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Development and Evaluation of Floating Matrix Tablets of Riboflavin

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Abstract: In the present study floating matrix drug delivery systems of model drug Riboflavin was developed and investigated in view of improving its oral bioavailability. The single and bilayer tablets were prepared by direct compression technique using polymers hydroxypropylmethyl cellulose (METHOCEL K4M), Carbopol 971P and other standard excipients. Calcium carbonate was incorporated as a gas-generating agent. The effect of polymers, diluents (lactose & microcrystalline cellulose) on drug release profile, floating properties were investigated. The tablets were evaluated for thickness, hardness, friability, swelling index, mucoadhesion and in vitro drug release. Polymer with lower viscosity (hydroxyl propyl methyl cellulose K4M) was found to be beneficial than higher viscosity polymer (Carbopol 971P) in improving the release properties of gastric floating drug delivery system. Incorporation of Carbopol in formulation helped in maintaining buoyancy of system. The mechanism of drug release was found to follow Higuchi matrix order release. The formulation F4 was optimized based on floating time (3±0.057 min) and in vitro drug release (98.60 %).

Keywords: Carbopol 971P, Gas generating agent, Floating matrix system, Hydroxyl propyl methyl cellulose K4M, Riboflavin.

Introduction

Gastroretentive drug-delivery systems are retained in the stomach and assist in improving the oral bioavailability of drugs that have an absorption window in a particular region of upper GI tract. Several approaches currently used to prolong gastric retention time include floating drug-delivery systems, swelling and expanding systems, polymeric bioadhesive systems, high-density systems, and other delayed-gastric-emptying devices[1].The principal of buoyant preparation offers a simple and practical approach to achieve increased gastric residence time of dosage form for sustained drug release [2].

Bioavailability of riboflavin in foods, mostly as digestible flavocoenzymes, is excellent at nearly 95%, but absorption of the free vitamin is limited to about 27mg per single meal or dose in an adult. Riboflavin is used for the treatment of Ariboflavinosis associated with weakness, throat soreness/swelling, tongue swelling (glossitis), angular stomatitis/cheilosis (skin cracking or sores at the corners of the mouth), dermatitis (skin irritation), and anemia. It is readily absorbed from the upper GIT being its absorption window, 60% of drug is bound to plasma proteins, its $t_{1/2}$ 66-84 min, 9% of drug is excreted unchanged in urine make it a suitable candidate for floating drug delivery system [3, 4]. This model drug is advantageous because it lacks adverse effects and has no pharmaceutical effect on gastric motility.

The present investigation shows a systematic balance between floating lag time, floating duration, in vitro drug release for the development of gastroretentive dosage forms of Riboflavin suitable for once-daily formulation with improved bioavailability.

Materials and methods

Materials:

Riboflavin was purchased from Dr. Reddy's Laboratories(Hyderabad,India). Methocel K4M,

Carbopol 971P, Ethyl cellulose, Polyvinyl pyrolidone K30 (PVP K30), Lactose, Microcrystalline cellulose were received as gift samples from FDC Limited, Mumbai. Glycerol monooleate was purchased from Milton chemicals (Mumbai, India). Citric acid and Calcium carbonate were purchased from Poona chemical laboratory (Pune, India). All other reagents and chemicals used were of analytical reagent grade.

Methods:

Preparation of single layer floating matrix tablets [5, 6]:

Drug was initially coated with the mixture of glycerol monooleate and ethyl cellulose prepared by melting and cooling. The polymers, effervescent mixture and other excipients were added to above mixture as shown in Table No. 1 by blending and sieving processes to form a homogenous mixture. Tablets were prepared by direct compression using 4 mm diameter punch at 4-5 kg/cm^3 pressure using a hydraulic press (Kimaya engineers, Thane, India).

Preparation of Bilayer floating matrix tablets:

Bilayer floating tablets were prepared by direct compression involving two steps.

The floating layer mixture was prepared by blending homogenously the polymer and effervescent mixture (Citric acid and Calcium carbonate) as shown in Table No. 2. The releasing layer mixture was prepared by coating the drug with glycerol monooleate and ethyl cellulose mixture, to which polymers and other excipients were added and blended homogenously.

Initially, the floating layer mixture (50mg) was compressed using 4 mm diameter punch at pressure 1-2 kg/cm^3 for 3 s. The upper punch was raised and the release layer mixture (152.7 mg) was placed on the above compact, the two layers were than compressed at a pressure of 4-5 kg/cm^3 for 15 s to obtain bilayer floating matrix tablets each weighing ~ 200 mg with thickness of 2 mm to 2.2 mm.

Tablet dimensions (Tablet thickness and diameter) [7]:

Five tablets of each batch were picked randomly and its thickness and diameter were measured individually using calibrated varnier calipers. Tablet thickness should be controlled within ±5% variation of a standard value.

Hardness[7]:

The hardness of tablet of each formulation was measured by Monsanto hardness tester. The hardness was measured in terms of kg/cm^2. Five tablets were randomly picked from each batch and the hardness of the tablets was determined. The mean and standard deviation values were calculated for each batch.

Friability[7]:

Roche friabilator was used for testing the friability using the following procedure. Ten tablets were weighed accurately and placed in the tumbling apparatus that revolves at 25 rpm dropping the tablets through a distance of six inches with each revolution. After 4 min, the tablets were weighed and the percentage loss in tablet weight was determined.

$$\% \text{ Loss} = \frac{\text{Initial wt. of tablets} - \text{final wt. of tablets}}{\text{Initial wt. of tablets}} \times 100$$

Weight variation[7]:

Weighed 10 tablets selected at random and calculated the average weight. Not more than the percentage as given in IP and none deviates by more than twice that percentage.

Content uniformity:

Ten tablets were weighed and triturated to get fine powder. Weight equivalent to 10 mg of riboflavin was dissolved in 10 ml of chloroform and sonicated for 10 min, the volume was adjusted to 100 ml using 0.1 N HCl with continuous sonication for 5min. 1 ml of this solution (withdrawn form supernatant aqueous part) was diluted to 100 mL with 0.1 N HCl. 3 ml of above solution was diluted with 0.1 N HCl up to 100 ml, filtered through 0.45 µm whatman filter paper, and analyzed at 450 nm using UV spectrophotometer (Shimadzu, Japan) [7]. The experiments were performed in triplicate.

In vitro buoyancy study [9, 10]:

This test was characterized by floating lag time and total floating time. The test was performed using USP XXIII type II paddle apparatus using 900 ml of 0.1 N HCl at paddle rotation of 100 rpm at 37 ± 0.5^o C. The time required for tablet to rise to surface of dissolution medium and duration of time the tablet constantly float on dissolution medium was noted as floating lag time and total floating time.

Swelling study [11, 12]:

Formulated tablets were weighed individually (W_0) and placed separately in petri dish containing 50 ml of 0.1 N HCl. The petri dishes were placed in an incubator maintained at 37±0.5^{o}C. At regular 1-h time intervals until 4h, the tablets were removed from the petri dish, reweighed (W_t), and the % swelling index was calculated using the following formula.

$\% WU = (W_t - W_o / W_o) \times 100$

WU – Water uptake

W_t – Weight of tablet at time t

W_o – Weight of tablet before immersion

Ex Vivo Mucoadhesion strength [13]:

Detachment force method was used to study the ex vivo mucoadhesion of tablets. The modified balance method was used to assess the tendency of mucoadhesive material to adhere to mucosal membrane. The left pan was replaced with a Teflon block B ring hung by a number of metallic rings. Sheep stomach mucosa obtained from slaughter house was cleaned and isolated. About 15 mm of the membrane was attached to Teflon block A with the mucus surface exposed on the upper side, the tablet was attached to Teflon B using an adhesive. Block B was lowered on block A kept in jacketed glass beaker filled with test medium (200ml of 0.1 N HCl at 37^{o}C). The right pan of the balance was replaced with a light weight beaker. By keeping suitable weight on the right hand side the pans were balanced so that Teflon block B attached with the tablet rest on the membrane attached to block A. After contact time of 4 min, weight was increased in the beaker on the right-hand pan by adding water until the tablet detached from the membrane. The excess weight in mg to the right hand side gave the mucoadhesive strength of the tablet.

Ex Vivo Mucoadhesion time [11]:

Isolated fresh sheep stomach mucosa obtained was tied on the glass slide; each tablet was wetted with 1 drop of 0.1 N HCl and pasted to the sheep stomach mucosa by applying light force with a fingertip for 30 s. The glass slide was then placed in the beaker, Since only mucoadhesive property was evaluated 200 ml of 0.1 N HCl was used for study, at 37°C ± 1°C with slow stirring speed of 50 rpm to simulate the stomach environment, tablet adhesion was monitored for 12 h. Time in min/s for the tablet to detach from the sheep stomach mucosa was recorded as the mucoadhesion time.

In vitro drug release study [9]:

The USP XXIII rotating paddle method was used to study drug release from the floating matrix tablets. 900 ml of 0.1 N HCl was used as dissolution medium. The release study was performed at 37±0.5^{o}C, with a rotation speed of 100 rpm.The tablet was entangled in a loosely wound thin wire mesh to prevent the tablet from floating. Samples of 5 ml were with drawn at predetermined time intervals and replaced with fresh medium. The samples were filtered through whatman filter paper and analyzed after appropriate dilution using UV spectrophotometer (Shimadzu, SPD-10 A VP) at 450 nm.

Results and Discussion

Formulated tablets were found to be satisfactory when evaluated for thickness (2±0.122 mm); Hardness (5.02±0.136 kg/cm^{2}), Friability less than 1% (as shown in Table No.3). The percent drug content of all formulations were found to be between 97.2 % to 99.9 % (Table No.3) which is within acceptable limits indicating dose uniformity in each batch.

All formulations showed good duration of floating i.e. floating time more than 12 h, as the amount of polymer and gas generating agent was constant. Formulations showed good buoyancy properties due to their low density than GI fluid. Single layer tablets show less buoyancy lag time (BLT) when compared with double layer tablets.(shown in Table No. 4). Formulation F2 showed lowest BLT while F8 showed highest BLT. This variation occurred due to the quantity difference of PVP K30 in single and double layer tablets. Carbon dioxide is formed within the tablet containing effervescent agent when it is brought in contact with acidic medium (0.1 N HCl). The low density as well as gelling capacity of polymers helps the tablet to float by entrapping the gas in the gel network.

Results of swelling index are shown in Table No.4, while the plot of swelling index against time (h) is depicted in Fig. I. In the present study, all formulations had same concentrations of polymer. The swelling index was highest for tablets of formulation F4 (146.3 %) and least F7 (93.0 %). This indicates that HPMC stores more water content in matrix than Carbopol. Rate of swelling for single layer formulation is more than for bilayer formulation. From the results it can be concluded that swelling increases with time because polymer gradually absorbs water due to its hydrophilicity. The outermost layer of the polymer hydrates, swells and a gel barrier is formed at the outer surface.

The ex vivo mucoadhesion strength and ex vivo mucoadhesion time of all formulations were determined for different contact times. Mucoadhesion studies reveal that formulations containing carbopol showed higher mucoadhesion property, due to which the formulation was retained for a longer duration in stomach (Table No.4) HPMC retains the dosage form due to swelling, where as Carbopol retains due to its mucoadhesive property.

The plot of cumulative drug release Vs time plotted for all formulations are depicted in Fig. II. The release of drug from HPMC K4M based floating tablets was more than Carbopol based tablets. Single layered tablets showed higher release than bilayered tablets due to its large surface area. Inclusion of PVP in the releasing layer of bilayered tablets showed higher drug release F7, F8 (73.33 %, 76.55 %) in comparison with PVP used in single layered F1, F2 (63.54 %, 69.45 %) respectively. HPMC K4M and Carbopol 971 P were used for matrix formation.

Effervescent mixture helps in maintaining the buoyancy of the tablet .The generated gas is entrapped

within the polymer matrix which helps in floating the tablets.

Carbopol containing tablets showed better controlled release when compared to HPMC. Microcrystalline cellulose as diluent increased drug release than lactose due to its hydrophobic nature. PVP K30 used as pore forming agent increases the water uptake from the tablet environment. The polymer, diluents nature and PVP K30 concentration in active layer influence the drug release. Model fitting studies revealed drug release mechanism followed Higuchi matrix order release.

Table No- 1 Formulations of single layer floating matrix tablets

Ingredients	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**
	Floating layer					
Citric acid	5	5	5	5	5	5
$CaCo_3$	5	5	5	5	5	5
HPMC K4M	-	-	40	40	20	20
Carbopol 971 P	40	40	-	-	20	20
	Releasing layer					
Riboflavin	10	10	10	10	10	10
Glycerol monooleate	2.2	2.2	2.2	2.2	2.2	2.2
Ethyl cellulose	0.5	0.5	0.5	0.5	0.5	0.5
HPMC K4M	-	-	40	40	20	20
Carbopol 971P	40	40	-	-	20	20
PVP K30	46	46	46	46	46	46
Lactose	30	-	30	-	30	-
MCC	-	30	-	30	-	30
Magnesium stearate	3	3	3	3	3	3
Citric acid	6	6	6	6	6	6
$CaCO_3$	15	15	15	15	15	15

All quantities in milligram. HPMC - Hydroxy propyl methyl cellulose, PVP – Polyvinyl pyrrolidone, MCC – Microcrystalline cellulose and $CaCO_3$ – Calcium carbonate.

Table No- 2 Formulations of bilayer floating matrix tablets

Ingredients	**Formulations**					
	F1	**F2**	**F3**	**F4**	**F5**	**F6**
Riboflavin	10	10	10	10	10	10
Glycerol monooleate	2.2	2.2	2.2	2.2	2.2	2.2
Ethyl cellulose	0.5	0.5	0.5	0.5	0.5	0.5
HPMC K4M	-	-	80	80	40	40
Carbopol 971P	80	80	-	-	40	40
PVP K30	46	46	46	46	46	46
Lactose	30	-	30	-	30	-
MCC	-	30	-	30	-	30
Magnesium stearate	3	3	3	3	3	3
Citric acid	11	11	11	11	11	11
$CaCO_3$	20	20	20	20	20	20

All quantities in milligram. HPMC - Hydroxy propyl methyl cellulose, PVP – Polyvinyl pyrrolidone, MCC – Microcrystalline cellulose and $CaCO_3$ – Calcium carbonate.

Table No.3: Physicochemical properties of Riboflavin Floating Matrix Tablets

Formulation code	Diameter (mm) Mean ± SD (n=5)	Thickness (mm) Mean ± SD (n=5)	Hardness (kg/cm^2) Mean ± SD (n=5)	Friability (%)	Avg Weight (gm) Mean ± SD (n=10)	Drug Content (%)
F1	10.02±0.008	2±0.122	6.18±0.111	0.29%	202.7±0.138	99.2
F2	10.01±0.007	2±0.044	6.10±0.045	0.28%	202.8±0.117	98.9
F3	10.01±0.04	2.2±0.1	5.02±0.136	0.37%	202.7±0.147	98.5
F4	10.01±0.008	2.1±0.083	5.08±0.094	0.34%	203±0.273	97.9
F5	10.01±0.013	2.5±0.164	5.46±0.122	0.31%	202.1±0.340	99.9
F6	10.01±0.007	2.3±0.130	5.53±0.158	0.33%	202.7±0.019	97.2
F7	10.02±0.01	2.1±0.070	6.15±0.061	0.28%	202.5±0.054	97.5
F8	10.01±0.005	2.5±0.192	6.70±0.134	0.25%	202.9±0.1	97.9
F9	10.03±0.008	2.3±0.114	5.18±0.198	0.38%	202.92±0.18	97.56
F10	10.02±0.004	2.5±0.192	5.10±0.054	0.36%	202.9±0.178	99.06
F11	10.01±0.008	2.2±0.109	5.49±0.079	0.30%	202.7±0.075	98.6
F12	10.01±0.004	2.25±0.120	5.51±0.109	0.32%	202.8±0.096	97.9

Table No- 4 Floating lag time, Floating time, Swelling index, Mucoadhesion timeand Mucoadhesion strength.

Formulation	Floating Lag time Mean±(S.D.)	Floating time (h)	Swelling index (%)Mean ± (S.D.)	Mucoadhesion time (h) Mean ± (S.D.)	Mucoadhesion strength (g) Mean ± (S.D.)
F1	0.30±0.057	›12	115±1	13± 0.288	16±0.288
F2	0.25±0.05	›12	118.9±1	13.2± 0.152	15±0.057
F3	3±0.321	›12	142.5±2	-	0.1±0.057
F4	3±0.057	›12	146.3±1	-	0.1± 0.057
F5	3±0.152	›12	122±1	0.3± 0.1	2±0.057
F6	3±0.115	›12	125±1	0.4 ±0.1	1.2±0.115
F7	4±0.1	›12	93.0±1	12± 0.288	15±0.288
F8	5±0.152	›12	96.0±1	14± 0.1	14±0.115
F9	3±0.115	›12	131.7±2	-	0.05±0.011
F10	2±0.057	›12	136.3±2	-	0.05± 0.028
F11	3±0.18	›12	106±1	0.1± 0.1	1±0.404
F12	3±0.07	›12	108.5±1	0.23± 0.1	2±0.152

± S.D- Standard deviation for (n=3)

Figure- 1 Swelling index:

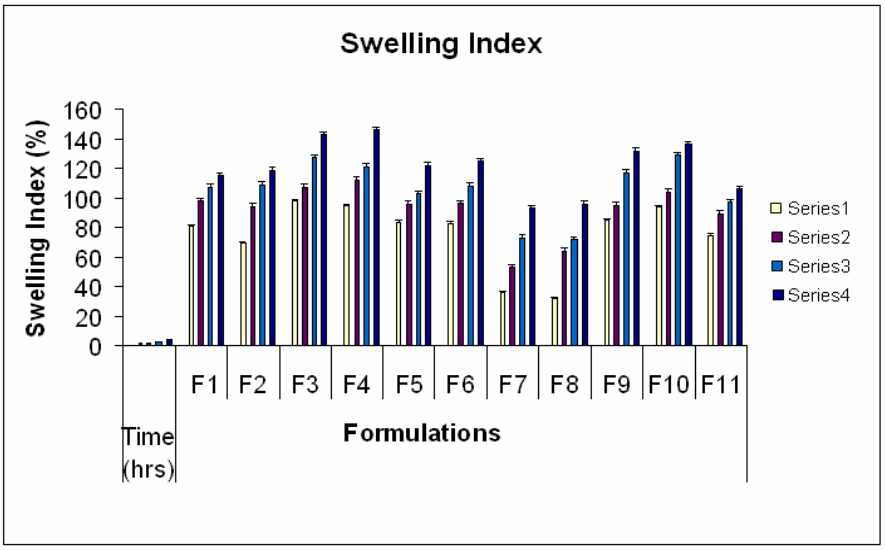
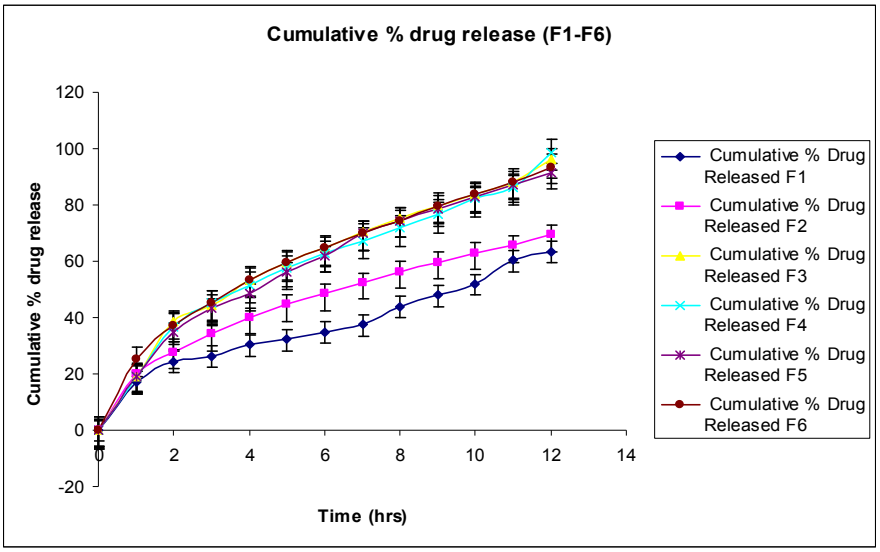
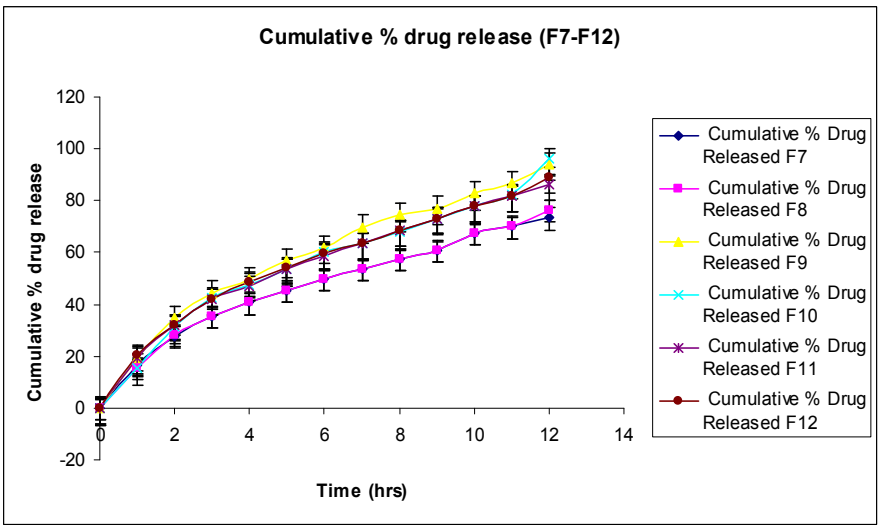


Figure- 2 In vitro drug release study (cumulative % drug release)





Conclusion

Results of mucoadhesion tests indicated that carbopol polymer increases mucoadhesion properties of tablets. Carbopol containing tablets were retained in stomach by mucoadhesion mechanism and HPMC containing tablets were retained in stomach by non-mucoadhesion (floating) mechanism.

From the results bilayer formulations showed better sustained release and buoyancy properties. Single layer formulations showed more drug release and swelling index. In vitro release results indicated that the drug release was more sustained in carbopol with lactose containing formulations.

From above studies it is concluded that floating matrix drug delivery systems can be a suitable approach to improve oral bioavailability of drugs having narrow absorption window in stomach.

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