RESEARCH ARTICLE

Formulation, Development, Evaluation and Optimisation of pH Dependent Drug Delivery System Containing Proton Pump Inhibitor

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ABSTRACT

The current study was involved the formulation and evaluation of Rabeprazole pellet. In current study the pellet formulation of Rabeprazole was formulated by using Extrusion and Spherization technique. Active Pharmaceutical Ingredient (APIs) and excipients selected for formulation was tested for preformulation study as well as by using analytical techniques like ultra violet (UV) spectoscopy, fourier transform infrared (FTIR) spectroscopy, differential scanning calorimetry (DSC). Initially cylindrical shaped structed mass formed by extruder then by using spheroniser it was transformed in to equal and sphere-shaped pellet. As Rabeprazole shows maximum drug absorption in basic pH condition, the strategy in current approach was used as a polymer coat. Before applying polymer, coat core pellet was coated for seal coating. Seal coat helps in protection of the core pellet from different environmental conditions as well as from another coat which applied on core pellet. After completion of seal coat polymer coat was applied by using Eudragit L 30. Polymer coat helps to release the formulation in appropriate location only. For seal coating and polymer coat Glatt instrument was used. After formulation the pellet was evaluated for all quality control parameters like Dissolution, Fourier Transform Infrared Spectroscopy, Differential Scanning Calorimetry study. Stability study was performed on optimised batch.

Keywords: Acid, Gastrointestinal tract, Peptic ulcer, Polymer, Stomach.

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INTRODUCTION

Rabeprazole belongs to proton pump inhibitor category. Among proton pump inhibitor Rabeprazole are used mostly currently in the treatment of the peptic ulcer. It is mainly used in the treatment of peptic ulcer, gastro oesophageal reflux disease. The main role of the proton pump inhibitor is to inhibit the acid secretion by formation of covalently bond of H+ / K+ ATP ase in parietal cell. Mostly gastrointestinal ulcer occurred in duodenum. The main cause of the peptic ulcer is due to *Helicobacter pylori*.[1] A group of proton pump inhibitors degrades in stomach where acidic condition present. Hence such strategy should use like there should no degradation take place in acidic condition. For this delayed release as well as targeted drug delivery system used. For formulation of such medicament if polymer coat applied it gets majority of chances that it releases its maximum dose at appropriate site. Also, basic polymer coat helps the formulation from degradation from acidic condition in stomach.[2] In current study initially pellet formulation was carried out by using extruder and spheroniser instrument. Seal coat was applied on core rabeprazole pellet so as to protect from different environmental condition as well as from another polymer coat on pellet. On the top of the pellet polymer coat was applied. The main role of the polymer coat was to protect the formulation from acidic condition in stomach and to release the formulation in appropriate site only.[3] Because of polymer coat site specificity is higher hence it increases the drug bioavailability.

MATERIALS AND METHODS

Materials

Rabeprazole, Sodium Carbonate, Mannitol, HPMC, Calcium Stearate, Opadry, Eudragite L-30D, Triethyl Citrate, Talc was supplied by Modern chemical.

Methodology

Melting Point

Melting point of the API was analysed by using capillary method.

Preformulation Study

Preformulation studies like Angle of repose, Bulk density, tapped density, carr's index was carried out.

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Table 1: Formulation of core pellet.

	Quantity (mg)					
Ingredient	*F1*	*F2*	*F3*	*F4*	*F5*	*F6*
Rabeprazole	20	20	20	20	20	20
Sodium Carbonate	8	8	9	12	13	14
Mannitol	4	6	6	7	8	9
HPMC	3	4	5	5	6	7
Calcium Stearate	2	2	3	3	4	4
Alcohol	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

Table 2: Composition of seal coating.

Ingredient	*Quantity %*
Opadry	22
Methylene dichloride	50
Isopropyl alcohol	50

Table 3: Composition of Polymer coating.

Ingredient	*Quantity (mg)*
Eudragite L-30D	52
Triethyl Citrate	10.15
Talc	11

Table 4: Organoleptic characters

Sr. No.	*Test*	*Observation*
1	Appearance	Crystalline
2	Colour	White
3	Odour	Characteristic
4	Melting Point	138-142^{0}C.

FTIR Spectroscopy

FTIR spectra of plain API and combination with all excipients were carried out at 4000–400 cm^{-1}. Initially mixture of 5 mg whose FTIR study should carried out was mixed with 0.1 gm of potassium bromide powder and pressed under pressurised vacuum for 3 to 4 minutes at 12 psi. Same process was carried out for API-Excipient compatibility study.[4]

UV Spectroscopy

10 mg of API was mixed in 100 mL of methanol to prepare standard stock solution; API was completely dissolved in methanol. Final volume was made up to 100 mL by using methanol. Then from this solution different aliquots were prepared hence 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, and 1.0 mL of solution withdrawals from stock solution and made final volume up to 10 mL with given solvent to make different aliquots. The given solvents were scanned under UV-spectrometer at 200–400 nm to get absorbance of each mixture by keeping blank as a solvent.[4]

DSC Study

Thermal study of the selected API was carried out under the differential scanning calorimetry. For this purpose, the pure drug sample was kept in instrument and heated at rate of 10ºC/min in between 25 and 35ºC and for 40 mL/min for the flow of the nitrogen. From the received data degradation study and purity can be carried out.[5]

Pellet Preparation

In first step Rabeprazole mixed thoroughly along with sodium carbonate, mannitol. Then in previously mixed blend granulating agent added along with solvent and make the mass wet. Hence all process was carried out by wet granulation process. Lastly calcium stearate added. Then prepared wet mass was placed in extruder, it formed the cylindrical shape structure mass. Then this cylindrical shape structured mass introduced in to spheronizer, in spheronizer the cylindrical mass converted in to round shape that is cut in to uniform sphere, this process is known as spheronization.[5] Table 1 shows Formulation of core pellet.

After preparation of core pellet of Rabeprazole, seal coating was completed. The main role of seal coating is to protect the core pellet from another coating i.e., to reduce incompatibility chances. For seal coating of pellet Opadry polymer was selected. Methylene dichloride and Isopropyl alcohol was initially mixed with 1:1 proportion then Opadry mixed thoroughly in solvent. Seal coating was completed in Glatt instrument. After completion of seal coating pellets were dried in warm temperature in Glatt instrument.[5] Table 2 shows Composition of seal coating.

After seal coating, polymer coating was completed which was outermost coat of the pellet. For polymer coating Eudragit L-30D was selected as a polymer coat. Triethyl citrate and talc mixed properly then Eudragit L-30D was mixed thoroughly. After completion of polymer coating pellets were dried in warm temperature in Glatt instrument. For polymer coating Glatt instrument was used.[6] Polymer coat is useful to deliver the formulation in appropriate site hence it increases bioavailability also. Table 3 shows Composition of Polymer coating.

RESULT AND DISCUSSION

Organoleptic Study

Organoleptic properties of API was carried out, in this appearance, colour, odour, melting point was studied.[7] Table 4 shows Organoleptic characters.

Preformulation Study

Preformulation study of the blend carried out, in preformulation study angle of repose, bulk density, tapped density,

compressibility index, hausnar's ratio study carried out.[7] Table 5 shows the preformulation result.

FTIR Spectroscopy

API and API-Excipient sample was scanned under FTIR spectroscopy. From the obtained result it was observed that API was pure and from the spectrum of API-excipient it was observed that excipients are not changing any property of the selected drug hence it was compatible with each other.[8] Figure 1 shows FTIR Study of API and Figure 2 shows FTIR Study of API and excipient.

UV Determination

100 mL standard stock solution of Rabeprazole were prepared by mixing 10 mg of API in solvent. API was mixed completely; then final volume was made up with selected solvent up to 100-mL. From this standard stock solution different aliquots were prepared of 1–10 µg/mL. Prepared solution was scanned under UV spectrophotometer under range of 200–400 nm. Maximum absorbance of API was found at 292 nm. Prepared different aliquoted also and scanned under UV Spectroscopy at 200–400 nm. From the obtained data calibration curve of API was plotted. Calibration curve of API was found in linear manner.[8] Figure 3 shows the calibration curve of Rabeprazole.

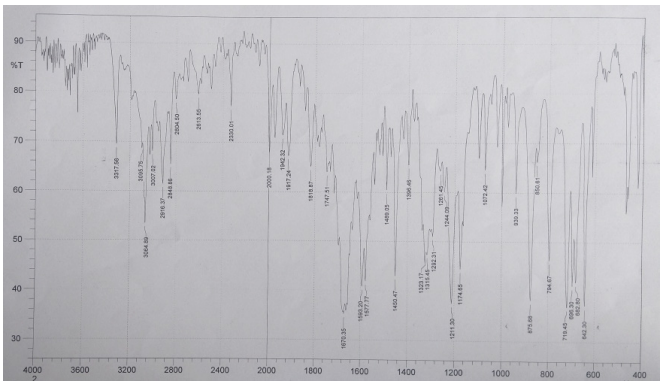

Figure 1 : FTIR study of API

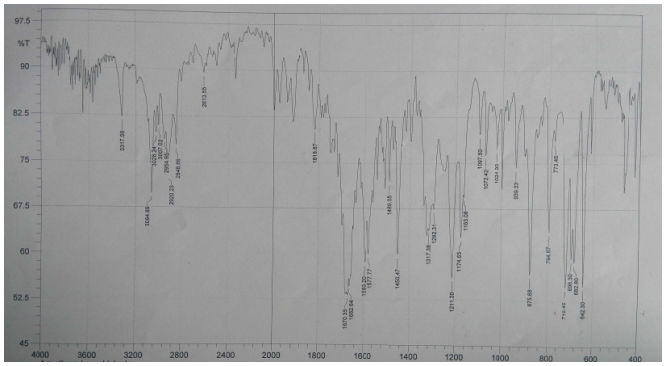

Figure 2: FTIR study of API and excipient

DSC Study

Thermal study of the selected API and formulation was conducted on differential scanning calorimetry. From the received data of the differential scanning calorimetry that is from thermogram it was observed that there was no any change in the selected drug with thermal effect. Hence it was observed the selected drug was pure in nature and not changed any characteristic in formulation. Figure 4 shows DSC study of Formulation.

In-vitro Release Study

In-vitro release study of formulation was carried out in 0.1 N HCL as well as in 7.4 phosphate buffer. In 0.1 N HCL formulation shows no any release. From obtained result of 7.4 dissolution study the plot was completed for all batches for comparitive study. Hence from the comparitive data of all dissolution result, t was found that batch 6 shows good

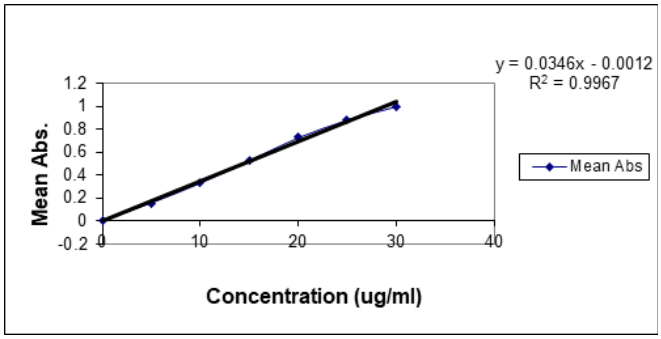

Figure 3 : Calibration curve of Rabeprazole

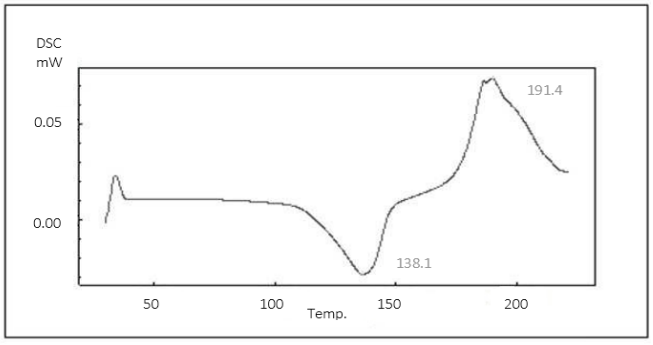

Figure 4: DSC study of formulation

Table 5: Preformulation result.

Batch	*Angle of repose (Θ)*	*Bulk density (gm/ml)*	*Tapped density (gm/ml)*	*Compressibility index (%)*	*Hausnar's ratio*
F1	21.41 ± 0.06	0.73	0.88	17.04	1.20
F2	41.26 ± 0.10	0.77	0.87	11.49	1.12
F3	23.27 ± 1.13	0.76	0.87	12.64	1.14
F4	23.92 ± 0.07	0.78	0.88	11.36	1.12
F5	30.61 ± 0.05	0.73	0.85	14.11	1.16
F6	31.97 ± 0.07	0.74	0.87	14.94	1.17

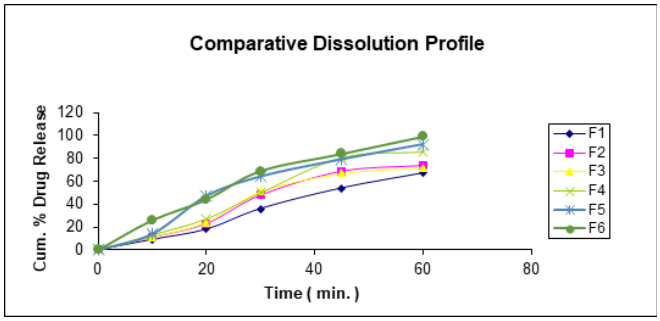

Figure 5: *In-vitro* dissolution comparitive study

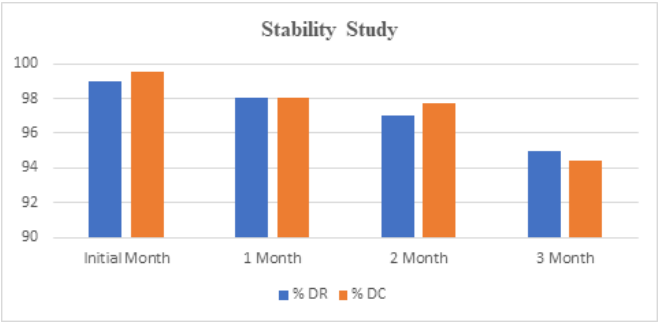

Figure 6: Stability study data

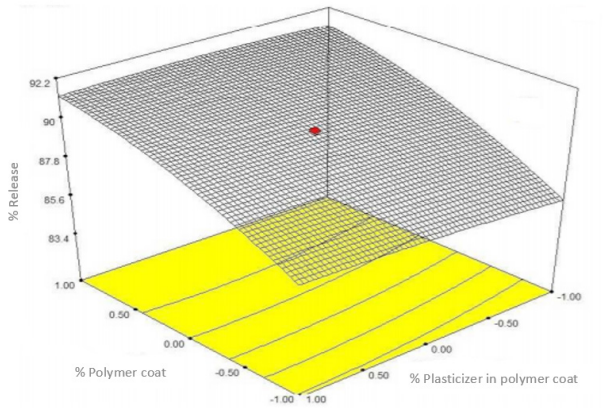

Figure 7: Response surface plot

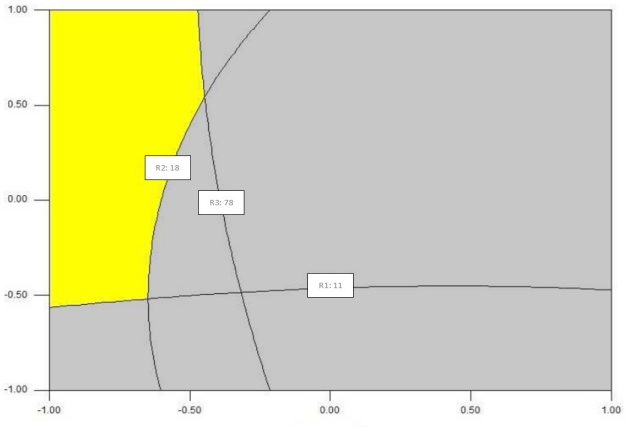

Figure 8: Overlay contour plot

dissolution result as compared to other batches.[9] Figure 5 shows *in-vitro* dissolution comparitive study.

Stability Study

From all the formlated batches, F6 was selected as a optimised batch as it shows best restult among all batches. Optimised batch formulation was kept in stability chamber to study the stability study. Selected formulation was stored in HDPE container at temperature condition of 40ºC/75% RH for 3 months.[10] Figure 6 shows stability study data.

Response Surface Plot and Overlay Contour Plot

Contour plot are designed for the optimisation of the formulation. Contour plot are multidimensional plot on which we can add multifactor for optimisation. Multifunctional response plot drawn to optimise the variation of response. Response surface plot mainly describes the co-relation between dependent factor and independent factor in formualtion. In seleced formulation release rate, %polymer coat and %TEC in coating parameters are selected for optimisation. In case of the contour plot different variables are plotted on one desired level as well as specific response noted for same in plotted graph. Axis of graph are mainly composed of experimental unit. From contour plot better value observed.[11] Figure 7 shows response surface plot and Figure 8 shows overlay contour plot.

SUMMARY AND CONCLUSION

The current study was performed to improve and increase the stability condition of the selected drug that is Rbeprazole in acidic condition. As mostly all proton pump inhibitors degrades in stomach where acidic condition present. Initially pellete formulation of Rabeprazole was prepared by using Extrusion and spheroniser instruments, pellets helps to increase surface area and hence increase dissolution rate. After pelete formulation core pellete was coated with opadry polymer for seal coat. Seal coat helps in minimising the interaction between core pellet and polymer coat as well as different humid and temperature condition. After seal coating Eudragit L 30D polymer used to coat the pellet. Hence polymer coat protects the pellete from degradation in acidic condition which is present in stomach. Formulated pellete was evaluated and passed all evaluation test. From different batches produced, the optimised batch was selected for stability study. Hence polymer coated pellete of Rabeprazole successfully formulated and evaluated.[11]

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