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FORMULATION AND EVALUATION OF BILAYER FLOATING TABLETS OF AMOXICILLIN AND RABEPRAZOLE

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ABSTRACT
Bilayer floating tablet is made up of two distinct layers compressed together with the individual layers lying one on top of another. In the present research work the bilayer floating tablets were formulated with Rabeprazole in Sustained release layer and Amoxicillin in immediate release layer. These tablets were prepared by both direct compression method and wet granulation method of different formulations (F1, F2, F3, F4, F5, and F6) by using different combinations and ratios of polymers. Evaluation parameters i.e. pre-compression parameters like bulk density, tapped density, Hausner's ratio, Carr's index and angle of repose were performed and post compression parameters like weight variation, friability, thickness, hardness, disintegration and dissolution were performed for all these formulations. Among all the formulations, F5 showed an optimized drug release profile. Polymer concentration was adjusted to get the maximum sustained release in 8 h and the effervescent agents were found to give floating lag time of about 1.3 min with total floating time of more than 8 h.

KEYWORDS: Bilayer floating tablet, direct compression, wet granulation, effervescent agents, floating lag time, floating time.

INTRODUCTION
Oral drug delivery has been known for decades as the most widely utilized route of administration among all the routes that has been explored for the systemic delivery of drugs of different dosage forms.[1] Gastro retentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of therapeutic agents. Prolonged gastric retention improves bioavailability, reduces drug waste and improves solubility for drugs that are less soluble in a high pH environment of small intestine.[2] It also helps to provide better availability of new products with new therapeutic possibilities and strong substantial benefits for patients.[3] Floating drug delivery systems have a bulk density lower than gastric fluids thus remain buoyant in the stomach for a prolonged period of time and while floating on the gastric contents, the drug is released slowly and almost completely at a desired rate form the system. After the release of the drug, the residual system becomes liable to be emptied from the stomach and this results in an increase in the gastro retentive time. Thus floating drug delivery system is a safe and efficient technology for drug delivery.[4]

Bilayer floating tablets are composed of two layers compressed together. These are prepared with one layer of drug for immediate release and with second layer to release drug later, either as second dose or in an extended release manner.[5] Bilayer tablet consists of one or more than one medicaments designed in a two layers system which can be suitable for combination therapy and biphasic release therapy. In case of combination therapy the two layers of this tablet is consist of two different medicaments and in case of bi-phasic release bilayer tablet both the layers content same drugs but the drug from one layer is immediately released and the drug from the second layer is released for an extended period of time to maintain the therapeutic concentration of drug within therapeutic window.[6] Bilayer Floating tablets contain immediate and sustained release layer. Immediate release layer delivers the initial dose, it contains super disintegrants which increase drug release rate and start onset of action whereas sustained release layer floats due to gas generating agent and releases drug at sustained manner for prolonged period.[7] These tablets are used to administer fixed dose combinations of different active pharmaceutical ingredients, prolong the drug product life cycle, and fabricate novel drug delivery

systems such as swelling device, buccal or mucoadhesive delivery systems, and floating tablets for gastro-retentive drug delivery.[8]

Amoxicillin is a broad-spectrum semi synthetic antibiotic and its resistance to gastric acid permits higher serum levels with oral administration. Amoxicillin is one of the main antibiotics given as part of treatment regimens to eradicate H. pylori infection in patients with peptic ulcer disease. For the eradication of H. pylori, amoxicillin is given with a proton-pump inhibitor.[9] For gastric ulcer patients, amoxicillin is ineffective even at high doses; apparently due to limited contact time with the target site when administered in a conventional oral dosage form. Rabeprazole is an antiulcer drug in the class of proton pump inhibitors. Rabeprazole inhibits the H+, K+ ATPase, the proton pump which involves in the acid secretion from gastric parietal cells.[10] 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.[11]

MATERIALS AND METHODS

Amoxicillin was obtained as a gift sample from Aurobindo Pharma, Hyderabad, India. Rabeprazole was obtained as a gift sample from Southern Pharma, Hyderabad, India. Crosscarmellose sodium, Cross povidone, HPMC K15 and HPMC K100 were obtained from Signet Chemicals Corporation. Microcrystalline cellulose, PVPK30, citric acid, Magnesium stearate and talc were obtained from SD fine chemicals. Sodium bicarbonate was obtained from Merck Chemicals Pvt Ltd., and Isopropyl alcohol was obtained from Universal Labs.

1. Preparation of Immediate release layer of Amoxicillin

The suitable formulation for IR layer was selected as in Table 1. Drug and super-disintegrants were passed through 40 #mesh separately and then transferred to a poly bag and mixed for 3 minutes. Then other excipients were added to the above mixture. Finally glidant was added to the above blend and mixed thoroughly.

2. Preparation of Floating Sustained release layer of Rabeprazole by Wet granulation method

The suitable formulation for SR layer was selected as in Table.2. Drug, polymer and gas generating mixture were passed through 40 # mesh separately and then transferred to poly bag and mix it for 3 minutes. Then binder is dissolved in isopropyl alcohol which is used as a granulating agent. The above blend was granulated by using the prepared binder solution. Then the damp mass was passed through 24 # mesh and dried at 400c for 20 min. Other excipients were added to the above mixture. Finally the glidant was added to the above blend and mixed thoroughly.

Table 1: Formulation of Immediate Release (IR) Layer.

Ingredients mg/tab	IR_1	IR_2	IR_3	IR_4	IR_5	IR_6
Amoxicillin	250	250	250	250	250	250
Cross carmellose sodium	20	30	40	-	-	-
Cros povidone	-	-	-	20	30	40
Micro crystalline cellulose	25	25	25	25	25	25
PVP k30	20	20	20	20	20	20
Magnesium stearate	10	10	10	10	10	10
Talc	15	15	15	15	15	15

Table 2: Formulation of Sustained Release (SR) Layer.

Ingredients mg/tab	SR_1	SR_2	SR_3	SR_4	SR_5	SR_6
Rabeprazole	20	20	20	20	20	20
HPMC k 15	75	-	37.5	50	56.25	60
HPMC k100	-	75	37.5	25	18.25	15
Sodium bicarbonate	37.5	37.5	37.5	37.5	37.5	37.5
Citric acid	5	5	5	5	5	5
PVPk30	2.5	2.5	2.5	2.5	2.5	2.5
Iso propyl Alcohol	qs	qs	qs	qs	qs	qs
Magnesium stearate	15	15	15	15	15	15
Talc	5	5	5	5	5	5

3. Evaluation of Pre-compression parameters

The powder of IR and SR layers were evaluated for the following pre-compression parameters.

A. Angle of Repose: The angle of repose of the pre compression blend was determined separately for IR and SR layers by the funnel-method. The accurately weighed blend was taken in a funnel. The height of the funnel was adjusted in such a manner that the tip of the funnel just touched the apex of the heap of the powder blend. The powder blend was allowed to flow through the funnel freely onto the surface. The diameter of the powder cone

measured and angle of repose was calculated using the following equation.

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

Where, h and r are the height and radius of the powder cone, θ is the angle of repose.

B. Determination of Bulk Density and Tapped Density: An accurately weighed quantity of the granules/ powder of IR and SR layer separately (W) was carefully poured into the graduated cylinder and volume (V_0) was measured. Then the graduated cylinder was closed with lid and set into the tap density tester (USP). The density apparatus was set for 500 tabs and after that the volume (V_f) was measured and continued operation till the two consecutive readings were equal. The bulk density and the tapped density were calculated using the following formulae.

$$\text{Bulk density} = \frac{W}{V0}$$

$$\text{Tapped density} = \frac{w}{vf}$$

Where, W= Weight of the powder, V_0 = Initial volume, V_f = final volume

C. Compressibility Index (Carr's Index): Carr's index (CI) is an important measure that can be obtained from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is.

$$CI = \frac{(TD-BD)}{TD} \times 100$$

Where, TD is the tapped density and BD is the bulk density.

D. Hausner's Ratio: It is the ratio of tapped density and bulk density. Generally a value less than 1.25 indicates good flow properties, which is equivalent to 20% of Carr's index.

$$Hausner's\,ratio = \frac{TD}{BD}$$

Where, TD is the tapped density and BD is the bulk density.

4. Tablet Compression

Then Bilayer floating tablets were prepared by taking formulations from both the individual layers. Then the accurately measured amount of sustained release layer powder mix was first introduced into the die cavity and compressed at mild compression force. After that accurately weighed Immediate release layer powder was introduced into the die cavity followed by final compression with optimum hardness to form the bi layer tablets of formulations F1 (IR1 and SR1), F2 (IR2 and SR2), F3 (IR3 and SR3), F4 (IR4 and SR4), F5 (IR5 and SR5) and F6 (IR6 and SR6).

5. Evaluation of Post-compression Parameters

After the Tablets were prepared, they were evaluated for the following post compression properties.

A. Thickness: Twenty tablets from the representative sample were randomly taken and individual tablet thickness was measured by using vernier calipers.

B. Hardness: Tablet hardness was measured by using Monsanto hardness tester. From each batch 10 tablets were measured for the hardness and averages of the 10 values were noted.

C. Friability Test: From each batch, ten tablets were accurately weighed and placed in the friability test apparatus (Roche friabilator). Apparatus was operated at 25 rpm for 4 minutes and tablets were observed while rotating. The tablets were then taken after 100 rotations, dedusted and reweighed. The friability was calculated as the percentage weight loss.

% Friability was calculated as follows

$$\%\ \text{Friability} = \frac{(W1 - W2)}{W1} \times 100$$

Where, W1 = Initial weight of the 20 tablets, W2 = Final weight of the 20 tablets after testing.

Friability values below 0.8% are generally acceptable.

D. Weight Variation Test: To study weight variation, individual weights (WI) of 20 tablets from each formulation were noted using electronic balance. Their average weight (WA) was calculated. Percent weight variation was calculated as follows

$$\%\ \text{Weight variation} = \frac{(WA - W1)}{WA} \times 100,$$

E. Floating time: Duration of time by which the dosage form constantly emerges on surface of medium called floating time. Tablets were placed in 400 ml flask of pH 1.2 solution and time need to go upward and float on surface of liquid was noted for 6 tablets in each batch.

F. Floating lag time: The in vitro buoyancy was determined by floating lag time method. The tablets were placed in 25^0 ml beaker containing 0.1 N HCl. The time between introduction of dosage form and its buoyancy in 0.1 N HCl and the time during which the dosage form remain buoyant were measured. The time taken for dosage form to emerge on surface of medium called Floating Lag Time (FLT) or Buoyancy Lag Time (BLT) was determined for 6 tablets in each batch.

G. *In-vitro* Disintegration time: In-vitro disintegration time of three tablets in each batch was determined by using digital tablet disintegration apparatus. *In-vitro* disintegration test was carried out at 37 ± 2 0C in 900 ml 0.1 N HCl.

H. *In-vitro* drug release studies: The *in-vitro* release of drug from the prepared tablets was carried out in 900ml dissolution media of pH1.2 (0.1N HCl) using rotating

paddle. Then the release pattern of the tablets was calculated.

RESULTS AND DISCUSSION

1. The pre-compression blend for IR layer and SR layer of bilayer floating tablets were characterized with respect to angle of repose, bulk density, tapped density and Carr's index. Angle of repose was found in between 250-35^0 and Carr's index values were found in between 13%-17% for the pre-compression blend of all the formulations indicating good flowability and compressibility.

2. Hausner's ratio was less 1.25 for all the formulations indicating good flow properties. The pre-compression evaluation results for IR and SR layers were given in tables 3 and 4 respectively.

Table 3: Evaluation of Precompression Blend for immediate release layer (Amoxicillin).

Formulation Code	Angle of Repose (°)	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Hausner's Ratio	Carr's index (%)
IR_1	26.32	0.56	0.53	1.04	7.20
IR_2	30.46	0.57	0.52	1.14	12.1
IR_3	29.05	0.62	0.60	1.06	13.07
IR_4	32.21	0.53	0.51	1.12	12.62
IR_5	23.2	0.55	0.52	1.02	5.1
IR_6	25.2	0.58	0.54	1.06	17.30

Table 4: Evaluation of Precompression Blend for Sustained release layer (Rabeprazole).

Formulation code	Angle of Repose (°)	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Hausner's Ratio	Carr's index (%)
SR_1	26.06	0.52	0.50	1.12	9.75
SR_2	27.85	0.46	0.44	1.14	12.08
SR_3	26.63	0.48	0.45	1.06	8.49
SR_4	26.78	0.52	0.51	1.12	12.48
SR_5	22.46	0.46	0.45	1.02	4.67
SR_6	27.08	0.44	0.42	1.06	11.73

3. The prepared tablets of formulations F1, F2, F3, F4, F5 and F6 were evaluated for physical parameters such as hardness, thickness, friability and weight variation. The results shown in table 5.The mean value of Hardness of bilayer floating tablets were in the range of 6.35-6.80 kg/cm2. All the tablets passed friability test as the loss of tablet material was less than 1%, indicating that tablets prepared were of sufficient strength. Floating time for all the formulations was found to be greater than 8 h, where floating lag time for formulations F1, F2, F3, F4, F5 and F6 were found to be 2 min, 2.1 min, 1.8 min, 2.0 min, 1.5 min and 1.9 min respectively. The In vitro disintegration time for all the 6 formulations varied from 1.30 to 3.55 minutes. Among all the formulations, F5 was found to show less floating lag time and disintegration time but more floating time of greater than 8h of SR layer.

Table 5: Evaluation of Post compression parameters of Bilayer Floating tablet.

Formulation Code	Weight variation (mg) n=20	Thickness (mm) n=20	Hardness (kg/cm^2) n=6	%Friability n=10	Disintegration Time (min)
F_1	398	4.24	6.75	0.44	3.55
F_2	401	4.27	6.42	0.46	3.34
F_3	403	4.23	6.35	0.45	2.44
F_4	402	4.45	6.75	0.41	2.87
F_5	392	4.25	6.77	0.43	1.30
F_6	399	4.23	6.80	0.42	1.56

4. The *in vitro* drug release profile of the formulations was observed by calculating % drug release of each formulation, as given in Fig.1 and Fig 2.

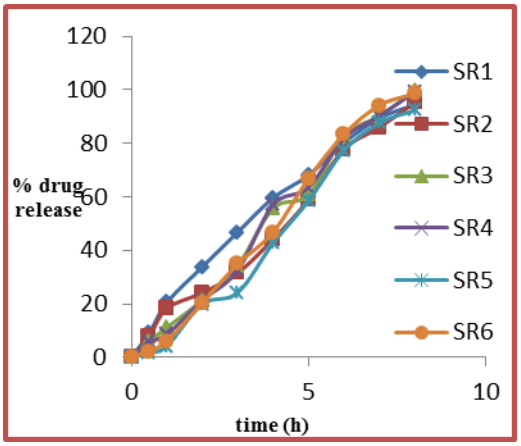

Fig.1. *In-vitro* Drug release data of layer of Rabeprazole

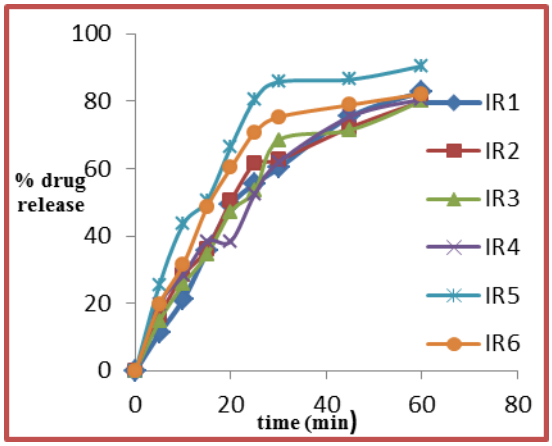

Fig.2. In-vitro drug release data of IR layer of Amoxicillin

5. Formulation F5 was found to be the optimized formulation with rapid disintegration time, faster floating lag time, longer floating time and SR layer with of percentage drug release 92.42% at 8 h and IR layer with 90.45 % at 60 min time. The FT-IR of the formulation showed no drug - drug interaction (between Rabeprazole and Amoxicillin) as in Fig 3.

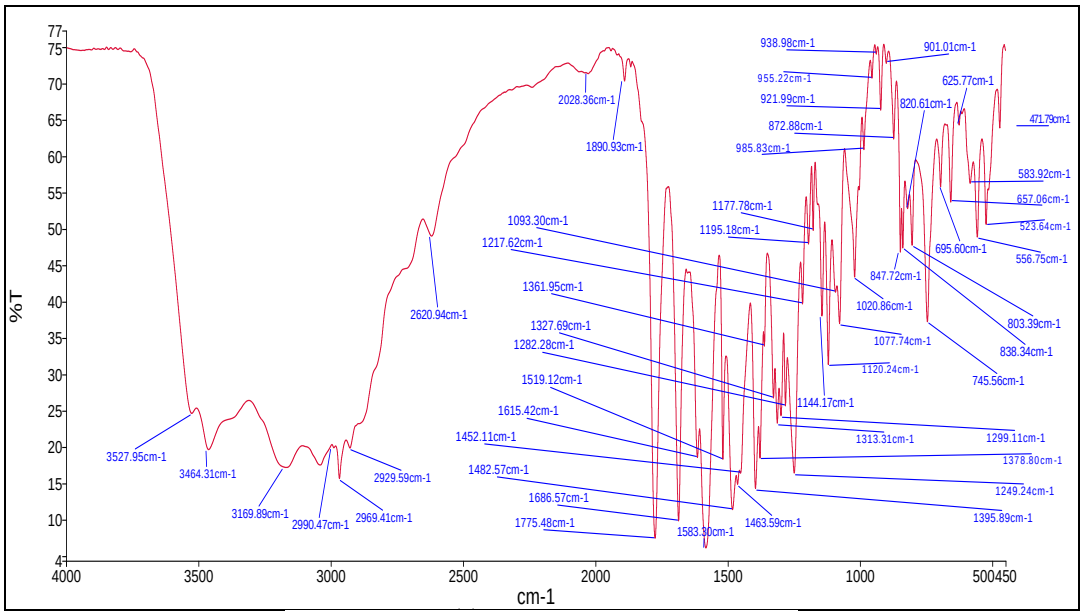

Fig 3: FT-IR of Amoxicillin and Rabeprazole

CONCLUSION

The present work demonstrated the successful formulation and evaluation of bilayer floating tablets of amoxicillin and rabeprazole in a single dosage form as bilayer tablet. Among the different formulations of bilayer tablets, the immediate release layer consisted of Amoxicillin prepared by direct compression method using various super disintegrants and sustained release layer consisted of prepared by wet granulation method using different release retarding agents, optimized formulation was found to be F5 (SR5 and IR5). The drug excipient compatibility studies carried out using FTIR revealed that there was no interaction found between drugs and excipients. All the pre- and post compression studies revealed that the results were found to be within the official limits. *In vitro* release studies reveal that Amoxicillin immediate release layer in bilayer tablet was found to be 90.45% within 1h and Rabeprazole sustained release layer was 92.42% at the end of 8hrs. Thus the prepared bilayer tablets achieved the objective of the research work in treating the *Helicobacter pylori* induced peptic ulcer with the sequential release of two drugs present in different layers.

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