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Research Article

IMPACT OF OVER COAT APPLICATION ON ENTERIC COATED DRUG PELLETS: DESIGNED TO PROTECT FROM STOMACH ENVIRONMENT

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ABSTRACT

Omeprazole is an antisecretory compounds called proton pump inhibitors. Omeprazole is an acid labile drug so enteric coated pellets were formulated using pan coating process. Two different groups of pellets were prepared, one group of pellets consists drug layer coat, enteric layer coat and another group of pellets consists of drug layer coat, enteric layer coat and over coat. The pellets were optimized with the acid resistance and drug release in simulated intestinal fluid as the process parameters. Other properties, such as moisture content, particle size, resistance to abrasion and drug content also studied. The over coat application played a vital role in acid resistance it protects the drug release in stomach environment. Three month accelerated stability studies, showed over coated pellets to be stable.

Key words: Omeprazole, pellets, proton pump inhibitors, enteric layer, acid resistance, drug release.

INTRODUCTION

Omeprazole (OMZ) belongs to a class of antisecretory compounds called proton pump inhibitors ("PPIs")[1] that are prescribed for duodenal ulcers, gastric ulcers, gastroesophageal reflux disease (GERD), severe erosive esophagitis and pathological hypersecretory conditions such as Zollinger Ellison syndrome[2]. The stability of OMZ is affected by stomach acid therefore it requires enteric coating applications[3]. Currently, there are many PPIs are available as gastro protected preparations which are necessary to protect the acid-labile PPI from acid degradation within the stomach namely; tablets, granules encapsulated in a gelatin shell and multiple unit pellet system moreover the available PPI formulations are considered as delayed release (DR) or Extended release preparations (ER)[4]. The formulations of PPIs will become an important strategy used by pharmaceutical companies, as they will be useful for the treatment of nocturnal acid secretion because of their modified release[5]. Multiparticulate drug delivery systems are predominantly suitable for achieving extended release oral formulations with low risk of dose deposition, flexibility of blending to get different release patterns, as well as reproducible and short gastric residence time[6]. Multiparticulate systems offer opportunities to improve bioavailability through the encapsulation of the API in a suitable matrix to promote solubility of the compound and can target release at the most appropriate location within the GIT for drugs with pH dependent solubility or a limited absorption window[7]. The main objective and purpose of the present research work is to formulate OMZ delayed release pellets containing an enteric layer of methacrylic acid copolymers of Eudragit L 100 and over coat layer of HPMC.

MATERIALS & METHODS

Materials

Omeprazole, Eudragit L 100 was kindly supplied as a gift sample by Yeluri formulations Hyderabad, India. HPMC, PEG6000 were gifted from Bioleo analytical laboratory Hyderabad, India. Other materials used were of analytical grade.

Methods

Preparation of delayed release OMZ pellets

Drug layering

500ml of purified water was taken in a beaker and kept for stirring under a mechanical stirrer. The binding polymer of HPMC, sucrose and Di sodium hydrogen phosphate are mixed until the materials are dissolved. Then the sodium lauryl sulfate (SLS) is added to the mixture with gentle stirring to avoid the formation of foam until it dissolves completely. Finally, OMZ is added to the mixture and gently stirring is continued until the OMZ is completely dispersed.

Enteric coating

The required quantity of Eudragit L100 was dissolved in 415.5 ml of 1:1 ratio of isopropanol and acetone on a magnetic stirrer until the entire polymer is dissolved. Then the plasticizer PEG 6000 is dissolved with agitation in this solution finally talc was added.

Over coating

Eudragit L100 is brittle in dry state. Thus, if they used as enteric polymer the film can suffer from severe damages which leads to loss of enteric properties of the dosage form. To overcome this restriction previous workers in the field of enteric coating have found it necessary to over coat with a cellulose derivatives to

prevent brittleness of the polymer and improve the stability of the product[8]. 2.25gms of HPMC and 3.87gms of PEG 6000 were dissolved in 207 ml of each of isopropanol and acetone under magnetic stirrer it would be considered as an over coating solution.

Coating process

1000 gm of non-pareil seeds (NPS) were placed in the lab model conventional coating pan (PCP-12" Prism Pharma machinery, Ahmadabad, India) and the suspension containing the OMZ is coated at a product temperature of 35-45 ^{o}C; an atomization pressure of 1.5 bar and a pump rate of 1-25ml/minute, starting with a slow rate of pumping to avoid agglomeration and increasing the rate of pumping consistent with the avoidance of the formation of agglomerates. After coating is complete the pellets are dried at a temperature of 50°C for 1hr and coated pellets were weighed to identify the weight gain. Next, 1012 gm of drug layered active pellets were placed coating pan and the enteric coating mixture was applied on to the drug layered active pellets, finally dried at a same temperature of 50°C and weighed again to know the weight gain. 1020 gm of coated pellets were divided in to two groups namely; A and A+ (50:50) 514 gm of A+ group of pellets were coated again with over coating polymer of HPMC under the same conditions. After completion of over coating process A+ pellets were weighed and identified the weight gain. The coating composition and process utilizes for coating were shown in Table 1-4.

CHARACTERIZATION AND EVALUATION OF PELLETS

Particle size and shape

The average particle size of the pellet formulations of OZ were analyzed by simple sieve analysis method[9]. The particle size of various batches of pellets was given in the table (5). The surface roughness of pellets were studied by scanning electron microscope (SEM) (JEOL JSM – 6490 LA, Japan) to characterize the surface of the pellets and the results are shown in Figure 1,2.

Loss on Drying

The moisture content (% loss on drying; % LOD) of the pellets of A & A* was determined by using Mettler Toledo Halogen Moisture Analyzer (Model: HB43, USA) where the working temperature was 105°C and the results are shown in Table 5.

Resistance to abrasion

Resistance to abrasion of the drug-layered cores or coated pellets was determined with a Roche friabilator. Briefly, 25 g of sample was mixed with 25 g of glass spheres (1.5–2 mm in diameter) and uniformly tumbled for 4 min at 25 rpm and subsequently strained through a 40-mesh sieve. Friability (%) was calculated based on the percentage of weight loss. The measurements were made in triplicate.

Initial weight - Final weight / Initial weight X 100

Assay

Standard preparation

Weigh accurately about 20 mg of OMZ working standard into 50ml volumetric flask and 25ml of 0.1N NaoH was added. The flask was shaken for 15 min and made the volume with remaining quantity of 0.1N NaoH. 3ml of this solution was withdrawn and transferred in to 100ml of fresh volumetric flask and diluted with same solution of 0.1N NaoH it would be consider as a standard solution.

Sample preparation

Enteric coated and over coated pellets were weighed accurately equivalent to 20 mg of OMZ in two 100 ml volumetric flasks separately then 0.1N NaoH solution was added and the contents were diluted to 100 ml and filtered through Whatman filter paper (No.41). 1 ml of each solution was then diluted to 50 ml of 0.1N NaoH solution separately. Absorbance of the sample solutions was recorded, at 302 nm by UV Spectrophotometer (Lambda 25, Perkin Elmer, Wellesley, (USA). Drug content was determined by following validated formula (Bioleo analytical laboratory, Hyderabad) Results of the triplicate analysis are given in Table 5.

$$\frac{\text{Sample Abs}}{\text{Std Abs}} \times \frac{W_{STD}}{50} \times \frac{3}{50} \times \frac{50}{W_{SPL}} \times \frac{}{3} \times 100$$

W_{STD} = Weight of the standard taken in (mg)
W_{SPL}. = Weight of the sample taken (mg)

Gastric resistance and in-vitro dissolution test

Dissolution testing of the pellets was performed using USP Type II Dissolution apparatus (Lab India) at 75 rpm starting with 750 ml solution at 37±0.5°C. The method of preparation of the dissolution medium was as follows. First, pellets were placed in a 0.1 M HCl solution for 2hrs and the samples were collected every 30 min up to 2hrs. Then, 250 ml of 0.05M phosphate buffer was added and the pH was adjusted with a solution of sodium hydroxide (NaOH) to pH 6.8. Samples were collected 10, 15, 30 and 45min finally the samples were analyzed at 302 nm by UV Spectrophotometer.

Stability studies

To investigate the influence of temperature and humidity onto the pellets. Pellets with enteric coating alone and pellets with over coating were placed in humidity chamber (Newtronics NW DSU 52) and exposed to a temperature of 40±2^{0}C and also a relative humidity of 75±5 % RH. The samples were removed from the humidity chamber at the end of 0, 15,30,45 and 60 days and checked for the shape, drug content, gastric resistant and in vitro dissolution studies and the results are shown in the Figures 5,6.

Scanning Electron Microscopy

The micrographs of the coated pellets were taken with a scanning electron microscopy (SEM) (S-3500N, SEM, Hitachi, Tokyo, Japan) to examine the surfaces and the morphology of the pellets. The pellets were mechanically cleaved transversely and sputtered with gold for 5min by a sputter.

RESULTS AND DISCUSSION

Omeprazole was loaded on NPS by solution layer technology. The prepared pellets were used to perform several physical parameters with in vitro dissolution study using the USP paddle method. Then 3 months stability study was performed at RT, 40°±2^{0}C, 75±5 % RH conditions. The results were mentioned on Table 6.

Physical characterization

Initially the colour of the pellet was white to off white and there were no difference in colour was found from A and A*. Hence, formulation variables have no effect on the colour of the pellets. Particle size of the pellets was in the range of 1685-1706µ determined by sieve analysis. The SEM result was revealed that, the enteric coated pellets were spherical in shape with rough surface (Figure 2). Whereas the over coated pellets were spherical in shape with smooth surface (Figure 1).

Table 1: Formula for preparation of OMZ pellets

S.No	Name of the materials (gm)	Drug layering	Enteric coating	Over coating
1	OMZ	213.85	-	-
2	HPMC	2.25	-	2.25
3	Sucrose	213.85	-	-
4	Mannitol	25.65	-	-
5	SLS	5.3	-	-
6	Eudragit L100	-	129.05	-
7	PEG 6000	-	7.74	3.87
8	Talc		64.5	
9	Isopropanol	-	415.5	207.8
10	Acetone	-	415.5	207.8
11	P.Water (ml)	500	-	-

Table 2: Parameters of coating process

S.No	Parameters	Value		
		Drug layering	Enteric coating	Over coating
1	Nozzle diameter (mm)	0.5	0.5	0.5
2	Pan Speed 12 RPM	12	12	12
3	Atomization Pressure (bar)	1.5	1.5	1.5
4	Inlet air temperature (^{o}C)	35	35	35
5	Outlet air temperature (^{o}C)	25-30	25-30	25-30
6	Spray rate(ml/min)	1-25	1-25	1-25
7	Coating time in (Min)	45	100	45

Table 3: Composition of over coating solution

S.No	Name of the materials and quantity in (gm)	
1	HPMC	2.25
2	Isopropanol	207.8
3	Acetone	207.8

Table 4: % weight gained for enteric coated and over coated pellets

S.No	Code	Wt. gained in mg (wt/wt)		Wt. gained in %
		Before	After	
1	Drug layering	1000	1012	1.2
2	Enteric coating	1012	1028	1.6
3	Over coating	514	519	0.96

Table 5: Physical properties of formulation codes of A & A*

S.No	Parameters	Formulation code (A)	Formulation code (A*)
1	Colour	Off-white	Off-white
2	Surface	Rough	Smooth
3	Particle size	1576±11	1604±19
4	LOD (%)	1.93±0.01	1.94±0.01
5	Resistance to abrasion (%)	0.792±0.00	0.751±0.00
6	Assay (%)	98.45±0.13	99.70±0.012

Table 6: Gastric resistance and in-vitro dissolution profile of A & A*

F. code	Amount of drug released in different dissolution media				
	$_{p}$H 1.2		$_{p}$H 6.8		
	Time in Min		Time in Min		
	30	60	120	150	180
A	7.21±0.02%	9.87±0.03%	16.12±0.09%	51.01±1.15%	86.15±1.13%
A*	0%	0%	4.43±0.10%	47.14±0.18 %	97.10±0.12%

Table 7: Accelerated stability study of A & A* batches

Parameters	Storage condition: 40 ± 2° C/ 75 ± 5% RH							
	Initial		1st Month		2nd Month		3rd Month	
	A	A*	A	A*	A	A*	A	A*
Colour	Off-white	Off-white	Off-white	Off-white	Off-white	Off-white	Off-white	Off-white
Surface	Rough	Smooth	Rough	Smooth	Rough	Smooth	Rough	Smooth
Drug content	98.45	99.70	98.40	99.67	98.38	99.64	98.35	99.60

Table 8: *In vitro* study of A & A* batches after accelerated stability study

F. code	Amount of drug released in different dissolution media				
	pH 1.2			pH 6.8	
	Time in Min			Time in Min	
	30	60	120	150	180
A	9.25±0.04%	30.17±0.01%	60.25±0.05%	74.00±1.18%	90.25±1.21%
A*	0%	0%	4.43±0.10%	47.14±0.18 %	98.00±0.12%

Figure 1: SEM image of over coated pellet

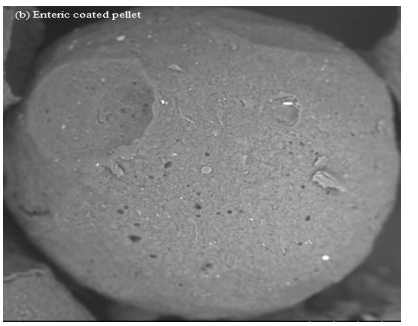

Figure 2: SEM image of enteric coated pellet

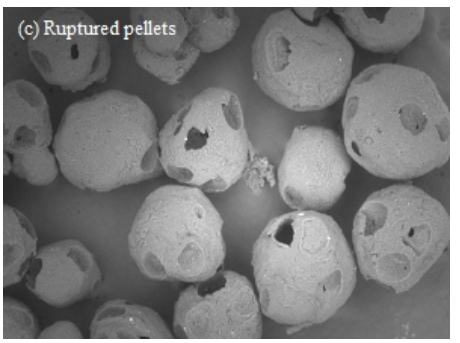

Figure 3: SEM image of enteric coated pellet after stability

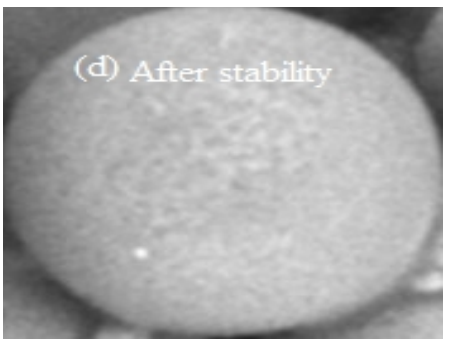

Figure 4: SEM image of over coated pellet after stability

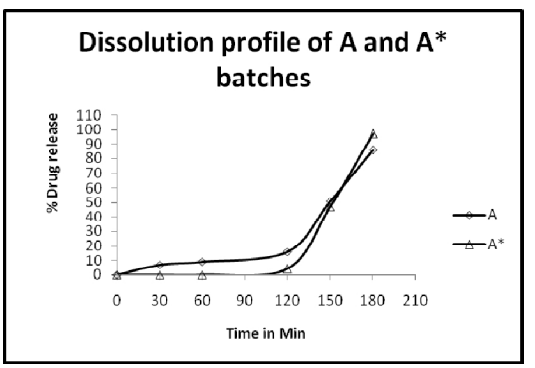

Figure 5: In-vitro dissolution Profile of A and A*

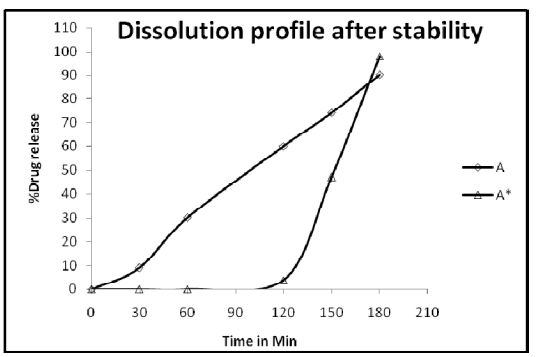

Figure 6: In-vitro dissolution Profile of A and A* at stability period

This might be owing to an over coat application of HPMC around enteric coated pellets. The friability loss of the all batches was in the range of 0.792-0.751%. The percentage of drug present in the formulations was found to be in the range of 98.45-99.70% and the loss on drying of pellets was in the range of 1.93-1.94% respectively. All the parameters evaluated for A and A* formulations of pellets were given in Table 5.

Gastric resistance and in-vitro dissolution

The effort of this work was to resist the enteric coated pellets in an acidic environment. The drug release of the pellets coated with HPMC and Eudragit L100 (A) and coated with drug and HPMC layer coat Eudragit L100 and HPMC over coat (A*) was performed for 2 h in acid media and later in PBS. At the end of 2h it was found that only 4% drug release occurred in group A* pellets whereas 16% of drug release was occurred in group A pellets. The most important properties of the extended release dosage form is its resistance against gastric conditions. It requires that no more than 10% drug release would occur after 2 h in 0.1N HCl solution[10]. The results confirmed that over coat application protect the drug in acdic conditions, moreover the over coat application provides uniform shapes Figure 1 and 4.

Stability studies

The results for 3 month stability testing revealed no significant change in color, drug content (98.4 – 99.7%). Pellets with only enteric coated alone (A) ruptured surface was observed Figure 3 moreover; more than 50% of drug were release at the end of 2h Figure 5, Table (8). Whereas Pellets with over coated (A*) was showed smooth surface Figure 4 and no significant change in drug release pattern Figure 5, Table 8.

CONCLUSION

Over coating application (HPMC) system on to the enteric coated pellets provided good acid resistance in 0.1N HCl. Those pellets exhibited spherical shape with uniform and smooth coating as evidenced by SEM photomicrographs. Based on the result, 0.96% weight gained over coated pellets provided excellent acid resistance than enteric coated pellets. From the present investigation, it can be concluded that the over coating application system can be used for many acid sensitive drugs to protect them from stomach environment.

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