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Formulation and Evaluation of Enteric Coated Pellets of Omeprazole

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Abstract

The objective of the present study is to formulate and evaluate delayed release pellets of Omeprazole comparable to the innovator product. The formulations of Omeprazole delayed release pellets of Omeprazole were developed by enteric film coating process varying the compositions of drug loading, barrier coating and enteric coating. Eudragit L 100 55 and HPMC Phthalate 55 S were used as enteric polymers. The process variables were standardized and the different batches prepared were evaluated for assay/drug content, water content, acid resistance and dissolution rate. The drug dissolution profiles of Omeprazole delayed release formulations developed were compared with that of innovators product. Based on the results formulation containing enteric coating polymer HPMC P 55 S (12%), and plasticizers diethyl phthalate, cetyl alcohol has been selected as the best formulation developed for Omeprazole delayed release pellets.

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Key words:
Omeprazole; Enteric Coating; Acid Resistance

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INTRODUCTION

The primary aim of using delayed release products is to protect the drug from gastric fluids, to reduce gastric distress caused by drugs particularly irritating to the stomach or to facilitate gastrointestinal transit for drugs that are better absorbed from intestine [1, 2]. Enteric polymers are becoming very popular due to their property of intact in the stomach, but will dissolve and release of the contents once it reaches the small intestine, their prime intension is to delay

the release of drugs, which are inactivated by the stomach contents or may cause bleeding or nausea by the irritation of gastric mucosa [3]. Omeprazole is a proton pump inhibitor used for short-term treatment of acid peptic disease, gastro esophageal reflux, gastric ulcer, duodenal ulcer, and Zollinger-Ellison syndrome and for maintenance treatment of Gastro Esophageal Reflux Disease (GERD) [4, 5]. It is highly acid labile and presents many formulation challenges and to protect it from acidic environment of the stomach an enteric coated pellets formulation was tried in the present study.

MATERIALS AND METHODS:

Chemicals/Excipients used

Chemical/Excipients	Manufactures /Supplier	Category
Omeprazole	Natco chemical division	Anti – ulcerative Gastric proton – pump inhibitor
Sugar spheres	J.R.S. Pharma(mfg), forum product Pvt Ltd (supp)	Seed pellets
PVP K30	Signet chemical corporation	Film former
HPMC E5	Signet chemical corporation	Film former
Di Basic Sodium Phosphate	Merck Ltd. (mfg), Vasco Scientifics (supp), Signet chemical corporation (supp)	Alkalizing Agent
Light Magnesium Carbonate	Merck Ltd. (mfg), Vasco Scientifics (supp), Signet chemical corporation (supp)	Alkalizing Agent
Sodium Lauryl Sulphate	Merck Ltd. (mfg), Vasco Scientifics (supp), Signet chemical corporation (supp)	Solubilising Agent
Mannitol	Roquette Ltd. (mfg) Signet chemical corporation (Supp)	Diluent
Eudragit L 100 55	Shin – Etsu (mfg)	Enteric Polymer
HPMC P55 S	Merck Ltd. (mfg), Vasco Scientifics (supp), Signet chemical corporation (supp)	Enteric Polymer
PEG 4000	Merck Ltd. (mfg), Vasco Scientifics (supp), Signet chemical corporation (supp)	Plasticizer
Tri Ethyl Citrate	Merck Ltd. (mfg), Vasco Scientifics (supp), Signet chemical corporation (supp)	Plasticizer
Di Ethyl Phthalate	Merck Ltd. (mfg), Vasco Scientifics (supp), Signet chemical corporation (supp)	Plasticizer
Cetyl Alcohol	VVF Ltd. (mfg) Sundeep Enterprises (Supp)	Plasticizer
Talc	Luzenac Pharma Ltd. (mfg) =, Signet chemical corporation (Supp)	Anti-Agglomerate
Titanium Dioxide	Merck Ltd. (mfg), Vasco Scientifics (supp), Signet chemical corporation (supp)	Opacifier
Isopropyl Alcohol	S.D Fine Chemical ltd. (mfg) Vasco Scientifics (Supp)	Solvent

Equipments Used:

Instruments/ Equipment	Model No & Manufacturer/ Supplier
Digital	Shimadzu AX- 200, Japan
Electronic balance	Oriental
HPLC	Alliance 2695, Waters India limited
Disintegration apparatus (disintegration tester USP)	ED2AL, electro lab
Dissolution test apparatus, USP XXII	Electro lab, six jars
Karl fisher titrator	Mettler Toledo DL50, Switzerland
Fluid bed dryer	Umang pharmatech Pvt Ltd

Preparation of Omeprazole Enteric Coated Pellets and Capsules:

Drug Loading

Specified quantity of non-pareil seeds were accurately weighed and dispensed. 500 ml of purified water is taken in a beaker and kept for stirring under a mechanical stirrer. Specified quantities of PVP K 30

or HPMC E 5, dibasic sodium phosphate or light magnesium carbonate and Sodium Lauryl sulphate were added slowly to form a uniform suspension. Specified quantity of Omeprazole is added and stirring is continued for 30 mins. Non pareil seeds were coated with the prepared drug suspension using Fluidized Bed Coater (FBC). Dried pellets were collected and coating efficiency was calculated.

Barrier Coating Stage

500 ml of purified water is taken in a beaker and kept for stirring under a mechanical stirrer. Specified quantities of PVP K 30 or HPMC E 5, dibasic sodium phosphate or light magnesium carbonate and mannitol were added slowly to form a uniform suspension. Drug loaded pellets were coated with the above suspension using Fluidized Bed Coater (FBC). Dried pellets were collected and coating efficiency was calculated.

Enteric Coating Stage:

300 ml of Iso propyl and 900 ml of Acetone were taken in a beaker and kept for stirring under a mechanical stirrer. Specified quantities of enteric coating polymer, plasticizers (Eudragit L 100 55, Tri ethyl citrate, PEG 4000 or HPMC P 55 S, Di Ethyl Phthalate Cetyl Alcohol), Titanium dioxide and Talc (previously passed through 200#) were added slowly to form a uniform suspension. Stirring was continued for 30 mins. Barrier coated pellets were coated with the above suspension using Fluidized Bed Coater (FBC). Dried pellets were collected and coating efficiency was calculated.

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Sugar spheres (18/20#)	460	460	460	460	460	460	460	460	460	460
DRUG LOADING										
Omeprazole	115	115	115	115	115	115	115	115	115	115
PVP K-30	8	16	16	16	-	16	16	16	16	16
HPMC E-5	-	-	-	-	16	-	-	-	-	-
Dibasic Sodium phosphate	10	10	10	-	-	-	-	-	-	-
Light Magnesium Carbonate	-	-	-	10	10	10	10	10	10	10
Sodium Lauryl Sulphate	1.7	1.7	1.7	1.7	1.7	2.7	2.7	2.7	2.7	2.7
Water	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
BARRIER COATING										
PVP k-30	30	30	30	30	-	30	30	30	30	30
HPMC e – 5	-	-	-	-	30	-	-	-	-	-
Dibasic Sodium Phosphate	10	10	20	-	-	-	-	-	-	-
Light Magnesium Carbonate	-	-	-	20	20	20	20.	20	20	20
Mannitol	218.3	210.3	200.3	200.3	200.3	199.3	179.3	219.3	199.3	179.3
Water	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
ENTERIC COATING										
Eudragit L 100 55	120	120	120	120	120	120	140	-	-	-
PEG 4000	12	12	12	12	12	12	12	-	-	-
Tri Ethy1 Citrate	3	3	3	3	3	3	3	-	-	-
HPMC P 55 S	-	-	-	-	-	-	-	100	120	140
Di Ethyl Phthalate	-	-	-	-	-	-	-	12	12	12
Cetyl Alcohol	-	-	-	-	-	-	-	3	3	3
Titanium Dioxide	4	4	4	4	4	4	4	4	4	4
Talc	8	8	8	8	8	8	8	8	8	8
Iso Propyl Alcohol	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Acetone	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S

Table No 1 Formula for preparation of pellets

Evaluation of Pellets

Angle of Repose:

Angle of repose is used to determine the flow properties of powders, pellets or granules. The method to find angle of repose is to pour the powder on a conical heap on a level, flat surface and measure the included angle with the horizontal.

$\tan \theta = h/r$

Where, h = height of the heap,

r = Radius of the heap.

Bulk Density

Bulk density of the coated pellets was determined by pouring pellets into a graduated cylinder via a large funnel and measuring the volume and weight.

$$\text{Bulk density} = \frac{\text{weight of granules}}{\text{Bulk volume of granules}}$$

Tapped Density:

Tapped density was determined by placing a graduated cylinder containing a known mass of granules and mechanical tapper apparatus, which was operated for a fixed number of taps until the powder bed volume has reached a minimum volume. Using the weight of the drug in the cylinder and this minimum volume, the taped density may be computed.

$$\text{Tapped density} = \frac{\text{weight of granules}}{\text{Tapped volume of granules}}$$

Carr's Index:

Carr's index is measured using the values of bulk density and tapped density. The following equation is used to find the Carr's index.

$$\mathbf{CI} = \frac{\mathbf{(TD-BD)}}{\mathbf{TD}} \mathbf{\times 100}$$

Where, TD = Tapped density

BD = Bulk density

Moisture Content (Or) Water by KF:

Take around 50ml of methanol in titration vessel of Karl Fischer titrator and titrate with Karl Fischer reagent to end point. In a dry mortar grind the pellets to fine powder .Weigh accurately about 0.5 g of the sample, transfer quickly to the titration vessel, stir to dissolve and titrate with Karl Fischer reagent to end point.

Calculation:

$$\textbf{Moisture content} = \frac{\mathbf{V \times F \times 100}}{\textbf{Weight of Sample in Mg}}$$

Where,

F= factor of Karl Fischer reagent.

V= volume in ml of Karl Fischer reagent consumed for sample titration.

Scanning Electron Microscope (SEM analysis):

SEM analysis is used to study the morphology of prepared pellets by Hitachi (Model: S-3400 N, Japan).

FTIR analysis

FTIR spectra of drug and optimized formulation were obtained. Sample about 5 mg was mixed thoroughly with 100 mg potassium bromide IR powder and compacted under vacuum at a pressure of about 12 Psi for 3 minutes. The resultant disc was mounted in holder in IR spectrophotometer and the IR spectrum was recorded from 4000 cm-1 to 625 cm-1 in a scan time of 12 minutes. The resultant spectra were compared for any spectral changes.

Assay:

Standard preparation:

Weigh accurately about 75 mg of omeprazole working standard into 100 ml of volumetric flask add 50 ml of Methanol sonicated and shake well and diluted to volume with Methanol, mixed well. Pipetted out 2 ml of this solution in to 100 ml volumetric flask diluted to volume with DM water and mix well.

Sample Preparation:

Weigh accurately about 75 mg drug equivalent pellets in a 100 ml volumetric flask, add 50 ml of Methanol, sonicated for 10 minutes. Cool and dilute to volume with Methanol. Filter the solution through what man filter paper. Then take 2 ml of filtrate into 100 ml volumetric flask. And dilute to volume with DM water.

Procedure:

Scan the solution of both standard and sample preparation against Blank preparation between 200 nm and 400 nm measure the absorbance for both standard and sample at 240 nm.

Calculation:

$$A = \frac{A_T}{A_S} \times \frac{W_S}{100} \times \frac{2}{100} \times \frac{100}{W_T} \times \frac{100}{2} \times P$$

A_T =Absorbance of the sample preparation.

P = Purity of the standard

A_S = Absorbance of the standard preparation.

W_S = Weight of the standard taken in mg

W_T = Weight of the sample taken in mg

***In-vitro* Dissolution:**

Apparatus: USP APPARATUS II

Medium: 0.1N HCl up to 1st two hours, pH 1.2

Phosphate buffer (pH 6.8 for) remaining hours

Sampling interval: 15, 30, 45 & 60 minutes.

Rpm: 100

Temperature : 37°C± 0.5°C

Procedure: Weigh and transfer the pellets equivalent to 100 mg of omeprazole individually in each of the 6 dissolution flasks, containing 900ml of 0.1N HCl. Previously adjust the temperature to37°C± 0.5°C. Collect the samples for first 2hrs and later replace the medium with phosphate buffer 6.8 and collect the samples for remaining 20hrs from a zone midway between the surface of the medium and the top of the rotating blade and not less than 1cm from the vessel wall and filter through 0.45µ membrane filter by discarding the first 5ml.The absorbance is measured at 271nm by using UV-spectrophotometer.

Stability Studies:

Selected formulation is subjected to stability studies as per ICH guidelines at 30°C/ 65 % RH and 40°C / 75% RH for 6 months. Sample are taken and analyzed at time interval.

RESULTS AND DISCUSSION

Formulation Development

In first trial (F1), improper coated sugar spheres were observed during drug loading, and would have been due to insufficient amount of binder. Sufficient amount of binder used in next trial. In trail 2 (F2), the binder concentration was increased in drug loading stage but the drug release was lesser than the innovator. So, to get better release, an attempt made with increasing amount of alkalizing agent dibasic sodium phosphate in barrier coating stage (F4). The drug release was observed to be lesser than the innovator. To get better release, strong alkalizing agent i.e. light magnesium carbonate was used (F4). The drug release was increased when compared to previous formulation but however the release was lower than the innovator. So, to get better release, another binder HPMC E 5 was used (F5). The release was almost same but still it was lower than the innovator. Another attempt, made with previously used binder i.e. PVP K 30 and also increased the concentration of solubilizing agent i.e. sodium lauryl sulphate (F6). The drug release was increased and did not match with the innovator, made another attempt with increased concentration of enteric polymer i.e. Eudragit L 100 55 (F7). The drug release in buffer media was matched with the innovator but in acidic media it did not match with the innovator. Another attempt made by changing the enteric polymer (F8). The drug release was not match with the innovator. The reason may be of enteric polymer, increased concentration of enteric polymer (F9). The drug release was as that of the innovator. This batch considered as an optimized batch however an attempt was made to know whether there is any change on increasing the enteric polymer concentration (F10). The drug release did not match with the innovator. It may be due to high concentration of enteric polymer. So the previous formulation was considered as an optimized formulation.

Evaluation Parameters

Result of angle of repose of powder showed the poor flow properties. Angle of repose of the different formulations were compared with bulk drug, omeprazole, which shows that after pellets formulation flow properties were excellent. Assay of Omeprazole was carried out using UV spectrophotemeter and it was found to be with in limits. The weight variation test for capsules was done results were in the prescribed limits. Results were shown in table no 2.

Parameters	Omeprazole	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Angle of repose	38.23	24.21	24.48	25.06	25.04	24.37	25.06	26.23	24.23	23.52	25.12
Bulk Density	0.4065	0.923	0.937	0.921	0.934	0.915	0.952	0.947	0.928	0.938	0.921
Tapped density	0.5813	0.989	1.004	0.988	0.991	1.032	1.012	0.996	1.031	1.037	0.989
Hausner's ration	1.43	1.07	1.07	1.07	1.06	1.04	1.04	1.08	1.06	1.04	1.05
Carr's Index		5.47	5.71	4.38	4.96	5.21	5.47	5.39	5.01	5.11	4.96
Moister content	0.19	1.88	1.86	1.89	1.92	1.89	1.91	1.91	1.95	1.86	1.94
Assay	99.91	98.12	98.23	98.87	99.23	99.12	98.56	98.39	99.12	99.85	99.12

Table No 2 Results of evaluation parameters

In vitro dissolutions studies

In vitro dissolution studies for first two hours in acidic medium had revealed the acid resistance capacity of pellets. Followed by dissolution behavior of pellets in basic medium (phosphate pH 7.4) revealed the *in vitro* drug release characteristics, F9 has shown the similar release characteristics as innovator. Result shown in fig no 1 and table no 3

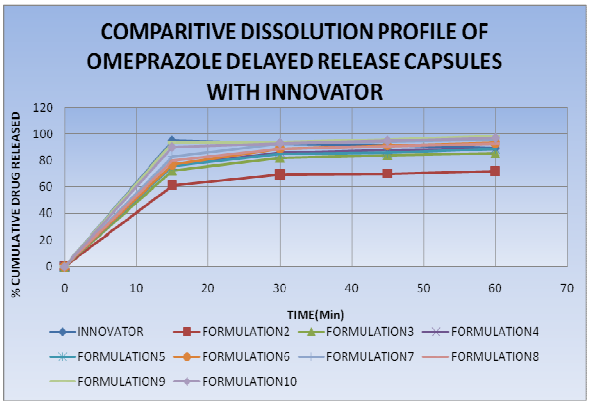

Fig No 1 dissolution behavior of different formulations

	% Drug Released										
	Innovator	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Acid Stage 0.1 NHCL,100 rpm, Paddle, (As per U.S.P)											
120 Min	5.3	-	3.2	3.1	3.6	3.4	1.6	7.8	3.8	2.1	5.3
Buffer Stage pH 6.8 Phosphate Buffer, 900 ml, rpm-100, Paddle (As per U.S.P)											
15 Min	89.6		61.3	72.7	76.7	75.9	76.9	83.2	80.0	94.0	90.3
30 Min	95.0	-	69.4	82. 0	86.1	85.0	89.2	92.8	89.0	94.3	93.2
45 Min	93.0	-	72.0	83.9	87.8	86.0	91.6	94.3	91.0	96.0	95.0
60 Min	92.0	-	70.1	85.4	89.0	89.0	93.5	96.0	93.1	98.6	97.0

Table No 3 Results of dissolution studies

Scanning Electronic Microscopy

Microscopy figures of optimized formulation (F9), the coated pellets appeared to exist as spherical discrete units whilst the surface morphology of the pellets was compact, continuous and uniform and is porous in nature. SEM demonstrated the spherical nature of the pellets. The average size of the pellets was found to be 1085±5 µm.

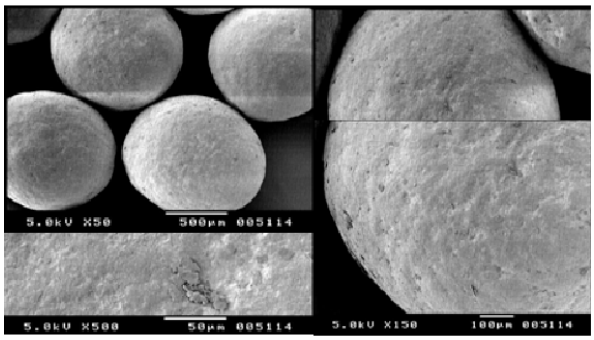

Fig No 2 Scanning Electron Microscopy figures of optimized formulation

FTIR

The FT-IR spectrum of the formulation showed the presence of the drug in its active form without alteration of its chemical structure.

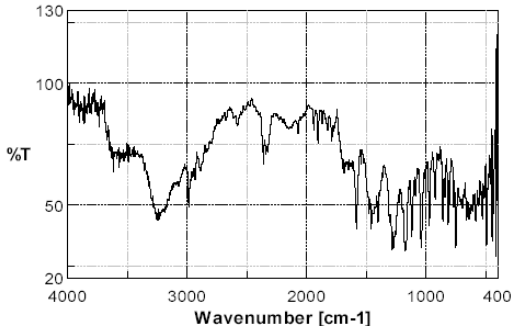

Fig No 3 FTIR spectra of Omeprazole

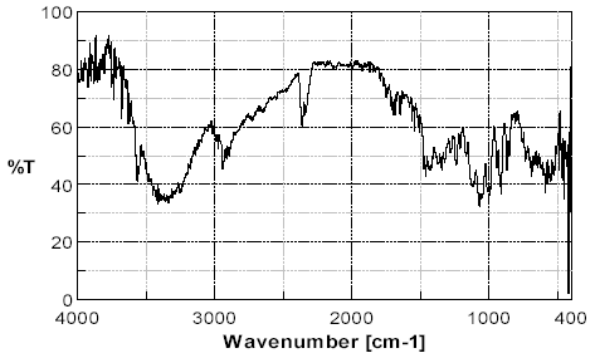

Fig No 4 FTIR spectra of F9 formulation

Stability Studies

There were no changes in appearances and percentage drug content of pellets stored at different temperature for drug remaining *vs.* time at 25°C/60% RH, 30°C/65% RH and 40°C/75% RH. All the parameters were within the limit after 90 days. Result were shown in table no.

S. No	Test	Result					
		Storage condition					
		Initial Analysis	40 0 C/75% RH			30 0 C/65% RH	250 C/60% RH
			1st Month	2nd Month	3rd Month	3rd Month	3rd Month
2	Assay	99.85%	99.82%	99.76%	99.75%	99.83%	99.80%
3	Dissolution	Acid stage : 2.1% Buffer stage :98.6%	Acid stage:2.2% Buffer stage :98.5%	Acid stage:2.3% Buffer stage:98.1%	Acid stage:2.3% Buffer stage:98.2%	Acid stage :2.3% Buffer Stage :98.5%	Acid stage :2.3% Buffer stage : 98.5%
3	Water content	1.86 %w/w	1.90%w/w	1.93%w/w	1.98%w/w	1.92%w/w	1.96%w/w

Table No 4 Results of stability studies

CONCLUSION

The objective of the present study was to formulate and evaluate delayed release capsules comparable to the innovator product. The formulations of Omeprazole delayed release capsules of Omeprazole were developed by enteric film coating process varying the compositions of drug loading, barrier coating and enteric coating using Eudragit L 100 55 and HPMC Phthalate 55 S as enteric polymers. The formulation F9 has shown similar drug release characteristics as innovator, it was selected as the optimized formulation and accelerated stability studies were done, formulation was stable for 3 months under accelerated conditions.

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