RESEARCH ARTICLE

Formulation and Optimisation of pH-Dependent Drug Delivery System Containing Proton Pump Inhibitor

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ABSTRACT

The objective of the current study was to formulate, evaluate, and optimize polymer coated pellets of rabeprazole. Rabeprazole is one of the productive drugs which show more effectiveness. Proton pump inhibitors are mostly used in ulcerative colitis. Rabeprazole acts by inhibiting last step of acid production. Rate of degradation of Rabeprazole increases as pH range decreases. Stability condition of proton pump inhibitor also affects by moisture content. Hence in current study, rabeprazole pellets were formulated and seal coat and polymer coat were loaded on pellets to protect from humidity and acidic condition. Rabeprazole was characterized by ultra violet spectroscopy (UV), fourier transform infrared spectroscopy (FTIR), differential scanning calorimetry (DSC) study. Drug-excipient compatibility study carried out by FTIR. Opadry was used for seal coating of pellet and Eudragit L100 was used as polymer coat. Optimized batch passes all evaluation tests. Stability data shows an excellent result.

Keywords: Coating, Compatibility, Peptic Ulcer, Proton Pump Inhibitor.

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INTRODUCTION

Proton Pump Inhibitors (PPI) are mostly used in the disease of Peptic ulcers. The disease is mainly related to gastric acid, and the ulcer is located in the gastrointestinal tract (GIT). Rabeprazole is the component of novel category of benzimidazole. Rabeprazole mainly act by inhibiting the last step of acid production. The stability of proton pump inhibitors decreases as pH decreases but increases as the pH range increases. Hence the stability of rabeprazole is reduced as the decrease in the humid atmosphere. If rabeprazole directly comes in contact with acidic conditions, it leads to a higher rate of degradation of rabeprazole.[1] As the acidic condition is present in the stomach, a delayed release or site-specific drug delivery system is used to protect the drug in acidic conditions and target the site-specificity. Such formulation consists of the core formulation with polymer-coated outer layer. It releases the formulation in some appropriate location and increases the bioavailability of the drug. Delayed-release or site-specific delivery system is used to target the colon and it also protects drug material from degradation through acidic conditions.[2] The objective of the current study was to formulate, evaluate, and optimize a stable Rabeprazole pellets formulation that employs less amount of polymer and consumes less operational time. Seal coat and polymer coat lead to an increase in stability and bioavailability of drug. Opadry are used for seal coating, whereas Eudragit L 100 used for polymer coat to achieve desired results.[3]

MATERIALS AND METHODS

Materials

Rabeprazole, Sodium carbonate, Hypromellose E15, Magnesium stearate, Opadry, Methylene dichloride, Eudragit L100, HPMC Phthalate, Talc, and Polyethylene glycol 600. Materials were obtained from Modern Pharma, Maharshtra, India.

Methodology

The preformulation study of Rabeprazole pellet formulation was carried out to select different excipients and better stability. The methodology used for preformulation and formulation is as follows:

Preformulation Study

Angle of Repose

Angle of repose of API Rabeprazole was identified by using the funnel method. API was transferred through a funnel to form a cone-like structure below the funnel in this method. The distance between the tip of funnel and the bottom was adjusted to 2 cm. The API was transferred through funnel till

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it touches the tip of the funnel. The dimeter of the cone formed by material was determined. From this, diameter, radius, and angle of repose were determined. The formula used to determine angle of repose is as follows:

$$\text{Tan}\,\Theta = \frac{h}{r}$$

Where h denotes height and r denotes radius of material cone.

Bulk Density and Tapped Density

Bulk density of the material is defined as the ratio of mass of powder to volume of powder. Unit used to describe the bulk density is gm/mL. Hence bulk density was calculated by transferring a known quantity of material to a measuring cylinder. Where, in tapped density material transferred in measuring cylinder, after transferring it was tapped for several time and it was observed until there was volume change. From this bulk density and tapped density were determined by using following formula:

$$\text{Bulk Density} \frac{\text{Mass of material}}{\text{Untapped volume of material}}$$

$$\text{Tapped Density} \frac{\text{Mass of material}}{\text{Tapped volume of material.}}$$

Compressibility Index

Compressibility index was calculated by carr's compressibility index. The carr's index generally used to identify the flow-ability of the material. Compressibility index of material was identified by using following formula:

$$\text{Compressibility index}: 100 \times \frac{\{\text{Tapped Density - Bulk Density}\}}{\text{Tapped Density}}$$

Table 1: Compatibility study of rabeprazole with different excipients

Mixture detail	*API-excipient proportion*	*40 ± 2°C/75% RH ± 5% RH (Weeks)*
Rabeprazole (API)	—	4
API + Sodium Carbonate	1:10	4
API + Lactose	1:10	4
API + Hypermellose E15	1:1	4
API + Magnesium Stearate	1:0.5	4
API + Opadry	1:1	4
API + Eudragit L100	1:1	4
API + Talc	1:0.5	4

Hausnar's Ratio

Hausnar's ratio is the statistical information that can give information of powder material or granule flowability. Hausnar's ratio is the ratio of tapped density to bulk density of powder. It was calculated by using following formula [4].

$$\text{Hausnar's Ratio}\,(H) = \frac{\text{Tapped Density}}{\text{Bilk Density}}$$

API – Excipient Compatibility Study

API and Excipients compatibility study were carried out by mixing the selected API with different excipients in different ratio. Mixture of API and excipient sealed in flint vial and Accelerated study carried out at the condition of 40 ± 2°C/75% RH ± 5% RH. The given study was performed for 4 weeks, and the study was compared with a controled condition of 2–8°C. Physical change in nature of blend was observed at regular interval of one-week duration. FTIR study was also carried out for compatibility study. Table 1 shows compatibility study of rabeprazole with different excipients.

Estimation of Rabeprazole

For estimation of rabeprazole, two different solutions were prepared, i.e., 0.1 N HCL and 6.8 pH phosphate buffer. UV spectra of solution were taken by spectrophotometer. The UV maxima of API were 270 and 280 in 0.1N HCL and in 6.8 phosphate buffer. The standard calibration curve of API was studied in buffer solution.[5]

Standard Calibration Curve

To perform the calibration curve 100 mg of drug was weighed and mixed in 100 mL of buffer solution. Further dilutions were prepared of range 2 to 18 µg/mL from this solution. The absorbance of each prepared dilution was measured at 280 nm. From this data standard calibration curve graph is plotted.

DSC Study of Rabeprazole

Thermal study of rabeprazole was carried out by using DSC methodology. Initially it was calibrated for the parameter of temperature condition and for the cell constant. Initially, sample of rabeprazole drug and reference standard pinched in pan of instrument and it was analyzed from temperature range of 20 to 200°C with the optimum and constant heating rate of 10°C/m.[6]

Formulation Development

Tables 2–4.

Table 2: Formulation of core pellet

	Formulation (Quantity in mg)					
Ingredients	*F1*	*F2*	*F3*	*F4*	*F5*	*F6*
Rabeprazole	20	20	20	20	20	20
Sodium carbonate	10	12	12	12	12	14
Lactose	12	12	11	11	10	9
Hypermellose E15	4	4	5	5	6	7
Magnesium Stearate	4	4	4	4	4	4
Iso propyl alcohol	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

Formulation of Rabeprazole Core Pellet

Preparation of core pellet of rabeprazole was completed by using powder layering technique. Initially rabeprazole was mixed with sodium carbonate, lactose, hypermellose E15 and iso propyl alcohol mixed to form the drug suspension. Sugar sphere then loaded in to the Glatt fluid bed processor machine and simultaneously previously prepared drug suspension was adjusted with spray gun and Glatt machine set for working parameter. The Glatt fluid bed processor instrument allows the spread and coat of the drug uniformly on the sugar sphere. After drug loading on core pellet, it was dried in warm air in pan of Glatt instrument.[7] This core drug pellets were used for further formulation.

Seal Coating of Core Pellet

After formulation of core rabeprazole pellet, seal coating of core pellets is completed. Seal coating protects pellets from direct interaction between core pellet and polymer coating. Seal coating solution was prepared by using Opadry polymer. Iso propyl alcohol and Methylene Dichloride is used to mix opadry polymer. Initially IPA and MDC were mixed in 1:1 proportion and mixed well for 20 to 25 minutes with stirrer. Then opadry polymer mixed in above solution and used for seal coating of polymer. After completion of seal coating pellets were dried in warm temperature condition in Glatt instrument.[8] Glatt instrument used for seal coating of pellet.

Polymer coat of Core Pellet

HPMC Phthalate initially mix with Iso propyl alcohol. After forming a homogeneous mixture, add Talc and PEG and Eudragit L100 in the IPA mixture. Mix the above solution well by using stirrer and used this solution for pH dependent coating for pellet. This coating solution was coated with Glatt fluid bed coater. After preparation of solution, it was placed in to the spray gun of Glatt coater and sprayed on the seal coated pellet to form the polymer coating.[9] This polymer coat mainly helps to deliver the formulation in an appropriate target.

Table 3: Composition of seal coating

Material	*Quantity %*
Opadry	25
Methylene dichloride	50
Isopropyl alcohol	50

RESULT AND DISCUSSION

Preformulation Study

From the study and data obtained from the Micromeritic study of rabeprazole, it was concluded that it possesses poor flow property and compressibility property (Tables 5 and 6). From the physical observation study and data, it was found that there is no any interaction between drug and excipients. Hence it was concluded that drug and excipients are compatible with each other. Table 7 shows the result of API-excipient compatibility data.

API–Excipient Compatibility Study

From the data obtained from physical observation and FTIR spectroscopy of API-Excipient mixture, it was concluded that API and excipients are compatible with each other. No any

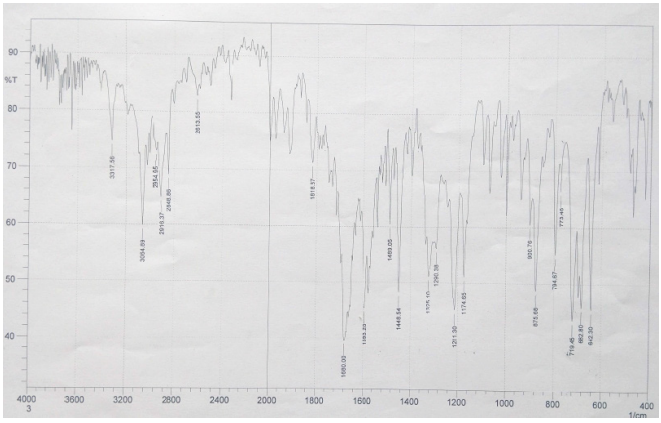

Figure 1: FTIR Spectroscopy of API

Table 4: Composition of polymer coating

Material	*Quantity (mg)*
Eudragit L100	30
HPMC Phthalate	4
Talc	1.5
Polyethylene glycol 600	3.5
Isopropyl alcohol	q.s.

Table 5: Micromeritic data of API

Sample	*Angle of repose (Θ)*	*Bulk density (gm/ml)*	*Tapped density (gm/ml)*	*Compressibility index (%)*	*Hausnar's ratio*
API	33	0.367	0.504	27.18	1.37

Table 6: Preformulation study of core pellets

Formulation	*Angle of repose (Θ)*	*Bulk density (gm/mL)*	*Tapped density (gm/ml)*	*Compressibility index (%)*	*Hausnar's ratio*
F1	22.41 ± 0.07	0.74	0.87	14.94	1.17
F2	40.26 ± 0.11	0.78	0.88	11.36	1.12
F3	24.27 ± 1.14	0.77	0.86	10.46	1.11
F4	24.92 ± 0.08	0.79	0.87	09.19	1.10
F5	31.61 ± 0.06	0.74	0.86	13.50	1.16
F6	32.97 ± 0.06	0.75	0.86	12.79	1.14

Table 7: API – Excipient Compatibility data (Physical observation)

Mixture detail	*API–excipient proportion*	*Initial observation*	*Final observation 1M (400 C/75%RH)*
Rabeprazole (API)	—	Off white	No Colour Change
API + Sodium Carbonate	1:10	White	No Colour Change
API + Lactose	1:10	White	No Colour Change
API + Hypermellose E15	1:1	White	No Colour Change
API + Magnesium Stearate	1:0.5	Fine white	No Colour Change
API + Opadry	1:1	White	No Colour Change
API + Eudragit L100	1:1	White	No Colour Change
API + Talc	1:0.5	Fine white	No Colour Change

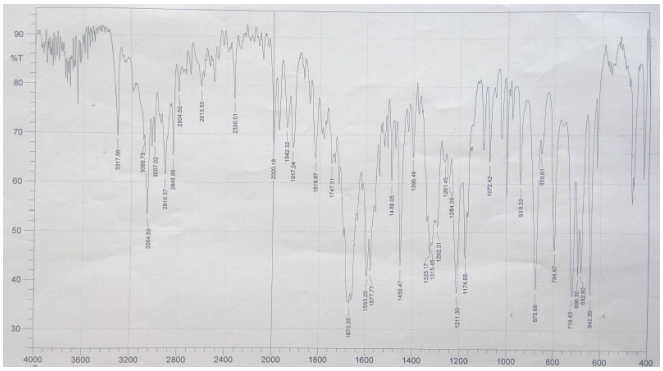

Figure 2: FTIR spectroscopy of API and excipients

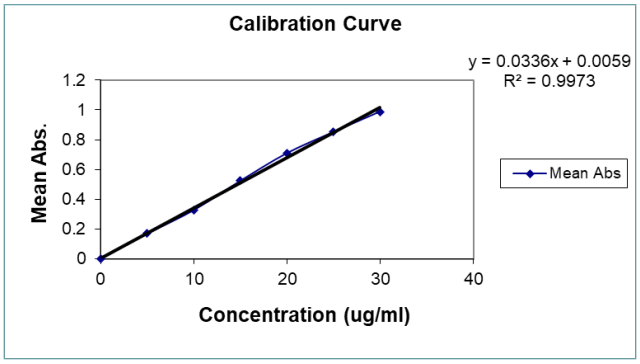

Figure 3: Calibration curve

physical change as well as separate peak was observed. Figures 1 and 2 shows API–Excipient compatibility data.

FTIR Study

Standard Calibration Curve

Standard calibration curve was plotted against Mean absorbance vs. concentration in ug/ml. From the data obtained, the graph was linear. Figure 3 shows the calibration curve.

Differential Scanning Calorimetry (DSC)

From the result of DSC study of optimized formulation, it was observed that there was no any interaction occurred between API and other excipients. Standard curve of drug represents that drug has retained its identity and other curve represents that presence of excipients other than drug material. Figure 4 shows DSC study of formulation.

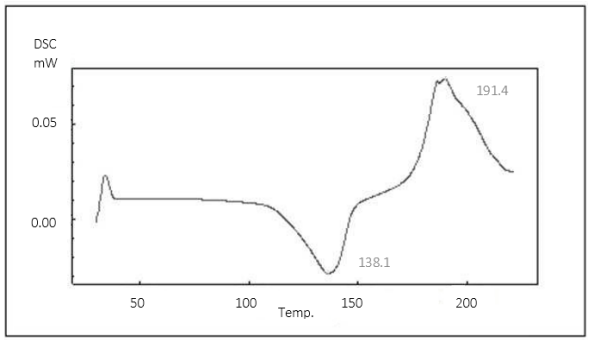

Figure 4: DSC study of formulation

% Loss on Drying (LoD)

The moisture content that is the % loss on drying of the product was determined by using LoD instrument at every step. For determination of % loss on drying two gm of sample was taken on aluminium plate and kept in LoD instrument and % LOD was checked at temperature of 105°C for 10 minutes.[10]

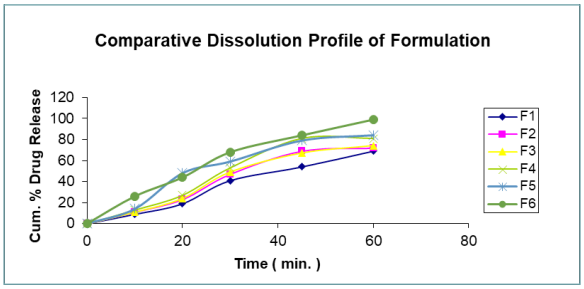

Figure 5: Comparative dissolution profile of formulation

In vitro Dissolution Study

Table 8 shows *In-vitro* dissolution study data. Figure 5 shows comparative dissolution profile of formulation. *In vitro* dissolution study was performed as per the specification. *In vitro* dissolution was performed in dissolution apparatus type II. Initially *in vitro* dissolution was performed in 0.1 N HCL for 2 hours. After 0.N HCL *in vitro* dissolution study was performed in 6.8 phosphate buffer. The respective dissolution concentration was scanned in UV spectrophotometer.[11] Optimized bath dissolution study was compared with marketed formulation. From comparative study with marketed

Table 8: *In-vitro* dissolution study

Time	*F1*	*F2*	*F3*	*F4*	*F5*	*F6*
0	0	0	0	0	0	0
10	9	11	11	13	14	26
20	19	23	24	27	48	44
30	41	47	49	53	59	68
45	54	69	67	81	79	84
60	69	72	74	81	84	99

Table 9: Comparative study of dissolution profile of optimized batch with market formulation

Time (Min.)	*F6*	*Marketed Formulation*
0	0	0
10	26	24
20	44	41
30	68	69
45	84	81
60	99	98

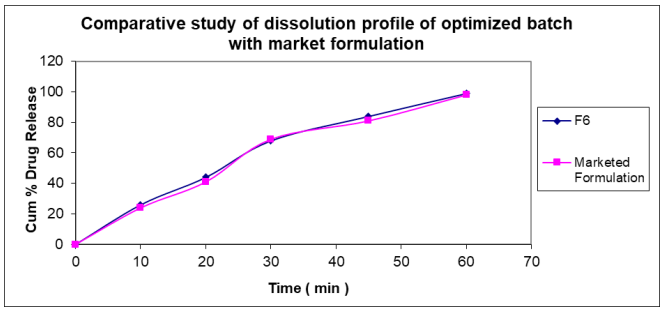

Figure 6: Comparative study of dissolution profile of optimized batch with market formulation

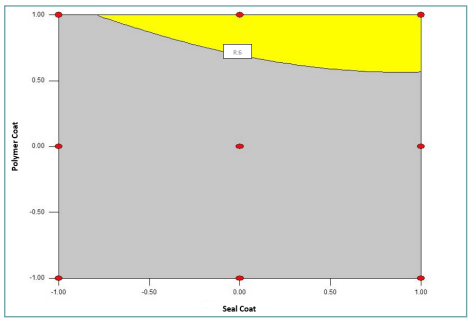

Figure 8: Overlay contour plot

Table 10: Result of Stability Study

Time Duration (Month)	*% Drug content*	*% Drug Release*
Initial	99.14 ± 0.01	99
1	98.54 ± 0.01	97
2	98.31 ± 0.01	96
3	98.19 ± 0.01	94

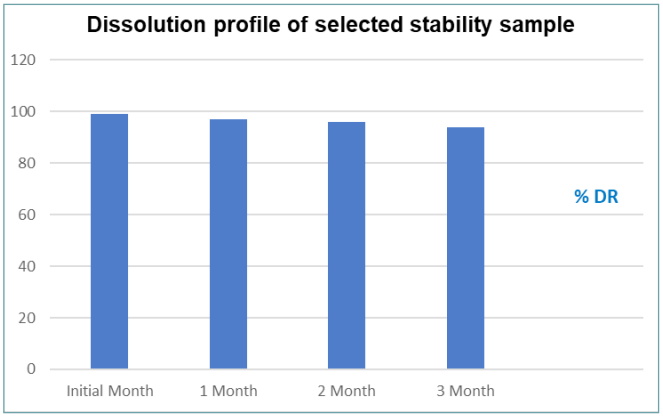

Figure 7: Dissolution profile of selected stability sample

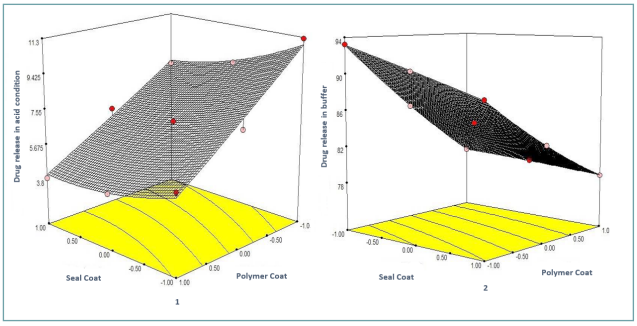

Figure 9: Response surface plot

formulation optimized batch show good result. Figure 6 and Table 9 shows comparative dissolution study of optimized batch and marketed formulation.

Stability Study

From all formulated batches, optimized batch was kept for the stability study. Stability study on optimized batch was performed as per International Council on Harmonisation guidelines. Capsule were filled in HDPE container and sealed. Container was kept in stability chamber at 40°C/75% RH for 3 months. Parameters such as % LOD, dissolution study, drug content was performed at 1, 2 and 3 months. Figure 7 and Table 10 shows results of stability data.

Overlay Contour plot & Respone Surface Plot

Figure 8 shows Overlay contour plot. Overlay contour plot for both polymer coat and seal coat was plotted. From the plot it was clear that the shaded part of the plot conist of the independent factors of formulation which leads to give better quality of the forjmulation. In case of the respone surface plot the factor that is f_2 taken as referance in given plot.[12] In surface plot area it mainly composed of both factor. In

this phenemenon plot of release profile vs coating parameter studied. Figure 9 shows Response surface plot.

SUMMARY AND CONCLUSION

The main aim and objective of this work was to formulate, evaluate and optimize the Rabeprazole pellet with polymer coating. As rabeprazole belongs to category of proton pump inhibitor also it degrades in acidic condition. Hence to protect the rabeprazole from acidic condition and to achieve the target in gastrointestinal tract polymer coating plays vital role. Hence different batches of rabeprazole were prepared and after formulating the core pellet barrier coat was applied on core pellet so as to avoid the interaction between pellet and polymer coat. After barrier coat polymer coat was applied on pellet so as to target the site specificity. Eudragit L100 was used as polymer coating. Among all batches F6 batch shows superior result and optimum result as compared to other bathes. Hence rabeprazole shows better stability as well as increase in bioavailability and dissolution rate.

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