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FORMULATION, DEVELOPMENT AND EVALUATION OF AN IMMEDIATE RELEASE BUFFER TABLET OF OMEPRAZOLE

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ABSTRACT

Gastro-oesophageal reflux disease (GERD) patients on proton pump inhibitors before breakfast or dinner have acid recovery at night. Bedtime immediate-release buffer omeprazole tablet demonstrated better control of nocturnal pH than pantoprazole before dinner. Buffered omeprazole is an oral preparation consisting of an inner core of non-enteric-coated omeprazole with a shell of sodium bicarbonate. The buffer protects against acid degradation of omeprazole in addition to immediate antacid action. The aim of this study was to assess the efficacy of Buffered omeprazole for raising and maintaining an intragastric pH of more than 6 in comparison to i.v. pantoprazole in equivalent dosing. Omeprazole can be used in the treatment of gastroesophageal reflux disease (GERD), peptic ulcers, erosive esophagitis, and Zollinger-Ellison syndrome. Omeprazole, as well as other PPIs, are only effective on active H+/K+ ATPase pumps. These pumps are stimulated in the presence of food to aid in digestion. For this reason, patients should be advised to take omeprazole with a glass of water on an empty stomach about 30–60 minutes before a meal to allow the drug to reach peak levels once food is ingested. Additionally, most sources recommend that after taking omeprazole, at least 30 minutes should be allowed to elapse before eating. The formulation is designed as a way to have release as well as, to give protection to drug part against acid environment of stomach, for that the strategy was followed in such a way that buffer part of final tablet provide protection to drug part by mechanism of raising pH as well as by maintaining that pH range for a period of sufficient time so that total drug from inner tablet is released and absorb from that pH.

KEYWORDS: Pantoprazole, Gastroesophageal reflux disease, Immediate release.

INTRODUCTION

Tablet is the solid dosage form usually prepared with the aid of suitable excipients for pharmaceutical . They may in vary in the size, shape, weight, hardness, thickness, disintegration and dissolution charecteristics and iI other aspect depending on their intended use. Maximum tablets are administered orally. Many of these are prepared with colorants and coatings of various types. Other tablets which administered sublingually, buccally or vaginally are prepared ato have features most applicable to their particular route of administration[1-3].

The controlled release formulation has become increasing popular in pharmaceutical industry. A number of product reaches in global markets and several brands have generated considerable

revenues. Many platforms are available for delivering small molecule drugs with good aqueous solubility in prolonged or delayed release forms. Those unmet technology needs create great opportunities for the development and innovation of research and the continuous improvement of current delivery technologies is also important when it comes to decreasing cost and increasing efficiency. Those advancements include novel excipients and equipment as new tools formulation scientists can use to develop oral controlled-release formulations[4-6].

In recent decades, a variety of pharmaceutical research has been prepared to develop novel dosage forms which considered quality of life and these efforts have been focused on ease of Medication[5]. Although the concept of pH does not apply to solids, the terms microenvironmental pH or surface pH have been used in conjunction with solid formulations. Those which have been used to describe hydrogen ion activity in non-crystalline regions such as sorbed water layers or water-plasticized amorphous domains[7].

The microenvironmental pH has been implicated as a factor influencing drug degradation of solid dosage forms. Microenvironmental pH also affects dissolution behavior and hence bioavailability of many compounds, especially weak bases. The concept of microenvironmental pH, however, is not well defined and there are no well-established techniques available to measure it.

Oral administration is the most popular and safe route for systemic effects due to its ease to take, avoid of pain and most importantly patient compliance. The developments of enhanced oral protein delivery technology by immediate release tablets which may release the drugs at an better rate before are very promising for the delivery of poorly soluble drugs high molecular weight protein and peptide[8]. The oral route remains the perfect route for the administration of therapeutic agents because the minimum cost of therapy, manufacturing, ease of administration. Many patients require quick onset of action in particular therapeutic condition and consequently immediate release of medicament is required. It is estimated that 50% of the population is affected by this problem, it means a high incidence of ineffective therapy[9-11].

Drug delivery systems (DDS) are a strategic tool for expanding in the indications, extend product life cycles and generating opportunities[12].

Oral route for systemic effects due to its ease of ingestion, avaidance of pain. Also solid oral delivery systems do not require sterile conditions and are therefore, less expensive to manufacture. Excipients and equipments choices will be significantly affected should solid dosage form technologies change in response to the unprecedented shifts in the drug discovery such as genomics. Injections generally are not favored for use by patients unless facilitated by

sophisticated injectors. Inhalation is one good alternative system to deliver these type of drugs, but the increased research into biopharmaceuticals so far has generate predominantly chemical entities with low molecular weights[13].

Manufacturing Methods for a Tablet Dosage Form

The product development stages for immediate release dosage forms may follow three, either direct compression or wet granulation or dry granulation[14].

Direct Compression:

It is a process in which tablets are compressed directly from the powder blend of active ingredient and suitable excipients, which will flow uniformly into a die cavity and form into a firm compact. To keep the direct compression formulation simple and elegant, the following factors have to consider:

Wet Granulation:

The most widely used method of granulation for low as well as high strength tablet is wet granulation method. Dosage strengths with 0.5 to 850 mg or more per tablet are considered suitable drug candidates for the high shear development route. It involves aqueous or non-aqueous granulation techniques.

Dry Granulation

Slugs are prepared by compacting powder of drug and excipients in a roller compactor and resulting slugs are milled to yield granules. Granules are compressed into tablets.

Immediate Release Tablet:

The term “immediate release” pharmaceutical formulation includes any formulation in which the rate of release of drug from the formulation and/or the absorption of drug, is neither appreciably, nor intentionally, retarded by galenic manipulations. In the present case, absorption. Thus, the term excludes formulations which are adapted to provide for “modified”, “controlled”, “sustained”, “prolonged”, “extended” or “delayed” release of drug. In this context, the term “release” includes the provision (or presentation) of rug from the formulation to the gastrointestinal tract, to body tissues and/or into systemic circulation. For gastrointestinal tract release, the release is under pH conditions such as pH=1 to 3, especially at, or about, pH=1.

Preformulation Studies:

Physical appearance:

The drug (Omeprazole) powder was examined for its organo-leptic whitish properties like colour and odour.

Solubility estimation:

The sample was qualitatively tested for its solubility in various solvents. It was determined by taking 10 mg of drug sample in 10 ml of solvent as water, methanol, ethanol, pH buffer 6.8 and pH buffer 7.4 in test tubes and well solubilized by shaking, according to I.P.

Melting point determination:

The Melting point was determined by the capillary method using Manual Melting point apparatus (E.I). The capillary tube was fused and filled by pressing the open end gently into pure drug sample and packed by tapping the bottom of the capillary on a hard surface so that the drug packed down into the bottom of the tube. When the drug was packed into the bottom of the tube, the tube was placed into the slot of the apparatus, the apparatus was started and the temperature was noted at which the drug melt.

Determination of partition coefficient:

25 mg of drug was taken in three separating funnels. The separating funnels were shaken for 2 hrs in a wrist action shaker for equilibration. Two phases were separated and the amount of the drug in aqueous phase was analysed spectrophotometrically. The partition coefficient of the drug in phases was calculated by using formula:

$$\text{Partition Coefficient, K} = \frac{\text{Amount of drug in organic layer}}{\text{Amount of drug in aqueous layer}}$$

Formulation of Omeprazole buffer tablet-in-tablet:

The formulation is based on two parts. Internal core and surrounding coat. Internal coat is based on immediate release omeprazole tablet and surrounding coat is sodium bicarbonate buffer powder. This formulation may be designed by two manner, firstly inner core was to give protection to drug part against acid environment of stomach and surrounding coat provide protection to drug part by mechanism of raising pH as well as by maintaining that pH range for a period of sufficient time so that total drug from inner tablet is released and absorb from that pH.

Formulation of Internal Core:

Immediate release tablets of omeprazole were prepared by wet granulation method according to the formula given in Table 6.1. omeprazole, microcrystalline cellulose and crosspovidone sifted through sieve No. 40 and thoroughly mixed in a Mixer Granulator (RMG) for 10 min. PVP K30 (Poly vinyl Pyrrolidone) dissolved in sufficient quantity of isopropyl alcohol (IPA), and used as a binder solution. Wet granules were dried in fluid bed dryer (FBD) at 60-65^{0}C till a LOD (Loss of drying) of dried granules obtained not more than 2% w/w. Dried granules were passed through sieve No.24. The dried granules were lubricated for 2 min with magnesium stearate and talc. The lubricated granules were then compressed into tablets on an eight station rotary machine to get a

tablet of 160 mg weight. The Formulation ratios given in table No. 1.

Table 1: Formulation of Inercore tablet of Omeprazole

Ingredients	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
Omeprazole	40	40	40	40	40	40
Microcrystalline Cellulose (PH-102) IP	116.54	111.45	107.45	116.54	111.45	107.45
Cross Carmellose Sodium	5.0	8.0	12.0	--	--	--
Crospovidone XL -10	--	--	--	5.0	8.0	12.0
Polyvinyl pyrrolidone (K-30)	0.13	0.13	0.13	0.13	0.13	0.13
IPA	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Talc	0.17	0.17	0.17	0.17	0.17	0.17
Magnesium stearate	0.25	0.25	0.25	0.25	0.25	0.25
Total Weight	160.0	160.0	160.0	160.0	160.0	160.0

Formulation of Outercoat tablet of Omoprazole:

After punching of inner coat, microcrystalline cellulose, sodium bicabnate, crosspovidone, sifted through sieve No. 40 and thoroughly mixed in a Rapid Mixer Granulator (RMG) for 10 min. PVP K30 dissolved in sufficient quantity of IPA, and used as a binder solution. Wet granules were dried in fluid bed dryer (FBD) at 60-65^{0}C till a LOD (Loss of drying) of dried granules obtained not more than 2% w/w. Dried granules were passed through sieve No.24. The dried granules were lubricated for 2 min with magnesium stearate and talc. The lubricated granules were then compressed into tablets on an eight station rotary machine to get a tablet of 1500 mg weight. The Formulation ratios given in table No. 2.

Table 2: Formulation of Outercoat tablet of Omeprazole:

Ingradients	F1	F2	F3	F4	F5	F6
Microcrystalline Cellulose (PH-102) IP	170.00	170.00	170.00	170.00	170.00	170.00
Peppermint flavor / Cardamom flavor	7.000	7.000	7.000	7.000	7.000	7.000
Sodium Bicarbonate(Crystalline powder)	1100.00	1100.00	1100.00	1100.00	1100.00	1100.00
Colloidal silicon dioxide(Aerosil)	3.00	3.00	3.00	3.00	3.00	3.00
Crospovidone XL -10	21.00	21.00	21.00	21.00	21.00	21.00
Polyvinyl pyrrolidone (K-30)	13.00	13.00	13.00	13.00	13.00	13.00
IPA	Qs	Qs	Qs	Qs	Qs	Qs
Talc	13.00	13.00	13.00	13.00	13.00	13.00
Magnesium stearate	3.00	3.00	3.00	3.00	3.00	3.00

Evaluation of Tablet:

Evaluation of powder blend:

Angle of repose (θ)

It is defined as the maximum angle possible between the surface of the pile of the powder and the horizontal plane. Fixed funnel method was used. A funnel was fixed with its tip at a given height 'h, above a flat horizontal surface to which a graph paper was placed. Powder was carefully poured through a funnel till the apex of the conical pile just touches the tip of the funnel. The angle of repose was then calculated using following equation:

Angle of repose Ø = tan-1(h/r) Where, h=height of the pile , r = radius of the pile

Bulk density

It is a ratio of mass of powder to bulk volume. The bulk density depends on particle size distribution, shape and cohesiveness of particles. Accurately weighed quantity of powder was carefully poured into graduated measuring cylinder through large funnel and volume was measured, which is called initial bulk volume. It is expressed in gm/ml and is given by the formula:

Bulk density=M/V_o Where, M = mass of the powder **,** V_o = bulk volume of the powder

Tapped density

Ten gram of powder was introduced into a clean, dry 100 ml measuring cylinder. The cylinder was then tapped 100 times from a constant height and the tapped volume was read. It is expressed in gm/ml and is given by:

Tapped density=M/V_t Where, M = mass of the powder **,** V_t = final tapping volume of the powder

Compressibility index (Carr's index)

Compressibility index is used as an important parameter to determine the flow behavior of the powder. It is indirectly related to the relative flow property rate, cohesiveness and particle size. It is Simple, fast and popular method for predicting flow characteristics. Carr's index can be represented by Equation:

$$\text{Carr"s Compressibility Index (\%)} = \frac{\text{Tapped density - bulk density}}{\text{Tapped density}} \times 100$$

Hausner's ratio

Hausner's ratio is used to predict the flow ability of the powders. This method is similar to compressibility index. Hausner's ratio can be represented by Equation:

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

Evaluation of Tablets:

All the tablets were evaluated for different parameters as thickness, hardness, friability, uniformity of weight, disintegration time, drug content and *in vitro* dissolution study.

Weight variation:

Randomly selected twenty tablets were weighed individually and together in a single pan balance. The average weight was noted and standard deviation calculated. The tablets pass the test if not more than two tablets fall outside the percentage limit and none of the tablet differs by more than double percentage limit.

PD = [(W_{avg} – $W_{initial}$) / (W_{avg})] x 100

Where, PD = Percentage deviation**,** W_{avg} = Average weight of tablet**,** $W_{initial}$ = Individual weight of tablet

Thickness:

The thickness and diameter of tablets was determined using Vernier Caliper. Twenty tablets from each batch were used and average values were calculated.

Hardness:

The Monsanto hardness tester was used to determine the tablet hardness. The tablet was held between affixed and moving jaw. Scale was adjusted to zero; load was gradually increased until the tablet fractured. The value of the load at that point gives a measure of the hardness of the tablet. It is expressed in kg/cm^2. For each formulation, the hardness of six tablets was determined and average value was calculated.

Drug content:

Tablets were crushed and the powder equivalent to 100mg of drug were accurately weighed and transferred to 50 ml volumetric flask. To this flask, sufficient amount of distilled water was added to dissolve the tablets completely. Then, the volume of flask was made up to the mark with same solvent. From this solution, 1ml of the sample was pipetted out and transferred to 10 ml volumetric flask. The volume in the second flask was made up to the mark with distilled water. From this 0.6ml, 0.8ml and 1ml samples were withdrawn and volume was made up to 10ml to maintain concentration within the beer's range. This final diluted solution was estimated UV spectrophotometrically at 298 nm.

Friability:

Twenty tablets samples were weighed accurately and placed in friabilator (Roche Friabilator). After the given specification (4 min at 25 rpm), loose dust was removed from the tablets. Finally tablets were weighed. The loss in weight indicates the ability of the tablets to withstand this type of wear. The % friability was then calculated by:

% Friability = (Loss in weight / Initial weight) × 100

Disintegration test:

Disintegration is evaluated to ensure that the drug substance is fully available for dissolution and absorption from the gastrointestinal tract. Disintegration test was carried out using tablet disintegration test apparatus (EI Instrument, India) using 0.1 N HCl without disk at room temperature (37±2°C).

In vitro Drug release studies:

In vitro drug release studies were carried out in 900 ml of 0.1M HCl for the first 2 h using a USP XXII type 1 dissolution apparatus (Electrolab TDT-08L) at 60 rpm and 37 ± 0.5 °C. At predetermined time intervals during the dissolution test, samples (10 ml) were withdrawn for assay and replaced with equivalent volume of fresh medium to maintain conditions. All dissolution studies were performed in triplicate. The samples were filtered, diluted appropriately and then analyzed spectrophotometrically (Systronics, India) for Omeprazole at 280 nm.

Kinetic analysis of dissolution data:

The release data were fitted to five kinetic models, viz, zero-order, first-order, Higuchi and Korsmeyer-Peppas to determine drug release mechanism.

Result & Discussion:

The objective of our work is to develop an oral and effective formulation for active pharmaceutical ingredient (API Omeprazole) which is acid labile. The main strategy was to develop a formulation giving protection to API as well as safe and effective release so as to impart its action in an effective manner. So first of all conventional formulations were designed having drug and buffer part compressed together (Tablet in Tablet), along with alkalizing agent. Tablets were evaluated for weight variation, hardness, friability, disintegration, *in-vitro* dissolution study and *in-vivo* release study.

The weight variation was prominent in the formulations with more lactose because of poor flow properties of the powder mixture. It ranged from 1480 mg to 1508 mg with very high values of standard deviation. The tablets from 4.21-4.81mm in thickness with minimum standard deviation values, it assumed that the tablets show uniformity in thickness. The hardness of the tablets was found to be 5.31 - 6.07 kg/cm^2. The friability of the tablets was found to be 0.40-0.58%. Drug content in the tablets was the limit of 97.61-98.83 %. The disintegration time was found to be 13.46-14.33. After *in-vitro* dissolution studies it was observed that drug release for different batches was found to be 91.69 to 95.96 within 45 minute. The maximum drug release was observed in F6 among all formulations in 45 minute. Comparative cumulative percentage drug release data of all formulations are given in table No. 3.

Table 3: Comparative *In vitro* % drug release profiles of formulations (F1-F6)

Time (Min)	Cumulative % of Drug release					
	F1	F2	F3	F4	F5	F6
0	0.000	0.000	0.000	0.000	0.000	0.000
5	44.93	45.79	45.63	44.0	40.90	41.91
10	57.16	49.40	48.54	48.84	47.72	48.43
15	62.68	54.37	55.06	55.04	54.30	55.01
20	67.09	58.86	62.64	60.22	58.38	59.03
25	71.62	63.23	67.74	67.62	65.53	66.26
30	74.87	67.94	80.34	77.27	72.21	72.80
35	70.54	72.94	81.67	80.43	76.86	78.46
40	81.45	81.86	87.68	87.02	82.25	86.59
45	91.69	93.73	94.24	94.30	93.52	95.96

On the basis of these drug-release profiles, mechanism of drug release was confirmed by Higuchi's plots that showed graphical representation of cumulative percent drug release versus square root of time. Drug release from omeprazole was almost similar to that from reference formulation. Plasma concentration profiles of omeprazole and test formulation exhibited as immediate release. All the pharmacokinetics parameters have shown good correlation and were found to be comparable, indicating their release patterns were similar. When the *in-vitro* dissolution of omeprazole tablet was compared with *in-vivo* data of F6 using the method of linear regression analysis, a good correlation coefficient was found. The data shown in figure No.1 and Table No. 4.

Table 4: Correlation coefficient (R^2) of different kinetic models for Buffer Tablet (F1-F6)

Formulations	Zero Order	First Order	Higuchi Equation	Pappas Equation
	R^2	R^2	R^2	R^2
F1	0.956	0.907	0.944	0.795
F2	0.966	0.835	0.974	0.801
F3	0.986	0.936	0.974	0.820
F4	0.994	0.693	0.977	0.821
F5	0.992	0.936	0.977	0.825
F6	0.993	0.925	0.976	0.693

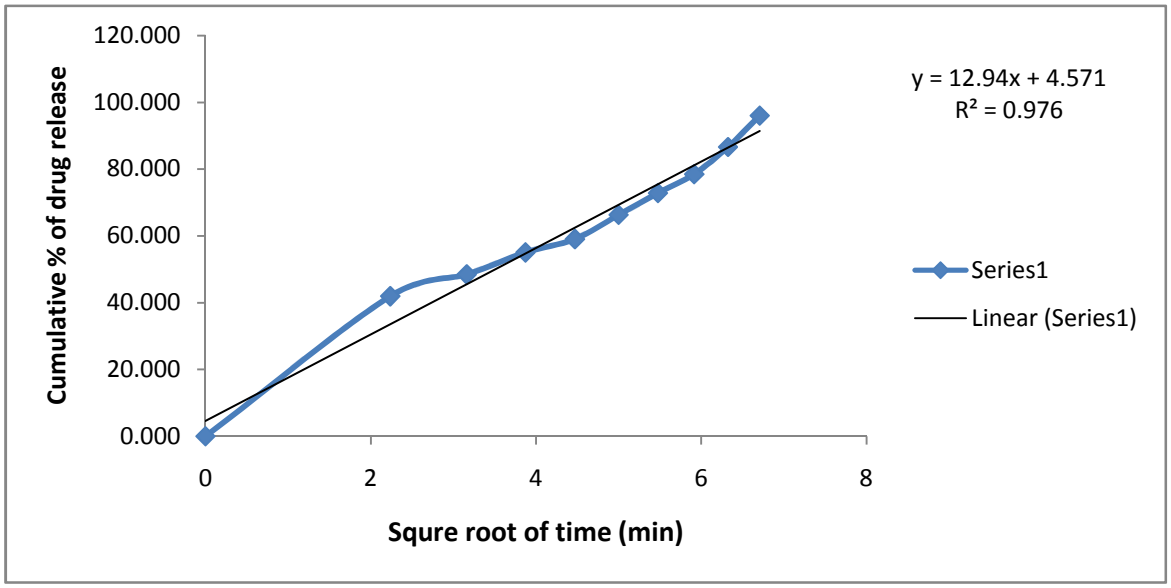

Fig. 1: Higuchi Equation of Omeprazole Buffer Tablet (F-6)

On the basis of drug release profile studies Formulation F6 was taken further for stability studies. The tablets were analyzed for hardness, uniformity of drug content and *in vitro* disintegration time at a time interval of 10days till a period of 30 days. Both the formulations showed no significant variations in all the parameters and were stable for a period of 30 days.

CONCLUSION

The Omeprazole is acid Habile, so the main strategy was to develop a formulation giving protection to Omeprazole as well as safe and effective release so as to impart its action in an effective manner. So first of all conventional formulations were designed having drug and buffer part compressed together (Tablet in Tablet), along with alkalizing agent. It can be concluded that super disintegrants concentration, granulation technique and both core play a key role in the development and optimization of the buffer tablet in tablet of omeprazole. The satisfactory drug release profile of omeprazole buffer tablet F6 dosage form provides an increased therapeutic efficacy.

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