International Journal of Science and Research (IJSR)
ISSN: 2319-7064
ResearchGate Impact Factor (2018): 0.28 | SJIF (2018): 7.426

Formulation and Evaluation of Floating Matrix Tablet of Riboflavin

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Abstract: ***Floating matrix tablets of Riboflavin were developed to prolong gastric residence time, leading to sustained action of the drug. The single layertablets prepared by wet granulation compression technique using polymers hydroxypropylmethyl cellulose (METHOCEL), Carbopol 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) in improving the release properties of gastric floating drug delivery system. Incorporation of Carbopol in formulation helped in maintaining buoyancy of system. The formulation F4 was optimized based on floating time (3±0.057 min).***

Keywords: Carbopol , Gas generating agent, Floating matrix system, Hydroxyl propyl methyl cellulose, Riboflavin

1. Introduction

Oral route has been the most predominant route of drug delivery due to its ease of administration, low cost of therapy, patient compliance and flexibility in its formulation. But drugs that are easily absorbed from gastrointestinal tract (GIT) and have short half-lives are eliminated quickly from the systemic circulation. Frequent dosing of these drugs is required to achieve suitable therapeutic activity. Recently oral controlled release drug delivery has been of great interest in pharmaceutical field to achieve improved therapeutic advantages. Variable and too rapid gastrointestinal transit has been the major limitation of oral controlled drug delivery which results in incomplete release of drug from the delivery device leading to diminished efficacy of the administered dose. Gastroretentive drug delivery system (GRDDS) is one such novel site-specific orally administered controlled release drug delivery [1-4] system in which the delivery system is retained in the stomach for prolonged period and release the drug in a controlled manner, so that the drug could be supplied continuously to its absorption sites in the GIT. Riboflavin is one such drug which has narrow absorption window in gastrointestinal tract (GIT). Hence, we intend to develop a simple floating matrix tablets of Riboflavin and prepare sustained release 'once daily' tablets. The once daily dosing regimen will be beneficial to the working population as well as for geriatric patients owing to its convenience.[5-6]

Bioavailability of riboflavin In foods , mostly as digestible flavocoenzymes , is excellent at nearly 95%, but absorption of the free vitamin is limited to about 27 mg per single meal or dose in adult. Riboflavin is used for the treatment of Ariboflavinosis associated with weakness. It is also used in treatment of throat soreness/swelling, tongue swelling (glossitis) ,angular stomatitis/cheilosis (skin irritation), and anemia.6-7

2. Materials and methods

Materials

All other reagents and chemicals used were of analytical reagent grade.Riboflavin was obtained as gift sample from Macleods. Pharmaceuticals Ltd. Hydroxyl propyl methyl cellulose, Ethyl cellulose, Carbopol 934, lactose, starch and Chitosan 75% were commercially obtained from Loba Chemicals Pvt. Limited, Mumbai, India. All other reagents and chemicals used were of analytical reagent grade.

Preparation of single layer floating matrix tablets

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/cm3 pressure using a hydraulic press.

Pre-Compression studies

Angle of repose

It is difined as the maximum angle possible between the surface of a pile of powder and the horizontal plane. Angle of repose of granules was determined by funnel method. Accurately weighed powder blend was taken in the funnel. Height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the powder blend. Powder blend was allowed to flow through the funnel freely on to the surface. Diameter of the powder cone was measured and angle of repose was calculated using the following equation.

$=\tan^{-1}(h/r)$

Wereθ = angle of repose
H= height in cms
R= radius in cms.

Density

1) Bulk density

It is the ratio of total mass of powder to the bulk volume of powder weigh accurately 25 gm granules, which was previously passed through 22# sieve and transferred in 100 ml graduated cylinder. Carefully level the powder without compacting, and read the unsettled apparent volume. Calculated the apparent bulk density in gm/ml by the following formula.

Bulk density = weight of powder / Bulk volume.
$D_b=M/V_O$
M= mass of powder
V_O=bulk volume of the powder.

2) Tapped density
It is the ratio of total mass of powder to the tapped volume of powder. weigh accurately 25 gm granules, which was previously passed through 22# sieve and transferred in 100 ml graduated cylinder of tap density tester which was operated for fixed number of taps the powder bed volume has reached a minimum, thus was calculated by formula.
Dt= (M) / (V_f).
M = mass of powder
V_f = tapped volume of the powder

Carr's Index:
Compressibility index of the powder blend was determined by carr's compressibility index. It is a sample test to evaluate the BD and TD of the powder and the rate at which it packed down. The formula for carr's index is as below.

$$\text{Compressibility index} = 100 \times \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}}$$

Post-Compression Studies

Evuluation of tablet characteristics

Weight variation
Twenty tablets were selected random and weighted individually.The average weight was calculated. Individual weights of the tablets were compared with the average weight.

Hardness
The hardness of tablet of each formulation was measured by monsanto hardness tester. The hardness was measured in terms of k/g cm2. Five tablet were randomly picked from each batch and the hardness of the was determined. The mein and standard deviation values were calculated for each batch.

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

Friability
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.

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

Drug Content
Five tablets were powdered in a mortar. Weighed accurately the quantity equivalent to 50mg of riboflavin transferred to a 100ml volumetric flask containing few ml of distilled water and mixed well, made up the volume up to 100ml with distilled water. Pipette out 10 ml from the stock solution into another 100 ml volumetric flask and made up the volume with distilled water. From the above solution withdrew the aliquots of 2ml, 2.4ml and 3.2ml (as per Beer's range 2-20 µg/ml) and the volume was made up to 10 ml with distilled water. The absorbance was measured at 445 nm using distilled water as blank.

In vitro buoyancy study
This test was characterized by floating lag time and total floating time. The test was performed using USP type II paddle apparatus using 900 ml of 0.1 N HCl at paddle rotation of 100 rpm at 37 ± 0.5o 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.

In-vitro Release studies
The in-vitro dissolution profile of the designed formulations of controlled release tablets was carried out using USP type II apparatus under conditions specified (temp 37± 0.50C, 100rpm). Tablets were subjected to dissolution for first two hrs in 0.1 N HCl next six hrs till the end of dissolution studies. From the dissolution medium withdrawn and replaced 1 ml for every 5 min, for the solution withdrawn volume was made up to 10 ml with distilled water and absorbance was measured at 445 nm using distilled water as blank. Dissolution profiles of the formulations were analyzed by plotting drug release versus time plot.

3. Results and Discussion

Formulated tablets were found to be satisfactory when evaluated for thickness (2±0.122 mm); Hardness(5.02±0.136 kg/cm2), Friability less than 1%. The percent drug content of all formulations were found to be between 97.2 % to 99.9 % 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. Formulation. 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 byentrapping 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 formulationshad 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.

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.

Evaluation of pre-compression parameters

Based on the results of pre-compression tests, all the formulations showed angle of repose ranging from 22.21o ± 0.84 to 27.5o ± 0.94 indicating a good flow property (Table No.2) and Carr's index ranging from 10.53 ± 0.01 to 23.22 ± 0.22%, indicating compressibility of the granules is fairly passable.

Evaluation of post-compression parameter

The tablet hardness, friability, weight variation and drug content uniformity of all tablet formulations were found to besatis factory and reproducible as observed from the data in Table 3. The hardness of allthe tablets was between 5.79±0.28 and7.5±0.31 kg/cm. In the present study, the lossin total weight in friability test was in therange of 0.28% to 0.58% that indicates, thepercentage friability for all the formulations was found below 1% indicating that friability (%) is within the acceptable limits. In a weight variation test, the pharmacopoeia limit for the percentage deviation for tablets weighing more than 250 mg is ±5%. The average percentage deviation of all tablet formulations was found to be within limit, and hence all formulations passed the test for uniformity of weight as per official requirement. Good uniformity in drug content was found among different batches of the tablets.

Stability Studies

The optimized formulation was found to be stable in terms of physical appearance, hardness and drug content after 2 months when it is stored under accelerated stability conditions as per ICH guideline.

Table 1: Working Formula: F1 – F5 by wet granulation method

Floating layer

S.No	Ingredients	F1	F2	F3	F4	F5
1	Citric acid	0.02 gm	0.2 gm	0.2 gm	0.2 gm	0.2 gm
2	CaCo3	0.2 gm	0.2 gm	0.2 gm	0.2 gm	0.2 gm
3	Hpmc	0	1.6 gm	1.6 gm	1.6 gm	0.8 gm
4	Carbopol	1.6 gm	1.6 gm	0	1.6 gm	0

Release layer

S.No	Ingredients	F1	F2	F3	F4	F5
1	Riboflavin	0.4 gm	0.4 gm	0.4 gm	0.4 gm	0.4 gm
2	Glycerol monooleate	0.088gm	0.088gm	0.088gm	0.088gm	0.088 mg
3	Hpmc	0	0	1.6 gm	1.6 gm	0.8 gm
4	Carbopol	1.6 gm	1.6 gm	0	0	1.84 gm
5	PVP	1.84 gm	1.84 gm	1.84 gm	1.84 gm	1.84 gm
6	Lactose	1.2 gm	0	1.2 gm	0	1.2 gm
7	MCC	0	1.2 gm	0	1.2 gm	1.2 gm
8	Magnesium stearate	0.12 gm	0.12 gm	0.12 gm	0.12 gm	0.12 gm
9	Citric acid	0.24 gm	0.24 gm	0.24 gm	0.24 gm	0.24 gm
10	Caco3	0.6 gm	0.6 gm	0.6 gm	0.6 gm	0.6 gm
11	Ethyl cellulose	0.02 gm	0	0	0	0

Table 2: Pre- Compression Parameter of Tablet

S.NO.	Formulation	Bulk density	Tapped density	Carr's index	Angel of repose
1.	F1	0.46±0.00	0.53±0.00	14.16±0.03	26.79±1.15
2.	F2	0.41±0.00	0.49±0.00	18.54±0.03	27.86±0.22
3.	F3	0.47±0.00	0.52±0.00	10.54±0.01	22.86±0.22
4.	F4	0.47±0.00	0.56±0.00	10.54±0.01	22.88±1.08
5.	F5	0.38±0.00	0.56±0.00	14.85±0.04	26.80±1.09

Table 3: Post-Compression Parameters of Tablets

S.NO	Formulation	Thickness	Hardness	Friability	Avg.Weight [gm]	Drug N Content [%]
1	F1	2.2±0.119	5.98±0.111	0.27	200±1.02	99.2
2	F2	2.1±0.122	5.88±0.109	0.26	199±1.32	98.2
3	F3	2.3±0.120	5.58±0.108	0.25	201±1.22	99.5
4	F4	2.1±0.123	5.68±0.11	0.27	200±0.01	99.7
5	F5	2.2±0.124	5.68±0.111	0.26	201±1.2	99.4

Table 4: Floating lag time, floating time, mucoadhesion time and mucoadhesion strength

Formulation	Floating lag time Mean±(S.D)	Floating time(H)	Mucoadhesion index (h) mean ±(S.D.)	Mucoadhesion strenght (g) mean ± (S.D.)
F1	120 sec	>12	09±0.130	12±0.635
F2	102 sec	>12	12±0.198	14±0.798
F3	108 sec	>12	13±0.203	16±0.788
F4	125 sec	>12	11±0.232	14±0.480
F5	130 sec	>12	10±0.215	13±0.288

Dissolution profile of formulation F1-F5

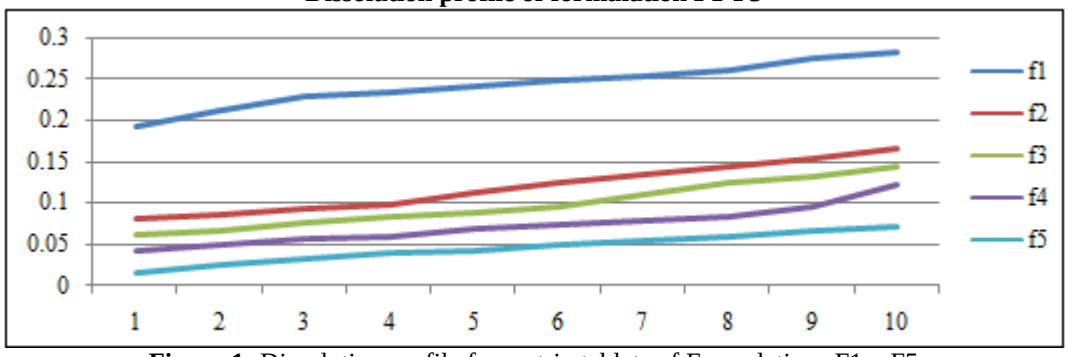
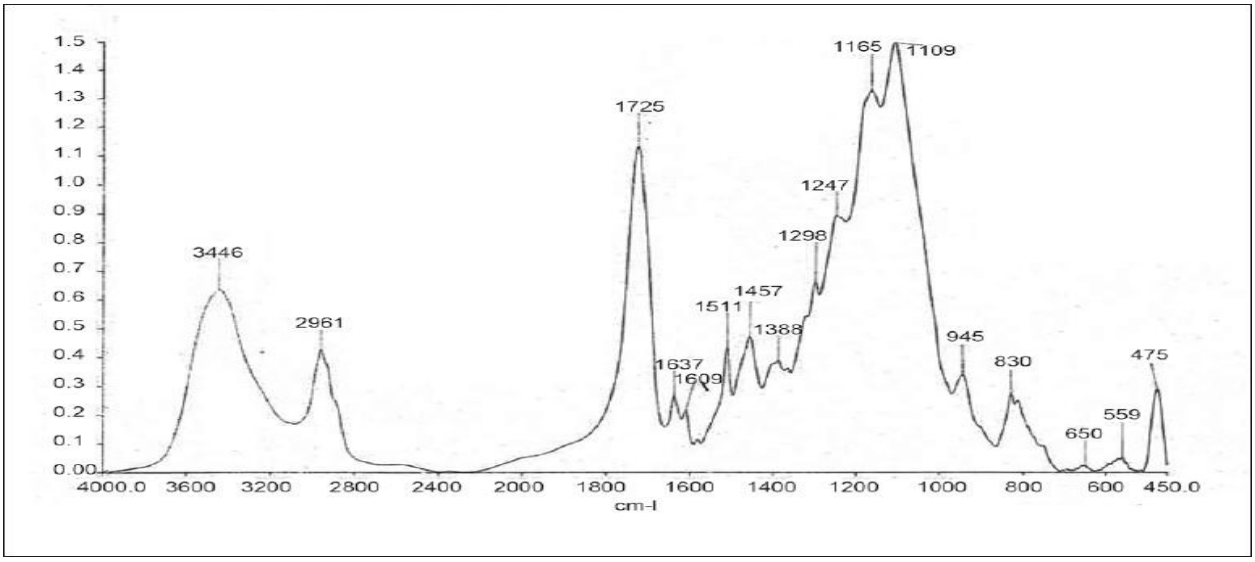


Figure 1: Dissolution profile for matrix tablets of Formulations F1 – F5

Picture = FT-IR Profile of Riboflavin



4. 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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