i.e., Eudragit L30D55 is the enteric polymer while Eudragit NE30D is pH-independent sustained-release polymer. In totality, the applied coating composition dissolves at pH ≥6.0.
3. *Prototype C* – Hypromellose phthalate HP55 alone with dibutyl sebacate (20% w/w of polymer) as the plasticizer, wherein the said polymer possesses only enteric property and dissolves at pH ≥5.5.
4. *Prototype D* – Eudragit L30D55 containing triethyl citrate as the plasticizer (applied to a level of 15% w/w of seal-coated pellets) as the first enteric coating, followed by a second enteric coating of hypromellose phthalate HP55 containing dibutyl sebacate as the plasticizer (applied to a level of 10% w/w of seal-coated pellets). The resulting enteric-coated drug pellets dissolve at pH ≥5.5.

The various enteric compositions used for preparing the four prototype drug pellets can be expressed in simple terms as given in Table 6.

The steps involved in the preparation of all the four prototype enteric-coated drug pellets are enlisted below:

1. Preparation of enteric-coating composition—the steps involved were:
   (a) *Preparation of aqueous polymeric dispersion*—the acrylic polymeric dispersion was diluted with water by stirring, followed by incorporation of plasticizer with agitation.
   (b) *Preparation of organic polymer solution*—the cellulosic polymer was dispersed and dissolved in acetone

Table 5: Composition of seal coating for application on rabeprazole sodium core pellets

Ingredients	Quantity (g)
Rabeprazole sodium core pellets (substrate for seal coating)	460.00
Hypromellose E5	36.60
Magnesium oxide, light	9.00
Red oxide of iron	0.40
Purified water*	184.00
Total	506.00**

*Removed during processing; **On anhydrous basis

Table 6: The enteric-coating compositions for the four prototype rabeprazole sodium pellet formulations

	Prototype A	Prototype B	Prototype C	Prototype D
Polymer type	Acrylic	Acrylic	Cellulosic	1st coat acrylic, 2nd coat cellulosic
Polymer nature	Enteric	Enteric (90%) + sustained (10%)	Enteric	Enteric
pH for polymer dissolution	≥5.5	≥6.0	≥5.5	≥5.5
Enteric polymer layers	One	One	One	Two
Solvent system	Aqueous	Aqueous	Organic	1st coat aqueous, 2nd coat organic
Plasticizer type	Water-soluble	Water-soluble	Oil-soluble	1st coat water-soluble, 2nd coat oil-soluble
Solid content of polymer dispersion	20% w/w	20% w/w	5% w/w	1st coat 20% w/w, 2nd coat 5% w/w
% coating in relation to core	25	25	25	1st coat 15, 2nd coat 10 (total 25)

Table 7: Coating compositions for the preparation of delayed-release rabeprazole sodium pellets

Excipients	Quantity	Function in formulation
Delayed-release coating composition A		
Rabeprazole sodium seal-coated pellets (16-20 mesh)	300 g	Core or substrate pellets
Eudragit L30D55 (on dry weight basis)	60 g (200 g)	Enteric coating polymeric dispersion
Triethyl citrate	15 g	Water soluble plasticizer
Purified water	100 g	Vehicle for enteric coating dispersion
Delayed-release coating composition B		
Rabeprazole sodium seal-coated pellets (16-20 mesh)	300 g	Core or substrate pellets
Eudragit L30D55 (on dry weight basis)	54 g (180 g)	Enteric coating polymeric dispersion
Eudragit NE30D (on dry weight basis)	6 g (20 g)	Sustained-release polymeric dispersion
Triethyl citrate	15 g	Water soluble plasticizer
Purified water	100 g	Vehicle for enteric coating dispersion
Delayed-release coating composition C		
Rabeprazole sodium seal-coated pellets (16-20 mesh)	300 g	Core or substrate pellets
Hypromellose phthalate HP55	60 g	Enteric-coating polymer
Dibutyl sebacate	15 g	Hydrophobic plasticizer
Acetone	1 500 g	Vehicle for enteric-coating composition
Delayed-release coating composition D		
Rabeprazole sodium seal-coated pellets (16-20 mesh)	300 g	Core or substrate pellets
Delayed-release coating composition D1 (60% by weight of total enteric coat)		
Eudragit L30D55 (on dry weight basis)	36 g (120 g)	Enteric coating polymeric dispersion
Triethyl citrate	9 g	Water soluble plasticizer
Purified water	60 g	Vehicle for enteric coating dispersion
Delayed-release coating composition D2 (40% by weight of total enteric coat)		
Hypromellose phthalate HP55	24 g	Enteric coating polymer
Dibutyl sebacate	6 g	Hydrophobic plasticizer
Acetone	600 g	Vehicle for enteric coating composition

with stirring to get clear solution, followed by addition of plasticizer with agitation.

2. Application of the enteric composition on seal-coated drug pellets in bottom spray fluid-bed processor utilizing the process parameters stated in Table 6 until the entire quantity has been deposited. This is then followed by drying of the pellets at 40°C for 1 hour to LOD ≤2% w/w and subsequent screening of the dried pellets to collect 14 to 18 mesh fractions.

Flow chart depicting the various steps in the preparation of delayed-release rabeprazole sodium pellets is illustrated in Figure 2.

In vitro Dissolution Studies on Delayed-Release Rabeprazole Sodium Pellets

Dissolution in acid stage is done to determine acid resistance of formulations, an essential criterion which must be fulfilled by delayed-release drug products. Subsequent to test for acid resistance, the formulations are exposed to buffer media to assess the rapidity of drug dissolution in alkaline buffer, a feature that too is essential for all enteric-coated formulations.

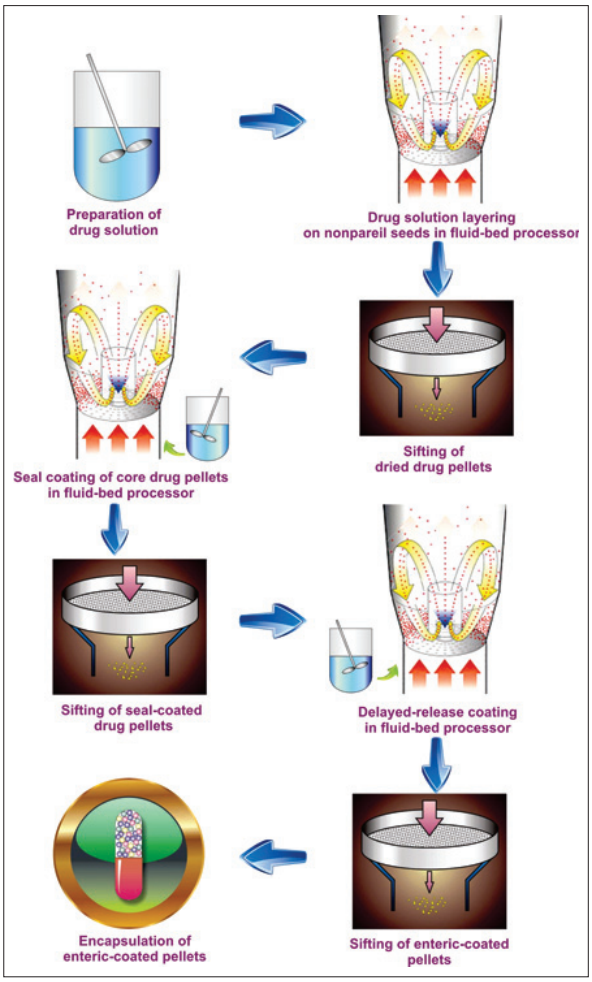

Figure 2: Flow chart depicting steps involved in the preparation of delayed-release rabeprazole sodium pellets

Dissolution tests were performed in accordance with pharmacopoeial method and using USP dissolution apparatus 2 (paddle). The selected *in vitro* dissolution conditions were in accordance with the US Food and Drug Administration CDER—dissolution methods for drug products, and indicated for rabeprazole sodium delayed-release tablets. Dissolution test conditions as recommended by the US FDA are given in Table 8.

Pellets equivalent to 20 mg rabeprazole sodium (253 mg pellets) were subjected to dissolution testing. The dissolution test comprised of following two stages as per US FDA guidance:

1. *Acid stage*: 700 ml of 0.1N HCl was used as the dissolution medium. The aliquots so removed at different time intervals in the acid stage (2 hours) were passed through a suitable 0.45-µm filter, and the filtrate was immediately diluted by a factor of 2 with 0.5N sodium hydroxide. The amount of drug dissolved in the acid stage was determined by high performance liquid chromatography (HPLC) using the assay procedure.
2. *Buffer stage*: Immediately after the completion of 2 hours of dissolution in acid stage, the pH of the dissolution media was raised to 8.0 by the addition of 300 ml of 0.6M tris-HCl buffer and further subjected to drug release study as stated in Table 9. The dissolution samples were collected at 10, 20, 30, and 45 minutes. The aliquots so removed at different time intervals in the buffer stage were passed through a suitable 0.45-µm filter, and the filtrate was immediately diluted by a factor of 2 with 0.5N sodium hydroxide. The amount of drug dissolved at various time points in the buffer stage was determined by the assay procedure.

Table 8: *In vitro* dissolution conditions for delayed-release rabeprazole sodium pellets as per USFDA-CDER

Dissolution parameters	Settings/requirements
Apparatus type	USP type 2 (paddle)
Speed	100 rpm
Dissolution media	700 ml (acid stage for 2 hours) 1 000 ml (buffer stage for 45 minutes)
Acid stage media	0.1N hydrochloric acid (pH 1.2)
Buffer stage media	Tris buffer, pH 8.0 (by addition of 300 ml of 0.6M tris-HCl buffer to medium of acid stage)
Sampling time points at acid stage	2 hours
Sampling time points at buffer stage	10, 20, 30, and 45 minutes
Stabilization of aliquots	Dissolution aliquots are stabilized by addition of 0.5 N sodium hydroxide solution

The criterion for acceptance of delayed-release product is given in Table 10.

Analysis of Rabeprazole Sodium Content in Prepared Formulations (Assay)

Rabeprazole sodium content of the prepared delayed-release pellets was determined by the method given in Indian Pharmacopoeia.[8] HPLC method was used for the assay of rabeprazole sodium.

RESULTS AND DISCUSSION

In the present study, an attempt was made to evaluate the enteric properties of acrylic and/or cellulosic polymers and their combination to produce a stable, delayed-release pellet formulation and their capsules. Delayed-release pellets of rabeprazole sodium were successfully prepared with each of the four different enteric compositions. The finer differences that accentuate the superiority of each of the four polymeric compositions are elicited in the results and discussion given below.

In vitro Drug Dissolution Studies on Delayed-release Rabeprazole Sodium Pellets

Results of acid resistance of enteric-coated pellets are presented in Table 11.

Dissolution profile of the product in buffer stage is presented in Table 12. Graphical representation of drug release at alkaline stage is depicted in Figure 3 (enteric-coated pellets).

Table 9: Comparison of evaluation characteristics of rabeprazole sodium delayed-release pellets

Evaluation parameters	A	B	C	D	Remarks
Pellet morphology	Smooth and glossy	Smooth and glossy	Smooth but less glossy	Smooth but less glossy	Pellets with outermost acrylic coating are glossier than those with cellulosic coating.
Acid release (in 2 hours)	<5%	<5%	<5%	<5%	All the products had good acid resistance. However, formulation A with lone coating of Eudragit L30D55 was poorest of all.
Buffer release (in 45 minutes)	>75%	>75%	>75%	>75%	Release was satisfactory for all pellets. However, the ones having a top coat of enteric cellulosic polymer were the best.

Table 10: Acceptance criteria or dissolution limits for delayed-release rabeprazole sodium pellets

Dissolution stage	Acceptance criteria/limits for amount dissolved
Acid stage	NMT 10% at the end of 120 minutes
Buffer stage	NLT 75% at the end of 45 minutes

Table 11: Amount of rabeprazole sodium released from enteric-coated pellets in acid stage in 2 hours

Percent rabeprazole sodium dissolved after dissolution in acid stage* from different formulations (±SD)			
A	**B**	**C**	**D**
4.6 ± 0.6	1.3 ± 0.2	2.5 ± 0.3	0.4 ± 0.3

*Results are mean of 6 readings

Table 12: Amount of rabeprazole sodium dissolved at various sampling time intervals from enteric-coated pellets after dissolution in buffer stage

Sampling time interval (min)	Amount dissolved (%) from various enteric-coated formulations* (±SD)			
	A	**B**	**C**	**D**
10	45 ± 3.2	33 ± 3.1	55 ± 2.9	53 ± 3.2
20	66 ± 3.8	51 ± 3.3	72 ± 3.1	68 ± 2.3
30	79 ± 2.8	68 ± 2.4	81 ± 2.2	77 ± 3.0
45	88 ± 2.4	79 ± 2.8	93 ± 2.5	90 ± 2.9

*Results are mean of 6 readings

A direct influence of polymer type, composition, and manner of coating on the drug release properties of delayed-release rabeprazole sodium pellets was observed. All the tested enteric-coated formulations—A through D, demonstrated comparable delayed-release properties owing to presence of thick polymeric coating on the surface of drug pellet.

Dissolution of drug in simulated intestinal fluid for all formulations was demonstrated to be dependent upon the following:

1. Type of enteric-coating polymer
2. Composition of enteric coating
3. Number of coating polymer(s), and
4. Manner of deposition of enteric coating.

Application of acrylic enteric coating (Eudragit L30D555) that contained additional sustained-release polymer (Eudragit NE30D) resulted in a product (formulation B) that demonstrated slowest drug release in buffer stage. The relative retarding effect on dissolution in buffer stage could be attributed to presence of sustained-release polymer that prevents the polymer from dissolving fast enough in the alkaline pH. This was followed by formulation A which was coated with a lone enteric acrylic polymer Eudragit L30D55. This was obvious since such a lone

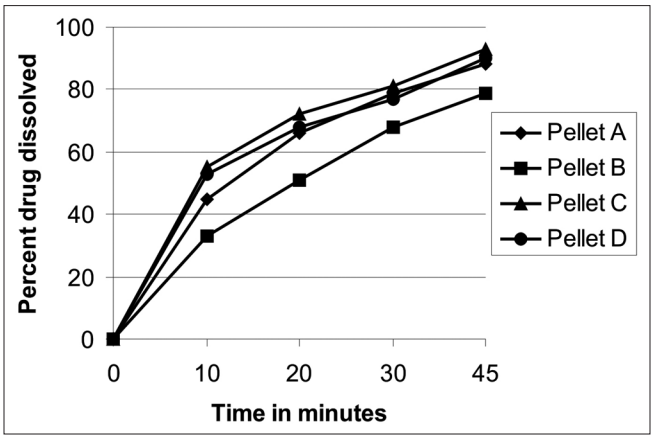

Figure 3: Comparative *in vitro* dissolution profile of rabeprazole sodium in buffer from various enteric-coated pellet formulations

enteric polymer has good and rapid solubility in alkaline pH compared with when it is mixed with a sustained-release polymer like Eudragit NE30D. In comparison with formulations A and B, formulation D was faster dissolving in simulated intestinal fluid. Formulation D was the one coated with enteric-coating composition, wherein the first enteric coat (in contact with the core drug pellet) was of acrylic polymer and the outer coat was of cellulosic enteric material. Its faster dissolution in relation to formulation B is understandable since the latter contained a portion of sustained-release polymer that retards drug dissolution to some extent. Although both the inner and outer coat comprised of enteric polymers in case of formulation D, the reason for faster dissolution in relation to lone acrylic polymer is that in the dissolution vessel, as the outer cellulosic enteric polymer dissolves, agglomeration of drug pellets do not occur. This is, however, observed during the dissolution of formulation A which is coated with lone acrylic enteric polymer. With such acrylic enteric polymers, when the polymer dissolves in the alkaline intestinal fluid, before the polymer completely goes into solution, a transition gel phase of polymer could be seen which favors agglomeration of coated drug particles in dissolution vessel, owing to which the dissolution rate is retarded to some extent.

The most rapid dissolving composition was found to be formulation C which was coated with a lone cellulosic enteric polymer hypromellose phthalate HP55. Enteric cellulosic polymers dissolve very well without showing any kind of pellet agglomeration in dissolution vessel as well as rapid dissolution in a media once a pH of more than 5.5 has been attained.

Thus, the sequence in which the formulations dissolve in buffer stage, i.e., the rapidity of dissolution, was as follows: $C > D > A > B$

CONCLUSIONS

Delayed-release pellets of rabeprazole sodium with desired physicochemical and stability attributes were successfully developed. pH-dependent, enteric acrylic, and cellulosic polymers were used either alone, in combination, or applied one over the other to impart delayed-release properties to the core drug pellets. Thus, the following four different enteric-coating compositions were evaluated:

- Enteric acrylic polymer alone (formulation A)
- Enteric + sustained-release acrylic polymers in combination (9 : 1 ratio)–formulation B
- Enteric cellulosic polymer (formulation C)
- Enteric acrylic polymer (inner layer) followed by enteric cellulosic polymer layer (outer layer)—formulation D.

All the four formulations were identical to each other with regards to composition of core drug pellets. They were also identical with respect to the total amount of enteric coating applied but differed from each other with regards to qualitative enteric-coating compositions.

A summary of results obtained as a result of comparison of all four pellet formulations, *viz.* formulation A through D, is presented in Table 9.

Designing a delayed-release pellet product of PPI has always been challenging, especially if it is highly water soluble, e.g., rabeprazole sodium. However, in the current study and with the approaches adopted, it can be concluded that as far as rabeprazole sodium is the drug under consideration, dual coating with two different enteric polymers—an inner acrylic coating followed by an outer cellulosic coating—yields the best product that provides all the desired characteristics.

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