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Formulation and Evaluation of Omeprozole Magnesium Delayed Release Tablets

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A B S T R A C T

The drawback of Omeprazole has complete unstable atmospheres at acidic pH of stomach. Many research studies have completed the solution of above mentioned anti-ulcer drug one technology among of all to provide drug with enteric coated polymers so delay release and make release of drug in proximal small intestine. The sugar spheres will be taken into a FBP and drug will be coated onto the spheres and then they will be sub coated and enteric coated. The enteric coated pellets will be compressed into tablets by direct compression. The tablets will be prepared by using sugar spheres HPMC3cps, HPMC5cps, EL30D5, GMS, and TEC etc. The prepared tablet will be coated by using opadry pink and various parameters evaluated as per standard procedure. FTIR studies will be conducted for optimized formula to prove that the formula will no incompatibility between the drug and excipients. The SEM studies will be conducted to know the surface morphology.

Keywords: Delayed release tablets, Omeprazole, Polymers, Pellets, FTIR, SEM

A R T I C L E I N F O

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1. Introduction

An ideal drug delivery system provides treatment for acute diseases or chronic Illness to the patients for many years. A number of oral dosage forms are available. Some are liquids whereas the most common ones are solids. Tablets and capsules are generally formulated to release the drug immediately after oral administration to hasten systemic absorption. These are called Immediate-release products [1]. Modified-release products fall in two categories: One is Extended-release dosage forms which allow a reduction in dosing frequency or diminishes the fluctuation of drug levels that observed on repeated administration of immediate-release dosage forms. Controlled and Sustained release products fall into this category. The second category is delayed-release dosage forms.

Delayed Release Dosage Forms

Delayed release systems release a bolus of the drug after a predetermined time in a predetermined location, i.e. they do not release the drug immediately after ingestion, for example enteric-coated tablets, Pulsatile-release capsules[2].

Delayed release dosage forms are designed to provide spatial placement or temporal targeted delivery of a drug to the distal human gut. Spatial placement relates to targeting a Drug to a specific organ or tissue, while temporal delivery refers to desired rate of drug release to target tissue over a specified period of treatment. 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.

Delayed Release Solid Oral Dosage Forms

The most commonly used pharmaceutical delayed release solid oral dosage forms today include tablets, capsules, granules and pellets.

Classification of Delayed Release Solid Oral Dosage Forms: Delayed 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.

Single Unit Dosage Forms: The single-unit dosage forms usually refer to diffusion controlled systems which include monolithic systems, where the diffusion of a drug through a matrix is the rate-limiting step reservoir or multilayered matrix systems, where the diffusion of the drug through the polymer coating or layer of the system is the rate-limiting step. However, generally, release of drugs will occur by a mixture of these two mechanisms [3].

Multiple Unit Dosage Forms

These can be formulated as 2 types of systems which comprises of

1. Pulsatile drug delivery systems

2. Enteric coated systems

Types of multiple unit dosage forms comprise

Pellets and Granules, Mini tablets, mini depots Micro particles, (Microspheres or Microcapsules) Nano particules, Multiple unit tablets, Multi particulates are Filled into hard-shell gelatin capsules, Compressed into tablets, Suspended in liquids or Packed in sachets.

Mechanism of Drug Release from Multi-Particulates

The mechanism of drug release from Multiparticulates can be occurring in the following ways:

Pellets: Pharmaceutical pellets are agglomerates of fine powder particles or bulk drugs and excipients, small, free-flowing, spherical or semi-spherical solid units, size ranges from about 0.5mm to 1.5mm (ideal size for oral administration), obtained from diverse starting materials utilizing different processing techniques and conditions.

Desirable properties of pellets: *Uncoated pellets:* Uniform spherical shape and smooth surface, Optimum size, Between 600 and 1000μm, Improved flow characteristics, High physical strength and integrity, High bulk density, Ease and superior properties for coating, Reproducible packing of beds and columns.

Coated pellets: Maintain all of the above properties. Contain as much as possible of the active ingredient to keep the size of the final dosage form within reasonable limits, desired drug release characteristics.

Figure 1: (a) Pellets, (b) Perfect pellet, (c) Coated pellet

Advantages of pellets [4]

- Improved appearance of the product and the core is pharmaceutically elegant.
- Pellets can be divided into desired dosage strength without process or formulation changes and also allows the combined delivery of two or more bioactive agents it may be the same site or at different sites within the gastrointestinal tract.
- They offer high degree of flexibility in the design and development of oral dosage form like suspension, tablet and capsule.

Disadvantages of pellets [5]: The manufacturing of multiple unit dosage forms is more complicated and more expensive, the filling into gelatin capsules is difficult to accomplish, especially in the case where different subunits are involved.

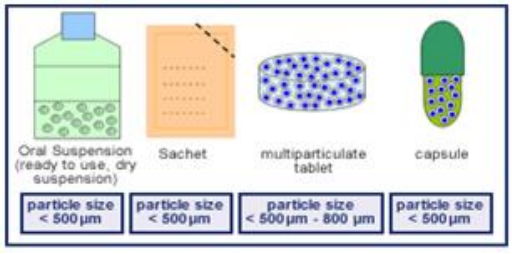

Figure 2: Flexibility of pellets in development of dosage form

Pelletization Techniques*:*

Pelletization is an agglomeration process that converts fine powders or granules of bulk drugs and recipients into small, free-flowing, spherical or semi-spherical units, referred to as pellets. The type of coating technique strongly affects the

film microstructure and thus affects the release mechanism and rate from pellets coated with polymer blends. There are several manufacturing techniques for production of spherical pellets.

2. Materials and Methods

Omeprazole was the gift sample of Aarthi Drugs Ltd in Hyderabad, Acrycoat 971 G, Lactose BP, Xanthan gum, Purified talc, Magneium stearate and analytical grades of chemicals.

Preparation of Delayed Release Tablets

Weigh all ingredients accurately, Sifted omeprazole, polymer, binder, diluent, lubricants through ≠ 40 sieve separately. Blended omeprazole, polymer, binder, diluents in a poly-bag. Lubricant and glident are added to the above blend. Compressed the blend of Step 4 materials into round concave shaped tablets with. The help of 7 mm concave shaped punches on double punch tablet machine

.

Table 1: Formulations of omeprazole Delayed Release Tablets

S. no	Ingredients (mg/Tab)	F1	F2	F3	F4	F5	F6	F7
1	Omeprazole	23.75	23.75	23.75	23.75	23.75	23.75	23.75
2	Xanthan gum	53	60	-	-	-	-	-
3	Acrycoat 971 G	-	-	53	60	65	74	89
4	Lactose	65.75	58.75	65.75	58.75	53.75	44.75	29.75
5	Purified talc	3.0	3.0	3.0	3.0	3.0	3.0	3.0
6	Aerosil	2.0	2.0	2.0	2.0	2.0	2.0	2.0
7	Magnesium sterate	2.5	2.5	2.5	2.5	2.5	2.5	2.5
8	Total weight (mg)	150	150	150	150	150	150	150

Evaluation of Delay Release Formulations [6]

The prepared omeprazole Delayed Release Tablets were evaluated for general appearance, thickness, hardness, weight variation, friability and drug content.

General appearance

The tablets prepared were white, round, spherical shape. They were smooth, uniform and free from cracking and chipping.

Hardness test:

Hardness (diametric crushing strength) is a force required to break a tablet across the diameter. The degree of hardness varies with the different manufactures and with the different types of tablets. The permissible limit for hardness is 4-12 kg/cm^2. The hardness was tested using Monsanto tester. "Hardness factor", the average of the five determinations was determined and reported.

Uniformity of weight:

This is an important In-process quality control test to be checked frequently. Average weight was calculated from the total weight of all tablets. The individual weights were compared with the average weight. The percentage difference in the weight variation should be within the permissible limits (7.5%). The percent deviation was calculated using the following formula**.** The limits are mentioned in the below table as per Indian pharmacopoeia (I.P)**.**

$$\% \text{ Deviation} = \frac{\text{Individual weight} - \text{Average weight}}{\text{Average weight}} \times 100$$

Friability test: Friability is the loss of weight of tablet in the container/package, due to removal of fine particles from the surface. Roche friabilator was used to measure the friability of the tablets. It was rotated at a rate of 25 rpm. Five tablets were weighed collectively and placed in the chamber of the friabilator. In the friabilator, the tablets were exposed to rolling, resulting from free fall of tablets within the chamber of the friabilator. Permitted friability limit is 1.0%. The percent friability was determined using the following

Formula

$$(W_1 - W_2)/W_1 \times 100$$

Where, W_1 = weight of the tablets before test, $W2$ = weight of the tablets after test

***In-vitro* drug release studies [7]**

In-vitro drug release studies were carried out using USP XXIV dissolution apparatus type II, with 500 ml of dissolution medium maintained at 37±0.5 °C for 20 hr, at 50 rpm, pH 6.8 ±0.2 phosphate buffers as dissolution medium. The commercial Toprol XL tablets were used as the reference formulation, and were also subjected to *In-vitro* drug release studies. The results of *In-vitro* release profile obtained for all the formulations were plotted in modes of data treatment as follows:

1. Log cumulative percent drug remaining versus time (first order kinetic model)
2. Cumulative percent drug release versus square root of time (Higuchi model)
3. Cumulative percent drug remaining versus time (zero order kinetic model)
4. Log cumulative Percent Drug released versus log time (korsmeyer's model)

Drug release kinetics-model fitting of the dissolution Data [8]

Whenever a new solid dosage form is developed or produces, it is necessary to ensure that drug dissolution occurs in an appropriate manner. Nowadays the pharmaceutical industry and the registration authorities focus on drug dissolution studies. Drug dissolution from solid dosage forms has been described by kinetic models in

which the dissolved amount of drug (Q) is a function of the test time, t or Q = f (t).

Similarity factor calculations

The Similarity factor (F2) is defined as the log reciprocal square root transformation of one plus the mean square difference in % dissolved between the test and the reference release profiles. There are several methods for dissolution profile comparison. The F2 is the simplest among those methods.

$$F_2 = 50 \text{ Log } \{[1+(1/n)\sum_{t=1}^{n} (R_t-T_t)^2]^{-0.5}.100\}$$

Where R_t and T_t are the cumulative % drug dissolved at each selected n time point of the reference and the test product respectively. Whereas factor f_2 is inversely proportional to averaged square difference between the two profiles with emphasis on the large difference among all the time points' .the similarity factor f2 and its significance is shown in the following table.

Compatibility studies [9]

In the preparation of drug and polymer may interact as they are in close contact with each other, which could lead to the instability of drug pre formulation studies regarding the drug – polymer interaction are therefore very critical in appropriate polymer. FT – IR Spectroscopy was employed to ascertain the compatibility between trospium chloride and the chitosan polymer.(Perkin Elmer Jasco FTIR- 401, Japan). The drug – excipients compatibility studies shows that there is no any physical incompatibility of omeprazole with excipients studied at given conditions.

FTIR spectroscopy was used to ensure that no chemical interaction between the drugs and polymers had occurred. From the FTIR spectral interpretation the following result were obtained. The FTIR of omeprazole show intense band at 1771.47 cm^{-1}, 1716.89 cm^{-1} , 1589.53 cm^{-1} and 1055.9 cm^{-1} corresponding to the functional groups C=O, COOH, NH and OH bending. The peaks observed in FTIR of Xanthan gum at 1771.36 cm^{-1}, 1716.93 cm^{-1}, 1589.89 cm^{-1}, 1055.33 cm^{-1} and 1771.47 cm^{-1}, 1716.44 cm^{-1}, 1589.12 cm^{-1}, 1055.49 cm^{-1} for Acrycoat 971 G and 1771.69 cm^{-1}, 1716.89 cm^{-1}, 1589.72 cm^{-1}, 1056.13 cm^{-1} for Aerosil and 1771.62 cm^{-1}, 1716.76 cm^{-1}, 1589.84 cm^{-1}, 1055.88 cm-1. The physical mixture of omeprazole, 1876.47 cm^{-1}, 1712.89 cm^{-1}, Acrycoat 971 G 1689.3n2 cm^{-1}, 1259.13 cm^{-1}, Xanthan gum 1615.93 cm^{-1}, 1488.89 cm^{-1}, 1255.33 cm^{-1}, Aerosil 1486.84 cm^{-1}, 1151.88 cm-1.

3. Results and Discussion

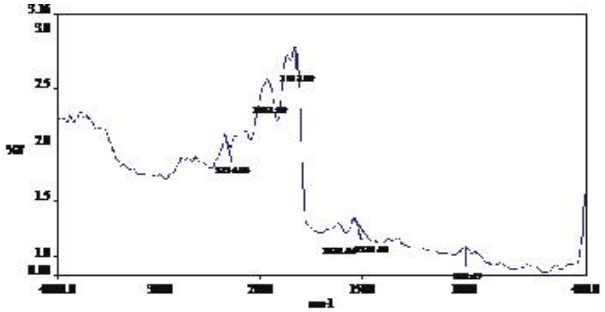

Figure 3: FTIR of Omeprazole

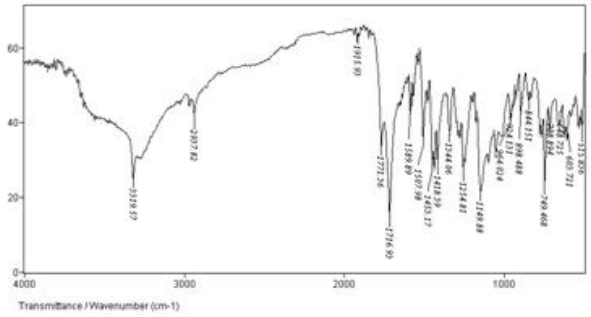

Figure 4: FTIR of Xanthan gum

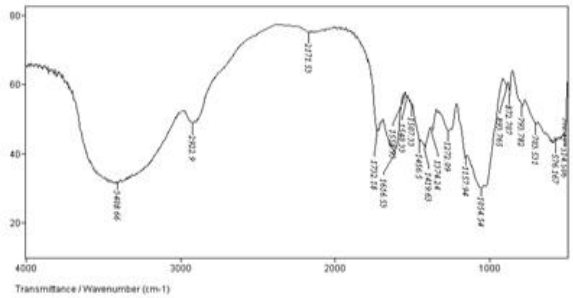

Figure 5: FTIR of Acrycoat 971G

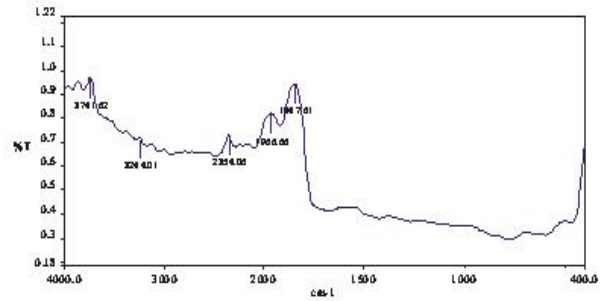

Figure 6: FTIR of Acrycoat 971G

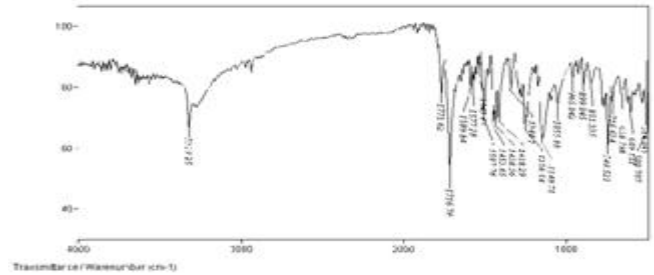

Figure 7: FTIR of Omeprazole, Xantham gum, Acrycoat 971 G, Aerosil

Table 2: Flow properties of omeprazole all formulation

S.No	Parameters	F1	F2	F3	F4	F5	F6	F7
1	Angle of repose	31.3	32.2	33.0	31.7	33.02	31.0	34.2
2	Bulk density(gm/ml)	0.296	0.307	0.313	0.301	0.320	0.301	0.301
3	Tapped density(gm/ml)	0.333	0.347	0.363	0.340	0.347	0.333	0.347
4	Hausner's ratio	1.13	1.13	1.15	1.12	1.08	1.10	1.15
5	Compressibility index (%)	11.1	11.5	13.7	11.3	12.0	10.4	13.2

Sub Coating Stage [10]

Step 1: HPMC 5cps was weighed and dissolved in water under stirring for 15 min.

Step 2: weighed quantity of SLS was dispersed under slow stirring in step 7 for 30min, results in uniform dispersion and talc was added to it

Step 3: drug loaded pellets (#25 passed and #60 retained) coated with dispersion in FBP.

Step 4: sub coated pellets were dried for 30min in FBP at lower temperature.

Table 3: Process parameters of FBP for Sub coating

S. No.	Process parameters	Range
1	Inlet temperature (^{0}C)	50-55
2	Product temperature (^{0}C)	35-45
3	Exhaust temperature (^{0}C)	33-43
4	Drive speed (CFM)	25-35
5	Atomization (Barr)	0.8-1.8
6	Peristaltic pump speed	2-15
6	Spray rate (g/min)	2-8

Table 4: Evaluation parameters of all formulations of omeprazole tablets

S.No	Parameters	F1	F2	F3	F4	F5	F6	F7
1	**Color**	Cream white	Cream white	Cream white	Cream white	Cream white	Cream white	Cream white
2	**Surface**	Smooth	Smooth	Smooth	Smooth	Smooth	Smooth	Smooth
3	**Thickness (mm)**	3.3-3.4	3.3-3.4	3.3-3.4	3.3-3.4	3.3-3.4	3.3-3.4	3.3-3.4
4	**Hardness (Kg/cm^2)**	4.0±0.1	4.2±0.2	4.3±0.1	4.1±0.2	4.2±0.1	4.0±0.1	4.3±0.1
5	**Weight (mg)**	148.20± 2.5	149.32±1 .5	149.35±1. 5	148.76±2. 5	148.36± 3.5	149.56±2. 5	149.23±1. 5
6	**Friability**	0.09±0.0 01%	0.05±000 1%	0.08±0.00 1%	0.09±0.00 2%	0.07±0.0 01%	0.09±0.00 1%	0.08±0.00 2%
7	**Assay (%w/w)**	99.96	100.2	98.65	99.23	100.6	99.3	99.52

Table 5: Sub coating optimization parameters

Sub Coating	B1	B2	**B3**
Drug loaded pellets	63.1	63.1	63.1
HPMC 5cps	1	2	4
SLS	1	2	4
Talc	1	1	2
Purified water	q.s.	q.s.	q.s.
Total(barrier layer)	3	5	10
Total amount per	66.1	68.1	**73.1**

1. Main aim of sub coating is to protect the drug coated pellets from enteric (Eudragit L30D55) material.
2. After enteric coating, some dark color pellets were observed in B1 & B2 formulation, whereas in B3 it was not observed. Hence enteric coating material was interacted with drug so discoloration was observed.
3. B1 and B2 formulation contain less % of sub coating, whereas compare with B3. To protect drug from enteric material, minimum sub coating build up required.
4. Hence, Based on the results B3 was finalized as a final sub coating formula for further development.

Enteric Coating Stage [11]

Step 1: Eudragit L30D55 was neutralized under stirring with aqueous solution of NaOH.

Step 2: TEC was slowly added to step 11 under stirring.
Step 3: GMS was gently added to water (at 60^0C), under stirring
Step 4: Talc was added to the step 13 under stirring for 5min, and the dispersion was homogenized for 10min.
Step 5: Homogenized dispersion was added to the step 12.
Step 6: Step 10 sub coated pellets (#25 passed and #60 retained) coated with step 15 dispersion in FBP.
Step 7: enteric coated pellets dried in FBP for 30min at 35-40°C.

Table 6: Process parameters of FBP for enteric coating

S. No	Process parameters	Range
1	Inlet temperature (^{0}C)	35-45
2	Product temperature (^{0}C)	28-35
3	Exhaust temperature (^{0}C)	25-34
4	Drive speed (CFM)	30-40
5	Atomization (Barr)	0.8-3.5
6	Spray rate (g/min)	2-8
7	Wurster height (cm)	2.5-5.0

Stability Study [12]

For all the pharmaceutical dosage forms it is important to determine the stability of the dosage form. This will include storage at both normal and exaggerated temperature conditions, with the necessary extrapolations to ensure the product will, over its designed shelf-life, provide medication for absorption at the same rate as when originally formulated. The design of the formal stability studies for the drug product should be based on the knowledge of the behavior and properties of the drug substances and formal stability studies on the drug substance. Specification which is list of tests, references to the analytical procedures and proposed acceptance criteria, including the concept of different acceptable criteria for release and shelf life specifications, is addressed in ICH guidelines.

Drug Release Kinetics

Table 7: Drug release kinetics for all 7 formulations with innovator

Batch	Zero order r^2	Higuchi r^2	n
Innovator	**0.9697**	**0.987**	**0.6611**
F1	0.877	0.9641	0.4611
F2	0.9313	0.6865	0.4811
F3	0.809	0.9149	0.4144
F4	0.8969	0.9719	0.4611
F5	0.9549	0.991	0.5333
F6	**0.9596**	**0.9849**	**0.710**
F7	0.9335	0.9905	0.6825

Release kinetics

The "n" value obtained from formulation 6 is 0.71 which is between >0.45 and < 0.89 hence it follows non fickian release. Showing anomalous transport.Also the drug release was best explained by the zero order equation as the plot showed the highest linearity with (r^2 value = 0.9969) followed by Higuchi equation (r^2=0.9849).Formulation F-6 was seemed to be close to the innovator's release profile. Then similarity factor was calculated between formulation F-6 and innovator. Similarity factor was 81, so formulation F-6 has similar release profile to the marketed formulation.

Stability Studies

Table 8: optimization of stability formulations

	cumulative % drug release	
Time (h)	**Initial**	**3 month**
1	11	11
4	31	30
8	54	53
20	99	98

The samples analyzed at initial stage and after three months at accelerated stage.

Table 9: Optimization of stability formulations

Parameters	Initial	3months
Color	Cream or White	Cream or White
Surface	Smooth	Smooth
Thickness	3.3-3.4	3.3-3.4
Hardness	4	4
Assay	100.6	99.5

Observation

Accelerated stability studies of the formulation 6 were done at 40°C ±2 °C / 75 % RH ± 5 % for 3months, seen that physically there was no change in appearance hardness, thickness and drug content. The dissolution profiles of first month and 3months are similar. When compared to formulation 6, indicates that the formulation was stable at 40°C ±2 °C / 75 % RH ± 5 % for 3months.

4. Conclusion

The optimised delayed release formulation (F-6) was found similar and comparable to the innovator product based on the f2 value (81) obtained. The release Mechanism was found to be "non fickian release n value is 0.71, which is between >0.45 and < 0.89. The results of *in-vitro* drug release profile of delayed release tablets depicts that increase in polymer concentration, increases the retardation of drug release from the omeprazole tablet. The flow properties of omeprazole formulation s Angle of repose of F6 was found to be 31.0^0, Bulk density F6 is 0.301 (gm/ml),

tapped density F6 is 0.333, Hausner's ratio was found to be 1.10, compressibility index was found to be 10.4%. The evaluation test of delayed release formulation perform the appearance is smooth surface & cream white in color, thickness is 3.3-3.4 mm, weight variation was found to be 149.56±2.5, friability was found to be 0.009±0.001%, & Assay was found to be 99.3. Drug content, invitro drug release studies by using basket method results was found to be 99 ± 7.77. The formulations F1 and F7 were suitable to sustain the drug release for a period of 12hrs, The "n" value obtained from F6 is 0.71 follows non fickian release. Accelerated stability studies of the F6 for three months, seen that there was no change in appearance hardness, thickness and drug content.

5. Acknowledgement

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