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Research Article

DEVELOPMENT AND CHARACTERIZATION OF GASTRORETENTIVE MUCOADHESIVE TABLETS OF RIBOFLAVIN

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ABSTRACT

Gastroretentive drug delivery system (GRDDS) is a novel site-specific orally administered controlled release drug delivery system in which the delivery system is retained in the stomach for a 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. GRDDS enable prolonged and continuous release of the drug to the upper part of GIT and this significantly extend the duration of drug release, improve bioavailability of drugs that have narrow therapeutic window, by this way they prolong dosing interval and increase compliance of the patient, reduces drug waste, and improves the drug solubility that are less soluble in a high pH environment. Mucoadhesion is one of the approach to prolong gastric retention. In these systems, Mucoadhesion is achieved by using Mucoadhesive polymers which adhere to the epithelial surface of gastrointestinal tract.Narrow absorption window mainly from upper part of GIT and short half-life makes riboflavin an ideal candidate for its formulation as a Mucoadhesive tablets. Hence we intend to develop a simple Gastroretentive Mucoadhesive tablets of Riboflavin and prepare sustained release 'once daily.

KEY WORDS: Gastroretentive drug delivery system, Riboflavin, Mucoadhesion, Narrow therapeutic window, Short half-life.

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 system in which the delivery system is retained in

the stomach for a 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. GRDDS enable prolonged and continuous release of the drug to the upper part of GIT and this significantly extend the duration of drug release, improve bioavailability of drugs that have narrow therapeutic window, by this way they prolong dosing interval and increase compliance of the patient, reduces drug waste, and improves the drug solubility that are less soluble in a high pH environment. Mucoadhesion is an approach to prolong gastric retention. In these systems, Mucoadhesion is achieved by using Mucoadhesive polymers which adhere to the epithelial surface of gastrointestinal tract. The formation of hydrogen and electrostatic bonding at the mucus polymer interface leads to Mucoadhesion. Riboflavin is one such drug which has narrow absorption window in gastrointestinal tract (GIT). Hence, we intend to develop a simple Gastroretentive Mucoadhesive 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.

Significance of the study

Bioavailability of riboflavin in foods, mostly as digestible flavor-coenzymes, is excellent at nearly 95%, but absorption of the free vitamin is limited to about 27mg per single meal or dose in an adult. This is as it is readily absorbed from the upper GIT being its absorption window, 60% of drug is bound to plasma proteins, its half-life is 66-84 min, and 9% of drug is excreted unchanged in urine. Narrow absorption window mainly from upper part of GIT and short half-life makes riboflavin an ideal candidate for its formulation as a Mucoadhesive tablets. Mucoadhesion will prolong the gastric residence time of riboflavin thus will help increase its bioavailability. Also this approach will avoid problems of acidity and gas generation caused due to the excipients used in floating systems. This model drug is advantageous because it lacks adverse effects and has no pharmaceutical effect on gastric motility.

MATERIALS AND METHODS

Materials

Riboflavin was obtained as gift sample from Macleods Pharmaceuticals Ltd. Hydroxyl propyl methyl cellulose K4M, Ethyl cellulose, methyl cellulose, Carbopol 934, Sodium alginate, 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.

Methods

Preparation of Gastroretentive Mucoadhesive tablets of Riboflavin:

Mucoadhesive tablets containing Riboflavin were prepared by wet granulation technique using variable concentrations of HPMC K4M, Ethyl cellulose, Carbopol 934, Sodium Alginate and Chitosan. Required quantity of drug and polymers (HPMC K4M, Ethyl cellulose, Carbopol 934, Sodium Alginate and Chitosan), were passed through 60 mesh sieve and mixed thoroughly. Then, granulating agent (starch paste) was added slowly with uniform mixing to get a wet mass. The wet mass was passed through sieve no. 16 to obtain wet granules which were dried at 50^{o}C for 2 to 3 hrs. in hot air oven. The dried granules were passed through sieve no. 22. After blending with lubricants (talc) tablet were compressed using tablet compression machine (08 mm diameter punches). Each tablet contained 10mg of Riboflavin and other pharmaceutical ingredients. The formulas of 9 formulations are mentioned in table 1.

Table No. 1 Formulations of Gastroretentive **Mucoadhesive tablets**

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Riboflavin	10	10	10	10	10	10	10	10	10
HPMC K4M	40	40	40	-	-	-	20	20	20
Ethyl cellulose	-	-	-	40	40	40	20	20	20
Sodium Alginate	20	-	-	20	-	-	-	-	10
Carbopol 934	-	20	-	-	20	-	-	10	-
Chitosan 75%	-	-	20	-	-	20	20	10	10
Lactose	210	210	210	210	210	210	210	210	210

All the quantities are in milligram. HPMC (Hydroxyl propyl methyl cellulose).

Physical characterization:

The fabricated tablets were characterized for weight variation (n=20), hardness (n=6, Monsanto hardness tester), tablet dimensions (n=5, Vernier calipers) and % friability (n=20, Roche friabilator).

Weight variation:

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

Tablet dimensions (Tablet thickness and diameter):

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

Hardness:

The hardness of tablet of each formulation was measured by Monsanto hardness tester. The hardness was measured in terms of kg/cm2. 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:

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.

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

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).

Table No. 2 Physicochemical properties of Riboflavin Mucoadhesive Matrix Tablets

Formulation code (n=10)	Diameter (mm) Mean ± SD (n=5)	Thickness (mm) Mean ± SD (n=5)	Hardness (kg/cm2) Mean ± SD (n=5)	Friability (%)	Avg. Weight (gm) Mean ± SD	Drug Content (%)
F1	10.05±0.008	2.2±0.119	5.98±0.111	0.27%	280.5±0.13	99.2
F2	10.01±0.003	2.1±0.122	5.88±0.109	0.26%	280.3±0.13	98.9
F3	10.09±0.005	2.3±0.120	5.58±0.108	0.25%	280.7±0.13	99.5
F4	10.10±0.001	2.1±0.123	5.68±0.11	0.27%	280.5±0.13	99.7
F5	10.03±0.006	2.2±0.124	5.68±0.111	0.26%	280.7±0.13	99.6
F6	10.04±0.004	2.0±0.118	5.98±0.111	0.28%	280.4±0.13	99.5
F7	10.03±0.002	2.3±0.119	5.98±0.111	0.25%	280.3±0.13	99.4
F8	10.08±0.001	2.25±0.122	5.98±0.111	0.26%	279.8±0.13	99.8
F9	10.04±0.003	2.12±0.120	5.88±0.111	0.28%	280.4±0.13	99.3

Swelling study:

Formulated tablets were weighed individually (W_o) 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°C. At regular 1-hour time intervals until 4-hour, the tablets were removed from the petri dish, reweighed (W t), and the % swelling index was calculated using the following formula.

$$WU = (W_t - W_o / W_o) \times 100, \text{ where}$$

WU – Water uptake

W_t – Weight of tablet at time t

W_o – Weight of tablet before immersion

Ex Vivo Mucoadhesion strength:

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:

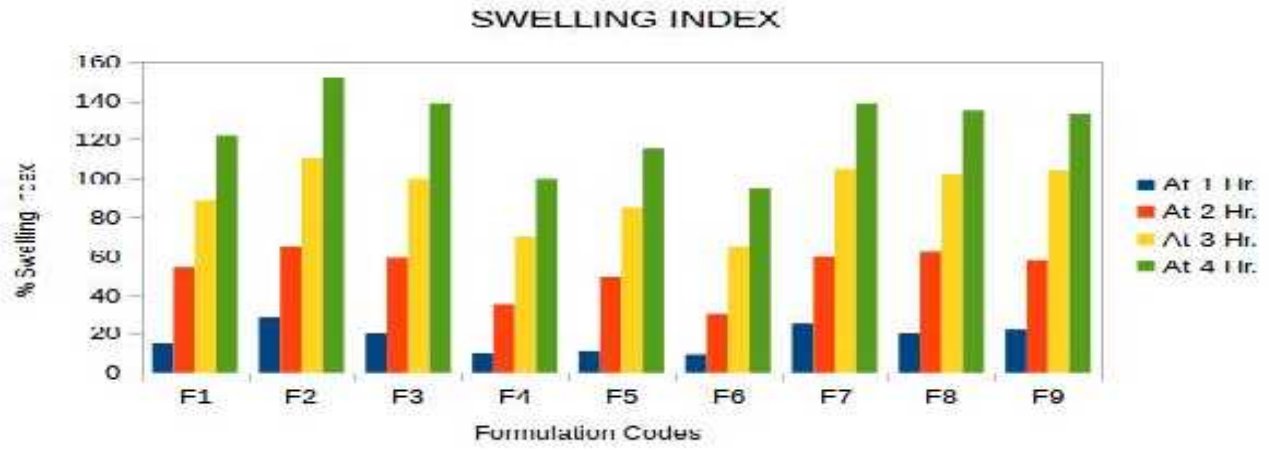
Isolated fresh sheep stomach mucosa obtained was tied on the glass slide; each tablet was wetted with 1 drop of 0.1 N HCl and pasted to the sheep stomach mucosa by applying light force with a fingertip for 30s. The glass slide was then placed in the beaker, since only Mucoadhesive property was evaluated 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.

Table No. 3 Evaluation of Mucoadhesive Parameters of Matrix Tablets

Formulation Code	Swelling index (%) Mean ± (S.D.)	Mucoadhesion time (h) Mean ± (S.D.)	Mucoadhesion strength (g) Mean ± (S.D.)
F1	**122**	**10± 0.134**	**13±0.870**
F2	**152**	**09± 0.129**	**12±0.636**
F3	**139**	**13± 0.206**	**16±0.588**
F4	**100**	**09± 0.221**	**13±0.660**
F5	**115**	**09± 0.210**	**12±0.90**
F6	**95**	**12± 0.198**	**14±0.798**
F7	**139**	**13± 0.203**	**16±0.788**
F8	**135**	**11± 0.232**	**14±0.480**
F9	**133**	**10± 0.215**	**13±0.288**

Figure- 1 Swelling index:



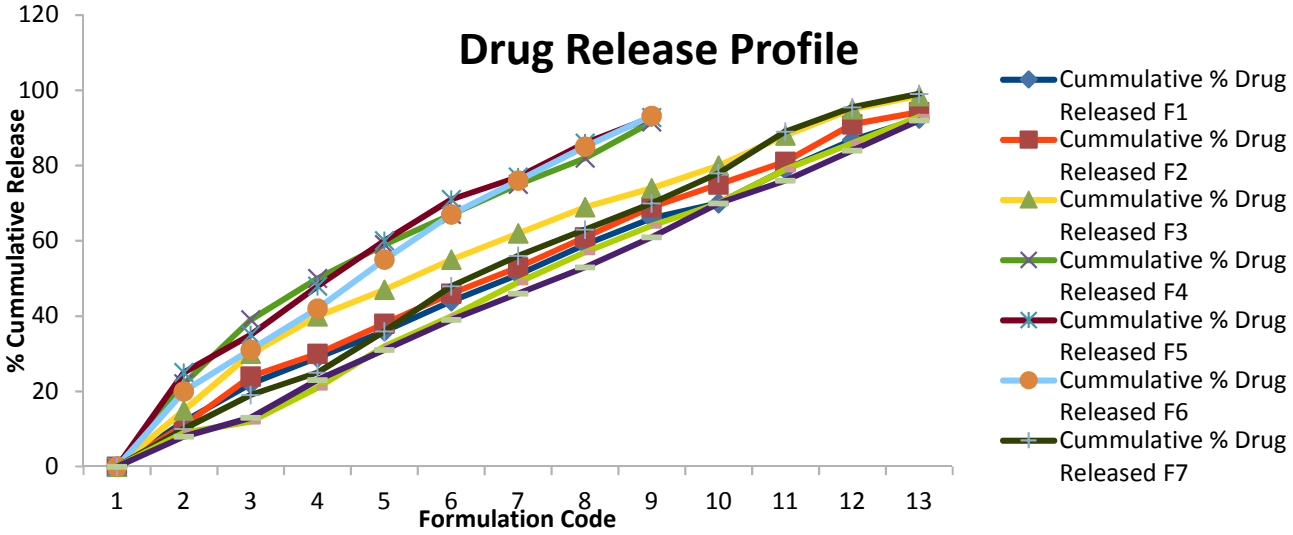
Drug polymer interaction:

Drug-polymers interaction was studied by using FTIR.

In vitro drug release study:

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 withdrawn 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 at 450 nm.

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



RESULTS AND DISCUSSION

Formulated tablets were found to be satisfactory when evaluated for thickness (2±0.122 mm); Hardness (5.62±0.136 kg/cm^2), Friability less than 1% (as shown in Table No.2). The percent drug content of all formulations was found to be between 97.2 % to 99.9% (Table No.2) which is within acceptable limits indicating dose uniformity in each batch. Results of swelling index are shown in Table No.3, 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 F2 (152.0 %) and least for F6 (95.0 %). This indicates that HPMC stores more water content in matrix than ethyl cellulose. From the results it can be concluded that swelling increases with time because polymer gradually absorbs water due to its hydrophobicity. 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 Chitosan showed higher Mucoadhesion property, due to which the formulation was retained for a longer duration in stomach (Table No.3) HPMC retains the dosage form due to swelling, whereas Chitosan retains due to its Mucoadhesive property. Chitosan was used as Mucoadhesive polymer. The plot of cumulative drug release Vs time plotted for all formulations are depicted in Fig. II. The release of drug from HPMC K4M (F3 - 99.5%) based Mucoadhesive tablets was more sustained than Carbopol and ethyl cellulose (F4, F5, F6 for 9 hrs.) based tablets. But the combination of HPMC K4M and Ethyl cellulose in (1:1) also gave comparative release as F3 (99.1%). HPMC K4M and chitosan were used for Mucoadhesive matrix formation. Model fitting studies revealed drug release mechanism followed Higuchi matrix order release.

CONCLUSION

Results of Mucoadhesion tests indicated that chitosan polymer increases Mucoadhesion properties of tablets. Chitosan containing tablets were more retained in stomach by Mucoadhesion mechanism than carbopol or sodium alginate. In vitro release results indicated that the drug release was more sustained in HPMC with lactose containing formulations than ethyl cellulose. From above studies it is concluded that Mucoadhesive 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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