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Formulation And *In Vitro* Evaluation Of Delayed Release Oral Dosage Forms For Omeprazole

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ABSTRACT

Omeprazole is a prototype member of a new class of substituted benzimidazoles which reduces gastric acid output both during basal conditions and stimulated acid secretion, irrespective of stimulus[1]. The objective of the present study is to develop a pharmaceutically equivalent, stable cost improved and quality improved formulation of omeprazole enteric coated pellets and to present in the form of tablets and capsules which were compared with the Innovators for its release efficiency. The enteric-coated drug pellets delivers the drug almost at a predetermined rate locally for a specified period of time at a specific site by reducing adverse effect. Main aim of this work is to formulate omeprazole enteric coated dosage forms , such as omeprazole enteric coated pellets and pellets in capsules, omeprazole enteric coated pellets compressed as tablets and coated with film coating material and omeprazole pellets compressed as tablets with enteric coated material were formulated and evaluated with respect to the various quality parameters such as dissolution, assay and impurity. The formula was finalized by comparing the in vitro dissolution profile with that of the Innovator in gastric and intestinal pH media.

INTRODUCTION

A peptic ulcer is a hole in the gut lining of the stomach, duodenum, or esophagus which results from ulceration of hyper acidity. A peptic ulcer of the stomach is called a gastric ulcer; of the duodenum, a duodenal ulcer; and of the esophagus, as an esophageal ulcer. An ulcer occurs when the lining of these organs is corroded by the acidic digestive juices that are secreted by the stomach cells. Peptic ulcer disease is common, affecting millions of people yearly. NSAIDs are medications for arthritis and other painful inflammatory conditions in the body. Aspirin, ibuprofen(Motrin), naproxen(Naprosyn), and etodolac(Lodine) are a few of the examples of this class of medications[2]. Prostaglandins are substances which are important in helping the gut linings to resist corrosive acid damage. NSAIDs cause ulcers by interfering with prostaglandins in the stomach.

Gastric ulcer(GU) and duodenal ulcer(DU) occur as a result of the imbalance between aggressive and defensive factors affecting the gastroduodenal mu-

cosa. Prostaglandins(PG) of E and I series are generated throughout the gastrointestinal tract, particularly in the gastric and duodenal mucosa, and are released into the gut lumen upon vagal and hormonal stimulation. Omeprazole was the first proton pump inhibitor to be marketed in the world. It has been marketed in many countries since the early 1980s and has proved to be a reliable therapy for gastric hyperacidity. Omeprazole inhibits secretion of gastric acid by irreversibly blocking the enzyme system K+Na+ATPase, or the so-called proton pump of the gastric parietal cell[3]. Enteric polymers are becoming very popular due to their property of remaining intact in the stomach, but will dissolve and release 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.

Enteric coating is normally used to protect the stomach from the irritating effect of the active ingredient as well as to protect the active ingredient from the stomach juices. Since enteric coating is itself an acid, it protects the whole pellet from dissolving so that it can reach the alkaline environment, where there is no longer any danger of the omeprazole dissolving and being destroyed. The essence of the pellet technique is in the protective layer which is produced from the neutral substance and safeguards the omeprazole. This specially developed neutral protective layer shields omeprazole not only from the acidic gastric juices, but also from the acidic layer of the enteric coating until the pellets reach the intestine and are dissolved.

The objective of the present study is to develop a pharmaceutically equivalent, stable cost improved and quality improved formulation of omeprazole enteric coated pellets and to present in the form of tablets and capsules that were compared with the innovators.

EXPERIMENTAL

Preformulation studies

Preformulation testing is an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. It is the first step in the rational development of dosage forms.

Physical properties

For a drug substance to formulate into a dosage form, it is necessary to study the physicochemical properties of the bulk drug.

Determination of bulk density and tapped density

An accurately weighed quantity of the powder(W), was carefully poured into the graduated cylinder and the volume(V_o) was measured, then the graduated cylinder was closed with lid, set into the density determination apparatus. The density apparatus was set for 500 taps and after that, the volume(V_f) was measured and continued operation till the two consecutive readings were equal.

The bulk density, and tapped density were calculated using the following formulas:

Bulk density=W/V_0; Tapped density=W/V_f

Where,

W=weight of the powder ; V_0=intial volume ; V_f=final volume

Sieve analysis

The main aim of sieve analysis is to determine the different size of drug particles present. A series of standard sieve were stacked one above the other so that sieves with larger pore size (less sieve number) occupy top position followed by sieves of decreasing pore size(larger sieve number towards the bottom). A series of sieves were arranged in the order of their decreasing pore diameter(increasing sieve number)i.e. sieve number 40, 60, 80, 100, 200#. About 25grams of drug was weighed accurately and transferred to sieve 40 which was kept on top. The sieves were shaken for about 5-10minutes. Then the drug retained on each sieves was taken, weighed separately and amount retained was expressed in terms of percentage.

Methods of preparing pellets

Compaction and drug layering are the most widely used pelletization techniques in pharmaceutical industry. Of the compaction techniques, extrusion and spheronization is the most popular method. Recently, however, melt pelletization has been used

frequently in making compaction pellets using a different type of equipment, eg.a high-shear mixer, pelletisation by extrusion and spheronization .The process involves first making the extrudes from the powder material and then converting the extrudes into beads using the spheronizer. The powder material could be any kind of powder(drug powder, ayurvedic powder, food ingredient powder, detergent powder, nuclear powder etc)

Manufacturing procedure of enteric coated pellets

Enteric coatings are those which remain intact in the stomach, but will dissolve and release 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 nausea or bleeding by irritation of gastric mucosa. Cracking of the film either during application or on storage will result in a loss of enteric properties. Therefore, consideration must be given to the mechanical properties of the applied film. Cracking problems can be effectively overcome by plasticization. Plasticizer can also be used to reduce the permeability of the polymer films to water vapor. The choice of suitable plasticizer is restricted to non-water soluble materials because these are likely to be most effective. Enteric coatings work , because they are selectively insoluble substances as they won't dissolve in the acidic juices of the stomach but will , when they reach the higher pH of the small intestine[4]. During all the stages of the manufacturing process temperature and humidity shall be maintained at 25±5^{0}C and 50±10% RH[5].

Dispense unmicronised drug and excipients as per order and micronization is carried out. Micronize omeprazole in the fluidized energy mill and transfer in to the double lined polythene bag. Sift sodium lauryl sulphate, mannitol through the #40and collect them in the polythene bag and label. Load sugar globules coat with HPMC. Load the sifted mannitol, sodium lauryl sulphate(SLS), micronized drug blend in to the blender. Blend for 30minutes. Unload the blend powder in to the double lined polythene bag. Weigh all the ingredients as per manufacturing formula. Dissolve binder in required quantity of purified water. Filter the solution through 200# mesh nylon cloth and collect them in the container. Disperse the drug mixed excipients in required quantity of purified water. Mix step-3 &4 and add this to drug dispersion. Use this dispersion for drug loading on sugar globules (#16/18). Dissolve the small quantity of binder in purified water and filter before using for mannitol outer layer. Load the seal coated pellets in to the coating chamber. Start and allow the beads to fluidize. Adjust the compressed air pressure accordingly. Start the peristaltic pump for spraying binder solution. Start spraying the binder solution by adjusting the pressure. Continue spraying till the beads become wet. Add the drug mixture and continue spraying. Load the wet coated pellets in to tray drier trays. Start the tray drier and dry the pellets in the tray drier between 30-40^{0}C. Sift the drug coated pellets through 14# mesh and collect the retains and passing separately in the HDPE containers. Sift the 14# passed pellets through 18# mesh and collect the retains and passing separately. Dissolve HPMC in purified water. Use this solution for sub coating of drug loaded pellets. Sift the sub coated pellets through 12# mesh and collect the retains and passing separately in the HDPE containers. Sift the 12# passed pellets through 18# mesh and collect the retains and passing separately. Weigh all ingredients as per manufacturing formula. Add enteric coating material in center of vortex of solvent scoop by scoop and stir for 5-10 min, Pass the whole dispersion through the #200 nylon cloth. Use this dispersion for enteric coating of sub coated pellets. After completion of coating, allow the pellets to dry in the coating pan Check the weight of enteric coated pellets for the build up. Sift the enteric coated pellets through 12# mesh and collect the retains and passings separately in the HDPE containers. Sift the 12# passed pellets through 18# mesh and collect the retains and passings separately.

Enteric coated pellets in capsule(equivalent to 40mg of omeprazole)

To prepare omeprazole capsules 40mg equivalent, omeprazole enteric coated pellets were taken from pellet formulation. Size'2' capsules were selected for capsule formulation. Dispence omeprazole

enteric coated pellets from previous formulation. Load these pellets in hard gelatin capsules No-2 with capsule filling machine. Transfer enteric coated pellets into capsules by spreading it into equal quantities equivalent to 40mg of omeprazole. Close the capsules by using caps.

Weight variation

Take individual weights of 20 capsules and calculate the average weight. Weight variation should not be more than 7.5%.

Weight variation=(weight of capsule-average weight)/Average weight of capsules×100

Omeprazole enteric coated pellets compressed as tablets (equivalent to 20mg of omeprazole)

Entericcoated pellets in tablets were formulated by conventional methods[6]. This study was mainly to check drug release, assay and acid resistance. Amount of omeprazole equivalent to 40mg of pellets were used[7].

Dispence omeprazole enteric coated pellets from pellets formulation. All excipients were sieved for extragranule preparation. Extra granules were prepared as wet granulation method. Pellets were dried and blended with the pellets. Pellets with extragranules were compressed as tablets in tablet compression machine using RPM-5.

Evaluation

Omeprazole enteric-coated tablets(equivalent to 40mg of omeprazole)

For better drug release and assay omeprazole enteric coated tablets were formulated. In this eudragit were used as a enteric coating material. Microcrystaline cellulose as a disintegrating agent and HPMC as a binder

Sieve all excipients including omeprazole. omeprazole granules work prepared as wet grand method and perform flow property by angle of repose method .

$$\tan\alpha = \frac{H^{13}}{R}$$

H=Height of the heat ; R=Radius of the hear

Good flow property of granules must be have tan α is less than 30^0. Flow property up drug granules were perform tan α was 38º. By addition of extra granules flow property must be improved. Omeprazole granules were blended with extra granules using poly bag for 15minutes. Angle of prepose of granules tan α was 27^0. This blend was used for tablet compression. Record all tablet parameters.

Analysis of the formulation

(A) Dissolution

Acid resistance stage

Medium	: 0.1N-Hcl
Type	: USP-II
RPM	: 100
Volume	: 300ml
Run time	: 2hrs
Temp	: 37±0.5^{0}C

Chromatographic system

Column	: Xterra RP.8 150×4.6 5µ
Wave length (λ)	: 280nm
Column temp	: 30^{0}C
Flow	: 1.0ml/min
Injection Volume	: 40µl
Run time	: 10min
Sample tray temperature	: 12^{0}C

Buffer PH 7.4

5ml TEA-1000ml, PH 7.4±0.05 with H_3PO_4

Mobile phase

PH 7.4 buffer	: Methanol
55	: 45
Diluent 1	: 0.1 NaOH
Diluent 2	: 3.8g of Borax in about 1000ml and mix with methanol in 3:1 ratio (Buffer:MeOH)(3:1)
Std Stock	: 46mg Esomeprazole Ws-250ml with diluent 1
Std	: 5ml-25ml with diluent 2(Std stock)

Test prep

Pellets(after 2hrs)-250ml with Diluent 1

5ml-25ml with diluent 2

Buffer stage: (PH 6.8)

Medium	: 300ml 0.1N Hcl+700ml of 0.086 Phos phate Buffer
Type	: USP - II
RPM	: 100
Volume	: 1000
Temp	: 37^0±0.5
Time	: 2hrs+45min

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(B)Assay

Chromatographic conditions

Column	: Xterra RP 8, 150×4.6
Flow	: 1.0ml /min
λ	: 280nm
Column temp	: 30^{0}C
Injection Volume	: 40µl
Run time	: 10min
Sample tray temperature	: 12^{0}C
Buffer PH 7.4	: 5mlTEA-100ml,PH 7.4 ±0.05 with H_3PO_4

Mobile phase

PH 7.4 buffer : Methanol
55 : 45
Diluent 1 : 0.1 NaOH
Diluent 2 : 3.8g of Borax in about 1000ml and mix with methanol in 3:1ratio(Buffer: MeOH 3:1)

RESULTS AND DISCUSSIONS

Among the three formulations omeprazole enteric coated pellets in capsule showed optimum drug release at 90 min time interval, as well as it was almost equivalent to innovator "x". The meptrozole enteric coated pellet's in capsule, drug release was constantly increased. At the time interval of 10min it showed 60%. At last it showed 96% drug release at 90min. In other hand enteric coated tablets were found to have less release at the time of 90min which was only of 88%. On comparing the three dosage forms, enteric coated pellet's in capsule showed better drug release and next comes the enteric coated pellets in tablets. There was no need to have disintegration time for pellets in capsule. When pellets were exposed to basic media such as intestinal fluids, it disintegrates immediately and makes the drug enter in to systemic circulation and this show maximum drug release. In case of enteric coated pellets in tablets, there was time required for the tablet to disintegrate and to release enteric coated pellets in stomach. The pellets then enters the intestine were enteric coated material dissolves. Finally the drug reaches the systemic circulation. It was clearly shown in drug release profile of enteric coated tablet (Figure 3)that at 10min 60.2% and at the time interval of 90 min 96%. For enteric coated tablets need more time to reach intestine because of its large volume, after some time the tablet has to enter in to the intestine and get its enteric coated material dissolved. For all these process the dosage delivery took more time for total drug to release. Thus it was shown that release rate at the time of 10min was 15%w/w and at the time of 90min was 88%.w/w.

TABLE 1 : Formula for omeprazole enteric coated pellets

Sl.No	Ingredients	Quantity (gm)/unit
	Drug loading stage	
1	Omeprazole	47.25
2	Mannitol	335.0
3	Sodium lauryl sulphate	1.5
1	Light magnesium carbonate	3.7
2	HPMC	15.5
3	Povidone	-
4	Sugar globules	92.5
5	Purified water	Quantity sufficient
6	Mannitol (outer layer)	4.48
7	Povidone	-
8	Purified water	Quantity sufficient
	Sub coating Stage	
9	HPMC	30.0
10	Purified water	Quantity sufficient
	Enteric coating stage	
11	Eudragit	54.0
12	Triethyl citrate	8.0
13	Glyceryl mono stearate	1.7
14	Talc	8.2
15	Sodium hydroxide	0.45
16	Purified water	Quantity sufficient

TABLE 2 : Compilation of capsules

S.No	Ingreadients	Mg/capsule	Innovator
1	Omeprazole enteric coated pellets	40.0	40.0
2	Hard Gelatin capsules	1	1
3	Talc	8.0	-

TABLE 3 : Formula for omeprazole enteric coated pellets compressed as tablets 20mg

S.no	Excipients	Mg/unit
1	Equivalent to omeprazole (as enteric coated pellets)	20.0
2	Aerosil	27.5
3	Pregelatinized starch	55.0
4	HPMC	27.0
5	Talc	27.15
6	Magnesium stearate	2.0
7	Sodium starch glycolate	87.35
8	Opadry brown	-
9	Purified water	Quantity sufficient

TABLE 4 : Evaluation of omeprazole enteric coated pellets compresed as tablets

Parameters	Limit
Disintegration time	Less than 1 minute
Percentage drug release	95 to 105% W/W
Acid resistance	3 to 5%
Assay	98 to 102% W/W

TABLE 5 : Formula for omeprazole enteric coated tablets

S.no	Excipients	Mg/unit
1	Omeprazole	20.0
2	Microcrystaline cellulose(AvicelPh101)	72.5
3	Hydroxy propyl cellulose	10.0
4	HPMC	28.6
5	Mannitol	22.0
6	Talc	31.0
7	Sodium lauryl sulphate	12.5
8	Na_2HPO_4	19.5
9	Purified water	q.s
	Extra granules	
10	Microcrystaline cellulose	65.0
11	Sodium starch glycolate	17.5
12	Aerosil	45.7
13	Magnesium stearate	0.3

TABLE 6 : Evaluation of enteric coated pellets

Drug loaded pellets	Value
Yield	98.2%
Bulk density	0.823 g/ml
Tapped density	0.880 g/ml
Sieve analysis	
#12 retained	1.25g
#18 passed	0.35g
#12 passed and 18 retained	489.4g
Assay	98-102%
Sub coated pellets	
Yield	99.6%
#12 retained	1.0g
#18 passed	0.1g
#12 passed and 18 retained	476.4g
Enteric coated pellets	
Yield	97.8%
Bulk density	0.781g/ml
Tapped density	0.836g/ml
#12 retained	2.0g
#18 passed	0.25g
#12 passed and 18 retained	545.75g
Assay	98-102%

TABLE 7 : Evaluation of enteric coated pellets in capsules

Parameters	Limits
Weight variation	7.5%
Percentage drug release	95-105%
Assay	98-102%

TABLE 8 : Evaluation of omeprazole enteric-coated tablets

Parameters	Limit
Disintegration Time	Less than 1 minute
Percentage drug release	95 to 105%
Acid resistance	3 to 5%
Assay	98 to 102%

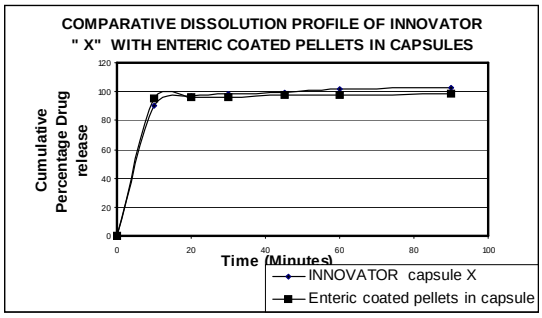

Figure 1 : Comparative dissolution profile of innovator "X" with pellets in capsules

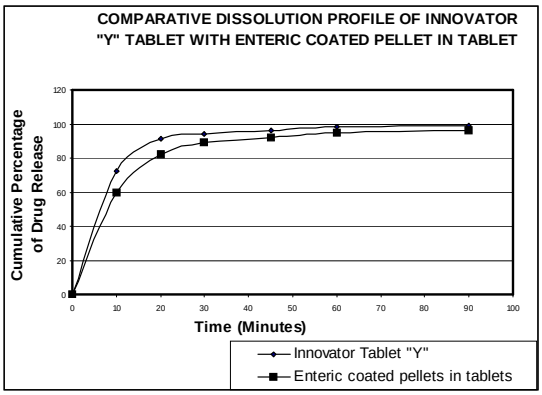

Figure 2 : Comparative dissolution profile of innovator "Y" with enteric coated pellets in tablets

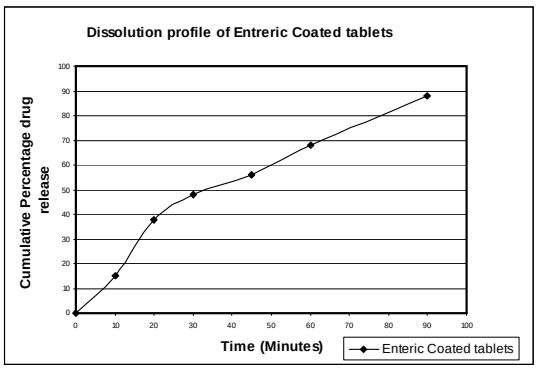

Figure 3 : Dissoltion profile of enteric coated tablets

CONCLUSION

Enteric coated pellets have minimum volume in size and has greater surface area and more surface activity. The area of the drug loaded enteric coated pellets exposed to intestine fluid was more and releasing rate was also more, more over there was no need for the dosage to disintegrate as in tablets. Small volume of pellets enters into the interstice very fast. Moreover there was no loss of drugs in acetic media like gastric fluid. Drug release rate was matches with innovator innovator "X".

In case of enteric coated pellets in tablets, there was time required for drug release because tablets need time for disintegrate has pellets. In this dosage form there was chance to break down of pellets while compression and to release the drug in acetic media. To minimize this character we used buffering agents.

The enteric coated tablet, which has large volume of size need more time to enter into the intestine and also need time for disintegrate in intestin leading to less drug release.

Finally it may be concluded that, enteric coated pellets in capsule has more drug release rate then enteric coated pellets in tablets and least amount of drug release was found in enteric coated tablets.

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