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Formulation and Evaluation of Floating Tablets of Riboflavin

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A B S T R A C T

Gastro retentive tablets of riboflavin were formulated using different water soluble polymers like HPMC, PVP, and Carbapol of different grades and magnesium stearate and lactose were used as lubricants all the pre formulation parameters like standard curve, melting point and FT-IR studies were performed. The pre compression studies were done angle of ripose to know the flow properties of drug and polymeric mixture and calculated the bulk density and tap density to know the compresability of a powder by hausners ratio all the formulations have show good flow property. The evaluation parameters like hatdness, friability, weight variation, drug content, swelling index, percentage of drug release were studied among all the 10 formulations F5 showed the maximum drug release of 96% because of the pvp polymer was present and the optimized formula F5 was filled to various kinetic models and the results showed the F5 formulation was following the zero-order kinetics and the mechanism of drug release from F5 tablet was anamolous non-fickians diffusion

Keywords: Riboflavin, floating drug delivery system, gastro retentive tablets, floating tablets

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1. Introduction

The development of an oral controlled-release drug delivery system is not just to sustain the drug release but also to increase the presence of dosage form within the gastrointestinal tract (GIT) until the total drug is completely released at the desired period of time Indeed. In the past few decades gastric drug retention has received significant interest. Most of the conventional oral delivery systems have shown some limitations related to fast gastric-emptying time. Drug absorption from the gastrointestinal tract is a complex process. The dosage form can show better bio availability and better rate of absorption by designing as floating drug delivery systems.

Definition

Floating systems are also known as hydrodynamically controlled systems which are low-density systems that have sufficient buoyancy to float over the gastric contents and remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration [1].

Advantages

a. Floating dosage forms such as tablets or capsules will remains in the solution for prolonged time even at the alkaline pH of the intestine.
b. FDDS are advantageous for drugs meant for local action in the stomach
   Eg: Antacids
c. FDDS dosage forms are advantageous in case of vigorous intestinal movement and in diarrhea to keep the drug in floating condition in stomach to get a relatively better response.
d. Acidic substance like aspirin causes irritation on the stomach wall when come in contact with it hence; HBS/FDDS formulations may be useful for the administration of aspirin and other similar drugs [2].
e. The FDDS are advantageous for drugs absorbed through the stomach
   Eg: Ferrous salts, Antacids.
f. Reduced dosing frequency
g. Better patient convenience and compliance
h. Reduced gastro intestinal (GI) side effects
i. Less fluctuating plasma drug levels
j. Improved efficacy/safety ratio
k. More uniform drug effect
l. Lesser total dose

Disadvantages

a. Floating systems are not feasible for those drugs that have solubility or stability problems in gastric fluids.
b. Drugs such as Nifedipine, which is well absorbed along the entire GI tract and which undergo significant first-pass metabolism, may not be suitable candidates for FDDS since the slow gastric emptying may lead to reduced systemic bioavailability. Also there are limitations to the applicability of FDDS for drugs that are irritant to gastric mucosa.
c. One of the disadvantages of floating systems is that they require a sufficiently high level of fluids in the stomach, so that the drug dosages form float therein and work efficiently.
d. These systems also require the presence of food to delay their gastric emptying [3].

Applications of floating drug delivery systems

1. Floating drug delivery systems offers several applications for drugs having poor bio availability because of narrow absorption window in the upper part of the gastro intestinal tract.
2. It retains the dosage form from the site of absorption and thus enhances the bioavailabity.
3. The applications include:
4. Sustained drug delivery: sustained release of floating capsules of nicardipine hydrochloride (8h)
5. Site specific drug delivery: furosemide [4].

2. Materials and Methods

Riboflavin and water soluble polymers like HPMC K4M, PVP K 30, Carbapol 934 and magnesium stearate and lactose were collected and used. The following analytical tests were carried out. The UV spectrophotometry method was developed for the analysis of drug using double beam Shimadzu 1800 spectrophotometer.

Determination of λ_{max} of Riboflavin using distilled water

Riboflavin 100mg was dissolved in 100ml of water in a 100ml volumetric flask, from this 10ml was withdrawn and transferred into a 100ml volumetric flask and made up the volume with water, in order to get standard stock solution containing 100µg/ml of the drug. From the stock solution, drug solution was suitably diluted with water to get 10µg/ml. UV scan was taken between the wavelength 300-500 nm which gives a highest peak at 444nm.

Determination of λ_{max} Riboflavin using 0.1N HCl

Riboflavin 100mg was dissolved in 100ml of 0.1N HCl in a 100ml volumetric flask, from this 10ml was withdrawn and transferred into a 100ml volumetric flask and made up the volume with 0.1N HCl in order to get standard stock solution containing 100µg/ml of the drug. From the stock solution, drug solution was suitably diluted with 0.1N HCl to get 10µg/ml. UV scan was taken between the wavelength 300- 500 nm which gives a highest peak at 446nm.

Standard Curve for Riboflavin

100 mg of riboflavin was accurately weighed and dissolved in 100 ml of distilled water to prepare stock solution. The aliquot amount of stock solution was further diluted with ethanol get 5 µg, 10 µg, 15 µg, 25 µg, 30 µg, 35 µg, 40 µg, and 45 µg. of drug per ml of the final solution. Then the absorbance was measured in a UV spectrophotometer at 444nm against distilled water as blank.

Preformulation studies

Melting Point Determination

Melting point of the drug was determined by taking small amount of drug in a capillary tube closed at one end and

placed in a melting point apparatus and the temperature at which drug melts was recorded. This was performed in triplicates and average value was noted [5].

Drug–Excepients Interaction Study

The infrared (IR) spectra were recorded using an FTIR spectrophotometer (Perkin Elmer Spectrum GX) by the KBr pellet method in the wavelength region between 4000 and 400 cm^{-1}. The spectra obtained for riboflavin and physical mixtures of riboflavin with polymers were compared to check compatibility of drug with polymers [6].

Angle of repose

The angle of repose a powder blend was determined by funnel method. The accurately weighed powder blend was taken into the funnel. The height of the funnel was adjusted in such a way the tip of the funnel just touched to the apex of the powder blend. The powder blend was allowed to flow through the funnel freely on to the surface. The diameter of the powder cone was measured and angle of repose was calculated using formula [7].

$$\text{Tan } \theta = \frac{h}{R}$$

Table 1

Comparison between angle of repose and flow property	
Angle of repose (θ)	Flow
< 25	Excellent
25- 30	Good
30- 40	Moderate
>40	Poor

Bulk density

Both bulk density and tapped density were determined. a quantity of 2 gm of powder blend from each formula, previously shaken to break agglomerates formed, was introduced in to 10 ml measuring cylinder was allowed to fall under its own weight on to a hard surface from the height of 2.5 cm at second intervals. Tapping was continued until no further change in volume was noted. Bulk density and tapped density were calculated by using following equation [8].

$$\text{Bulk density} = \frac{\text{Weight of the powder blend}}{\text{Untapped volume of the packing}}$$

$$\text{Tapped density} = \frac{\text{Weight of the powder blend}}{\text{Tapped volume of the packing}}$$

Hausner's ratio

It indicates the flow property, measured by the ratio of tapped density to the bulk density [9].

Table 2

Hausner's ratio	Property
0 - 1.2	Free flowing
1.2- 1.6	Cohesive powder

Development of floating tablets of Riboflavin

Riboflavin, polymers like HPMC, Carbopol, PVP and lubricants like magnesium stearate, lactose were added by blending and sieve the drug and polymers mixture to get uniform and homogeneous mixture. Tablets were prepared by direct compression using 4mm diameter punch at 4-5kg/cm^2 pressure.

Evaluation of Floating Tablets of Riboflavin

The floating tablets which have been prepared were evaluated for the following parameters:

Hardness

The hardness of the tablet of each formulation was measured by hardness tester. The hardness was measured in terms of kg/cm^2. 5 tablets were randomly yield from each batch and the hardness of the tablets was determined. The mean and standard deviation values were collected for each tablet [10].

Friability

Friability was used for the testing the friability using the following procedure. The friability using the following procedure ten tablets are 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 that tablet was weighed and the percentage loss in tablets weight was determined [11].

$$\text{Percentage loss} = \frac{\text{Initial weight of the tablets} - \text{Final weight of the tablets}}{\text{Initial weight of the tablets}} \times 100$$

Table 3

Formulation no.	HPMC (mg)	PVP (mg)	Carbopol (mg)	Magnesium stearate (mg)	Lactose (mg)	Riboflavin (mg)	Total weight of the 1 tablet (mg)
F1	15	-	-	3	2	5	25
F2	10	5	-	3	2	5	25
F3	10	-	5	3	2	5	25
F4	5	5	5	3	2	5	25
F5	-	15	-	3	2	5	25
F6	5	10	-	3	2	5	25
F7	-	10	5	3	2	5	25
F8	-	-	15	3	2	5	25
F9	-	5	10	3	2	5	25
F10	5	-	10	3	2	5	25

Swelling study

Formulated tablets were weighed individually and placed separately in petridish containing 50ml of 0.1N HCl. The petridishes were placed in an incubator maintained at 37±0.5˚c. At regular 1hr time intervals until 4hrs the tablets were removed from the petridishes re-weighed (wt) and the % swelling index was calculated using the following formula [12].

% W_u = (W_t - W_u/ W_o) X 100

W_u = water uptake

W_t = weight of tablet at time t

W_o = weight of tablet before immersion

Weight uniformity

Weigh the tablets of individual batch randomly and calculated the average weight [13].

Drug Content Analysis

The tablet was taken into a 100 ml volumetric flask and dissolved in water and volume was made up with 0.1N HCl. Subsequent dilutions were made and analyzed by UV spectrophotometer at 444nm [14].

***In- vitro* drug release study**

To prevent the floating of tablet the tablet was entagled in a loosely wound thin wire mesh the USP rotating paddle method was used to study drug release from floating tablets of riboflavin 900 mL of 0.1N HCl was used as dissolution medium the release study was performed at 37±0.5˚c at rotational speed of 100rpm. Samples of 5ml were withdrawn at pre-determined time intervals and replaced with fresh medium the samples were filtered through whatmann filter paper and analyzed for appropriated dilution using UV spectrophotometer [15].

Release kinetics

Data obtained from invitro drug release studies was evaluated to check the goodness of fit to various kinetic equations or quantifying the phenomena controlling the release from the tablets. The kinetic models used were zero order, first order, higuchi and kosmeyer- peppas model. The goodness of fit was evaluated using the correlation coefficient values (R^2).

Zero order:

it describes the system in which the drug release rate is independent of its concentration.

$Q_t = Q_0 + K_0 t$

Q_t= the amount of drug dissolved in time t,

Q_0= initial amount of drug in the solution (0)

K_0= zero order release constant

If the zero order drug release kinetic is obeyed, then a plot of Q_t versus t will give a straight line with a slope K_0 and intercept at zero.

First order:

It describes the drug release from the system in which the release rate is concentration dependent.

$\text{Log } Q_t = \log Q_0 + K_t / 2.303$

Q_t= the amount of drug dissolved in time t,

Q_0= initial amount of drug in the solution (0)

K= first order release constant

If the first order drug release kinetic is obeyed, then a plot of log (Q_t-Q_0) versus t will be straight line with a slope of K_t/ 2.303 and an intercept at t= 0 of log Q_0

Higuchi model:

It describes the fraction of drug release from a matrix is proportional to square root of time

$M_t / M_\infty = Kt^{1/2}$

M_t and M_∞ are cumulative amount of drug release at time t, and

K = higuchi diffusion constant reflection formulation characteristics.

If the higuchi model of drug release (i.e Fickian diffusion) is obeyed, then a plot of M_t / M_∞ versus $t^{1/2}$ will be straight line with slope of K.

Kosmeyer-peppas model (Power law):

The power law describes the drug release from the polymeric system in which release deviates from fickian diffusion as expressed in following equation

$M_t / M_\infty = Kt^n$

$\text{Log } (M_t / M_\infty) = \log K + n \log t$

Where M_t and M_∞ are cumulative amount of drug release at time t, and infinite time

K= constant incorporating structural and geometrical characteristics of CR device.

n= diffusion release exponent indicative of the mechanism of drug release for drug dissolution.

To characterize the release mechanism

The dissolution data ($M_t / M_\infty < 0.6$) are evaluated.

Table 4

n	Mechanism
0.5	Fickians diffusion
0.5 < n< 1	Non fickians diffusion
1	Class II transport
> 1	Super class II transport

3. Results and Discussion

Standard Curve for Riboflavin

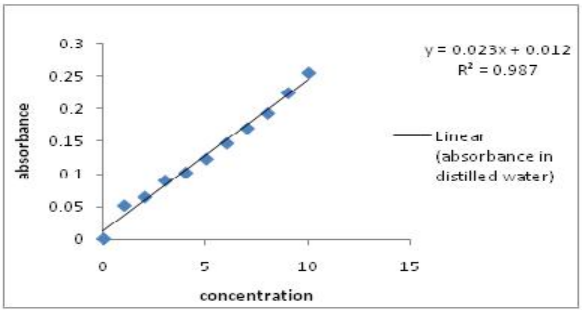

Figure 1: standard graph of riboflavin in distilled water

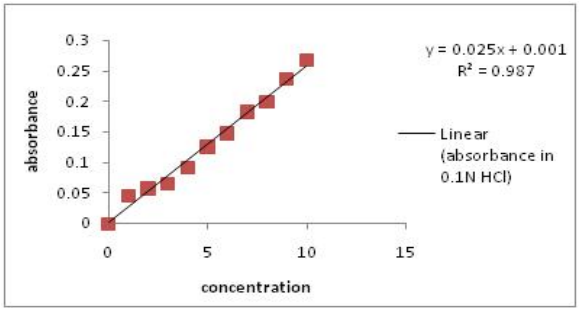

Figure 2: standard graph of riboflavin in 0.1N HCl

Table 5: Spectrophotometric Data for the Estimation of riboflavin

S.No	Concentration	Absorbance in 0.1N HCl	Absorbance in distilled water
1	0	0	0
2	1	0.046	0.051
3	2	0.058	0.064
4	3	0.065	0.089
5	4	0.092	0.101
6	5	0.126	0.122
7	6	0.148	0.146
8	7	0.183	0.169
9	8	0.199	0.192
10	9	0.236	0.223
11	10	0.267	0.254
Equation of line		y = 0.025x + 0.001	y = 0.023x + 0.012
R^2		0.9872	0.9879
Beer's law limit		1-10mcg/ml	1-10mcg/ml
λ_{max}		444nm	444nm

Preformulation studies

Melting Point:

Melting point of riboflavin was determined by capillary tube method and it was found to be 283.2ºC (*n* = 3). This value is same as that of the literature citation.

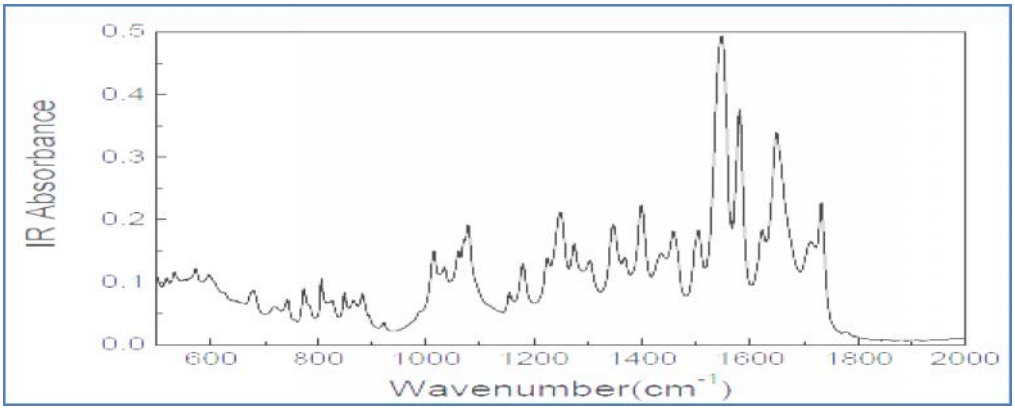

Figure 3: Drug–Excepients Compatibility Studies

As described in the methodology section the infrared spectroscopy studies were carried out for pure drug and along with polymers and there was no incompatibilty found.

Table 6: Bulk density, tap density, angle of repose, hausner's ratio and angle of repose for F1 to F10

Formulation code	Bulk density g/cm^3	Tap density g/cm^3	Hauner's ratio	Angle of repose
F1	0.624	0.740	1.185	25.12±0.594
F2	0.679	0.727	1.070	24.99±0.613
F3	0.612	0.735	1.200	25.06±0.232
F4	0.698	0.740	1.060	25.23±0.690
F5	0.711	0.802	1.127	24.65±0.481
F6	0.699	0.851	1.102	23.98±1.01
F7	0.702	0.865	1.032	25.04±1.178
F8	0.689	0.762	1.105	22.35±0.998
F9	0.568	0.745	1.111	23.74±1.160
F10	0.634	0.877	1.083	21.50±1.143

Bulk density was in the range between 0.568 to 0.711g/cm^3, tapped density was in the range between 0.727 to 0.865 g/cm^3, hausner's ratio were between 1.060 to 1.2.

Table 7: Hardness and Friability of Different Formulations

Formulation Code	Hardness(kg/cm^2)*	Friability*(%)
F1	2.5	0.25
F2	2.4	0.24
F3	2.5	0.24
F4	4.1	0.25
F5	3.5	0.24
F6	2.1	0.23
F7	2.5	0.23
F8	4.0	0.24
F9	5.0	0.25
F10	7.4	0.24

Dropping the tablets through a distance of six inches with each revolution after that tablet was weighed and the percentage loss in tablets weight was determined in the range between 0.23- 0.25% according to procedure. The hardness of the tablet of each formulation was measured by Pfizer hardness tester the average range is in between 2.1-7.4 kg/cm^2.

Swelling studies:

Formulated tablets were weighed individually and placed separately in petridish containing 50ml of 0.1N HCl. The petridishes were placed in an incubator maintained at 37±0.5°c. At regular 1hr time intervals until 4hrs the tablets were removed from the petridishes re-weighed (wt) and the % swelling index was in the range between 65- 105%. The optimized formulation F5 showed the maximum swelling index of 105%.

Table 8: Swelling studies for F1 to F10

Time (h)	Swelling(%)									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
0	0	0	0	0	0	0	0	0	0	0
1	34	33	29	35	50	35	35	25	20	25
2	40	40	35	46	57	45	42	32	27	34
3	47	45	40	56	69	55	53	40	35	40
4	55	52	47	64	85	68	62	46	43	48
5	64	65	53	77	96	75	67	58	57	60
6	75	73	67	89	105	89	75	65	64	71

Weight uniformity:

The weight uniformity test has been carried out by using the digital weighing balance and all the formulations are showing the uniformity weight in the range from 24-26 mg.

Table 9: weight uniformilty

Formulations	Weights (mg)
F1	25±0.763
F2	24.02±0.219
F3	25.1±0.368
F4	24±0.412
F5	26.03±0.156
F6	25.2±1.003
F7	25±0.224
F8	26.01±0.438
F9	25±0.294
F10	24.9±0.708

Drug content analysis:

The riboflavin tablets contain not less than 90% and not more than 110%. The optimized formlation F5 showed 98.167%.

Table 10: Percentage Drug Content of All the Formulations

S. No	Formulation Code	% Drug Content*
1	F1	92.57 ± 0.2078
2	F2	95.198 ± 0.2273
3	F3	91.770 ± 0.1889
4	F4	94.73 ± 0.1868
5	F5	98.167 ± 0.2044
6	F6	94.398 ± 0.2230
7	F7	95.917 ± 0.1805
8	F8	90.996 ± 0.2006
9	F9	93.485 ± 0.2162
10	F10	93.798 0.2191

Floating lag time: All the formulations showed the 11.54 to 82.32 sec. the formulation F2 has shown the floating lag time of 15.89sec.

***In- vitro* dissolution study:** USP rotating paddle method was used to study drug release from floating tablets of riboflavin 900 mL of 0.1N HCl was used as dissolution medium the release study was performed at 37±0.5˚c at rotational speed of 100rpm. The maximum drug release was shown by formulation F5 was 96.108% after 6 hours. Because of the highly water soluble polymer PVP was used alone in the formulation.

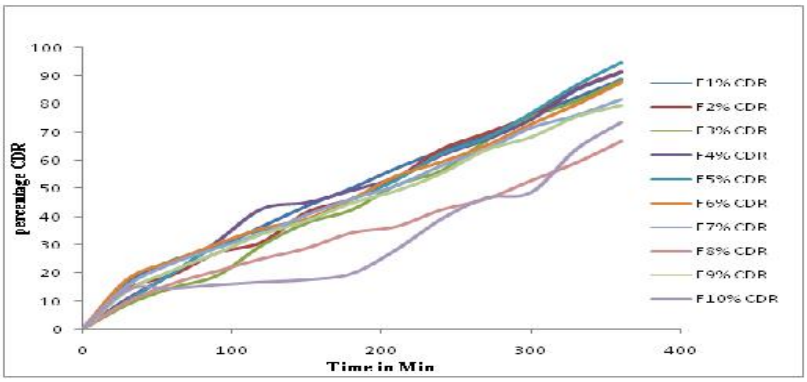

Figure 7: *In Vitro* % Drug release of Riboflavin in Formulations F1- F10

The correlation coefficients of the formulation describes the formulation F5 following the anomolous non fickians zero order release kinetics.

Table 11: Correlation coefficients of different mathematical models for formulation F5

Formulation code	Zero- order		Higuchi model		Kosmeyer-peppas		First order	
	R^2	K_O	R^2	Intercept	R^2	n	R^2	K_1
F5	**0.982**	**5.468**	**0.9434**	**-12.796**	**0.9874**	**0.1606**	**0.918**	**2.047**

4. Conclusion

From the present study, the following conclusions can be drawn Gastroretentive non- effervescent floating tablets of riboflavin using different polymers HPMC, PVP, Carbopol were prepared by direct compression technique by maintaining the each tablet weight around 25mg by using magnesium stearate and lactose as lubricants. The content was uniform in all the 10 formulations of tablets prepared. The low value of standard deviation indicates the uniform drug distribution in a tablet. The drug polymer compatibility was studied by FTTR spectroscopy and there was no incompatibilities were noted. F5 formulation showed the maximum drug release in 6 hrs about 96.108%. Finally these results are concluding that the formulation and evaluation of floating tablets of riboflavin have shown better drug release and it is concluded that the rate gastric residence time was increased than other formulations of marketed products of riboflavin comparatively.

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