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Research Article

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Formulation development of enteric coated tablets of a proton pump inhibitor for stability enhancement

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ABSTRACT

In the present investigation enteric coated formulation of proton pump inhibitor which is a substituted benzimidazole derivative was developed to enhance its stability. The tablets were coated with HPMC phthalate based enteric polymer with different amount of plasticizers and talc. Prior to enteric coating core tablets were seal coated to prevent interaction between core and enteric layer. The core tablets were separated into three groups and seal coated with a colour coding scheme to coverage levels of 2% (white colour), 2.5% (yellow colour), 3% (orange colour) weight gains. The purpose of colour coding was to carry out the coating simultaneously to reduce the number of experiments and eliminate potential differences that may exist during separate coating processes. The tablets were coated with three HPMC phthalate based enteric formulations containing different amounts of plasticizer and talc. During each enteric coating process, a predetermined amount of labeled tablets were removed after attaining 6, 8, and 10% weight gains. Dissolution results revealed that all enteric coated formulations inhibited drug release for 2 h in 0.1 N HCl and drug release at most intermediate sampling time points in phosphate buffer, pH 6.8.

Keywords: Enteric coat, seal coat, delayed release, colour coding, stability

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INTRODUCTION

Stability is an important issue for the successful development of drug products. Unfortunately, most of the drugs are vulnerable to chemical degradation. If a drug is chemically degraded, its therapeutic efficacy begins to decline. Furthermore, drug degradation can accompany not only a loss in potency, but also formation of harmful and toxic byproducts. Therefore, maintaining drug stability is critical to successful product development [1]. Drug stability in formulated solution has been investigated extensively. However, another important aspect of drug stability is in physiological fluids such as gastrointestinal fluids. When taken orally, drugs are exposed to acidic and/or enzymatic conditions. Several acid-labile drugs from different chemical classes are currently on the market, demonstrating varying degrees of acid-lability. Due to their sensitivity to the acidic conditions, acid-labile compounds present many challenges during manufacturing and production and, therefore, should be dealt with appropriately. Some drugs are extremely acid-labile, including proton pump inhibitors (PPIs), penicillin G, didanosine, peptides and proteins, to name a few. The therapeutic activity of such drugs can be compromised when exposed to acidic conditions; hence, they require suitable formulation technologies or structural modifications to remain stable and efficacious [2].

Site-specific, drug delivery of a therapeutic agent to the intestinal region can be readily accomplished by the application of an enteric coating on a solid dosage form [3]. The application of an enteric coating to a solid dosage form is a well established approach to prevent drug release in the stomach and allow release in the small intestine [4-6]. It is used to preclude the degradation of acid-labile actives in the gastric environment or to protect the stomach from irritant compounds. The most commonly used enteric coatings employ pH-dependent polymers which contain carboxylic groups. Commercially available polymers commonly employed for enteric coating consist of cellulose

acetate phthalate, hydroxypropylmethylcellulose phthalate, copolymers of methacrylic acid and acrylic acid esters. These substances are anionic polymers or copolymers which remain un-ionized in the low pH environment of the stomach, and become ionized in the higher pH conditions of the small intestine, due to ionization of functional groups along the polymer chain thus allowing the dissolution of the coating and drug release [7].

PPI is substituted benzimidazole derivative and are administered as enteric coated tablet that pass through stomach intact and absorbed in proximal small intestine. Enteric coating of tablets is frequently used since decades, prevents oral medication from being digested in stomach and leads to the controlled release of the active substance in the upper intestine. Such enteric properties, for example, are useful for substances that have an irritant effect on the stomach or for drugs that are acid unstable or are designed to act in the small intestine. PPI is acid labile, rapidly degraded in acidic atmosphere of stomach so to make it gastro-resistant tablets are marketed as enteric coated tablets. The drug is highly sensitive to acid and moisture. It rapidly absorbs moisture from atmosphere and starts degradation.

The primary objective of the present study are to examine the role of seal coating on the stability of enteric coated tablets, and to optimize an enteric coat formulation composed of plasticizer, detackifier, and enteric polymer for these tablets.

EXPERIMENTAL SECTION

Materials

A PPI bulk drug was procured from Cadila Healthcare limited as a gift sample. The excipients used in formulation development were purchased from market. All excipients used in formulation development are of Ph.Eur. grade.

Preparation of tablets

The tablets were prepared using formula using drug, L-HPC, MgO, Mannitol were granulated by fluid granulation using HPC as binder. The dry granulation was sized using a Quadro Comil. The milled granulation was blended for 5 min with L-HPC in Conta blender. L-HPC was added both intra and extra granularly (50:50). Tablets were produced using 16 station rotary press with 8 mm punch and die set (Ajas component, Mumbai) was used to obtain tablets of mass 150 mg and crushing strength of 8 kp.

Coating of tablets

Seal/barrier coating

Tablets were coated using polymeric dispersion of diacetylated monoglyceride (DAMG) (10% based on polymer weight) was dissolved into ethyl cellulose solution using ethanol as solvent. MgO is used as permeability modifier and anti tacking agent with suitable pigments were homogenized in ethanol and added into above dispersion. The total solid content for final dispersion was 10% as given in Table 1. The coating level recommended for seal coating depends upon whether it provides effective barrier between core tablet and enteric coated polymer, to protect the drug in core tablet from enteric polymers, as they are acidic in nature. The seal coating polymer were applied at coverage levels of 2, 2.5, and 3% weight gain. Prior to an enteric coating process, 50 of each seal coated tablets at 2% (white, uncoated), 2.5% (yellow), and 3% (orange) weight gains (150 total) were sequentially numbered with a marker pen and weighed in order to identify the precise level of enteric coat and weight gain variability among the tablets. The tablets were coated using neocota. The tablets were mixed with a sufficient quantity of readily identifiable `bulking' placebo tablet cores of the same shape, size, and mass to obtain a total 900 g pan charge. After coating tablets were cured for 60 minutes in oven at 40°C.

Enteric coating

Tablets were coated using polymeric dispersion of HPMC phthalate based enteric coating dispersion containing 100 parts HPMC phthalate (dry polymer weight) with different amounts of plasticizer (5-15parts) and talc (10-30 parts), as listed in Table 1. Diacetylated monoglyceride DAMG was dissolved in HPMC phthalate solution with acetone. Talc added as anti tacking agent was homogenized in acetone and added to above dispersion enteric coating dispersions containing a total of 10% w/w solids content was prepared. The polymer was equilibrated with the plasticizer for at least 30 min prior to application of the enteric coating dispersion. During each enteric coating process, 10-15 tablets of each seal coating level were removed after attaining 6 and 8% weight gains, without adding replacement tablets. After coating tablets were cured for 120 minutes in oven at 40°C. Curing is a necessary step to ensure the complete film formation and drug release stability.

The coating parameters for seal coating and enteric coating are given in Table 2.

Evaluation of tablets

Tablets were evaluated in triplicate using USP disintegration and dissolution test procedures for enteric coated tablets. Accordingly, tablets were tested without disks in a USP disintegration apparatus using 900 ml of simulated gastric fluid (SGF), without enzymes maintained at 37 ±0.5°C. At the end of 1 h, the tablets were visually inspected for any evidence of enteric coat failure. Thereafter, tablet disintegration was completed by transferring the tablets into 900 ml simulated intestinal fluid (SIF), without enzymes maintained at 37 ±0.5°C. Dissolution testing was carried out using a USP Apparatus 2 set at 75 rev/min. Tablets were placed into 900 ml of 0.1NHCl (37 ±0.5°C) for 2 h then transferred into 900 ml of pH 6.8, 0.05 M phosphate buffer (37 ±0.5°C). Samples of the dissolution media were taken without replacement at the end of 2 h of acid exposure and every 15 min thereafter while in the phosphate buffer for a total of 4 h. Sink conditions were maintained throughout the dissolution procedure. All samples were analyzed using UV spectroscopy at 291 nm.

RESULTS AND DISCUSSION

In the present investigation, an efficient, practical and systematic strategy of colour coding was employed to evaluate and optimize stability of enteric coated tablets, its composition and assess the variability of a given coating operation. In addition, the role of a seal coat thickness on the stability of the enteric coated tablet is examined. In this study, identical tablet cores tablets were formed, the values of bulk and tapped density of the final granulation were 0.674 g/ml and 0.890 g/ml, respectively. Carr's compressibility index of the formulation was 21%, indicating a passable flow character. Physical properties of the uncoated tablets are listed in Table 3. The friability of 20 tablets was below 0.34% and tablets were of acceptable hardness (7.80 ± 0.80 kp). Great uniformity regarding diameter (8.0 mm ± 0.03%), thickness (3.44 ± 0.05%), and weight (150.50 ± 1.50%) indicated an evenly applied coating. Tablet core with three different seal coating levels of 2% (white), 2.5% (yellow), and 3% (orange) weight gains were combined and simultaneously enteric coated. During coating no significant loss of coating dispersion was observed. Furthermore, during each enteric coating trial, a predetermined amount of tablets were removed upon attaining theoretical coverage levels of 6, 8, and 10%, thus resulting in a combined nine-fold reduction in the number of enteric coating experiments.

In Seal coating process ethyl cellulose and MgO with plasticizer were utilized in a particular concentration. The purpose of incorporating ethyl cellulose film was to provide protective barrier between core tablets and enteric coating for a stable formulation and MgO acted as a permeability modifying agent which aided in drug release through ethyl cellulose film. The plasticizers incorporated played a key role in the mechanical, adhesive and dissolution properties of films and film-coated products.

Table 1: Coating dispersion Preparation Parameters

Parameter	Seal coat Layer	Enteric Coat
Dispersion Solids Content (%)	5	10
Theoretical Weight Gain (%)	2	10-14
Coating Application Level (mg/cm^2)	2.2	11.0-15.4
Powder (g)	EC–8.0 MgO–14.2 DAMG–0.80	HPMC-P –31.4 DAMG –4.71 TALC –3.15
Solvent (g)	Ethanol –460	Acetone –440
Total Dispersion (g)	483	480
Dispersion Mixing Time (min)	30	30

Table 2: Coating Process Parameters for Sealcoat Layer and Enteric Coating

Parameter	Seal Coat Layer	Enteric Layer
Pan Volume (L)	1.3	1.3
Pan Charge (kg)	1.0	1.0
Inlet Temperature (ºC)	50	55
Outlet Temperature (ºC)	35	40
Fluid Delivery Rate (g/min)	5	8
Process Air Flow (CFM/CMH)	40/68	40/68
Pan Rotational Speed (rpm)	7	8
Atomization Air Pressure (bar)	1.3	1.3

Table 3. Physical Properties of Uncoated Tablets

Parameters	Range
Weight (mg)	150.50 ± 2.50
Breaking Force (kp)	7.80 ± 0.80
Diameter (mm)	8.0 ± 0.03
Thickness (mm)	3.44 ± 0.05
Friability (%)	0.34± 0.02
Content Uniformity (%)	101.80 ± 2.90

Table 4. Disintegration results and coating level variability of enteric coated tablets

Enteric coat formulations	Enteric coat solids, parts			Seal coat	Enteric coat	Coating level (%RSD)	Disintegration time (min:s)
	HPMC-P	DAMG	Talc				
I	100	10	20	2.5	6 8 10	6.3 7.2 9.7	9:40 14:20 15:55
II	100	5	30	2.5	6 8 10	8.5 10.1 8.0	9:10 12:30 16:00
III	100	15	10	2.5	6 8 10	11.1 4.2 6.2	12:05 14:25 17:40

Table 5. Stability data of Core, seal, enteric coated tablets

Type of Product	Impurities					
	Known		Unknown		Total	
	Initial	Stability	Initial	Stability	Initial	Stability
Core tablets	0.19%	0.28%	BQL	0.32%	0.19%	0.60%
Enteric coated (seal coat 2%)	0.23%	0.27%	0.04	0.30% & 0.60%	0.27%	1.07%
Enteric coated (seal coat 2.5%)	0.22%	0.27%	BQL	0.29% & 0.55%	0.22%	1.11%
Enteric coated (seal coat 3%)	0.18%	0.24%	BQL	0.30% & 0.38%	0.24%	0.92%

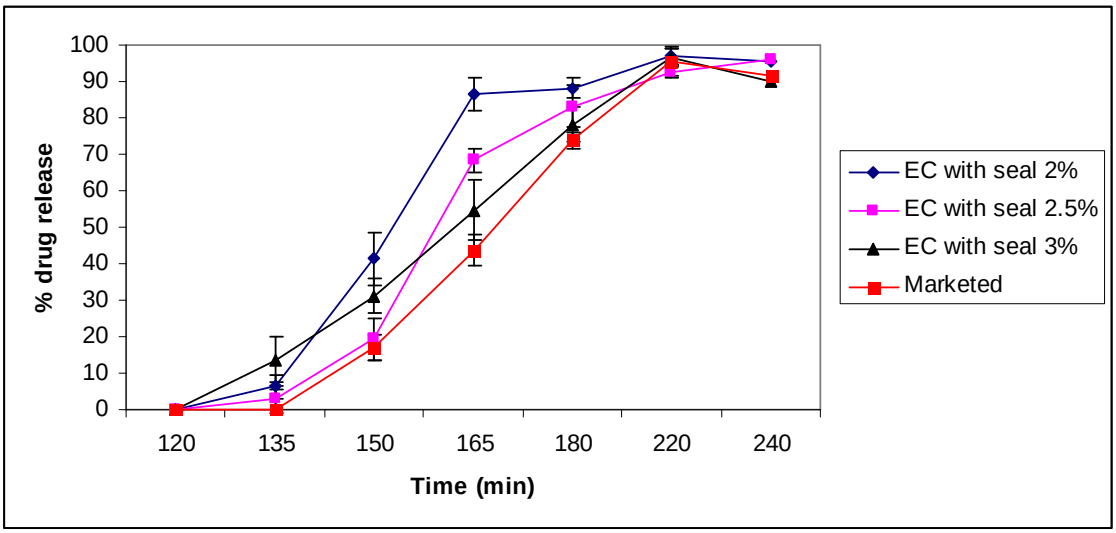

Figure 1: Dissolution profile of enteric coated tablets with different seal coat

Table 4 summarizes the enteric coating and disintegration results of seal coated tablets using formulations I-III. Functional qualities of the enteric coat during exposure to simulated gastric fluid (SGF) was employed as a tool to evaluate the disintegration analysis. Immediately after SGF exposure, each tablet was visually inspected for any evidence which would indicate improper function of the enteric coat then transferred to a phosphate buffer media with a disk placed on top of the each tablet as described in the methods section. It can be seen in Table 4 that the high levels of talc present in formulations I and III (30 parts) reduced the tablet disintegration times. The enteric films of formulation I and III probably fractured under the repeated impact of the disk on the tablet surface instead of deforming, leading to more rapid disintegration time. In addition, it was found that the disintegration time of

tablets increases as the coverage level of the enteric coat increases. For example, tablets with a 2.5% w/w seal coat that were subsequently enteric coated to 6, 8, or 10% w/w weight gain using formulation I disintegrated completely in approximately 10, 15, and 17 min, respectively.

Dissolution analysis was employed to assess the effect of the enteric coat composition and coverage levels on the release of the drug. The impact of a different seal coat on drug release was evaluated. In general, it was found that all enteric coat formulations effectively inhibit drug release during the acid exposure phase of the dissolution procedure. Dissolution analysis revealed that seal coated tablets which were enteric coated with exhibited a retardation in the release as shown in Figure 1.

The core and enteric coated tablets were subjected to stability studies at 40°C/75%RH for 1 month in Alu-Alu blister for estimating the impurity level. The impurity data of core and enteric coated tablets after stability are shown in Table 5. The stability data revealed that the 3% seal coat is required for stable formulation to keep the impurity below levels, important consideration for the accurate comparison of different seal formulations is impurity levels in the final tested tablets. However, selecting individual tablets with the precise coating level can be problematic due, in part, to and recorded prior to enteric coating, as illustrated in Fig. Quantification of the weight gain permited the selection of the most suitable labeled tablets for analytical testing. In addition, the variability of a given coating operation can be readily calculated by weight analysis of the labeled tablets. Analysis of the final tablets selected for stability studies indicate that the seal coating levels were on target (2, 2.5, 3% w/w). Overall, it was found that the 3% seal coating process is required for stable formulation.

CONCLUSION

In the present work enteric coated tablets of proton pump inhibitor were coated using polymeric dispersion of HPMC phthalate based enteric coating dispersion. The utility of seal coating was also demonstrated. The application of enteric coating coupled with seal coat was able to enhance the stability of drug.

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