FORMULATION AND EVALUATION OF FLOATING PELLETS OF OMEPRAZOLE BY EXTRUSION SPHERONIZATION METHOD

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Abstract

Objective: The aim of the present study was design, develop and to evaluate a model of floating sustained release pellets formulations for Omeprazole by extrusion and spheronization technique.

Methods: Omeprazole at different drug to polymer ratios were prepared by extrusion and spheronization technique and the release rate of the drug from the pellets was studied. Further, the *in-vitro* release studies of pellets were carried out in 0.1N HCL for 12 hours. Prepared pellets were subjected to characterization by different techniques such as loose bulk density, tapped bulk density, compressibility index and angle of repose. To optimize the formulation on the basis of acceptable pellet properties friability, drug content, moisture content, and loss on drying and *in-vitro* drug release tests were done. In addition, the compatibility studies were performed by using FTIR and DSC.

Results: These above studies indicated that the drug release can be modulated by varying the concentration of the polymer**.** The resulting formulation produced robust pellets with acceptable drug content and low friability. Further, release data was fitted to various mathematical models such as, Higuchi, Korsmeyer-Peppas, First-order, and Zero-order to evaluate the kinetics and mechanism of the drug release. Kinetic modeling of *in-vitro* dissolution profiles revealed the release mechanism ranges from Quasi-Fickian transport to Anomalous (non-Fickian transport), which was only dependent on the type and amount of polymer used. The drug release of the optimized formulation (F5) follows Zero order kinetics and the mechanism was found to be diffusion controlled. The FTIR and DSC studies reveal that there is no interaction between the drug and the polymer/excipients mixture.

Keywords: Floating**,** Ethyl cellulose, HPMC, Pellets, Omeprazole.

Introduction

Omeprazole is widely used in the management of acid secretion and in the treatment of the peptic and duodenal ulcers. The bioavailability of Omeprazole is high and protein binding was found to be 91-93 %. The half-life of Omeprazole is about 1-1.2 hours with short half-life leads to poor compliance and adverse reactions. To combat this there is a need in development of Omeprazole in sustained release dosage form to achieve better therapeutic effects and to improve patient compliance[1]. The primary use of extrusion and spheronization technique was the production of multiparticulates for oral controlled drug delivery system. The correct selection and balance of excipients and processes in solid dosage formulations are designed either for improving the micromeritic or macromeritic properties of materials during manufacture and/or for providing a desired drug delivery system. The most commonly used pharmaceutical delayed release solid oral dosage forms today include tablets, capsules, granules and pellets[2]. Sustained release solid oral dosage forms are available either as single-unit (non-divided formulations- tablets, capsules) or as multiple-unit (divided formulations-pellets, mini- tablets) forms. Sustained release dosage forms are in two types that contain single unit dosage forms where diffusion of a drug through a matrix is the rate limiting step[3]. The other one is multiple dosage form where it comprises of pellets and granules. Where, multiple dosage forms have advantages over single dosage forms, it Maximize drug absorption, reduce peak plasma fluctuations, minimize local irritation of the mucosa by certain irritant drugs and minimize potential side effects without appreciably lowering drug bioavailability[4]. Moreover multiple dosage forms avoids risk of dose dumping[4]. Pelletization a technique helps in case of immediate release products, larger surface area of pellets enables better distribution[5]. Further, chemically incompatible products can be formed into pellets and delivered in a single dose by encapsulating them[5]. The ultimate dosage forms for pellets can be capsule or they may be compressed into disintegrating tablets. Interest in this area has been increasing continuously, since it offers

some important pharmacological as well as technological advantages. So in this present study Extrusion-spheronization technique was selected to prepare the floating pellets of omeprazole.

Material and Methods:

Preparation of omeprazole floating pellets:

 Omeprazole sustained release pellets were prepared by a laboratory scale mini melt extruder and spheronizer by extrusion and spheronization technique. All the ingredients of sustained release pellets (F1-F5) were passed through the sieve no 40 and weighed according to the formulation. Ingredients were blended for 10 min. a precisely determined amount of solvent mixture was then added to the powder mixture and the mass was kneaded for 10 min. of time after solvent mixture addition. Finally the dry powder was made into dough mass[6].

Extrusion

 The wet powder mass was immediately extruded at 25 rpm through a radial screen with a 1mm aperture screen.

Spheronization

A radial plate spheronizer with a plate diameter (12cm) was used. The friction plate speed in the spheronizer was maintained at 1200 rpm. The was spheronized for 30 min. the wet pellets were dried in a hot air oven at 40 c For 12 hours and then stored in desiccator[6].

 Table 1: Formula for one capsule

Ingredients	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9
Omeprazole	30mg	30mg	30mg	30mg	30mg	30mg	30mg	30mg	30mg
Sodium Bicarbonate	35mg	35mg	35mg	35mg	35mg	35mg	35mg	35mg	35mg
Citric acid	10mg	10mg	10mg	10mg	10mg	10mg	10mg	10mg	10mg
HPMC K15M	25mg	50mg	75mg	----	-----	------	-----	-----	------
HPMC K100M	-----	----	-----	25mg	50mg	75mg	------	-----	------
HPMC E15	-----	----	-----	-----	-----	-----	25mg	50mg	75mg
Ethyl cellulose	10mg	10mg	10mg	10mg	10mg	10mg	10mg	10mg	10mg
Mcc	50mg	50mg	50mg	50mg	50mg	50mg	50mg	50mg	50mg
Talc	20mg	20mg	20mg	20mg	20mg	20mg	20mg	20mg	20mg
Starch	30mg	30mg	30mg	30mg	30mg	30mg	30mg	30mg	30mg
Iso propyl alcohol	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

CHARACTERISATION OF PELLETS[7]
1. Shape and Surface roughness
Shape and morphological features of pellets were observed by scanning electron microscopy (SEM). SEM has been used to determine the surface topography, texture and to examine the morphology of fractured or sectioned surface. The optimized formulation was selected for scanning electron microscopy (SEM) by using JEOL-JSM-840A, Japan. The pellet surface morphology was studied at 2nd, 6th and 12th hour.
2. Angle of repose
The angle of repose of Omeprazole pellets was determined by the funnel method (Repos gram). The accurately weighed quantity of pellets was taken in a funnel. The pellets were allowed to flow through the funnel freely onto the surface. The diameter of the pellet cone was measured and angle of repose was calculated using the following equation.
Angle of repose $(\theta) = \tan^{-1}$ (h/r)
Where h and r are the height and radius of the pellets cone, respectively
3. 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_0) was measured. Then the graduated cylinder was set into the density determination apparatus. The density apparatus was set for 100 taps and after that, the volume was measured. The bulk density, and tapped density were calculated using the formulae**.**
Bulk density = Mass of the pellets/ Bulk volume
Tapped density = Mass of the pellets / Tapped volume
4. Flow rate:
30 grams of pellets were filled in a glass funnel with a 6 mm internal stem diameter fixed on a clamp. The time was recorded from when the pellets started to flow until finish. Flow rate was expressed as g.s-1.
5. Compressibility index (Car's indices)
Carr's compressibility index:
Compressibility indices are a measure of the tendency for arch formation and the ease with which the arches will fail. It is calculated by using the formula,
Carr" s index (%) = [(TBD – LBD) x 100]/TBD
Where,
TPD is Tapped bulk density LBD is loose bulk density
6. Hausner's Ratio
Hausner"s ratio was measured by the ratio of tapped density to bulk density. Hausner"s ratio = Tapped density/ Bulk density
7. Sieve analysis:
Arrange the sample collector and sieves as per specification. Weigh and transfer around 100 g of the sample through the sieves and continue to sieve for 5

minutes. The retains were collected on larger sieve (A) and passed through the smaller sieve (B) from the sample collector separately.

Calculation Formula: Weigh the retains (Wa) and passes (Wb) and calculate the %retains and passing as follows.

8. Friability

The friability of pellets was determined by using USP friability tester. Friability of the pellet formulation was evaluated over 5g sample in Roche friabilator at 25rpm for 4min. Prior to and following the test, the weights of the formulation were accurately recorded and friability ratios were calculated with the given equation

$F = W_1 - W_2/W_1 \times 100$

Where, W1 = Initial weight of the formulation, W_2 = Final weight of the formulation

9. Moisture Content:

Transfer about 25 ml Methanol into Karl Fischer titration vessel, titrate with Karl Fischer Reagent and determine the end point potentio-metrically. Weigh accurately about 0.15g of disodium tartrate and transfer quantitatively into the Karl Fischer titration vessel. Titrate with Karl Fischer-reagent and determine the end point potentio-metrically. Note down the volume of Karl Fischer-reagent consumed. The strength of Karl Fischer-reagent is expressed as water equivalence (mg/ml).

Wt. of disodium tartrate x 15.66 x 1000 Water equivalence = ------------

100 x volume of KF reagent consumed

Standardization should be done at least in duplicate.

Determination of Water:

Weigh accurately about 1.5g of sample such that a minimum of 5ml KF reagent should be Consumed and transfer into the titration vessel containing, previously titrated methanol with KFreagent. Titrate with KF reagent and determine the end point potentio-metrically.

Titre Value X water equivalence X 100 Water (%) = ------------------

1000 X Weight of sample

Note: The moisture content of the pellets must be less than 3%w/w.

10. Loss on drying:

The empty crucible was taken and it is dried for about 30 minutes and weighed(W1), place the sample of about 1gm and again crucible was weighed(W2), now the crucible was kept in furnace for about one hour which is maintained at a temperature of 250-300ºC. Now the crucible is taken out from the furnace and kept for cooling in desiccator. After the crucible was cooled it is again weighed (W3). Now LOD is calculated in percentage using the following formula.

LOD = W2-W3/ W2-W1 X 100

Where,

W1= weight of empty crucible, W2= weight of crucible+ weight of the sample, W3= weight of crucible+ weight of the sample (after drying).

***In-vitro* release study[8].**

In-vitro drug release studies were carried out using USP XXII dissolution apparatus type II(Electrolab, Mumbai, India) at 50 rpm. The dissolution medium consist of 900 ml of pH 1.2 phosphate buffer for first two hour and pH 6.8 phosphate buffer for remaining hour , maintained at 37 ± 0.50C. The drug release at different time intervals was measured using an ultraviolet visible spectrophotometer (Labindia, Mumbai, India) at 281nm. The study was performed in triplicate.

Kinetic analysis of in-vitro release rates of controlled release pellets of Omeprazole:

The results of *in-vitro* release profile obtained for all the formulations were plotted in modes of data treatment as follows:-

1. Zero – order kinetic model – Cumulative % drug released versustime.

2. First – order kinetic model – Log cumulative percent drug remaining versus time.

3. Higuchi„s model – Cumulative percent drug released versus square root of time.

4. Korsmeyer equation / Peppa„s model – Log cumulative percent drug released versus log time.

COMPATABILITY STUDY OF DRUG WITH EXCIPIENTS[7].

FTIR study of Omeprazole with excipients

FTIR spectra of the selected formulation were taken and compared with the spectrum of pure drug. The characteristic peaks of drug were checked in the formulation spectra.

Differential Scanning Calorimetric (DSC) Studies

Compatibility studies of drug with other excipients used in optimized formulation under experimental condition was carried out by using differential scanning calorimetry.

RESULTS AND DISCUSSION

Formulation development

Ethyl cellulose of different grades like N10, N7 and N20 were selected as retardant materials. HPMC E5, PVP K30 were used as binders and iso propyl alcohol, methylene dichloride and diethyl phthalate as solvents, sunset yellow is used as colorant and talc as glidant for the formulation of sustained release pellets. Ethyl cellulose is a non-toxic, biocompatible, hydrophobic and cost effective and also reduces the risk of systemic toxicity due to dose dumping. As the different grades of ethyl cellulose has been used the properties of ethyl cellulose remains same but the release pattern is found to be changed as the porosity and viscosity of different grades of ethylcellulose differs. So they were used to sustain the release of the drug according to specification given in USP.

Evaluation parameters

Values of angle of repose are rarely 20^oC and values up to 40^oC indicate reasonable flow properties. Above 50^oC however the powder flows only with great difficulties. The angles of repose of the pellets were in the range of 21.36° to 25.23°. They are particularly sensitive to changes in particle size distribution and to the moisture content, and they provide a rapid means of monitoring significant batch to batch differences in these respects. Values of Carr's Index (Compressibility) below 15% usually give rise to good flow properties but readings above 25% indicate poor flow properties. It was found that the compressibility values of the pellets were below 15% and hence they exhibit good flow characteristics.

The Carr's index (compressibility) of the pellets was in the range of 8.42 to 11.80 (Table 2).

Friability and loss of drying

The friability of the pellets was found to be less than 1% and it was within the range of standard specification. Loss on drying was found to be in the range of 0.172 to 0.263% (Table 2). It was within the range of monograph specification.

Moisture content and assay

The moisture content of all the batches was found to be in the range of 1.958 to 1.210 which was within the range of monograph specification. Assay was conducted for all the batches and it was also found to be in the range of 99.15 to 101.56 (Table 2)

Table 2: Physico-chemical parameters of Omeprazole sustained release pellets (F1 to F9)

| PARAMETERS	FORMULATION CODE								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Angle of repose	22.01	22.35º	21.2º	23.2º	20.32	20.1º	21.65º	23.48º	24.1º
Loose bulk density (LBD)(g/ml)	0.350	0.282	0.270	0.279	0.268	0.262	0.276	0.268	0.254
Tapped bulk density (TBD) (g/ml)	0.390	0.310	0.295	0.295	0.291	0.289	0.296	0.291	0.273
Compressibility index (%)	7.203	9.032	8.474	8.42	10.25	9.342	6.756	7.903	6.959
Hausner"s ratio	1.114	1.099	1.092	1.057	1.085	1.103	1.072	1.085	1.074
Flow rate (g/s)	9.235	7.843	7.625	7.389	7.764	8.913	8.782	8.478	8.652
Loss on drying (%)	0.197	0.199	0.249	0.198	0.263	0.198	0.235	0.242	0.238
Moisture content (%w/w)	1.2555	1.21	1.25	1.267	1.8	1.683	1.958	1.751	1.899

In-vitro release study

The formulations were subjected to *in-vitro* dissolution study; using USP XXII dissolution apparatus type II (Electro lab, Mumbai, India) at 50 rpm. The dissolution was carried out for the duration of 12 hour. The formulations were subjected to dissolution study in pH 1.2. Samples were removed at the interval of 4 hour. Each time 5 ml of sample was removed and replaced with 5 ml of solvent. Sample was analyzed by double beam UV-spectrophotometer at 248nm. The release profile was compared with that of company specification and the formula which fits in accordance with that of specification is finalized and considered as optimum.

The dissolution test was carried out for all the formulations. F1 (without the coat of polymer) release was found to 99.88% at 4 hours which is due to the absence of polymer. The formulations F2 to F13 was prepared by coating the sustained release polymer ethyl cellulose of different grades (N10, N7, N20). The concentration of different grades of ethyl cellulose for all the formulations was maintained in the range of 0.5% to 1.5%. The formulations from F2 to F5 have the presence of sustained release polymer (ethyl cellulose N10), the release profile of these formulations was not found to be within the limits specified in monograph. The release profile of these formulations is shown in the table 28. The formulations F6 to F9 were coated with

ethyl cellulose N7. The release of F6 (concentration of ethyl cellulose N7 is maintained at 0.5%) was not in the limit whereas the release of F7 was found to be within the limits (concentration of ethyl cellulose N7 was maintained at 0.75%). In F8 and F9 the concentration of ethyl cellulose N7 was increased to 1 and 1.5% and checked whether the formulations comes and falls in the limits are not, but these formulations are also failed. Then another grade of ethyl cellulose N20 was coated to the formulations F10 to F13 (same concentration from 0.5 to 1.5% was maintained), but the release for these formulations was out of the limits. Therefore these formulations are also rejected. Ethyl cellulose N10 and N20 are highly viscous and less porous the release was found to be less compared to the formulations coated with the ethyl celluloseN7.

Then the dissolution profile of the optimized formula (F7) was compared with the innovator. The release profile is shown in the Table 3. The release profile of the innovator at 4th hour was found to be deviated from the limits specified. The drug release of the innovator at the 8th hour was found to be released more i.e. about 89.8% of the drug was released at 8th hour itself. Whereas the prepared Domperidone pellets were within the limits specified and the prepared pellets have shown about 89.14% of drug release at 12th hour. This shows that the prepared pellets were more sustained than the innovator. The dissolution profile is given in the. Fig. 1 & 2.
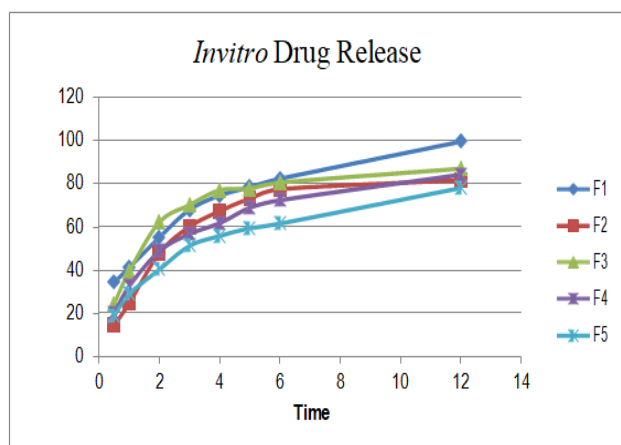
Figure 1: *In-vitro* Drug release profile of OmeprazoleF1-F5
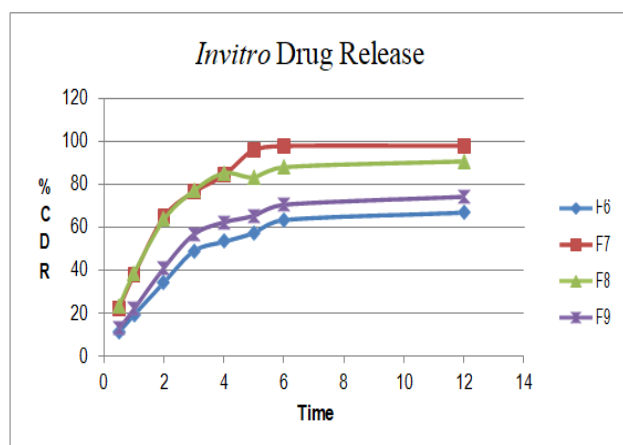
Figure 2: *In-vitro* Drug release profile of OmeprazoleF5-F9

RELEASE KINETICS

The release data was fitted to various mathematical models to evaluate the kinetics and mechanism of drug release. The kinetic data of all formulations F-1 to F-13 could be best expressed by zero order equation as the plots showed highest linearity (R^2: 0.879 to 0.992), than first order release kinetics (R^2: 0.814 to 0.938)

Table 3: Kinetic fitting model for optimized formulation (F1).

| TIME	LOG TIME	SQRT	%CDR	LOG% CDR	%CRR	LOG% CRR
0.5	-0.3010	0.7071	34.281	1.5350	65.719	1.8176
1	0	1	41.13	1.6141	58.89	1.7700
2	0.3010	1.4142	55.17	1.7417	44.83	1.6515
3	0.4771	1.7320	68.011	1.8325	31.989	1.5050
4	0.6020	2	74.062	1.8727	25.398	1.4047
5	0.6989	2.2360	78.493	1.87211	25.507	1.4066
6	0.7781	2.4494	82.35	1.9156	17.65	1.2467
12	1.0791	3.4641	99.551	1.9980	0.449	-0.3477

FTIR Spectroscopy

Drug polymer interaction was checked by comparing the IR spectra of the formulations with the IR spectra of the pure drug. There was no significant change in the functional groups between the IR spectrums of the pure drug and also no additional peaks were seen in the selected formulations This confirms that no interaction between drug and excipients (Fig 3).
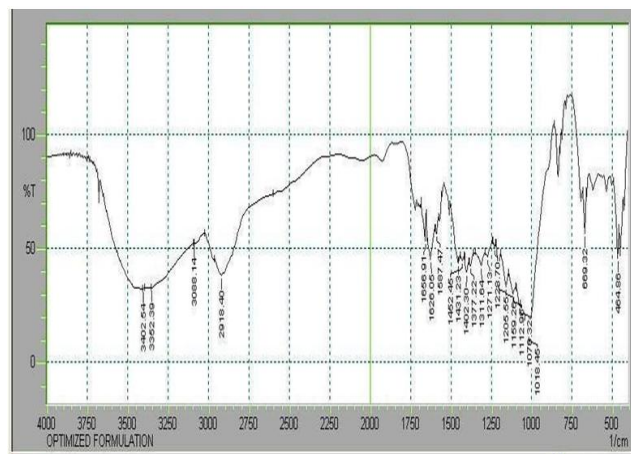
Figure 3: FTIR Spectroscopy of Optimized formula

DSC STUDIES

In order to find out drug and excipients compatibility DSC analyses were also performed. Pure omeprazole displayed sharp endothermic peak at 243.10C. The DSC curve of formulation F-1 demonstrated endothermic peak at 238.12C. DSC results did not show any major interactions.
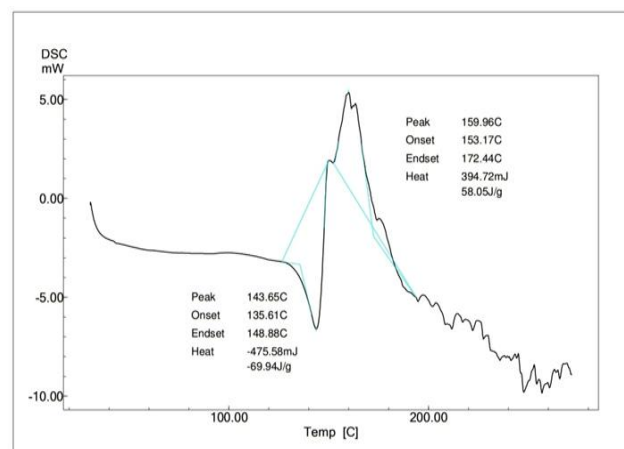
Figure 4: DSC Thermogram of Optimized formulation

Conclusion

From the present research work "Formulation and evaluation of floating pellets of Omeprazole by extrusion spheronization" for anti ulcer the following points were concluded. The Omeprazole floating pellets were prepared by extrusion spheronization method. The

prepared pellets were evaluated for characterization of pellets for different parameters and *in vitro* drug release assay. The prepared formulations showed acceptability quality control property. Formulation F1 having the polymer HPMC K 15M shows good *in vitro* drug release. All the formulation showed acceptability quality control property. Formulation F1 having the polymer HPMC K 15M shows good *in vitro* drug release. Hence F1 formulation is considered as optimized formulation. The kinetic release study shows that the optimized formulation F1 follows zero order release and the n value is less than 0.5 hence it follows fickanian diffusion. The FTIR and DSC studies show that there is no interaction between drug and excipients. The result suggests that the floating pellets of omeprazole could perform the better conventional dosage form leading to improved efficacy and better patient compliance

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