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Research Article

Formulation and *in vitro* evaluation of Esomeprazole delayed release multi-particulate capsules

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ABSTRACT

The present research was aimed to formulate and evaluate Esomeprazole magnesium dihydrate delayed release multi-particulate capsules. The delayed release multiple units were prepared by solution/suspension layering using fluid-bed Wurster (bottom-spray) technology, a well recognized process for providing excellent coating uniformity and efficiency. The prepared multiparticulates consists of successive layers of seal coat, drug coat, barrier coat, enteric-polymer coat, over coat on existing inert seeds and finally filled into capsules. The filled capsules were evaluated for drug content, acid resistance test, *in vitro* drug release and compared with the marketed product. The dissimilarity (f1) and similarity (f2) factors for optimized and marketed formulations were found to be 3.56 and 72.49, respectively. Accelerated stability study conducted as per ICH guide lines at 40^0C/75% RH for six months showed that the finalized formulation (E5 multiple units filled into capsules) was stable during the study period.

Keywords: Esomeprazole Magnesium Dihydrate; Delayed Release; Multi-Particulates; Solution/Suspension layering; Wurster

INTRODUCTION

Pharmaceutical invention and research have been focused on the development of drug delivery systems which enhance desirable therapeutic objectives with minimizing side effects. Among all, Multiparticulate oral dosage forms have acquired a centre stage in the arena of pharmaceutical research and development for achieving delayed release oral formulations; thus provide tremendous opportunities and extending the frontier of future pharmaceutical development. These formulations release the drug at a time rather than promptly after administration, offers design flexibility and clinical benefits than single units such as short gastric residence time, most patient convenience means of drug administration, maximum drug absorption, reduce peak plasma fluctuations, minimize the potential side effects due to dose dumping and numerous technological, physiological, therapeutical advantages over single-unit dosage forms (Digenis, G.A., 1994; Nastruzzi, C., et al., 2000; Roy, P. and Shahiwala, A., 2009).

Various techniques to prepare multiparticulates, which includes solution/suspension layering, powder layering, extrusion spheronization etc. Solution/suspension layering technique is one of the prominent techniques for preparation of delayed release multiple units. Various inert cores used as starting materials for solution/suspension layering include saccharose and microcrystalline cellulose (MCC) based inert cores. Sugar spheres have been used as inert cores for a long time and are monographed in the major pharmacopeias (Werner, D., 2006). These multiple sub units require relatively complex manufacturing processes compared to single unit tablets. The potential risks include quality assurance, time consuming due to the challenges associated with reproducibility and uniformity within or among the batches (Bodmeier, R., 1997).

Proton Pump Inhibitors (PPIs) are substituted benzimidazoles. All these shares a similar core structure and mode of action, but differ in substituent groups. The type of substituents affects the chemical properties of the compounds that directly influence their rates of reactions and therefore, their stability in different media. PPIs are used in the treatment of acid related gastro duodenal disorders by reducing gastric acid secretion by irreversibly inhibiting the gastric parietal H+/K+ ATPase enzyme involved in the production of hydroch-

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Table 1: Optimization of Seal Coating

S.No.	INGREDIENTS	mg/unit		
	SEAL COATING	F1	F2	F3
1	Sugar spheres	38.000	38.000	38.000
2	Hypromellose, 3cps	1.000	2.000	3.000
3	Purified water	20.000	40.000	60.000
	Total weight of seal coated pellets	39.000	40.000	41.000
	% weight build up of seal coating	2.63	5.26	7.89
	% yield	65.00	95.00	95.00

Table 2: Optimization of Drug Coating

S. No	INGREDIENTS	mg/unit				
	DRUG COATING	D1	D2	D3	D4	D5
1	Seal coated multiple units F2	40.000	40.000	40.000	40.000	40.000
2	Esomeprazole magnesium dihydrate	43.504	43.504	43.504	43.504	43.504
3	Hypromellose, 3cps	-	10.000	15.000	17.500	22.000
4	Povidone (pvp k-17)	10.000	-	-	-	-
5	Meglumine	2.000	2.000	2.000	2.000	2.000
6	Polysorbate 80	1.000	1.000	1.500	2.000	2.000
7	Methyl alcohol	100.000	100.000	100.000	120.000	120.000
8	Methylene chloride	100.000	100.000	100.000	120.000	120.000
	Total weight of drug coated pellets	96.504	96.504	102.004	105.004	109.504
	% weight build up of drug coating	141.26	141.26	155.01	162.51	173.76
	% drug coated (% drug content)	69.00	80.00	91.00	99.00	98.00

Table 3: Optimization of Barrier Coating

S.No.	INGREDIENTS	mg/unit		
	BARRIER COATING	B1	B2	B3
1	Drug Coated multiple units D4	105.004	105.004	105.004
2	Hypromellose, 3cps	3.000	4.000	6.000
3	Sodium Lauryl Sulphate	-	0.400	1.000
4	Talc	1.000	1.500	1.500
5	Isopropyl Alcohol	50.000	60.000	75.000
6	Methylene chloride	50.000	60.000	75.000
	Total of sub coated pellets	109.004	110.904	113.504
	% weight build up of sub coating	3.81	5.62	8.09
	% yield	85.00	91.00	96.00

loric acid in the stomach (Digenis, G.A., 1994; Bodmeier, R., 1997; Martindale: The Extra Pharmacopoeia, 2005; Scott, L.J., 2002).

Esomeprazole is a PPI and *S*-isomer of Omeprazole. It is used in the treatment of gatroesophageal reflux disease (GERD), erosive esophagitis, gastric ulcer, etc. It has acceptable stability under alkaline conditions but rapidly degrades in acidic pH (Thomson PDR, 2007). To protect the drug from gastric fluids, to reduce gastric distress caused by the drug, particularly to prevent irritation to the stomach or to facilitate gastrointestinal transit for drug to be better absorbed from an intestine, an enteric coating is applied.

The drug release criteria of Esomeprazole delayed release dosage forms has been reported that more than 90% of drug content must be resistant to acid (i.e., less than 10% drug content loss) after two hours in compendial acid media, 0.1N HCl (pH 1.2) followed by rapid release of the drug (not less than 80% of the labeled amount) within 45 minutes in pH 6.8 phosphate buffer. The objective of the present work was to formulate and evaluate Esomeprazole multiple unit delayed release capsules.

MATERIALS AND METHODS

Materials

Esomeprazole magnesium dihydrate (Hetero Drugs Ltd.), Sugar spheres – 250 µm to 425 µm (JRS Pharma), Hypromellose, 3 cps (DOW Chemicals), Povidone (pvp k-17) (BASF), Meglumine (Spectrum), Polysorbate 80 - Crillet 4 (Croda Chemicals), Triethyl Citrate (Morflex, Inc.), Talc (Luzenac Pharma), Sodium Hydroxide (Merck), Methacrylic Acid Copolymer (type C) (Evonik), Glyceryl Monostearate (Sasol), Sodium Lauryl Sulfate (Stepanol WA-100) (Stepan), Methyl alcohol, Methylene chloride, Isopropyl alcohol (Runa chemicals). All other chemicals and reagents were of analytical grade.

Table 4: Optimization of Enteric-Polymer Coating

S.No	INGREDIENTS	mg/unit					
	ENTERIC-POLYMER COAT-ING	E1	E2	E3	E4	E5	E6
1	Barrier coated multiple units **B3**	113.504	113.504	113.504	113.504	113.504	113.504
2	Methacrylic acid copolymer (Type C) dry polymer	30.000	-	-	-	-	-
3	Methacrylic acid copolymer (Type C) 30% aqueous dispersion	-	134.000 (40.200)	167.000 (50.100)	217.000 (65.100)	234.000 (70.200)	250.000 (75.000)
4	Triethyl citrate	-	-	5.000	6.500	7.000	7.500
5	Polyethylene glycol 400	3.000	4.000	-	-	-	-
6	Talc	6.000	8.000	10.000	13.000	14.000	15.000
7	Sodium Hydroxide	0.200	0.250	0.300	0.350	0.350	0.350
8	Polysorbate 80	0.450	0.600	0.750	0.970	1.050	1.130
9	Purified water	150.000	105.000	130.000	170.000	180.000	200.000
	Total of enteric coated pellets	153.154	166.554	179.654	199.424	206.104	212.484
	% weight build up of enter-ic coating	34.93	46.74	58.28	75.69	81.58	87.20
	% yield	83.00	95.00	96.00	98.00	98.00	98.00

Table 5: Over Coating

S.No.	INGREDIENTS	mg/unit					
	OVER COATING	E1	E2	E3	E4	E5	E6
	Enteric-Polymer coated multiple units	153.154	166.554	179.654	199.424	206.104	212.484
1	Glyceryl mono stearate	0.500	0.500	0.500	0.500	0.500	0.500
2	Talc	0.500	0.500	0.500	0.500	0.500	0.500
3	Isopropyl alcohol	15.000	15.000	15.000	15.000	15.000	15.000
	Total of polished pellets	154.154	167.554	180.654	200.424	207.104	213.484
	% weight build up of polishing	0.65	0.60	0.55	0.50	0.48	0.47
	% yield	98.00	95.00	95.00	97.00	98.00	99.00

Methods

Preparation of Different Coating Solution/Suspensions

Seal coating solution: Required quantity of purified water was taken into a suitable vessel and Hypromellose, 3 cps were added slowly under continuous stirring for 45 minutes to get clear solution. This solution was coated onto the inert starting material, i.e., sugar spheres to provide mechanical strength for multiple units to withstand for further coating process.

Drug coating suspension: Hypromellose, 3cps or Povidone (pvp k-17) was added to the mixture of Methyl alcohol and Methylene chloride (in the ratio 1:1) under continuous stirring and stirred for 30 minutes to get a clear solution. This solution was cooled and maintained below 10°C.

Meglumine and Polysorbate 80 were added to the above solution and stirred for 30 minutes. Then, Esomeprazole magnesium dihydrate was added slowly under stirring and stirring was continued for 45 minutes to get homogeneous suspension. The drug suspension was maintained between 5° - 10°C until the end of the coating process, i.e., coating of drug suspension on to the seal coated multiple units.

Barrier coating suspension: Hypromellose, 3 cps were added slowly to Isopropyl alcohol (50%), under continuous stirring. Then Methylene chloride (50%) was added and stirred until clear solution was obtained.

To the remaining quantity of Isopropyl alcohol (50%), Sodium Lauryl Sulphate and Talc were added slowly under continuous stirring and stirred for 15-20 minutes to get uniform suspension. This suspension was passed through a colloid mill for 10-15 minutes to get homogenized suspension. Then, this suspension was added to the above mixture of Hypromellose - Isopropyl alcohol - Methylene chloride. Then, the remaining quantity of Methylene Chloride (50%) was added and stirred for 15 minutes.

Enteric- polymer coating dispersion: Purified water (40%) was taken in a suitable vessel and Methacrylic acid copolymer (type C) (dry polymer/dispersion sifted through a mesh #80) was added slowly under stirring and stirred for 10 minutes. Purified water (10%) was taken into another suitable vessel; sodium hydroxide

Table 6: Coating Parameters of Different Coating Solution/ Suspensions

Process parameters	Seal coating	Drug loading	Barrier coating	Enteric coating	Over coating
Product /Bed temperature	40 ± 5°C	35 ± 5°C	38 ± 5°C	33 ± 5°C	35 ± 5°C
Drive speed	20-50	20-50	20-50	20-50	20-50
Atomization (Barr)	1.2 – 2.0	1.2 – 2.0	1.2 – 2.0	1.2 – 2.0	1.2 – 2.0
Spray rate (gram/minute/gun)	1-5	1-10	3-6	2-6	1-5
Wurster height (mm)	20 – 40	30 – 50	20 – 50	30 – 50	30 – 50

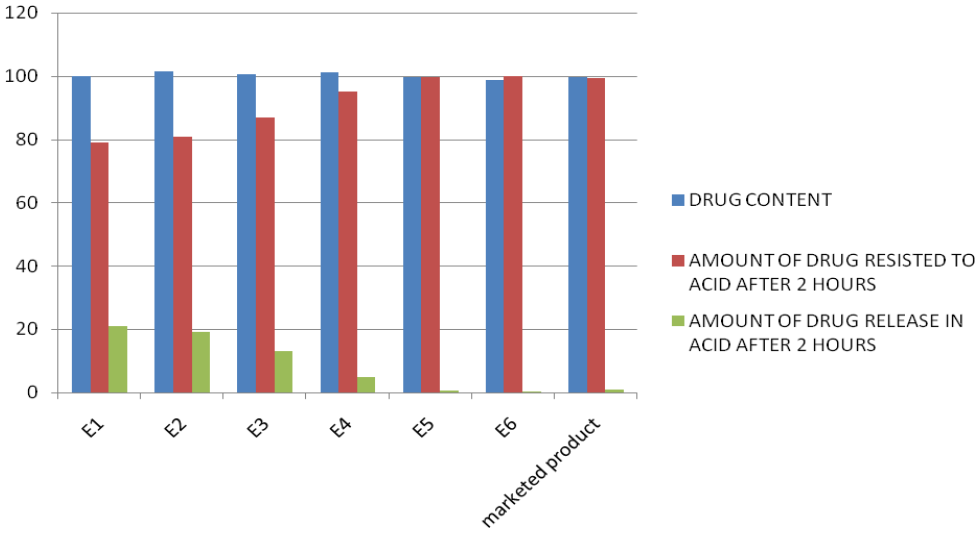

Figure 1: Graph showing amount of drug content, drug resisted and drug release of over coated multiple units (E1-E5) in 0.1 N HCl, 300ml, II, 100rpm after 2 hours

was added and agitated for 10 minutes to get clear solution. This solution was added to the mixture of Methacrylic acid copolymer dispersion - water. The stirring was further continued for 30 minutes.

Plasticizer (Polyethylene glycol 400 or Triethyl citrate) was taken into a beaker and purified water (25%) was added and mixed for 30 minutes. This was added to the above Methacrylic acid dispersion under stirring.

To the remaining quantity of purified water (25%), Polysorbate 80 was added under continuous stirring and stirred for about 10-15 minutes. Talc was added to this solution and stirring was continued for about 20 minutes. This was added to the dispersion of Methacrylic acid copolymer.

Over coating suspension: Isopropyl alcohol was taken in a suitable vessel. Glyceryl mono stearate and Talc were added under stirring and continued stirring for 15 minutes. Finally, the suspension was passed through a colloid mill to get a uniform suspension. The suspension was kept under continuous stirring during the coating process.

FORMULATION OF DELAYED RELEASE CAPSULES

Different formulations and coating parameters of Esomeprazole delayed release capsules 40 mg were tabulated in **Table 1, 2, 3, 4, 5 and 6.** After a coating process, these multiple units were filled into size '2' capsules and analyzed for drug content, acid resistance, in vitro dissolution and stability.

EVALUATION PARAMETERS

The coated multiple units and/or capsules were evaluated for drug content, amount of drug content resisted to acid (acid resistance), *in vitro* drug release.

Estimation of drug content, amount of drug content resisted to acid (acid resistance) and *in vitro* drug release.

The amount of drug present, amount of drug content resisted to acid and *in vitro* drug release of the over-coated multiple units and/or capsules were estimated by HPLC using C_{18} column at a wavelength - 302 nm, flow rate - 1.5 ml/minute, run time - 10 minutes at ambient column temperature. The diluent was 0.1N Methanolic NaOH and the mobile phase was the degassed mixture of pH 7.4 phosphate buffer and methanol in the ratio 50:50 v/v.

Preparation of standard solution for drug content estimation, acid resistance test and in vitro dissolution: Working standard was prepared with about 45mg of Esomeprazole magnesium dihydrate accurately weighed and transferred into 100ml volumetric flask. To this, about 60ml of diluent was added and sonicated to dissolve. The volume was diluted with diluent. From this 5ml of the solution was transferred into 50ml volumetric flask and diluted to volume with mobile phase.

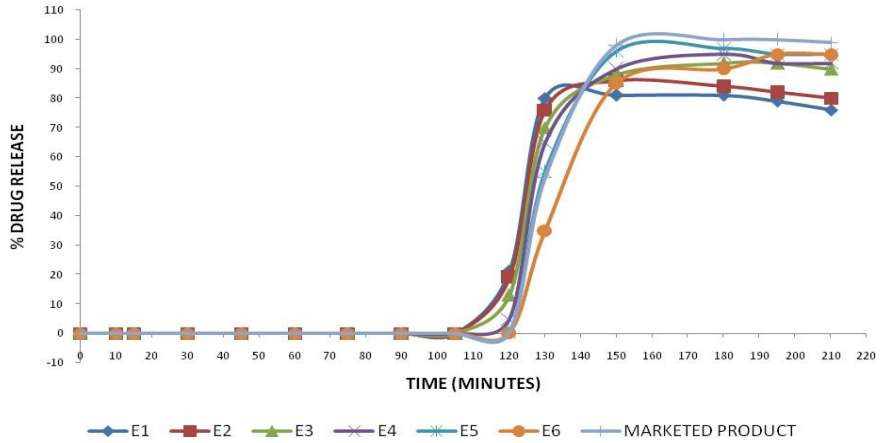

Figure 2: Graph showing comparative dissolution profile of over coated multiple units (E1-E5) in 0.1N HCl, 300ml, II, 100rpm followed by pH 6.8 Phosphate Buffer, 1000ml, II, 100rpm with marketed product

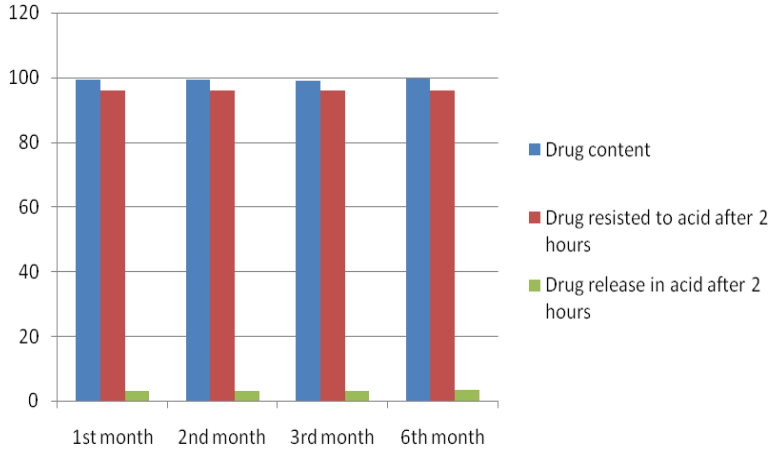

Figure 3: Graph showing amount of drug content, drug resisted and drug release of Esomeprazole delayed release capsules (E5) at AST - 40±2°C/75±5% RH for 6 months in 0.1 N HCl, 300ml, II, 100rpm after 2 hours

Preparation of sample solution for drug content estimation: Sample solution was prepared by Esomeprazole magnesium dihydrate multiple units or filled capsules equivalent to 80 mg of Esomeprazole accurately weighed and transferred into a 200ml volumetric flask. To this, about 120ml of diluent was added and sonicated for 30 minutes with shaking until multiple units were dissolved (sonicator bath temperature to be maintained between 20-25^{0}C). The volume was diluted with diluent. A portion of solution was centrifuged at about 5000 rpm for 10 minutes. 5ml of the above solution was transferred into 50ml volumetric flask and diluted to volume with mobile phase. Filtered a portion of solution through 0.45µ filter and first few ml of filtrate was discarded. 20µl of mobile phase, standard solution (five times) and sample solution were separately injected into HPLC. The chromatograms and peak responses were measured.

For determination of drug resisted to acid (gastro/ acid resistance test): 300ml of 0.1N HCl was transferred into each vessel and allowed the medium to maintain at a temperature of 37±0.5^{0}C. One capsule in each vessel was placed and operated at 100 rpm for 2 hours. At the end of 2nd hour, 0.1N HCl was discarded from each vessel. Sample solution was prepared with entire quantity of multiple units of each vessel, immediately transferred into dry individual 100ml volumetric flasks with the aid of suitable filter or mesh and ensured a complete transfer of multiple units to the volumetric flask. About 60ml of diluent was added and sonicated for 30 minutes with shaking until the multiple units were completely dissolved. The volume was diluted with diluent. A portion of solution was centrifuged at about 5000 rpm for 10 minutes. 5ml of the above solution was transferred into 50ml volumetric flask and diluted to volume with mobile phase. A portion of solution was filtered through 0.45µ filter and first few ml of filtrate was discarded. 20µl of mobile phase, standard solution (five times) and sample solution were separately injected into HPLC. The chromatograms were recorded and peak responses were measured. Drug release in acid and drug resisted to acid were calculated by the following formulae.

% labeled amount of Esomeprazole dissolved in 0.1N HCl = Total drug content of the over-coated multiple units/ filled capsules – amount of drug content resisted to acid (0.1N HCl) after two hours.

% labeled amount of Esomeprazole resisted to 0.1N HCl = % Drug content of pellets resisted to acid (0.1N HCl) after two hours.

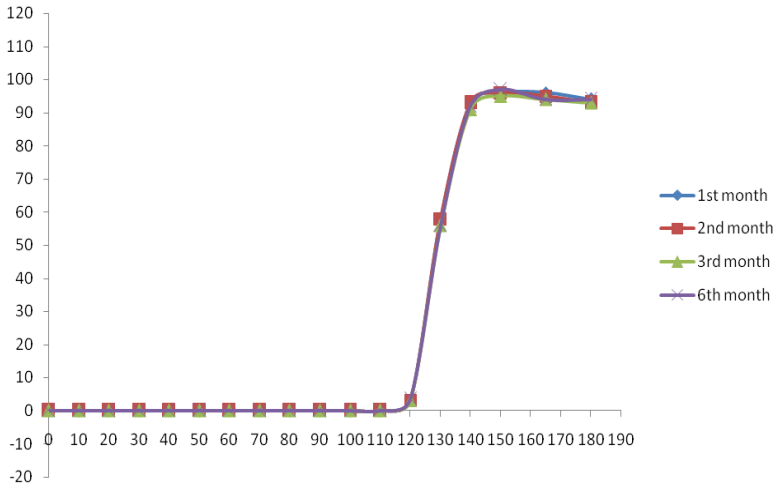

Figure 4: Graph showing comparative dissolution profile of Esomeprazole delayed release capsules (E5) at AST - 40±2°C/75±5%% RH for 6 months in 0.1N HCl, 300ml, II, 100rpm followed by pH 6.8 Phosphate Buffer, 1000ml, II, 100rpm

***In vitro* Dissolution:** In vitro dissolution studies were carried out in 0.1N HCl, 300 ml, USP II, 100 rpm for two hours followed by pH 6.8 phosphate buffer, 1000ml, USP II, 100 rpm for one hour at a temperature of 37±0.5^{0}C. Sampling points in pH 6.8 phosphate buffer includes 10, 20, 30, 45 and 60 minutes.

Preparation of sample solution for in vitro drug release studies: Sample solution was prepared as directed under acid stage mentioned above with a new set of samples from the same batch. After the multiple units/ filled capsules were run for two hours in 0.1N HCl, HCl was discarded and 1000ml of pH 6.8 Sodium Phosphate buffer was transferred into the dissolution vessel and run at 100 rpm for specified time. 10ml of samples were withdrawn from each dissolution vessel. The sample was filtered through 0.45µm membrane filter and first few ml of the filtrate were discarded. 5ml of the filtered sample solution was immediately transferred into test tubes containing 1ml of 0.25N NaOH in a test tube. Same procedure was followed as directed above for release profile by maintaining the sink conditions. 20µl of dissolution medium, standard solution (5 times) and sample solution were separately injected into HPLC. Chromatograms and peak responses were recorded and measured.

SIMILARITY AND DISSIMILARITY FACTORS (Moore, J.W. and Flanner, H.H., 1996; Shah, V.P., et al, 1998; Food and Drug Administration, 1997).

The dissimilarity factor *(f1)* and similarity factor *(f2)* were calculated to compare the dissolution profile of optimized formulation ***(E5)*** with marketed formulation. The difference factor *(f1)* calculates the percent difference between the reference and test curve at each time point and is a measurement of the relative error between two curves. The similarity factor (*f*2) is a logarithmic reciprocal square root transformation of one plus the mean squared (the average sum of squares) differences of drug percent dissolved between the test T_t and references products R_t, over-all time points, *n*.

The dissimilarity factor (f1) values ranges from 0-15 and similarity factor (f2) value should lie between 50–100. It is 100 when two comparative groups of reference and test are identical and approaches 0 as the dissimilarity increases.

The following equations are used to calculate the dissimilarity and similarity factors:

$$f_1 = \{[\sum_{n=1}^{n} |R_t - T_t|] / [\sum_{n=1}^{n} R_t]\} \times 100$$

$$f_2 = 50 \times \log\{[1 + (1/n)\sum_{n=1}^{n} |R_t - T_t|^2]^{-0.5} \times 100\}$$

where, n is the number of dissolution sample times; R_t and T_t are the individual or mean percent dissolved at each time point, t, for the reference and test dissolution profiles, respectively.

ACCELERATED STABILITY STUDIES

Stability study of the best-fit formulation was conducted as per ICH guidelines under accelerated conditions at 40±2°C/ 75±5% RH for about six months in a stability chamber (thermo lab). Samples were collected and analyzed for % drug content, drug content resisted to acid and drug release at 1st, 2nd, 3rd & 6th months.

RESULTS AND DISCUSSION

Optimization Studies of Different Coating Layers

Seal coating: Different polymer concentrations of Hypromellose, 3 cps was coated for the formulations F1, F2, F3 at a weight buildup of *2.63% w/w, 5.26% w/w and 7.89% w/w* to the weight of sugar spheres. In formulation F1, breakage of sugar spheres was observed during coating whereas in F2 and F3 formulations, enough mechanical strength was observed for multiple units as breakage of sugar spheres were not observed during coating. For optimum % w/w of seal coating, *F2* formulation was finalized for further coating stages, i.e., drug coating.

Drug Coating*:* The five batches D1, D2, D3, D4, D5 were developed with different binders (Hypromellose, 3cps and Povidone pvp k-17) and binder concentrations (10, 15, 17.5 and 22 mg/unit) for ***F2*** seal coated multiple units by using suspension layering technique in a fluid bed processor and analyzed for the amount of drug coated (drug content estimation) onto the seal coated pellets. D1 and D2 were formulated with binders Povidone (pvp k-17) and Hypromellose, 3 cps respectively. The amount of the drug content (%drug coated) for these formulations was 69% and 80% respectively. By this, it was clear that D2 formulation coated using Hypromellose, 3 cps as a binder showed better binding of drug on to the seal coated pellets than D1 coated using povidone (pvp k-17) with the same binder concentration. To improve the amount of drug to be coated, further trails were planned with increased Hypromellose concentration. D3 formulation showed that the drug content was about 91%. The decrease in the amount of drug bound to F2 multiple units may be due to inadequate binding of drug on to seal coated multiple units. So, in D4 formulation, the binder concentration was increased to 17.5 mg/unit and found that drug content was 99%. Even no process problems were observed during coating in D4. To check the process feasibility with a further increase in binder concentration, D5 was formulated with 22 mg/unit of binder and found to have a drug content of 98% but lumps were observed during a coating process. From these observations, 17.5 mg/unit of Hypromellose, 3 cps ***(D4)*** was an optimized binder concentration for drug coating.

Barrier Coating: Main aim of barrier coating is to protect the drug coated multiple units from direct interaction with acidic enteric coating polymer and environmental conditions. It also reduces surface roughness of the coating substrate and enhances adhesion of the enteric film on the substrate surface. Barrier coating was given to D4 drug coated multiple units. In B1, barrier coating was given with Hypromellose, 3cps and Talc where as in B2 and **B3** Hypromellose, 3cps, Sodium Lauryl Sulphate, Talc were used. In B1 and B2 formulations, yield was found to be low. Hence these formulations don't show better protection for drug coated multiple units. In **B3** formulation, both Hypromellose and Sodium Lauryl Sulphate concentrations were increased for better film formation there by better protection was obtained to drug coated multiple units.

Enteric-Polymer coating: To prevent drug degradation and protect the drug from acidic environment of the stomach and release the drug component in the intestinal region, a delayed/ gastro-resistant coating is given with enteric coating polymers like Polymethacrylates (Methacrylic acid/ethyl acrylate), Cellulose esters (Cellulose acetate phthalate, Cellulose acetate trimellitate, Hydroxypropylmethylcellulose acetate Succinate), Polyvinyl derivatives (Polyvinyl acetate phthalate). The polymeric backbone of an enteric coating polymer generally has free carboxylic acid groups and the number of carboxylic acid groups in the polymer composition influences its solubility. These polymers are insoluble in acidic juices of the stomach (pH ~3) but become de-protonated and dissolved in basic/alkaline media at nearly neutral pH values (pH>5). In the present formulation, *Methacrylic acid copolymer (type C)* was chosen for enteric coating. In E1 formulation, *Methacrylic acid copolymer (type C) dry polymer* was used and this formulation does not comply with USP limits for the % drug release in 0.1N HCl. So, further trials E2, E3, E4, **E5**, E6 were conducted with *Methacrylic acid copolymer (type C) 30% aqueous dispersion*. E2 formulation does not comply with USP limits for the % drug release in 0.1N HCl. Hence, further trials were planned with increased polymer concentration. E3 formulation was found to have drug release of 13% in acid media and in buffer stage, drug release profile was found to be high. To retard the release profile and protect the drug from acidic pH, trials were planned with the further increase in enteric polymer concentration. E4 formulation was found to be good in acid stage but doesn't comply with USP limits in buffer stage. Further trials were planned with increased plasticizer concentration because the success of enteric coating efficiency mostly relies on the addition of plasticizers. The major function of the plasticizers is to improve elasticity and spreadability of the rigid and breakable polymers on the surface of the coating substrates by reducing the minimum film forming temperature (MFFT) of the polymers and softening the polymeric film at a lower temperature (Thoma, K. and Bechtold, K., 1999). The amount of plasticizer also influences film flexibility. Insufficient amount of plasticizer causes film blistering, which could lead to a premature drug release in acidic media. However, the high amount of plasticizer reduces the strength of the film and may accelerate the water uptake into the cores upon storage. The formulation **E5** with increased plasticizer concentration complies with USP limits and marketed product for % drug release in acid and buffer stages. To study the affect of polymer and plasticizer concentration on the %drug release in acidic and basic media; trial E6 was conducted with further increased polymer and plasticizer concentration. In E6 formulation, % drug release was found to comply in acid stage, but in buffer stage, release was found to be retarded. Based on the above results, **E5** was finalized as a best-fit formulation.

Over coating: To produce the characteristic gloss, enteric coated pellets of all the formulation trails from E1 to E6 were coated with the mixture of Glyceryl mono stearate and Talc. After over coating, pellets of all batches were elegant. The drug content, the amount of drug content resisted and drug release in acid (in 0.1 N HCl after 2 hours) was depicted in **Figure 1** and the comparative dissolution profile of different

formulations with a marketed product was depicted in **Figure 2**.

Similarity and dissimilarity: For *in vitro,* dissolution curves to be considered f1 values should be in the range of 0-15 while values of f2 should lie within 50-100**.** The *dissimilarity (f1) and similarity (f2) factors* for optimized ***(E5)*** and marketed formulation were found to be 3.56 and 72.49, respectively.

Accelerated stability studies: Results of AST showed that the formulation ***E5*** pellets filled into size ***'2'*** capsules were stable at 40°C/75% RH for 6 months **(Figure 3 and 4)**.

CONCLUSION

In line with the above results and observations, it can be concluded that seal coating on to inert sugar spheres with Hypromellose, 3 cps at an optimized average weight build up of 5.26% w/w **(F2)** gives better mechanical strength to withstand for further coatings. In drug coating, 17.5 mg/unit Hypromellose, 3 cps **(D4)** was found to have efficient binding of drug compared to different concentrations of Hypromellose and Povidone (pvp k-17) with respect to % yield and drug content. Barrier coating was given with Hypromellose, Talc and Sodium Lauryl Sulphate combinations at an average weight build up of 8.09% w/w **(B3)** offers better protection of the drug from acidic enteric polymer. Enteric-polymer coating given by Methacrylic acid copolymer type C (30% aqueous dispersion) was optimized at an average weight build up of 81.58% w/w of barrier coated multiple units and release profile complied with the marketed product. In enteric coating, plasticizer plays major role in film formation. Among Triethyl citrate and Polyethylene glycol 400, Triethyl citrate was found to have good film forming capacity and plasticizer concentration optimized was about 10% w/w to dry polymer weight. Over coating was given to enteric coated pellets with Glyceryl mono stearate and Talc to have characteristic gloss. Finally, it was concluded that **E5** as best fit and stable formulation for formulation of Esomeprazole delayed release multiparticulate capsules.

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