Research Article

Design, Development and *In-Vitro* Evaluation of Floating Bilayer Tablet of Domperidone and Rabeprazole for the Treatment of Gastro Esophageal Reflux Disorder

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ABSTRACT

Bilayer tablets of Domperidone (IR) Rabeprazole (SR) were formulated for the management of gastro esophageal disorder.Immediate layer of Domperidone formulated using Tulsion T-339 as super disintegrant. For sustained release of Rabeprazole HPMC as the rate controlling polymers was used. Preformulation studies were performed prior to compression. The individual layers of the bilayer tablets were evaluated for weight variation, dimension, hardness, friability, drug content, and disintegration time and *invitro* drug release using USP dissolution apparatus type II (paddle). It was found that the optimized formulation showed 12.8%, 18.0%, 38.8%, 59.5%, 74.9%, 88.5% and 98.9%release for rabeprazole in 0.5,1,2, 4, 6, 8, 12 hours respectively. However, domperidone released 98.28% at the end of 30 minutes. The IR spectrum studies revealed that there is no disturbance in the principal peaks of pure drugs. This further confirms the integrity of pure drugs and no incompatibility of them with excipients. The stability studies were carried out for the optimized batch for three months and it showed acceptable results. The kinetic studies of the formulations revealed that diffusion is the predominant mechanism of drug and release follows first order kinetics.

Keywords: gastric retention time, domperidone, rabeprazole, *invitro* dissolution study.

INTRODUCTION

Per oral dosage forms for gastric retention have attracted more and more attention for their theoretical advantage in gaining control over the time and the site of drug release[1]. Gastric retention has received significant interest in the past few decades as most of the conventional oral delivery systems have shown some limitations related to fast gastric emptying time[2, 21].

The stomach is divided into 3 anatomic regions: fundus, body, and antrum (pylorus). The separation between stomach and duodenum is the pylorus. The part made of fundus and body acts as a reservoir for undigested material, whereas the antrum is the main site for mixing motions and act as a pump for gastric emptying by propelling actions.

Gastric emptying occurs during fasting as well as fed states. A gastro retentive dosage form (GRDF) can overcome this problem and is particularly useful for drugs that are primarily absorbed in the duodenum and upper jejunum segments. The pattern of motility is however distinct for the two states. During the fasting state an inter-digestive series of electrical events take place, which cycle both through stomach and intestine every 2–3 h. This is called the inter-digestive myloelectric cycle or migrating myloelectric cycle (MMC), which is further divided into following 4 phases [3,4] -

- Phase I (basal phase) lasts for 40 to 60 min with rare contractions.
- Phase II (preburst phase) lasts for 40 to 60 min with intermittent action potential and contractions. As the phase progresses the intensity and frequency also increases gradually.
- Phase III (burst phase) lasts for 4 to 6 min. It includes intense and regular contractions for short period. It is due to this wave that all the undigested material is swept out of the stomach down to the small intestine. It is also known as the housekeeper wave.
- Phase IV lasts for 0–5 min is a transition period of decreasing activity until the next cycle begins. [17,18,]

Food effects and the complex motility of the stomach play a major role in gastric retention behavior. Several approaches of non-

effervescent and effervescent formulation technologies have been used and patented in order to increase gastric residence time of the GRDF [19,20].

The bilayer tablets drug delivery system is preferred for the following reasons to co-administer two different drugs in the same dose, to minimize physical and chemical incompatibilities, for better drug release, IR and SR in the same tablet, for chronic condition requiring repeated dosing.

The current investigation aims at development of floating bilayer tablets of Rabeprazole by using a gas generating agent. Rabeprazole is an antiulcer drug in the class of proton pump inhibitors. Rabeprazole inhibits the H^+, K^+ ATPase of the coating gastric cells and dose-dependent oppresses basal and stimulated gastric acid secretion.

However, the recent failure of PPIs to prevent night-time gastric acid surge (which is associated with high nocturnal histamine concentration) brings open a new door for delivery of Rabeprazole at specific times in relation to onset of symptoms. Colonic metabolism is partly responsible for poor bioavailability of Rabeprazole, thereby, favoring gastro-retentive delivery. [5,6]

The gastro retentive drug delivery systems can be retained in the stomach and assist in improving the oral sustained delivery of drugs that have an absorption window in a particular region of the gastrointestinal tract. These systems help in continuously releasing the drug before it reaches the absorption window, thus ensuring optimal bioavailability. [7]

Domperidone, a specific blocker of dopamine receptors speeds gastrointestinal peristalsis, causes prolactin release, and is used as antiemetic and tool in the study of Dopaminergic mechanisms. Combination of Rabeprazole and Domperidone improve the disease condition with the combination form.

MATERIALS AND METHOD.

Domperidone and Rabeprazole is the gift sample from Cipla, HPMC K4M, Sodium citrate, Talc were purchased from Colorcon Asia Pvt Ltd, Mumbai; and Tulsion T-339 from Thermax Ltd Pune ,Sodium bicarbonate, Lactose, , Lactose monohydrate, Magnesium stearate were purchased from S.D Fine Chemicals Pvt Ltd (INDIA) . Tartrazine was from Central Drug House. All other chemicals are of analytical grades.

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Preparation of bilayer tablet with floating matrix layer

Tablets were prepared by direct compression technology using cadmach single punch machine. Bilayer tablets consist of floating matrix layer as bottom and immediate release layer as top layer were prepared in two stages

Preparation of domperidone immediate release layer

Domperidone immediate release layer were prepared by using direct compression method. The drug (20 mg), tulsion T-339, sodium citrate, lactose monohydrate and magnesium strearate were passed through sieve no.30 and mixed homogenously for 5 minutes. Finally the colorant tartrazine was sieved through sieve no.100 mesh and then mixed with the dry mix homogenously to get uniform blend without mottling.

Table 1: Composition of the IR layer of Domperidone

Ingredients	M1-M4 batch Mg/ tab
Domperidone	20
Tulsion T-339	5
Sodium citrate	5
Lactose monohydrate	12.5
Magnesium Stearate	1.5

Preparation of rabeprazole sustained release layer

Rabeprazole sustained release layer were prepared by direct compression method. The hydroxyl propyl methyl cellulose (HPMC K4M), sodium bicarbonate, sodium citrate, lactose, Tulsion T-339 and Rabeprazol were passed through sieve no.30 and mixed homogenously.

Table 2: Composition of the SR layer of Rabeprazole

Ingredients	M1 Mg/tab	M2 Mg/ tab	M3 Mg/ tab	M4 Mg/ tab
Rabeprazole	20	20	20	20
HPMC K4M	15	18	22	15
sodium bicarbonate	10	12	14	16
sodium citrate	4	6	8	10
Lactose	5	5	5	5
Tulsion T-339	5	5	5	5
Magnesium stearate	Qs	Qs	Qs	Qs
Talc	Qs	Qs	Qs	Qs

Fabrication of floating bilayer tablets

The mixture was then compressed using a 8-mm-diameter die in a CADMACH tablet compression machine. As the upper punch was raised the immediate release layer of Domperidone was placed on the above compact; the 2 layers were then compressed into a floating bilayer tablet. Each tablet weighed 50 mg with density less than 1.

Fig. 1: Bilayer floating tablet

Evaluation of granules flow properties

The prepared granules were evaluated for parameters like bulk density, tapped density, Carr's index, Angle of repose, and Hausner's ratio [11] .

Table 3: Flow characters of granules of IR Layer

Parameters	Immediate Release Layer (M1-M4)
Angle of Repose	θ= 20.3°
Bulk Density	0.61
Tapped Density	0.75
Hausner's Ratio	1.22
Carr's Index	18.6

Table 4: Flow characters of granules of SR layer

Batch	Angle of Repose	Bulk Density	Tapped Density	Hausner's Ratio	Carr's Index
M1	θ= 16.6°	0.62	0.68	1.07	8.8
M2	θ= 20.9°	0.56	0.60	1.18	16.7
M3	θ= 26.4°	0.43	0.58	1.09	7.2
M4	θ= 17.5°	0.78	0.80	1.54	20.1

Physical evaluation of tablets

Bilayer tablets were evaluated for the mechanical strength using Monsento hardness tester and Roche friabilator.

Buoyancy lag time and the floating time of the tablets were determined in 900ml of 0.1 N HCl maintaining the pH 1.2 at 37±0.5 ° C using USP type II dissolution apparatus with the agitation speed of 50 rpm. Time required to float the tablet to the surface of the acidic dissolution medium was determined and expressed as buoyancy lag time. The time period for which tablet remains floating, expressed as tablet floating time. The time over which the tablet remain intact considered as the tablet integrity[16], [24 26, 27].

Tablet parameters [12 ,21]

Table 5: Tablet parameters for immediate release layer

Batch	Weight Variation % (for 10 tab's)	Hardness kg/cm^2 (For 6 tab's)	Friability % (For 10 Tab's)	Thickness (for 10 tab's) mm
IR layer	42±2.5	4.7± 0.35	0.18	1.00±0.04

Table 6: Tablet parameters for sustain release

Batch	%Weight Variation	Hardness kg/cm^2	% Friability	Thickness	Floating lag time (min)	Floating duration (hrs)
M1	67±2.5	4.4 ±0.35	0.13	1.50±0.04	5.25±0.23	10.76±0.124
M2	66±2.0	4.5 ±0.47	0.15	1.53 ±0.05	4.75±0.39	11.23±0.245
M3	64±1.5	4.4 ±0.32	0.12	1.48 ±0.06	4.18±0.44	12.45±0.133
M4	65±2.5	4.5 ±0.54	0.16	1.55±0.02	6.85±0.45	9.678±0.008

Evaluation of tablets

Determination of drug content In tablets

Six tablets from each batch were selected randomly and transferred to a 100ml volumetric flask containing 0.1N HCL. Kept it for 48hours, then took 1ml from each and was transferred to the test tubes. Samples were then filtered, suitably diluted and analyzed spectrophotometrically at a suitable wavelength of 285 and 287 nm. The sample mean and standard deviation were calculated[8, 9].

Determination of *In – vitro* dissolution study

In Vitro dissolution studies (n = 6) for the formulations were performed by USP type II (paddle method)[8] dissolution apparatus, 50

rpm in 900ml 0.1(N) HCl medium (pH-1.2) at 37°C. A sample (10 mL) of the solution was withdrawn from the dissolution apparatus at specified time intervals and the samples were replaced with 10ml of fresh dissolution medium. The samples were filtered through a 0.45-µm membrane filter and diluted to a suitable concentration with 0.1N HCl. Absorbance of these solutions was measured at 287 nm using a Shimadzu UV-1601 UV/Vis double-beam spectrophotometer (Kyoto, Japan). Cumulative percentage drug release was calculated using an equation obtained from a standard curve [10,22, 23, 25].

Stability studies

The optimized formulation was subjected to stability at 40 ± 2 ^{0}C and 75 ± 5 % RH for period of 3 months in a stability chamber. After each month tablet sample was analyzed for physical characteristics and drug release profile.[13]

Kinetic studies

The following plots were made to study the kinetic drug release profile. Cumulative % drug release vs. time for zero order kinetic models; Log cumulative of % drug remaining vs. time for the first order kinetic model; cumulative % drug release vs. square root of time for the higuchi model to understand the kinetic release pattern for the floating drug formulation . The regression coefficient R^2 value nearer to 1 indicates the model best fits the release mechanism [28.]

RESULTS AND DISCUSSION

Various formulations of bilayer were prepared and evaluated with an aim of presenting Rapeprazole as sustained release and Domperidone as immediate release for improving the patient's compliance.

Both immediate release and extended release formulations were prepared and contain in a single dosage form. The study describes the formulation of both immediate and extended release drug for increased therapeutic efficacy and patient convenience.

Micrometric study

Bulk density, tapped density, compressibility index, hausner's ratio and angle of repose of the granules were determined. The pre-compressed parameters of the formulation were showed satisfactory flow property in table No 3 and 4 for the IR layer and SR layer individually.

Physical Parameters

The physical parameter of the compressed tablets was determined. The friability was found within the limit. Hardness of the formulations were satisfactory within the range of the 4 - 4.5 Kg/ cm ^{2} and it was sufficient to prevent the chipping and breaking during transportation the drug content of the formulation was also calculated table No.5 and 6 for individual layers.

Floating character

All formulation floated for more than 12 hrs with a floating lag time up to 6 min.During the floating time, formulation maintained the matrix integrity. Floating duration and the floating lag time were found to be dependent on the amount of the polymers incorporated in the formulation and carbon dioxide generating excipients incorporated in the formulation.

Dissolution study of Immediate layer

There is no alteration of the drug release from the immediate release formulation as the concentration and the amount use for the preparation of the immediate release drug. The release of the drug Domperidone for the immediate release layer of all the batches takes place within 15-25 min (n=6 for each batch). Use of Tulsion T-339 as super disintegrant found to optimum for the release of the immediate drug within 15 min with the disintegration time of 2 min.

Dissolution study of sustained release floating layer

The floating sustain release of the rabeprazole formulation was formulated with different concentration of the polymer HPMC and the different concentration of gas generating excipients. The M1 and M2 are unable to retard the drug for the longer time. The drug was release within the end of 4 and 7 hrs. The polymer concentration was not sufficient to prolong the drug release. Whereas the formulation M3 shows the satisfactory drug release over the period of 12 hrs containing the polymer of 10% of the formulation and 8% of gas generating agent of total weight. The formulation M4 shows good sustain action of 18.5 hrs but bad floating character.

Table 7: Drug content and drug release of the SR layer

Batch	%Drug content	Drug release 30 min	Drug release 1 hr	Drug release 2 hrs	Drug release 4hrs	Drug release 6hrs	Drug release 8hrs	Drug release 12hrs	Drug release 18hrs
M1	99.5±0.2	20.3±0.7	38.8±0.1	67.5±0.8	97±0.2	-	-	-	-
M2	98.90±0.7	15.65±0.4	26.8±0.1	58.4±0.4	71.8±0.1	98.7±0.6	-	-	-
M3	99.8±0.0	12.8±0.9	18±0.4	38.8±0.3	59.5±0.7	74.9±0.1	88.5±0.2	98.9±0.7	-
M4	97.4±0.3	10.3±0.8	17.4±0.9	36.1±0.3	54.7±0.1	69.3±0.7	80.1±0.2	91.6±0.6	99.6±0.3

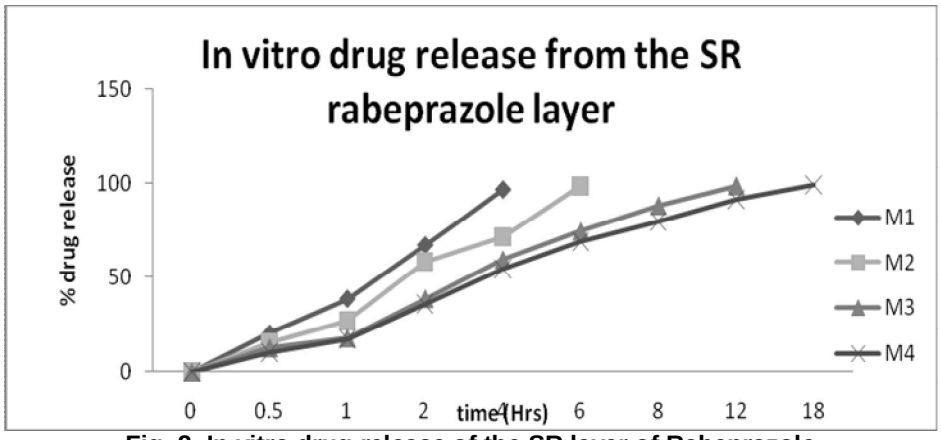

Fig. 2: In vitro drug release of the SR layer of Rabeprazole

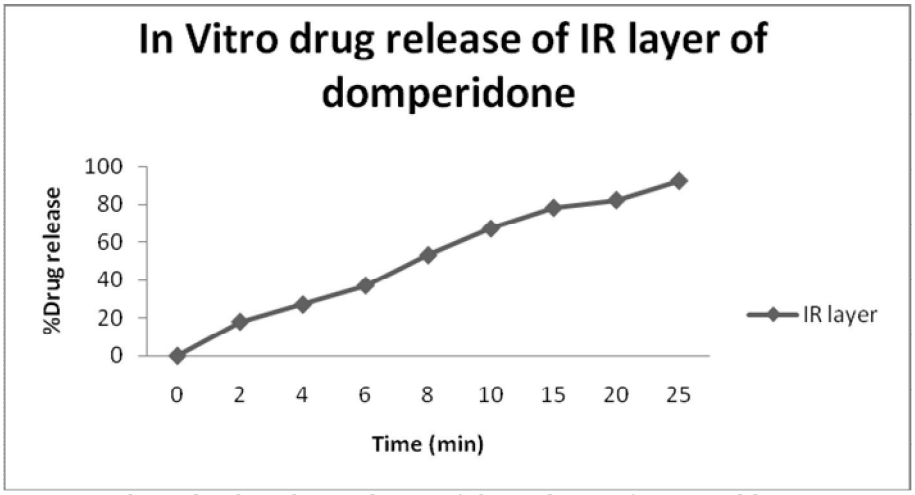

Fig. 3: in vitro drug release of the IR layer of Domperidone

Stability study

The stability studies were carried out on the optimized formulation *i.e.* M3. The formulations were stored at 40 ± 2°C/75 ± 5% RH for 3 months to assess their long term stability. The protocol of the stability studies confirmed to WHO guidelines for stability testing of protocols intended for the global market. After an interval of 15, 30, 60 and 90 days, samples were withdrawn and retested for drug content, buoyancy lag-time, buoyancy time . The results indicated that, irrespective of the concentration of polymer, these formulations remained stable for three months.

Table 8: Stability study

Characteristic	15 days	1 month	2 months	3 months
Physical appearance	Flat faced distinguishable two layers. SR layer is orange in colour	Flat faced distinguishable two layers. SR layer is orange in colour	Flat faced distinguishable two layers. SR layer is orange in colour	Flat faced distinguishable two layers. SR layer is orange in colour
Hardness (kg/cm^2)	4.4 ±0.32	4.4 ±0.67	4.4 ±0.87	4.4 ±0.91
Drug content (mg/tablet)	99.8±0.0	99.1±0.23	98.2±0.08	97.6±0.12
Buoyancy lag time (s)	4.18±0.44	4.98±0.47	5.23±2.78	6.78±2.3
Total buoyancy time (h)	>12	>12	>12	>12
***In vitro* drug release**	98.9±0.7	97.10±0.70	96.35±0.68	95.80±0.10
All values are mean ± S D of three determinations				

KINETIC STUDY FOR THE OPTIMIZED BATCH

Optimized formulation M3 was subjected to curve fitting analysis, zero order, and first order, Higuchi Kinetics, Korsemeyer and Peppas model [28]. The slope and R^2 are shown in Table 8 and graphs in Figure 3 to 6. Optimized formulation fitted best for Korsemeyer – Peppas equation with R^2 value of 0.9959.

Table 9: Kinetic release data of different model for optimized formulation (m3)

Model	Slope	R^2value
Zero order	4.2369	0.9528
First order	-0.729	0.9475
Higuchi	23.761	0.9924
Korsemeyer Peppas model	0.6901	0.9959

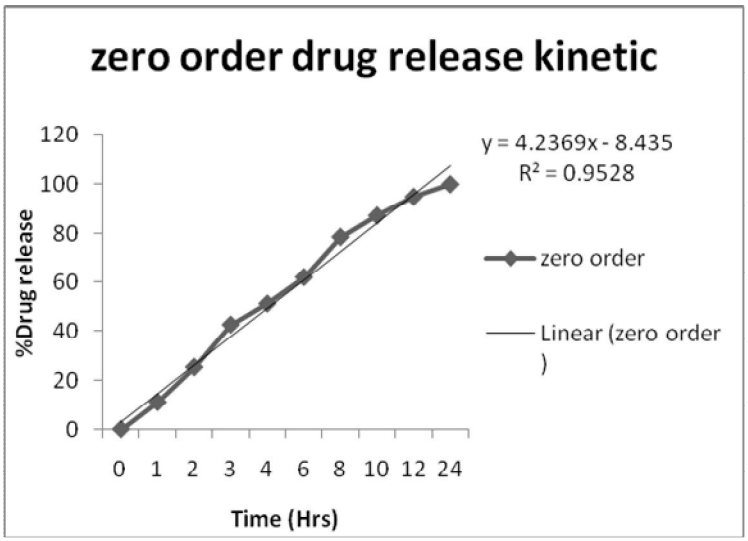

Fig. 4: Zero order kinetic

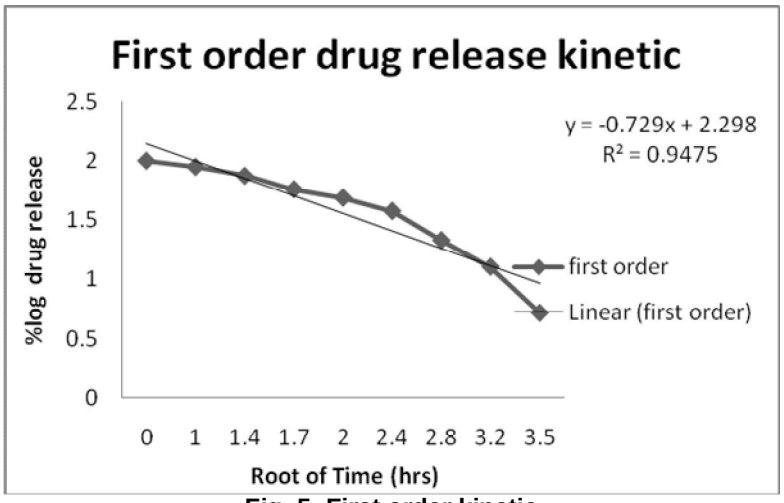

Fig. 5: First order kinetic

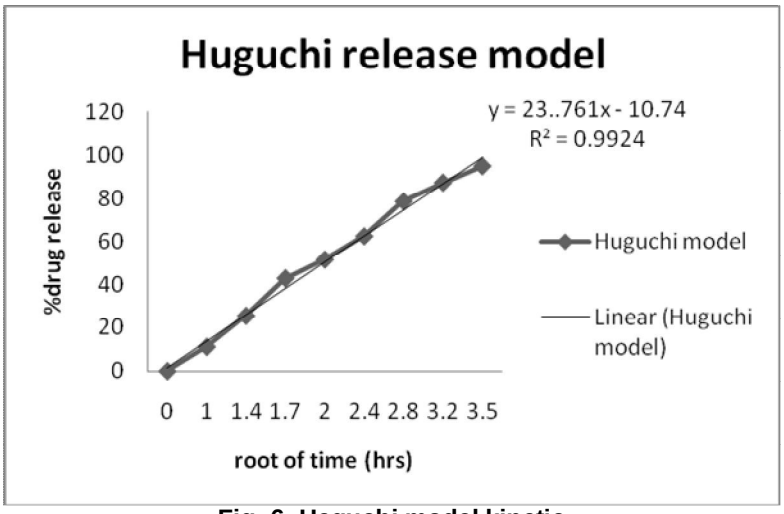

Fig. 6: Heguchi model kinetic

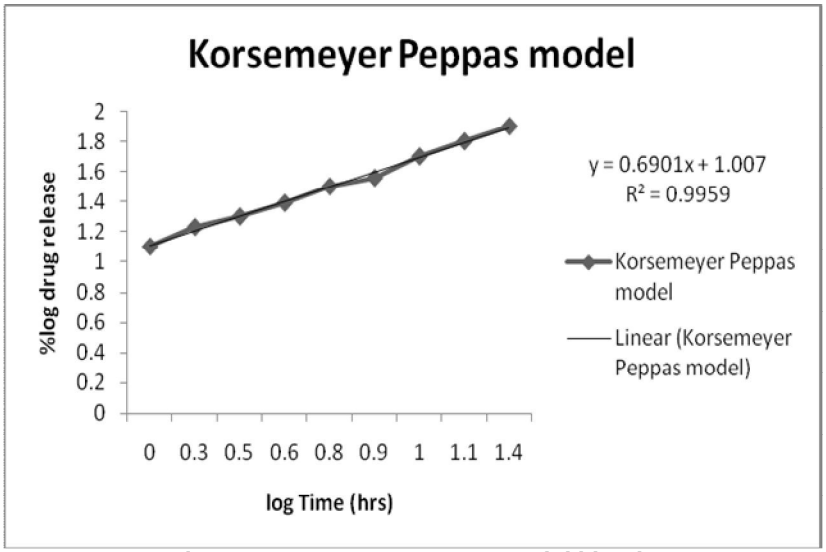

Fig. 7: Korsemeyer peppas model kinetic

CONCLUSION

Oral solid dosage form of bilayer tablets drug delivery is the promising to achieve the bimodel drug delivery. After the immediate release of the Domperidon the Rabeprazol is release for a prolong period of time to maintain the sustained therapeutic activity. In this study, we successfully developed optimized bilayer and floating dosage forms which exhibit a unique combination of floatation and prolonged residence in the stomach. The optimized M3 tablet formulation showed a satisfactory dissolution profile, detachment stress and floating characteristics. The tablets remained floated in the stomach for up to 12 hrs. For sustained release portion HPMC polymer was used in granulation stage and also extra granularly.

Prior to compression the granules were evaluated for angle of repose, bulk density, tapped density, compressibility index, Hausner's ratio. The compressed bilayer tablets were also evaluated for weight variation, dimension, hardness, friability, drug content, and disintegration time and *invitro* drug release. The stability studies were carried out for the optimized batch for three months and it showed acceptable results. The kinetic studies of the formulations revealed that diffusion is the predominant mechanism of drug release. So M3formulation was considered as the optimized formulation. It may be concluded that bilayer floating Domperidone and Rabeprazole tablets by direct compression technology had shown good floating property and sustained drug release characters However; it needs further *in vivo* studies to show how bilayer floating dosage forms act in fed state. More clinical trials and statistical data are required for the bilayer floating dosage forms to enter the pharmaceutical market.

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