Original Article

Enteric Dissolution Enhancement of Engineered Gastro Resistant Omeprazole Tablets using Hydroxypropyl Methylcellulose Acetate Succinate

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ABSTRACT

Purpose: Oral drug delivery system has always been a preferred choice for the treatment of peptic ulcer and gastroesophageal reflux diseases. Being a proton pump inhibitor omeprazole restricts gastric acid secretion but the foremost downside is its degradation in acidic environments. The systemic absorption of gastro-unstable drugs can be improved by the enteric coating. **Materials and Methods:** This study was aimed at developing an effective enteric coating for omeprazole tablets using HPMC E5-LV and Hydroxypropyl Methylcellulose Acetate Succinate (HPMC-AS) polymers. The core tablets were subcoated with HPMC E5-LV which acted as a barrier between core tablet and enteric coated tablet. The enteric coating was applied using HPMC-AS. **Results:** Dissolution information unveiled that the enteric coat remained in place for 2 hr in acidic medium (0.1N HCl) and later dissolved when came in contact with basic media (acetate buffer pH 6.8), it dissolved within a jiffy. **Conclusion:** The release profile showed 91 to 98% drug release within 1hr in pH 6.8 Acetate buffer. Further instrumental analysis was performed to ascertain drug-polymer interaction.

Key words: Proton pump inhibitor, Enteric coating, HPMC, Omeprazole, Dissolution enhancement.

INTRODUCTION

The first "Proton Pump Inhibitor (PPI)" Omeprazole, is one of the major active ingredient in antiulcerative drug products, extensively used for prevention and treatment of gastric and duodenal ulcers, symptomatic gastro-esophageal reflux,[1] gastric bleeding[2] and dyspepsia.[3] The omeprazole drug product is kenned to degrade in acidic media as a function of pH but has acceptable stability under alkaline conditions.[4] The PPI irreversibly blocks the parietal proton pump of the gastric mucosa.[5,6] This ion gated pump is responsible for eluting protons into the gastric environment. Inhibition of the pump result in lowering of overall acid secretion by gastric mucosa.[7,8] Decrementing acid can lead to the rejuvenation of duodenal ulcers and provide relief.

In the delayed release tabet the dosage form is relinquished after certain time interval so that it can pass through the upper GI and reach the intestine. To achieve this goal the dosage form is often coated with a polymer which acts as a barrier and prevents drug dissolution in acidic pH.[9] Enteric coating also acts a mean to barricade the drugs from degradation which are unstable in the gastric environment. Enteric coating is additionally an efficacious method to obtain drug targeting (such as gastro-resistant drugs). The enteric coated tablet formulations are considered as delayed action delivery systems. Omeprazole is acid-labile and decomposes rather rapidly at pH < 5.[10] Polymers like hydroxypropylmethylcellulose, hydroxypropyl-methylcellulose phthalate, cellulose acetate

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phthalate, polyvinylacetate phthalate, methylmethacrylate are commonly utilized in enteric coating.[11] HPMC-AS is a semi synthetic compound prepared by addition of hydrophobic acetate group and ionizable succinic acid group to the hydrophilic hydroxyl groups of the HPMC backbone. This change in chemistry results in increased inherent lipophilicity and pH specific solubility which was not previously native to the polymer. This modification makes HPMC-AS an unique enteric coating candidate over its contemporaries.[12]

Several attempts were made to increase the bio-availabilty of omeprazole. Choi *et al.* 2000 prepared bucco-adhesive omeprazole tablets using HPMC to bypass Hepatic fast-pass metabolism and gastric degradation but disadvantages like low permeability,[13] small absorption area, chances of swallowing and the effect of salivary scavenging make it a less preferable formulatory approach. Tu¨rkoglu *et al.* 2004 prepared enteric-coated omeprazole pellets employing microcrystalline cellulose as an aid in plastic deformation in the compression process.[14] Though microcrystalline cellulose enhanced the compressiblility of omeprazole, variation in it's concerntration played a key role in the degradation of drug itself in acidic medium. Choudhury *et al.* 2010 prepared omeprazole mucoadhesive tablets containing 20 mg omeprazole coated with carbopol 934P achieved satisfactory % swelling index,[15] drug content and promising mucoadhesive strength, appears to be a potential candidate for the development of mucoadhesive tablet for effective therapeutic use as well as controlled drug delivery but with some disadvantages like drug loss during coating. The presnt research is aimed at a stable omeprazole oral formulation by taking HPMC AS as enteric coating material due to it's contribution in enhancing dissolution and stability.[16]

MATERIALS AND METHODS

Materials

All the Materials employed for the development of omeprazole enteric coated tablets were, Omeprazole (Aurobindo Pharma), Lactose Monohydrate (DFE Pharma), Sodium Starch Glycolate(SSG) (DMV), Sodium Steryl Fumarate(SSF) (JRS Pharma), Methocel E5 premium LV (The DOW Chemical), Sodium Lauryl Sulfate (SLS) (BASF), Sodium Hydroxide Pellets (Rankem), Polyethylene Glycol 6000 (PEG 6000) (Clariant Chemicals), Hydroxy Propyl Methyl Cellulose Aetate Succinate (HPMC AS) (Ashland), Triethyl Citrate (TEC) (Vertellus), Ammonia Solution (Merck), Talc Ultra Micronized (Imerys Talc Austra) and Opadry Brown (Colorcon). All the other ingredients used were of analytical grade

Methods

Preparation of core tablets

Omeprazole delayed release tablets were prepared by wet granulation method.[17] All the material were accurately weighed and co-sifted through 30 mesh. The material was loaded into RMG (model-HSMG-2, Gansons) and dry mixed for 10 min with impeller at low speed and chopper off. Dry mix material was checked for LOD (Loss on drying) in Moisture Balance (model-MX 50 AND) at 105°C: 0.85%. Binder solution was prepared by using HPMC E5 LV, NaOH and sodium stearate. The binder solution was added to the dry mix materials for 2 min 30 sec under slow impeller and fast chopper. Further kneading was carried out for 15 sec under slow impeller and slow chopper.

Wet mass was dried at 50°C for 30 min at fluidization 25 to 30 CFM (Cubic Feet per Minute) in rapid dryer (model-TG100, Retsch). Dried granules were checked for LOD at 105°C i.e. 0.90%. Dried granules were sifted through 30 mesh. The retained granules were co-milled (model-U5 0280, Quadro) at slow speed and again passed through 30 mesh and all the materials were mixed properly. In prelubrication stage, extra granular materials excepts sodium stearyl fumarate were sifted through 30 mesh and blended in blender (VB 3/5/10, San) with intragranular materials for 10 min in low shear blender at 16 rpm. Sodium stearyl fumarate was shifted through 30 mesh and blended with pre lubrication materials for 5 min in the low shear blender. Lubricated blend was compressed in compression machine (model-CMD 4, Cadmach) into tablets with the following tooling and parameters i.e. 12.0 × 6.0 mm length, Capsule shape, Plain on both side. Formulation of different core trial tablets is depicted in Table 1.

All trial batches were evaluated basing on the physicochemical parameters like weight wariation, friability and disintegration time as per USP guidelines. The batch which showed promising results in physicochemical characterizations was selected for further study.

Sub coating of core tablets

Sodium hydroxide and PEG 6000 were dissolved in purified water under stirring. HPMC E5 LV was further added slowly to the solution with constant stirring to urge clear solution. Talc UM was added to the above solution under stirring for 20 min. The sub coating solutions were prepared in different concentrations i.e 2.5%, 5% and 7.5% of coating (Table 2).

Table 1: Formulation for omeprazole core tablets.

	Trial 1	Trial 2	Trial 3	Trial 4	Trial 5	Trial 6	Trial 7
Ingredients	**Mg/tab**	**Mg/tab**	**Mg/tab**	**Mg/tab**	**Mg/tab**	**Mg/tab**	**Mg/tab**
Omeprazole	20.08	20.08	20.08	20.08	20.08	20.08	20.08
Lactose Monohydrate	202.52	195.62	201.37	197.92	201.37	197.92	200.22
Sodium Starch Glycolate	2.3	9.2	4.6	4.6	4.6	4.6	4.6
Hypromellose E5 LV	2.3	2.3	2.3	2.3	1.15	4.6	2.3
Sodium Steryl Fumarate	2.3	2.3	1.15	4.6	2.3	2.3	2.3
NaOH	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Core tablet weight	230	230	230	230	230	230	230

Table 2: Formulation of sub coating solution.

	Batch 1(2.5%)	Batch 2(5%)	Batch 3(7.50%)
Ingredients	**Mg/tab**	**Mg/tab**	**Mg/tab**
Hypromellose E5 LV	4.60	9.20	13.79
PEG 6000	0.46	0.92	1.38
Talc UM	0.63	1.27	1.90
NaOH	0.060	0.12	0.18

Table 3: Parameters of coating.

Sl. No.	Parameters	Data
1	Inlet Temperature(°C)	44-47
2	Exhaust Temperature(°C)	39-41
3	Bed Temperature(°C)	37-41
4	Pan RPM	8-12
5	Spray Pump RPM	4-6
6	Atomization	bar-1.6 bar

Core tablets were loaded into the coating machine (model-GAC 250/375, Ganson) and pre warmed at an inlet temperature 45°C with an intermittent inching for 10 min. Sub coating dispersion was sprayed onto pre warmed core tablets with parameters mentioned in Table 3.

Enteric coating sub coated tablets

Sodium lauryl Sulfate was dissolved in purified water under stirring. Triethyl citrate was integrated to solution with constant stirring. Further HPMC AS was integrated gradually to solution under stirring for 15 min. Liquid ammonia solution was added to adjust the pH between 7 to 9. Micronized talc was added slowly to solution under stirring for another 15 min. Lastly Opadry Brown was added to the above mixture and stirring was continued for another 30 min to attain uniformity.[18] The enteric coating solutions were prepared in different concentrations like 20%, 25% and 30% of coating (Table 4). Enteric coating dispersion

Table 4: Formulation for enteric coating solution.

	Batch 1(20%)	Batch 2(25%)	Batch 3(30%)
Ingredients	**Mg/tab**	**Mg/tab**	**Mg/tab**
HPMC AS MF	25.20	31.5	37.80
Triethyl citrate	7.05	8.82	10.58
SLS	0.75	0.94	1.12
Talc UM	9.00	11.25	13.50
NH_3	NA (Qs to pH-7-9)	NA (Qs to pH-7-9)	NA (Qs to pH-7-9)
Opadry brown	6.30	7.88	9.46

Table 5: Parameters of coating.

Sl. No.	Parameters	Data
1	Inlet Temperature(°C)	43-47
2	Exhaust Temperature(°C)	39-41
3	Bed Temperature(°C)	38-41
4	Pan RPM	10-13
5	Spray Pump RPM	3-5
6	Atomization	1.2-1.6 bar

was sprayed onto pre warmed sub coated tablets with following parameters mentioned in Table 5.

Evaluation of coated tablets

Formulated Omeprazole enterric coated tablets were evaluated (as per USP) for the weight variation, hardness, friability and disintigration time. The formulations were assessed by dissolution testing. Initial dissolution study was administered by USP type II Paddle (Electro Lab) at 100 rpm in 750 ml of 0.1 N HCl for 120 min and later in 900ml of pH 6.8 acetate buffer for hour.

Instrumental characterization

Powder X-Ray diffraction(XRD)

The X-ray powder diffraction (XPRD) pattern of omeprazole and with other excipients were analysed utilizing a Rigaku (Ultima-IV) diffractometer. It shows

the scattering angles (2θ) values, the interplanar d-spacing (A°), observed for the major diffraction peaks. The angular range was within 5° to 60° (2θ).

Differential scanning calorimetry (DSC)

Differential scanning calorimetry studies were performed for the drug and excipients utilizing a Mettler Toledo DSC-1 Stare system (Mettler Toledo) underneath the subsequent conditions: sample weight 3-5 mg, scanning speed 10°C/min, within the 25-200ºC temperature range. The samples were heated in hermetically sealed aluminum pans and indium was utilised as standard (Brittain, 2010).

Fourier transform infrared (FTIR) spectroscopic

The infrared (IR) absorption spectrum of omeprazole and other excipients were obtained in a KBr pellet using a Jasco (FT/IR-4600) IR spectrophotometer.

RESULTS AND DISCUSSION

Evaluation of core tablets

The physicochemical charecters under evaluation for both core and coated tablets were found to be compliant to USP guidelines for the said concern. Different parameters such as hardness, thickness, strength and weight variation were evaluated. For core tablets thickness of all tablets ranges between 3.21 to 3.28 mm and hardness was found within the vary of 5.10 to 5.82 KP. Percentage weight loss for all the batches was less than 1 chronicles in the fibrillation apparatus. It has been found from the weight variation and drug content analysis that all the formulations were within permissible USP range (average weight- 229 mg to 235 mg and individual weight- 227 mg to 235 mg). Disintegration time of core tablets were found to be within 5 min 30 sec to 6 min 10 sec. which is in compliance with the USP.

Drug release study

The drug release of all formulations i.e. Batch one (20%), Batch 2 (25%) and Batch 3 (30%) of enteric coated tablets was carried out in 0.1N HCl for two hours and one hour in acetate buffer pH 6.8.[19]

Acid resistance

All the three batches (1,2 and 3) were observed in acidic medium i.e. 0.1N HCl. In Batch 1 demonstrated degradation upto 87% for all the tablets and failed to adher USP specifications. In Batch 2 and 3 all the tablets degraded were in the range of 0.8% and 0.3% respectively. Further characterization was carried out on batch 2 and 3.

Drug release profile

The dissolution study was done in pH 6.8 acetate buffer 900ml for 1 hr. The dissolution profiles of batch 2 and 3 were displayed in Figure 1. In this Figure the batch 3 drug release is slower compared to batch 2 due to excess concentration of enteric coating polymer and other excipients coated during enteric coating. As per USP guidelines for the enteric coated tablets, for immediate release formulations the drug release in pH 6.8 acetate buffer should be more than 80% in 10 min. In pH 6.8 acetate buffer all the enteric coated tablets behaved like immediate release formulation. Basing on the release profile batch 2 was selected for further stability studies. Kinetic modeling approach has been applied to the dissolution data to understand the underlying mechanism. Zero order, first order, Higuchi, Hixson Crowell and Korsmeyer Pappas equation models were tried.[20] Selection of best fit was made on the basis of highest regression coefficient (r^2) value depicted in Table 6. The correlation coefficient value for peppas model were found to be highest. Peppas kinetic release exponent value (n) was more than 0.5 and less than 1 for both the trials,which indicates that the drug release is both diffusion and erosion dependent.

Stability study

Batch 2 was selected for the stability studies. The omeprazole tablets were packed in two different type of packaging i.e. alu-alu blister and HDPE bottle. The packed tablets were subjected to accelerated stability

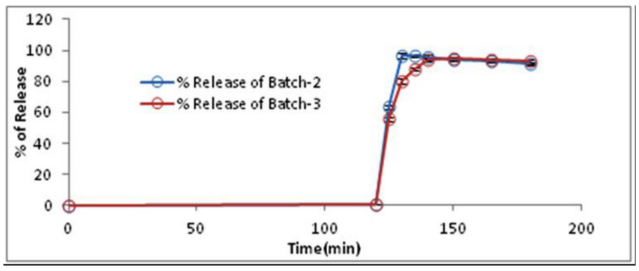

Figure 1: Dissolution profile of Batch 2 and Batch 3.

Table 6: Kinetics of in-vitro drug release.

	Zero order	First order	Higuchi	Peppas	
Batch	r^2	r^2	r^2	r^2	n
Batch -2	0.5546	0.5142	0.5052	0.9241	0.5394
Batch -3	0.5861	0.5656	0.5101	0.9248	0.5302

testing (40°C/75% RH) for 3 months. After the study period the tablet showed no physical changes in their appearance. Acid resistance and the dissolution study was carried out for stability charged batches (Table 7).

Acid resistance

The acid degradation of tablets charged in alu-alu blister packaging and HDPE packaging were found to be 2.1% and 1.9% respectively. According to USP guidelines the degradation should not be more than 10%, so the two batches passed as per USP monograph.

Dissolution (6.8 acetate buffer-900 ml/paddle-100 RPM/1 hr)

After 2 hr of acid resistance all the tablets were transferred into pH 6.8 acetate buffer and was observed for 1 hr. Drug release of the Stability batches remained same as that of Batch 2 (Figure 2).

Powder X-Ray diffraction (XRD)

The diffractogram of the pure omeprazole showed the typical peaks appearing at 10.6, 12.34, 19.80, 23.93 and 27.62 (2θ) (Figure 3).[21] The high intensity pointed peaks of omeprazole pure drug established its inherent crystallinity. The diffractogram of physical mixtures corresponding to Omeprazole, HPMC AS, HPMC E 5, Lactose, SSG, SSF, Talc, PEG6000 and SLS depicted in Figure 3 potrayed lower intensity peaks due to the presence of polymers. The diffractogram of omeprazole tablet showed only one characteristic intensity peaks appearing at 29.31 (2θ). The intensity of characteristic peaks of omeprazole has been lowered substantially in the tablet formulation. The increase of the full width at half maximum (FWHM) in the diffraction pattern of the formulation was may be the result of possible conversion of microstate of crystalline drug to amorphous form.

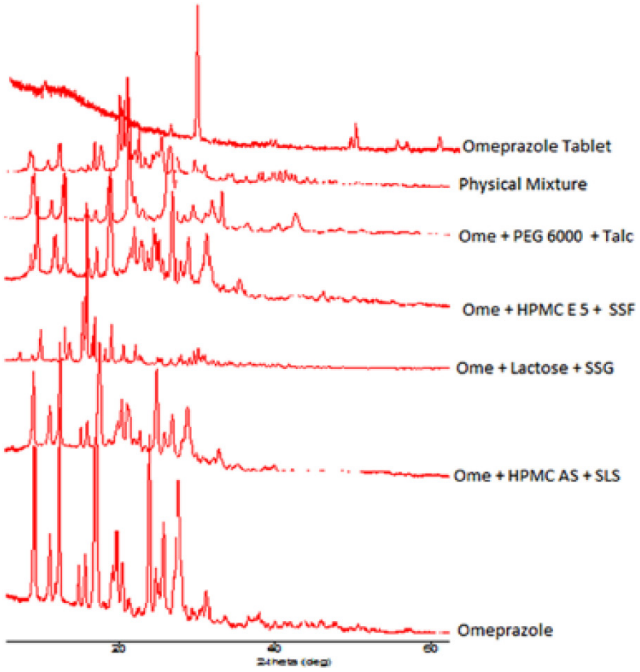

Figure 3: XRD pattern of omeprazole, drug polymer physical mixtures and Tablet.

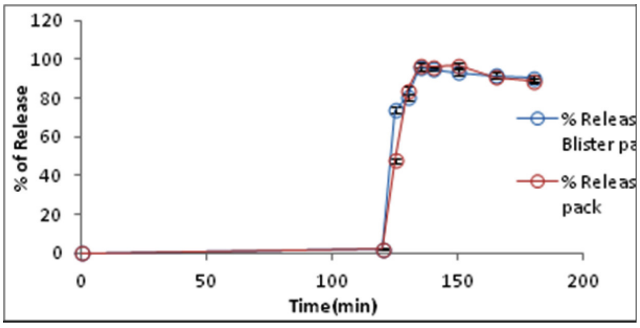

Figure 2: Dissolution profile of omeprazole delayed release tablet after loaded at 40°C/75% RH in stability chamber.

Table 7: Kinetics of *in-vitro* drug release of stability charged batches.

	Zero order	First order	Higuchi	Peppas	
Batch	r^2	r^2	r^2	r^2	n
Alu-Alu package	0.5805	0.5618	0.5302	0.9355	0.5377
HDPE package	0.5584	0.4982	0.4932	0.9066	0.5299

Differential scanning calorimetry (DSC)

The DSC thermogram was employed for the derivation and characterization melting point and crystalline behaviour of the drug.[22] DSC thermogram of pure omeprazole revealed a charecterstics endothermic peak with sharp melting point at 159°C, which confirmed its crystalline characteristics. The endothermic peaks of physical mixtures containing omeprazole and polymers (HPMC AS, HPMC E 5, SSG, SSF, SLS, Lactose, Talc and PEG 6000) depicted in Figure 4 shows lowering in intensity and shifting of endothermic peaks as compared to the pure drug. In case of tablet, the endothermic peak of omeprazole was found to be 143.46°C. The shifting of peaks are the outcomes of the dispersion of crystalline drug entity in the polymeric matrix.

Fourier transform infrared (FTIR) spectroscopy Analysis.

An overlay of FTIR spectra of the pure omeprazole, drug polymer physical mixtures and tablets with spectral

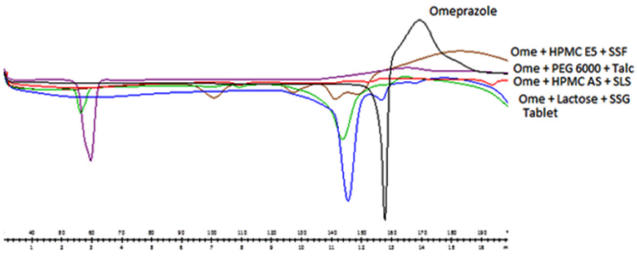

Figure 4: DSC thermogram of omeprazole, drug polymer physical mixtures and Tablet.

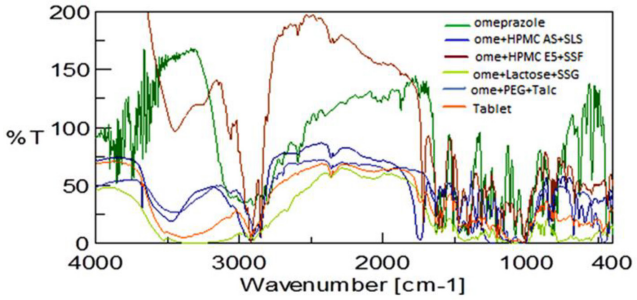

Figure 5: FTIR spectra of omeprazole, drug polymer physical mixtures and Tablet.

shifts were depicted in Figure 5. Spectra of pure omeprazole potrayed characteristics band at 2902.34 cm^{-1}, 1627.60 cm^{-1}, 1586.16 cm^{-1}, 1158.01 cm^{-1} and 1074.16 cm^{-1} due to C-H stretch, C=C stretch, C=N stretch, CH_2 stretch, C=O stretch and C=S stretch respectively. Spectra of characteristics peaks band at (1407.78 cm^{-1}, 1310.39 cm^{-1}) is due to CH bending and 1510.95 cm^{-1} due to CH_2 bending respectively. Peak bands at 965.19 cm-1, 885.166 cm^{-1}, 822.49 cm^{-1} is also due to C-H bending. In the tablet formulation, characterisics peaks corresponding to pure omeprazole overlapped to form strong asymmetric envelope assembled arround 822.49 cm^{-1} to 1627.60 cm^{-1}. The characteristics peaks were broad as compared to omeprazole pure drug. In this region all the formulation Frequency of stretching and bending were either shifted or masked due to the drug-excipients interaction i.e. intramolecular hydrogen bonding.

CONCLUSION

All the batches (1, 2 and 3) of omeprazole delayed release tablet were observed in dissolution media. It was found that the batch 2 and 3 had resisted acidic medium for 2 hr and got released in pH 6.8 acetate buffer due to maximum concentration of enteric coating polymer, other excipients used and the smaller diffusion pore size. The release of omeprazole from batch 2 (97%) was significantly high as compared to batch 3 (76%) due to the abundancy of enteric coating polymer. Instrumental characterization such as FTIR, DSC and XRD revealed that the crystalline drug has been amorphised in the tablet formulation.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

HPMC: Hydroxylpropylmethycellulose; **FTIR:** Fourier transform infrared spectroscopy; **SEM:** Scanning electron microscopy; **DSC:** Differential Scanning Calorimeter; **PPI:** Proton Pump Inhibitor.

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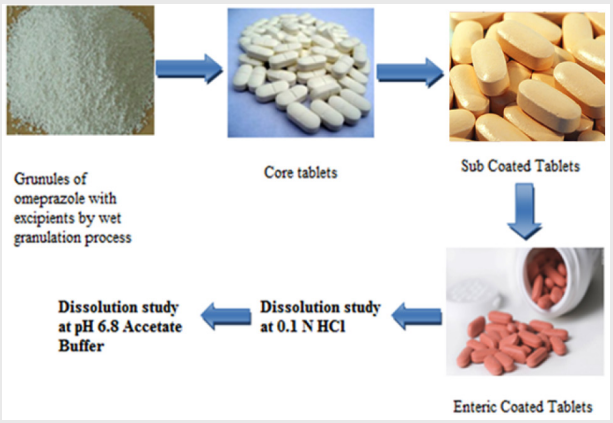
PICTORIAL ABSTRACT



SUMMARY

In recent years omeprazole has been extensively used for inhibition of acid secretion in stomach. Omeprazole is available in various types of dosage forms namely, pellets, capsule, suspension and injection. These kind of preparations generally suffers from disadvantages like difficulty in administration and stability. To overcome the above mentioned lacuna omeprazole tablets were prepared for easy oral administration. The inherent poor flow property of omeprazole was addressed by carrying out wet granulation using HPMC E5 LV as binder. Omeprazole gets degraded in the stomach; to prevent this enteric coating was done employing HPMC. This formulatory approach can be transferred to local pharmaceutical industries.

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