

Formulation and in Vitro Evaluation of Bio adhesive Tablets Using Hydrophilic Gum Blends

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Abstract- Controlled release matrix tablets of theophylline were designed with hydrophilic gum blends as a bioadhesive polymer. Combinations of natural hydrophilic polymers such as Xanthan gum and Locust bean gum were used in different concentrations to formulate bioadhesive tablets. Tablets of theophylline were prepared by direct compression method and were subjected to in vitro bioadhesion strength and in vitro drug dissolution for 12h by using USP dissolution apparatus basket type at speed of 100rpm at a temperature of $37 \pm 0.5^\circ\text{C}$ using simulated gastric fluid (pH 1.2). The bioadhesive strength of the tablets was measured as force of detachment against porcine gastric mucosa. The in vitro release study as well as retention time of bioadhesive tablets on mucous membrane were investigated to develop a bioadhesive polymer based controlled release delivery system and to evaluate the performance of such delivery device. Combination of xanthan gum: locust bean gum (4:6) in concentration of 1:0.5 (drug: gum) showed significant bio-adhesive strength and were dissolved in the gastric fluid with maximum release of 96.95% in 12h. Increase in gums concentration increases the drug release profile as well as bio-adhesive strength of tablets.

Index terms- Theophylline, Xanthun gum, Locust bean gum, Controlled release

INTRODUCTION

Oral controlled release (CR) systems continue to be the most popular ones among all the drug delivery systems.[1] Mucoadhesive delivery systems offer several advantages over other oral CR systems by virtue of prolongation of residence time of drug in the gastrointestinal tract, targeting, and localization of the dosage form at a specific site.[1"4] Also, these mucoadhesive systems are known to provide intimate contact between dosage form and the absorptive

mucosa, resulting thereby in a high drug flux through the absorbing tissue.[11,2,51] In addition, bioadhesive dosage forms have been used to target local disorders at the mucosal surface to reduce the overall dosage required and to minimize the side effects that may be caused by the systemic administration of the drugs. Bioadhesive formulations use polymers as the adhesive component. These polymers are often water soluble and when used in a dry form, they attract water from the mucosal surface and this water transfer leads to a strong interaction. These polymers also form viscous layers when hydrated with water, which increases the retention time over the mucosal surfaces and leads to adhesive interactions.[6] Several studies reported bioadhesive oral drug delivery systems in the form of tablets, films, patches, and gels for oral, buccal, nasal, ocular, and topical routes; however, very few reports on bioadhesive tablets using natural hydrophilic polymers are available.[7"10] Prolonged contact time of a drug with a body tissue through the use of a bioadhesive polymer can significantly improve the performance of many drugs. In our study, theophylline anhydrous is used as a model drug. The objective of this study is to develop, characterize, and evaluate mucoadhesive matrix tablets of theophylline employing various natural hydrophilic bioadhesive polymers such as xanthan gum, locust bean gum, gum karaya, and guar gum for prolonged gastrointestinal absorption. The prepared tablets were evaluated for different parameters such as swelling index, in vitro drug release rates, and in vitro mucoadhesive strength.

MATERIALS AND METHODS

Theophylline anhydrous was a kind gift from M/S. Lupin Pharmaceuticals Ltd., Aurangabad, India. Gum Karaya and Locust bean gum were gift samples from Krystal Colloids and Lucid Gums, Mumbai, India. Xanthan gum and Guar gum were gift samples from Loba Chemie Pvt. Ltd., Mumbai, India. Lactose (direct compressible), magnesium stearate, and Aerosil were procured from Research Lab, Mumbai, India. For determining the bioadhesive strength, the porcine gastric mucosa was obtained from a local slaughter house. All other reagents employed were of analytical or pharmaceutical grade.

Preparation of the mucoadhesive tablet

A sustained release mucoadhesive oral tablet of theophylline was prepared by the direct compression method. In all the cases, the amount of the active ingredient is 100 mg. All the ingredients of the tablet were blended to obtain uniform mixing. Matrix tablets were prepared using a Cadmach single punch tablet machine (M/S Cadmach Machinery Co. Pvt. Ltd., Ahmedabad, India) using 8-mm flat surface punches. All the theophylline-loaded matrix tablets were stored in airtight containers at room temperature for further study. Tablets of Batch F1-F4 contain only single mucoadhesive polymer having a drug:gum ratio of 1:1, Batch F5-F7 contain combinations of various mucoadhesive polymers having a drug:gum ratio of 1:1, Batch F8-F11 contain only single mucoadhesive polymer having a drug:gum ratio of 1:0.5, and Batch F12-F14 contain combination of various mucoadhesive polymers having a drug:gum ratio of 1:0.5. Compositions of various formulations

are shown in Table 1. following official parameters: Hardness, Friability, Weight variation, Thickness, and Drug content as per official procedures. The values of all the evaluation parameters are shown in Table 2.

In vitro drug release study

The in vitro drug release studies of the matrix tablets were conducted in a USP type II dissolution apparatus equilibrated at temperature $37 \pm 0.5^\circ\text{C}$ and 100 rpm speed. The dissolution studies were carried out in triplicate for 12 hours in 900 ml of gastric fluid (pH 1.2). The dissolution samples were collected at every 1 hour interval and replaced with an equal volume of gastric fluid to maintain the volume constant. The sample solution was diluted sufficiently and analyzed at 272 nm as mentioned in USP and BP by a UV spectrophotometer (Shimadzu, Kyoto, Japan). The amount of drug present in the samples was calculated with the help of appropriate calibration curves constructed from the reference standard of the respective drug. Drug dissolved at specified periods was plotted as a percent release versus time (hours) curve.

The in vitro release study of formulation F1-F14 is given in the plot of percentage cumulative drug release against time (hours), depicted in Figure 1.

Evaluation of the mucoadhesive tablets

All the mucoadhesive tablets prepared were evaluated for the Analytical method validation. The method was validated according to the International

Table 1: Composition of the mucoadhesive tablets

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14
Theophylline	100	100	100	100	100	100	100	100	100	100	100	100	100	100
Xanthan gum	100	-	-	-	40	-	-	50	-	-	-	20	-	-
Karaya gum	-	100	-	-	-	60	70	-	50	-	-	-	30	35
Guar gum	-	-	100	-	-	40	-	-	-	50	-	-	20	-
Locust bean gum	-	-	-	100	60	-	30	-	-	-	50	30	-	15
Aerosil	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Magnesium stearate	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Lactose (DC)	16	16	16	16	16	16	16	16	66	66	66	66	66	66

Table 2: Physical parameter of the mucoadhesive tablets

Batch code	Hardness (kg/cm ²)	Friability (%)	Weight variation	Thickness (mm)	% drug content	mean ± SD	mean ± SD
SD (mg)	mean ± SD	mean ± SD					
F1	6.92 ± 0.23	0.67	220 ± 0.44	4.92 ± 1.01	94.81 ± 0.68		

F2	6.57 ± 0.52	0.62	220 ±	0.23	4.02 ±	0.56	96.72 ± 0.54
F3	7.02 ± 0.48	0.37	220 ±	0.85	4.90 ±	0.62	97.98 ± 0.84
F4	6.42 ± 0.41	0.66	220 ±	1.00	4.34 ±	0.48	92.18 ± 0.47
F5	6.63 ± 0.36	0.58	220 ±	0.64	4.08 ±	1.00	94.25 ± 0.72
F6	7.20 ± 0.57	0.38	220 ±	0.96	4.37 ±	0.68	96.80 ± 0.69
F7	6.67 ± 0.53	0.68	220 ±	1.00	4.12 ±	0.29	98.12 ± 0.83
F8	5.21 ± 0.71	0.59	220 ±	0.56	4.29 ±	0.43	94.43 ± 0.74
F9	6.33 ± 0.32	0.35	220 ±	0.63	4.68 ±	0.56	97.63 ± 0.68
F10	6.87 ± 0.42	0.42	220 ±	0.58	4.45 ±	0.83	98.92 ± 0.46
F11	7.00 ± 0.86	0.40	220 ±	0.47	4.28 ±	0.72	95.13 ± 0.83
F12	6.12 ± 0.77	0.51	220 ±	0.43	4.49 ±	0.79	92.68 ± 1.00
F13	6.13 ± 0.85	0.47	220 ±	0.68	3.39 ±	0.62	98.89 ± 0.56
F14	6.17 ± 0.75	0.45	220 ±	0.41	3.27 ±	0.47	96.68 ± 1.00

Conference of Harmonization guidelines for validation of analytical procedures.[13] The validation parameters were accuracy and precision. The accuracy and precision were investigated at three concentration levels of theophylline with six independent replicates on the same day and on six consecutive days. The intraday and interday bias values were found to be less than 1.65% and 1.12% and the intraday and interday relative standard deviation values were less than 2.16% and 1.84%, respectively.

In vitro mucoadhesive study[14-17]

The mucoadhesive strength of the tablets was measured on a modified physical balance [Figure 2]. The apparatus consist of a modified double beam physical balance in which the right and the left pan have been replaced by lighter pans. The left side of the balance was made 5 g heavier than the right side by placing a 5 g weight on left side pan. Another Teflon block of 3.8 cm diameter and 2 cm height was fabricated with an upward protrusion of 2 cm height and 1.5 cm diameter on one side. This was kept in a beaker, which was then placed below the left hand set of the balance.

The porcine gastric mucus membrane was used as the model membrane and pH 1.2 solution was used as the moistening fluid. The porcine stomach mucosa[18,19] was kept in Tyrode solution at 37°C for 2 hours. The underlying mucus membrane was separated and washed thoroughly with a pH 1.2 solution. It was then tied to a Teflon-coated glass slide and this slide was fixed over the protrusion in the Teflon block using a

thread. The block was then kept in a beaker containing pH 1.2 buffer solution at the level that just touches the membrane so as to moisten the membrane. By keeping a 5 g weight on the right pan, the two sides of the balance were made equal. The beaker with the Teflon block was kept below the left hand set up of the balance. The tablet was stuck on to the lower side of the left hand side pan. The 5 g weight from the right pan was then removed. This lowered the left pan along with the tablet over the membrane with a weight of 5 g. This was kept undisturbed for 3 minutes. Then, the weight on the right hand side was slowly added in an increment of 0.5 g till the tablet just separated from the membrane surface. The excess weight on the right pan i.e., total weight minus 5 g was taken as a measure of the mucoadhesive strength. From the mucoadhesive strength, the force of adhesion was calculated using the following formula:

Mucoadhesive strength

Force of adhesion (N) = $\frac{W}{9.81}$

Results are summarized in Table 3. Stability study

Stability study was carried out on the optimized formulation F13. The tablets of formulation F13 were first wrapped in an aluminum foil and then placed in an amber-colored bottle. This was stored at $40 \pm 2^\circ\text{C}$ and $75 \pm 6\%$ relative humidity for 6 months. The tablets were evaluated for mucoadhesive properties and in vitro drug release after 2, 4, and 6 months.[20] Figure 1: Percent cumulative drug release of formulation F1-F14

Figure 3: Comparative percent cumulative release of formulation F13 after the stability study

Figure 2: In vitro mucoadhesive strength measurement apparatus (A) Right pan, (B) Left pan,

(C) Teflon block, (D) Stomach membrane, (E) Teflon-coated glass slide, (F) Beaker containing 1.2 pH buffer, (g) Threads, (H) Pointer, and (i) Scale Results obtained were compared with the data obtained for zero time at room temperature and humidity (temperature $28 \pm 2^\circ\text{C}$ and humidity $42 \pm 2\%$).

The results of the in vitro release study of formulation F13 after the stability study are shown in Table 1 and the plot of comparative release is shown in Figure 3.

RESULT AND DISCUSSION

All the batches were evaluated for the physical properties and hardness of the tablet in the range of 6-7 kg/cm². Percentage weight loss in the friability test was less than 0.7% in all the batches and all the batches contained Theophylline within $100 \pm 5\%$ of the labeled content. Overall, the prepared tablet batches were of good quality with regard to hardness, friability, and drug content.

The in vitro mucoadhesive strength study was performed on the modified physical balance to measure the force (N) required for detaching the tablet. The bioadhesion characteristics were affected by the type and concentration of the bio adhesive polymers [Table 3]. Viscosity of the polymer also affects the bio adhesive strength of the tablet.

From the overall dissolution profiles, it was concluded that the drug release rate decreased as the concentration of the polymer increased, which was also affected by the type of polymer used. This can probably be attributed to the different diffusion and swelling behaviors of the polymer.

The stability study showed that there was no change in the appearance and on drug release pattern of the tablets.

From the results of the dissolution data, the Korsmeyer and Peppas model was found to be best fitted in all dissolution profiles having a higher correlation coefficient. Thus, it was

Table 3: In vitro mucoadhesive strength study of the prepared mucoadhesive tablets

Batch code	Mucoadhesive strength (mean \pm SD) force (N)	Mucoadhesion(g)
F1	13.35 ± 0.95	2.27
F2	24.15 ± 0.36	2.35

F3	23.41 ± 0.57	2.25
F4	19.68 ± 0.24	1.86
F5	15.52 ± 0.84	2.52
F6	18.73 ± 0.51	2.83
F7	12.18 ± 0.84	1.19
F8	21.77 ± 0.38	2.06
F9	16.04 ± 0.79	1.56
F10	22.14 ± 0.16	2.15
F11	18.92 ± 0.41	1.89
F12	27.72 ± 0.65	2.64
F13	30.62 ± 0.81	2.94
F14	19.12 ± 0.76	2.25

Concluded that the drug release occurred via a diffusion mechanism and due to the affinity of natural hydrophilic polymers toward water, there is bio adhesiveness of the natural hydrophilic polymers.

CONCLUSION

Review of the literature indicates that gastro retentive drug delivery systems can be used to increase the gastric residence time of dosage form, which led to an increased bioavailability of various drugs.

Thus, in the present investigation, an attempt was made to deliver Theophylline via an oral mucoadhesive drug delivery system to the vicinity of the absorption site by prolonging the gastric residence time of the dosage form. For the formulation of the oral mucoadhesive tablet, various hydrophilic polymers and their combinations were used in varying concentrations.

Tablets were subject to various evaluation parameters such as Hardness, Friability, Drug content, Mucoadhesive strength study, and in vitro drug release study. It was revealed that tablets of all batches had acceptable physical parameters. Tablets of batch F13 have good mucoadhesion along with in vitro drug release. It was observed that tablets of all batches followed the equation of Korsmeyer and Peppas drug release profiles. Tablets of Batch F13 were selected as an optimum batch.

Stability studies revealed that there was no significant change in the hardness, friability, drug content, and dissolution profile of formulation F13. Thus, this formulation was stable at different conditions of temperature.

The present study shows that the hydrophilic gums obtained from natural sources can be used for designing a mucoadhesive CR drug delivery system.

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