ISSN 2249-3875

International Journal of Pharmaceutical Erudition

Research Paper

Enteric Coating Formulation Design of Omeprazole Tablets

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The effect of seal coat polymer, concentration of seal coat polymer, and enteric coat polymer on the permeability simulated gastric juice has been evaluated. There were significant differences between each polymer, particularly with regard to acid resistance. Suitable formulations of each polymer were used to enteric coat 20 mg Omeprazole tablets, which were subsequently subjected to both the Disintegration Test for Enteric Coated Tablets and a dissolution procedure to monitor the release of drug in simulated gastric juice and simulated intestinal fluid. Both polymers demonstrated their suitability for producing enteric coatings. However, Eudragit L30D55 yielded a faster release of Omeprazole in simulated intestinal fluid than did Hypromellose phthalate. Controlled and localized release of drugs in the intestine can be achieved by enteric coating. The design of enteric-coated tablets has so far remained empirical, in part because of the lack of a quantitative description of the drug release kinetics. Explicit relationships between the release rates and factors (seal coat polymer and enteric coat polymer) are derived.

Keywords: Omeprazole, HPMC phthalate HP55, pellets, Eudragit L30D55

INTRODUCTION

Enteric coating of drug tablets is used to prevent the release of drugs in the stomach, either to reduce the risk of gastrointestinal side effects or to maintain the stability of the drugs which are subject to degradation in the gastric environment (Porter S.C. et. al. 1982). An important example of enteric coating of aspirin to protect the gastric mucosa from corrosion. This application is particularly important for those on chronic aspirin medication e.g. for arthritic patients. Erythromycin, Pancreatin, Potassium chloride and diethylstilbestrol are other examples of drugs that have been formulated as enteric coated products. (Chambliss W.G.1983)

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An enteric coated dosage form should not allow significant release of the drug in the stomach yet provide rapid dissolution of the polymer layer and complete release of the drug at the desired site in the intestine. Most polymers used for enteric coating are polyacids, whose solubility in aqueous media is strongly pH dependent [1-3].

Hypromellose phthalate, Cellulose acetate phthalate, polyvinyl acetate phthalate, and methacrylic acid / methacrylate copolymers are often used for enteric coating. These polymers are weak acids containing carboxyl groups in a substantial proportion of their monomeric units. Rapid dissolution of these polymers requires pH values that are much higher than that which are normally present in the stomach.

However when hydrate these polymers are permeable to the confined drug even at pH lower than the dissolution pH. The important factors in the design of enteric coated dosage forms include the choice of appropriate polymer [4, 5].

The standard basis of determining the efficacy of the enteric coated tablets is the 1985 USP modified disintegration tests (USP Convention United States Pharmacopoeia). This requires the product remains physically intact for specified period when exposed to simulated gastric fluid (SGF) and yet disintegrate readily in the simulated intestinal fluid (SIF) [6-7]. Drug release has been modeled for a variety of dosage forms and conditions for the purposes of determining the factors that affect the drug release.

Chemically, Omeprazole is a substituted benzimidazole, 5-methoxy-2-[[(4-methoxy 3,5-dimethyl-2-pyridinyl) methyl] sulfinyl] -1H-benzimidazole, a compound that inhibits gastric acid secretion. Omeprazole is a proton pump inhibitor used in the treatment of dyspepsia, peptic ulcer disease, gastro esophageal reflux disease, laryngopharyngeal reflux, and Zollinger–Ellison syndrome. Omeprazole is a white to off-white crystalline powder. The stability of Omeprazole is a function of pH; it is rapidly degraded in acid media, but has acceptable stability under alkaline conditions [8].

MATERIALS AND METHODS

Omeprazole USP (Yashica pharmaceuticals Pvt. Ltd.), Sodium starch glycollate(Roquette), Lactose mono-hydrate (DMV international), Sodium Lauryl Sulfate, NF (Stepan Company Northfield), Hypromellose, NF (Shin – Etsu Chemicals Co. Ltd. Tokyo Japan), Talc, USP (Luzenac America Plainfield, NJ), Hypromellose Phthalate, NF (Shin – Etsu Chemicals Co. Ltd.Tokyo, Japan), Magnesium hydroxide(S.V.Enterprises, Mumbai), Triacetine (Sigmachem Corporation), Magnesium stearate (Amishi Drugs & Chemicals, Ahmedabad), Polyviny alcohol(BASF), Eudragit L30D55(Evonik).

All organic solvents were of high performance liquid chromatography (HPLC) grade. All other chemicals were of reagent grade.

Manufacture of Omeprazole Enteric Coated Tablets [9-14]

(I) Dispensing

Weigh accurately require quantity of Omeprazole, Lactose , Sodium starch glycolate , Sodium Lauryl Sulfate, Magnesium hydroxide.

(II) Sifting

Passed the Omeprazole from 20#, Lactose from 40#, Magnesium hydroxide from 40#, Sodium starch glycolate from 40#,

Table no.1: Parameters of Rapid Mixer Granulator for wet granulation

For Immediate Release part			
Process	Time	Speed of Impeller	Speed of Chopper
Dry mixing	5 minute	150 rpm	Off
Binder addition	2 minute	150 rpm	Off
Kneading	1 minute	150 rpm	1500 rpm

Sodium Lauryl Sulfate from 40# sieve.

(III) Granulation

Wet granulation method was used for granulation of Immediate Release part. For wet granulation prepare a binding solution by dissolving HPC in water and stir binder solution for 10 minutes. Granulation was done in Rapid Mixer Granulator (RMG). Parameters of Rapid Mixer Granulator for wet granulation of Immediate Release part was shown in Table no.1

(IV) Drying

Dry the granules of Immediate Release part in Fluidized Bed Dryer (FBD) at 40^{o}C temperature till Loss on Drying (LOD) lie between 1.0-1.5%.

(V) Sizing

Pass the dried granules of both Immediate Release part from by using sieve no.#20.

(VI) Lubrication

Pre lubricate the granules with Sodium starch glycolate (40#) in cage blander at 18 rpm for 10 minute. Finally lubricate above granules with Talc (60#) Magnesium stearate (60#) at 18 rpm for 3 minute. Now blend was ready for compression. Measure the Angle of repose, Bulk density, Tapped density, Carr's Index and Hausner's Ratio of both Immediate Release and Sustain Release part of granules.

(VII) Compression

Compression was done 8 Station D-tooling machine using 9.00 mm, round shape, SC (sub convex), PL/PL (plain on both side) punch set.

(VIII) Seal coating

Prepare sub coating solution using HPMC or PVA in Purified water. Coat the uncoated tablets with the enteric coating suspension to achieve required weight gain.

(IX) Enteric coating suspension preparation

Prepare enteric coating suspension using HPMC Phthalate, Triacetine, and Talc in Acetone IPA mixture or Prepare enteric coating suspension using Eudragit L30D55, Triacetine, and Talc in Water.

(X) Enteric coating

Coat the uncoated tablets with the enteric coating suspension to achieve required weight gain.

Characterization of tablet Blend [15-17]

Determination of Particle Size (Randall CS et al., 1995)

Particle size of drug was determined by Malvern particle size analyzer which based

Table no.2: Influence of different seal coating polymers on enteric coated tablets

Sr. No.	Ingredients	Qty (g/ml)	F001	F002
	Dry mix			
1	Omeprazole	G	200	200
2	Lactose hydrate	G	928.6	928.6
3	Sodium starch glycolate	G	40	40
4	Sodium lauryl sulphate	G	15	15
5	Magnesium hydroxide	G	60	60
	Binding			
6	Hydroxypropyl cellulose	G	10	10
7	Purified water	Ml	q.s	q.s
	Lubrication			
8	Sodium starch glycolate	G	40	40
9	Talc	G	13.2	13.2
10	Magnesium stearate	G	13.2	13.2
	Seal Coating			
11	PVA	G	16	
12	HPMC E15			16
	Purified water	Ml	q.s	q.s
			1336	1336

Table no.3: Influence of different enteric coating polymers at different level on enteric coated tablets

Sr. No.	Ingredients		F003	F004	F005	F006	F007
	Dry mix						
1	Omeprazole	g	200	200	200	200	200
2	Lactose monohydrate	g	928.6	928.6	928.6	928.6	928.6
3	Sodium starch glycolate	g	40	40	40	40	40
4	Sodium lauryl sulphate	g	15	15	15	15	15
5	Magnesium hydroxide	g	60	60	60	60	60
	Binding						
6	Hydroxypropyl cellulose	g	10	10	10	10	10
7	Purified water	ml	q.s	q.s	q.s	q.s	q.s
	Lubrication						
8	Sodium starch glycolate	g	40	40	40	40	40
9	Talc	g	13.2	13.2	13.2	13.2	13.2
10	Magnesium stearate	g	13.2	13.2	13.2	13.2	13.2
	Seal Coating						
11	HPMC E15	g	16	30	30	30	30
	Purified water	ml	q.s	q.s	q.s	q.s	q.s
	Enteric Coating						
12.	Eudragit L30D55				55.72		
12.	HPMC Phthalate	g	55.72	55.72		55.72	70.00
13.	Triacetine	g	3.94	3.94	3.94	3.94	3.94
14.	Talc	g	3.94	3.94	3.94	3.94	3.94
15.	Iso propyl alcohol	ml	q.s	q.s	q.s	q.s	q.s.
16.	Acetone	ml	q.s	q.s	q.s	q.s	q.s.
	Total		**1399.6**	**1413.6**	**1413.6**	**1413.6**	**1427.88**

Table no.4: Final formula of Omeprazole DR tablets

Sr. No.	Ingredients		F007
	Dry mix		
1	Omeprazole	mg	20.0
2	Lactose hydrate	mg	92.86
3	Sodium starch glycolate	mg	4.0
4	Sodium lauryl sulphate	mg	1.5
5	Magnesium hydroxide	mg	6.0
	Binding		
6	Hydroxypropyl cellulose	mg	1.0
7	Purified water	ml	q.s
	Lubrication		
8	Sodium starch glycolate	mg	4.0
9	Talc	mg	1.32
10	Magnesium stearate	mg	1.32
	Seal Coating		
11	HPMC E15	mg	3.0
	Purified water	ml	q.s
	Enteric Coating		
12.	HPMC Phthalate	mg	7.0
13.	Triacetine	mg	0.394
14.	Talc	mg	0.394
15.	Iso propyl alcohol	ml	q.s
16.	Acetone	ml	q.s
	Total		**142.79**

on principle of light scattering.

The particles were analyzed by two methods

- Dry method
- Wet method

Determination of Bulk Density

Weigh accurately 25 g of drug, which was previously passed through 20 # sieve and transfer in 100 ml graduated cylinder. Carefully level the powder without compacting, and read unsettled apparent volume (V0). Calculate apparent bulk density in g/ml by following formula,

Determination of Tapped Density

Weigh accurately 25 g of drug, which was previously passed through 20 # sieve and transfer in 100 mL graduated cylinder. Then mechanically tap cylinder containing sample by raising cylinder and allowing it to drop under its own weight using mechanically tapped density tester that provides a fixed drop of 14± 2 mm at a nominal rate of 300 drops per minute. Tap the cylinder for 100 times initially and measure tapped volume (V1) to the nearest graduated units, repeat the tapping an additional 200 times and measure tapped volume (V2) to the nearest graduated units.

Carr's Compressibility Index &Hausner's Ratio

The compressibility index and Hausner's

Table no.5: Characterization of tablet blend

Batch No.	Appearance	Loose Bulk Density (g/ml)	Tapped Bulk Density (g/ml)	Angle of Repose (θ)	Sieve analysis > 40#	Sieve analysis <40#
F007	++	0.449	0.555	23.66	89.5	10.5

++= off white to yellow coloured blend

Table no.6: Evaluation of uncoated tablet

B.No.	Appearance	Avg. Weight (mg)	Thickness (mm)	Friability (%)	Hardness (kg/cm^2)
F007	+++	132.0	2.54	0.059	5-6

+++= off white to yellow colored uncoated tablets

ratio were measured of propensity of powder to be compressed. Carr's compressibility index and Hausner's ratio can be calculated as follows

$$\text{Carr s Index} = \frac{\text{Tapped density} - \text{Bulk densi}}{\text{Tapped density}}$$

$$\text{Hausner s Ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Determination of angle of repose

The frictional force in powder can be measured by angle of repose. Angle of repose was calculated by fixed funnel method. Angle of repose can be calculated by using following formula

$$\text{Tan} = \frac{h}{r}$$

Where, h = Height of heap in cm

r = Radius of heap in cm

Evaluation of Tablets

Appearance

The general appearance and elegance of tablet was identified visually, which include tablet size, shape, color, presence or absence of an odor, taste, surface texture etc.

Weight Variation

Twenty tablets were weighed individually and average weight was determined. The individual tablet weight was compared with average tablet weight. The tablet weight for Immediate release tablet was 135 mg and the maximum percent difference allowed is 5% i.e. ± 15.00 mg.

Thickness

Tablet was selected at random from individual formulations and thickness was measured by using vernier caliper scale, which permits accurate measurement. Tablet thickness should be controlled within a ± 0.5% variation of standard value.

Hardness

Uncoated Tablet was selected at random from individual formulations and hardness was measured using Scheluniger hardness tester.

Friability Test

Friability of uncoated Tablets was determined using Friability Tester made by Electrolab. Friability for uncoated tablets

was determined at 100 revolutions. Friability of tablets should be less than 1%.

Disintegration time

Disintegration testing of coated dosage forms was carried out in the six tablet basket rack USP disintegration apparatus. One tablet was introduced into each tube of the basket rack assembly of the disintegration apparatus without disc. The assembly was positioned in the beaker containing 0.1N HCl (pH 1.2) maintained at 37±2°C and operated the apparatus for 2 hours. After 2 hours 0.1N HCl was replaced with phosphate buffer 8.0 pH. A disc was added to each tube and operated for further 60 minutes. The disintegration time of each tablet was recorded.

Dissolution test

The tablets were evaluated for in vitro drug release was carried out using USP dissolution apparatus. The following conditions were applied.

Specification:

Acid stage:

Not more than 10 % of the labeled amount of Omeprazole is dissolved in 2 hours.

Buffer stage

Not less than 75 % (Q) of the labeled amount of Omeprazole is dissolved in 45 minutes.

For DR Tablet

Stage A : Acid stage

Medium : 0.1 N Hydrochloric acid; 900 mL

Apparatus : USP I (Basket)

RPM : 100

Temperature : 37°C ± 0.5°C

Time : 2 hours

Stage B : Buffer stage

Note: The standard preparation and sample preparation should be analyzed immediately without delay.

Medium : 0.05 M pH 6.8 Phosphate buffer; 900 mL

Apparatus : USP I (Basket)

RPM : 100

Time : 45 minutes

Temperature : 37°C ± 0.5°C

Omeprazole DR tablets Stability Study[18-20]

The stability studies were performed on the most promising tablet formulation i.e.

007. The study has done to know the effect of aging and temperature on the in-vitro drug release. The study was performed by keeping the prepared tablets in air tight high density HDPE bottle pack at 40° C and relative humidity of 75% according to ICH guidelines.

RESULTS AND DISCUSSION

Characterization of tablet blend

The results of evaluation of powder blend formulations F007 mentioned in table no.7, suggests that it has fair to passable

Table no.7: Characterization of DR tablet

B.No	Appearance	Water content	Thickness	D.T.	Avg. Wt. (mg)	Dissolution Acid stage	Dissolution Buffer stage	Assay (%)
F007	$$$	0.99	2.50	C	141.35	C	98.7	99.7

C=Complies, $$$=Off white to pale brown tablets

compression property and moderate flow property (Damodaran et al., 2010).

Evaluation of uncoated tablet

The core tablets were evaluated for various parameters and their result are mentioned in table no.8. Weight variation data of all trial batches indicated that they were in range of official standards and no significant difference between individual weights of tablets from the average value. Hardness of all the tablets was kept between 5-8 kg. Friability test for both wet granulation and direct compression was in the range of less than 1%. All the batches pass in content uniformity test as per official requirement. The assay results showed that the percentage drug content was found to be in the range of 92.13% to99.74% for all the seven formulations, which is acceptable. (Singh et al., 2009).

Seal coating trial was taken on core tablets with two different polymers (F001, F002). PVA in seal coating gave sticky coating, whereas HPMC gave good seal coating. Hence HPMC for seal coat finalized.

Further for optimization of seal coat

Table no.8: Omeprazole DR tablets Stability Study

Parameters	Specifications	F007 (0M)	F007/40°C/ 75%RH/ 3M
Appearance	Off white to pale brown tablets	Off white to pale brown tablets	Off white to pale brown tablets
Dissolution Acid stage	Stage A : after 2 hrs, the average of the 6 units not more than 10% dissolved	complies	complies
Dissolution Buffer Stage	Stage A : Not less than 80% of the labelled amount of Omeprazole is dissolved in 45 mins	98.7%	89.3%
Assay	90% to 110% of the labelled amount of Omeprazole USP	99.7%	94.2%
Impurities	Omeprazole related compounds F and G (%) NMT 0.5%	BQL	0.09%
	5-Methoxy-1H-benzimidazole-2-thiol (%) NMT 0.5%	BQL	0.09%
	Any other individual Impurity (%) NMT 0.5%	0.05%	0.4%
	Total Impurties (%) NMT 2.0%	0.05%	1.2%

percentage on core tablet (F003, F004); two different percentage of coating solution was applied on core tablets. The weight gain was found to be in the range of 15 to 30mg. Seal coated tablet containing 15mg seal coat were devoid of full coating. It was partially coated with seal coating solution. Core tablet containing 30mg seal coat were fully coated with barrier coating without any kind of coating defect. So, 30mg/tablet seal coating on core tablet was optimized concentration of seal coating (Crotts and Sheth, 2000; Nair et al., 2010). Dissolution in 0.1N HCl, 900ml, 2hrs, drug release with 15mg and 30mg seal coat was 5% and 1.0% respectively. Hence 30mg/ tablet HPMC seal coat was finalized.

Enteric coating was performed using Eudragit L30D55 and HPMC Phthalate 55 was used in batches F005, F006 respectively. Solvent Water for Eudragit and IPA:Acetone

HPMC Phthalate 55 for was used in 60:40 ratio to prepare coating solution. 4.12% enteric coating was performed in all batches. Enteric coated tablet of all batches pass in weight gain test. Enteric coated tablet of batch F005 failed in official disintegration test, while other batch F006 tablets passed in this test. The assay result of all the trial batches of enteric coated tablets was within official limit. Enteric coated tablet of F005 shows less resistance in 0.1N HCl it may be because it contains less amount of Eudragit L30D55 also it fail in disintegration test.

Characterization of DR tablet

Enteric coated tablets of optimized batch F007 were passed in weight variation, Water content , D.T., thickness as per official requirement as depicted in table. The % drug content was obtained to be 99.7% which is acceptable under the limits. The cumulative % drug release after 165 minutes was found to be 98.7%. From the results of comparative study of dissolution profile of final batch with reference product, it was concluded that final formulation F007.

Omeprazole DR tablets Stability Study

Formulation (F007) was put on stability as below mentioned condition.

F007 at40°C ± 2°C / 75% RH ± 5 % RH,Packaging: HDPE bottle pack.

From the results of the accelerated stability study (table no.10) of final formulation F007 for 3 months, it was concluded that with storage conditions no significant changes were found in final formulation F006. From the results of similarity factor (f2) applied in accelerated stability study, it was concluded that final formulation F007 after 3 months has shown good similarity (i.e., more than 50)

CONCLUSION

Seal coat polymer trial it was concluded that F002- HPMC seal coating. Trials were taken to optimize level coating of seal coat as compared to 15mg and 30mg. Enteric coating was performed by two different polymers, HPMCP 55 and Eudragit L30D55. It was concluded after study that HPMCP 55 was more effective as enteric coating polymer at same concentration than Eudragit L30D55 on seal coated tablet. As concentration of enteric coating polymer increases in formulation, acid resistance increases. It was concluded that 70mg enteric coating on seal coated tablet was optimum to protect core tablet from acidic environment of stomach in-vivo. From the stability result we have concluded that there was no change in the formulation after 3 month accelerated stability study. So, prepared delayed release tablet of proton pump inhibitor was stable.

ACKNOWLEDGEMENT

The authors are grateful to the management of Cadila healthcare ltd., India, for providing reagents, raw materials and manufacturing facilities for this study.

REFERENCES

1. Ansel, C.H., and Poppovich, N.G. , Pharmaceutical Dosage Forms and Drug Delivery Systems, 6th Ed. B.I. Waverly Pvt. Ltd, New Delhi, 1995, 213.

2. Aoki, S. (2005) Preparation composition containing acid unstable physiologically active compound and process for producing same, U.S Patent No. US 2005/0163846 A1.

3. Aulton, M.E., Wells T.I. Pharmaceutics: The Science of Dosage Form Design. London, England: Churchill Livingston, 1998, 247.

4. Bruce, L.D., Hans-Ulrich Petereit, Thomas Beckert, James W., McGinity. Properties of enteric coated sodium valproate pellets. International Journal of Pharmaceutics, 2003, 264(1-2): 85-96.

5. Cole, G., Pharmaceutical Coating Technology, Taylor and Francis Ltd., 1998, 6-52.

6. Cooper, J. Gun, C. Powder Flow and Compaction. Inc Carter SJ, Eds. Tutorial Pharmacy. New Delhi: CBS Publishers and Distributors, 1986, 211-33.

7. Crotts, G., Sheth A., Development of an enteric coating formulation and process for tablets primarily composed of a highly water soluble Organic acid. European Journal of Pharmaceutics and Bio pharmaceutics, 2000, 71-76.

8. Damodaran, N., Manimaran, V., Sravanthi, B. Formulation Development and evaluation of enteric coated Doxicycline Tablet. Indian Journal of Pharmacy and Pharmaceutical Science;

2010, 2(1): 119.

9. Goodman, Gilman. The Pharmacological basis of Therapeutics. 10th edition, 2001, 1007-08.

10. ICH International Conference on Harmonization. Stability testing: Accelerated stability testing of new drug substances and products, 1996, 32.

11. Lachman, L., Lieberman, H.A., Kanig, J.L.,Theory and Practice of Industrial Pharmacy. Bombay: Varghese House Publication. 3rd ed., 2009, 371-72.

12. Libermen, H.A., Lachman, L. Pharmaceutical Dosage Forms: Tablets. N.Y.: Marcel Dekker Inc., 1-3. 1989, 85-143.

13. Martin, A. . Micromeretics. In: Martin A, Physical Pharmacy. Baltimores, MD: Lippincott Williams and Wilkins, 2001, 423-54.

14. McTavish, D., Buckley, M.M., Heel R.C. Omeprazole: An updated review of its pharmacology and therapeutic use in acid-related disorders Drugs; 1991, 42(1), 138-70. [DOI] PMid: 1718683.

15. Nair, A., Gupta, R., Jacob, S. Formulation and evaluation of enteric coated tablets of proton pump inhibitor. Journal of Basic and Clinical Pharmacy, 2010, 215-21.

16. Singh, C., Kumar, R., Agarwal, K., Nema, R.K. Development and Evaluation of Enteric Coated Tablet Containing Diclofenac Sodium. Int. J. of Pharm. Sci. and Nanotechnology; 2009, 2(1), 443-45.

17. The United states Pharmacopoeia, The National Formulary, USP 27, NF 22. Asian-edition, 2004, 2303.

18. Wilde, M.I., McTavish, D. Omeprazole: An update of its pharmacology and therapeutic use in acid related disorders. Drugs; 1994, 48(1), 91-132. [DOI] PMid: 7525198.

19. Porter S.C. and K.Ridgeway. J.Pharm. Pharmacol. 1982, 34: 5-8.

20. Chambliss W.G. Pharm Tech 1983, 7:124-40.