Formulation and Evaluation of Floating tablets of Theophylline

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Abstract

Plan*: Formulation of oral gastro retentive floating tablets of Theophylline.*

Prologue*: The primary aim of the present study is to design a sustained release gastro retentive oral dosage form using intra gastric floating as formulation strategy. Theophylline, an antiasthmatic is used as the model drug.*

Methodology*: Oral gastro retentive floating tablets of Theophylline was formulated using gel-forming hydrophilic polymers, HPMCK4M, HPMCK100M and HPMC 15cps. The work also focused on in vivo evaluation of buoyancy by x-ray imaging. Suitable In vitro methods for estimating the drug release from the tablet as a function of time were developed and compared with marketed product (TheoSR200mg)*

Outcome*: The prepared Tablets exhibited satisfactory physicochemical characteristics. All the prepared batches showed good in vitro buoyancy. The tablets with HPMCK4M and HPMCK100M floated for longer duration and had more matrix integrity as compared to formulations containing HPMC 15cps. Formulations with HPMCK100M & HPMCK4M showed better control of drug release and the drug release was similar to that of marketed product.*

Keywords: *Theophylline, Gastro retentive floating tablets, Polymers HPMCK4M, HPMCK100M and HPMC 15cps.*

1. Introduction

The Oral[1] route of drug administration is the most important method of administering drugs for systemic effect. To achieve and maintain the concentration of administered drug within therapeutically effective range, it is often necessary to take drug dosage several times and this result in fluctuating levels in plasma. Controlled drug delivery systems have been introduced to overwhelm the drawbacks of fluctuating drug levels associated with conventional dosage forms.

Controlled [11, 12] and Targeted drug delivery systems to the stomach could be achieved via prolongation of the gastric residence time. Gastro retentive systems are important for drugs which exert local effect in the stomach; drugs which are poorly soluble in the intestine, such systems improve gastrointestinal absorption of drug with narrow absorption window as well as controlling release of drugs having site specific absorption limitations. Drugs that are slowly absorbed from G.I.T can be given as slow release gastric retention system to improve the absorption and bioavailability. To design such a system many factors are to be considered. Recently several approaches have been developed to increase gastric residence time of drug formulation[5, 6, 10].

Floating system, Bioadhesive system, Low density system, High density system, Expandable system, Super porous, biodegradable hydrogels, Magnetic system,Slowed motility of the Gastro Intestinal Tract by concomitant administration of drugs.

Floating system[2, 3, 4, 9] has the property of retaining the dosage unit in the stomach for prolonged period of time and is useful for drugs with absorption in the G.I.T. The main objective of developing these systems is to increase the safety of product to extend its duration of action and decrease side effects of drug. Drugs, which are predominantly absorbed from the upper part of gastrointestinal tract[6, 7] such as Furosemide, Albuterol and Theophylline are worth considering candidates for improving and prolonging their limited oral bioavailabilities.

Three major requirements for FDDS formulations are,

❖ It must form a cohesive gel barrier
❖ It must maintain specific gravity lower than gastric contents (1.004- 1.01g/cc)
❖ It should release contents slowly to serve as a reservoir.

Selection of excipients[2,3,6,8] is an important strategic decision for designing a dosage form with consistence and controlled residence in the stomach. Water soluble cellulose derivatives represent a typical class of polymers best suited for such purposes. It has been suggested that higher molecular weight polymers and slower rates of polymer hydration are usually associated with better floating behaviour. Therefore, high molecular weight and less hydrophilic polymers are expected to improve floating properties of delivery systems.

2. Materials and Methods

2.1. Floating tablets of Theophylline

A 3^2 full factorial design was employed for the optimization of floating tablets of Theophylline using HPMCK4M, HPMCK100M, HPMC15cps. The total weight was fixed as 500 mg. Each tablet contained 200mg of Theophylline. The independent variable factors selected were the compression load (4,5,6 tones) and the quantity of HPMC 40,50,60%) in the formulation. The dependent variables selected were the cumulative % drug release after 6 hour (R6), 12 hour (R12), 24 hour (R24), similarity factor (f_2), time to release 50 % drug (t_{50}) and *in vitro* Buoyancy time (BT).

Pre-optimization studies were carried out before choosing the level of each independent factor. MCC was added in formulations in required quantities to adjust the tablet weight to 500 mg. Ingredients were passed through a No. 44 sieve, mixed by geometric dilution and mixed in a mortar for 15 minutes. Then the powder mixture was compressed using a Cadmach 16 station rotary tablet press with 13 mm round shaped flat punches. 1 % Magnesium stearate and 0.5 % Aerosil were included in the formulation as lubricant. The drug release profiles from the prepared tablets were determined by *in vitro* dissolution study performed in USP Type-2 Dissolution Apparatus using 0.1N HCl as dissolution media at a speed of 50 RPM samples are analyzed by UV spectrophotometer at 273nm (V-560, UV-VISIBLE Spectrophotometer, JASCO, Japan).

The formulation with the highest similarity factor was chosen as the optimized formulation.

3. Evaluation of the optimized formulations
3.1. Flow and Consolidation properties

The content of tablets of optimized formulation from each batch was evaluated for angle of repose, bulk density, tapped density, Hausner ratio and Carr's index.

3.2. Friability, Crushing strength and Drug content

The optimized formulations from each batch were evaluated for friability, crushing strength and Drug content.

3.3. In Vitro Buoyancy Test

The *in vitro* buoyancy was determined by (floating lag time) The FODDS took to emerge on the dissolution medium surface and (duration of floating) the time the tablet constantly floated on the water surface, were evaluated in dissolution vessel (apparatus USP –XXIV type 11) filled with 500 ml of 0.1NHCl with paddle rotation of 100rpm

3.4. Swelling Study

Swelling Index was determined by placing weighed tablet in glass beaker containing 0.2N HCl at regular time intervals, tablets were removed, excess surface liquid was removed and swollen IGF tablets were then re-weighed (W2)

Swelling index was calculated using the formula SI= (W2-W1)/W1

3.5. Kinetics of drug release

To study the release kinetics, data obtained from the *in vitro* drug release studies were plotted in various kinetic models: Zero order as cumulative amount of drug released Vs time, first order as log cumulative percentage drug remaining Vs time Higuchi's model as cumulative percentage of drug released Vs square root of time and Hixson-Crowell rate equation as the cube root of the percentage of drug remaining in the matrix Vs time.

3.6 Mechanism of drug release

To evaluate the mechanism of drug release from the optimized tablet formulations, data for first 60 % of drug release were plotted in Korsmeyer et al's equation as log cumulative percentage of drug released Vs log time, and the exponent n was calculated through the slope of the straight line portion of the curve. All the parameters of the drug release kinetics were analyzed using Microsoft Excel-2007. The regression coefficient (r^2) was also determined in all cases.

3.7. In Vivo Assessment of Floating

Rabbits were used for the study (1.5-2 kg). Divided 8 rabbits into two groups, each comprise 4 (n = 4) rabbits.

Group I   -   Standard (Receives tablets devoid of Floating polymers)
Group II   -   Test (Receives optimized Floating tablet)

Animals were deprived of food (with *ad libitum* access to water) 18 h before the experiment and during the experiment. Before administration of the tablets, the animals were given with 8 ml of phosphate buffer (pH 7.4) via an oral gastric tube. Radiology was used for imaging the tablets. Ingested one optimized tablet containing 40 % barium sulphate to each animal of group I and blank tablets to group II. X-ray imaging was performed at times 2, 4, 8 and 24 hr from two perpendicular recumbencies (ventral-dorsal and right lateral).

3.8. Accelerated Stability Studies

3.8.1. Controlled temperature and humidity condition

Optimized formulations were strip packed for stability studies under controlled temperature and humidity condition. 30 tablets from each optimized formulations of Theophylline were packed in strips of 0.04 mm thick aluminium foil laminated with PVC.

The packed tablets were placed in a humidity chamber maintained at a relative humidity of 75 %. The humidity chambers were created by placing a beaker of saturated aqueous sodium chloride solution in a desiccator. The humidity chambers were kept in a hot air oven maintained at 40°C. The packed tablet samples were withdrawn from the humidity chambers at time intervals of 0, 1, 2 and 3 months. The tablets were evaluated for appearance, color and odor, moisture absorption, tablet crushing strength, friability, assay and *in vitro* dissolution study. Different humidity chambers and strip packs were used for the different sampling intervals such that the tablets were not in contact with external environment during the storage interval in the chambers.

4. Results and Discussion

4.1. Flow and consolidation properties

Angle of repose of the optimized formulation

Formulation	Height of the pile h (cm)	Radius of the pile r (cm) ± SD	Angle of repose, $\theta = tan^{-1} (h/r)$
K4-7	2	2.265 ± 0.48	37.04
K100-8	2	2.35± 0.93	40.40
15cps-8	2	2.95 ± 1.21	34.13

All values are mean ±SD of three determinations

Tapped and bulk density of the optimized formulation

Formulation	Weight (g)	Bulk volume (ml)	Tapped volume (ml)	Bulk density (g/ml)	Tapped density (g/ml)
K4-7	5	13	8.5	0.3846	0.5882
K-100-8	5	12	9	0.4166	0.5555
15-cps	5	11.5	7.5	0.4348	0.6666

All values are mean ±SD of three determinations

Hausner ratio and Carr's index of the optimized formulation

Formulation	Hausner ratio	Carr's index
K4-7	1.5294	34.6140
K100-8	1.3334	25.0045
15cps-8	1.5331	34.77

From the above results, it could be concluded that the flow and consolidation properties are in acceptable range.

4.2. Physicochemical Characterization

Crushing strength, Friability and Drug content of the optimized formulations.

Evaluation parameters	K4-7	K100-8	15cps-8
Thickness(mm)	5.05±0.042	5.15±0.041	5.25±0.035
Weight variation (%)	0.469±0.0.005	0.398±0.004	0.521±0.004
Crushing strength(cm^2)	5.5±0.146	5 ±0.125	5.5±0.142
Drug content(mg)/tablet	98.4% ±0.202	98.7%±0.165	99.5%±0.172
Buoyancy lag time(m)	7±2.6	8±4.1	6±3.4
Total buoyancy time(h)	>24h	>24h	>24h
Friability (%)	0.2122	0.2432	0.2212

All values are mean ±SD of three determinations.

Results indicate that Crushing strength, friability and drug content of the optimized formulations were within the limit. All the formulations were floated for more than 24hrs. Thickness (5-5.5) and compression ton were adjusted to obtain satisfactory floating. HPMCK4 and HPMCK100 showed higher swelling index and matrix integrity.

4.3. Kinetics of drug release

Release rate constant and regression coefficient from various kinetic models such as Zero order, First order, Higuchi's model and Hixson-Crowell plot for the optimized formulations are given in the table.

Release rate constant and regression coefficient of optimised formulation

Formulation	Zero order		First order		Higuchi		Hixson-Crowell	
	K_o	r^2	K	r^2	K_H	r^2	K_{HC}	r^2
K-4	3.257	0.988	0.036	0.871	19.93	0.993	0.099	0.895
K-100	2.802	0.997	0.025	0.895	16.91	0.999	0.069	0.829
15cps	2.521	0.662	0.027	0.598	17.46	0.772	0.071	0.626

HPMC matrix formulations followed Higuchi's release profile.

4.4. Mechanism of drug release

Korsmeyer-Peppas release exponent and regression coefficient for the optimized tablet formulations

Formulations	n	r^2
K4-7	0.532	0.724
K100-8	0.631	0.774
15cps-8	0.522	0.463

The values of 'n' indicate anomalous behaviour and the drug followed non-Fickian diffusion mechanism, both diffusion and matrix erosion from the polymeric matrix system.

4.5. Accelerated stability studies

No change in colour, appearance and odour were noted with samples withdrawn for stability testing.

4.5.1. Moisture absorption

Percentage moisture absorption of optimised formulation

Optimized formulation	Mean moisture absorption (%)		
	1 month	2 month	3 month
K4-7	0.6422	0.6318	0.6895
K100-8	0.4216	0.4226	0.4763
15cps-8	0.4110	0.4502	0.4432

4.5.2. Tablet crushing strength

Crushing strength of Optimised tablet formulations

Optimized formulation	Crushing strength ± SD (kg/cm^2)			
	0 month	1 month	2 month	3 month
K4-7	5.5± 0.11	5.5± 0.13	5.5 ± 0.61	5.5± 0.63
K100-8	5.4± 0.92	5.4 ± 0.66	5.4 ± 0.33	5.4 ± 0.11
15cps-8	5.3 ± 0.17	5.3 ± 0.17	5.3± 0.53	5.3± 0.26

All values are mean ±SD of three determinations

4.5.3. Friability

Friability % of optimised formulations

Optimized formulation	Friability (%)			
	0 month	1 month	2 month	3 month
K4-7	0.2122	0.2120	0.2123	0.2109
K100-8	0.2432	0.2432	0.2412	0.2421
K100-8	0.2212	0.2213	0.2210	0.2212

All values are mean ±SD of three determinations

4.5.4. Drug content

Percentage drug content of tablet formulations

Optimized formulation	Drug content (%)			
	0 month	1 month	2 month	3 month
K4-7	98.4% ±0.202	97.9% ±0.202	97.9%±0.165	97.9±0.123
K100-8	98.7%±0.165	98.6%±0.165	98.5±0.202	98.6±0.142
K100-8	99.5%±0.165	99.4%±0.165	99.3±0.123	99.4±0.312

All values are mean ±SD of three determinations

5. Conclusion

Tablets of anhydrous Theophylline were prepared by direct compression using gel forming polymers such as HPMCK4M, HPMCK100M, HPMC15cps, and were subjected to various evaluation parameters. All the formulations were found to conform to the standards. Final strength of tablets was fixed as 500mg incorporating 200mg of drug. A 3^2 factorial design was adopted to get 9 combinations in each formulation. It was found that both the amount of polymer and compression load had significant influence on the percentage drug release and buoyancy time. The floating tablets were evaluated for uniformity of weight, hardness, friability, drug content, in vitro buoyancy and dissolution studies. The effect of hardness (5-5.5kgm/cm^2) on floating behaviour of the tablets was evaluated. An increase in hardness from 5 to 6kgm/ cm^2 resulted in significant increase in floating lag time of 15-30 minutes.

5.1.7 In Vitro dissolution study

In vitro drug release profiles of the optimized tablet formulations subjected to accelerated stability studies at regular time intervals during the period of 0 and 3 months

In vitro drug release profile of optimised formulation

Time (hr)	Cumulative % Drug Release ± SD					
	K4-7		K100-8		15cps-8	
	0 month	3 month	0 month	3 month	0 month	3 month
1	14.15± 2.03	14.22 ± 0.45	12.85± 1.04	12.76 ± 1.45	18.84 ± 0.92	18.83 ± 0.93
2	18.16 ± 1.82	17.82 ± 1.73	19.35 ± 0.04	19.32 ± 0.16	29.31± 0.57	29.20 ± 2.04
3	24.01± 1.04	23.53 ± 0.55	22.72± 0.42	22.07 ± 0.36	40.45 ± 0.83	40.60 ± 0.03
4	31.41± 1.11	31.32 ± 0.72	26.47± 0.93	26.30 ± 1.25	50.63± 0.52	49.93 ± 0.90
5	38.52± 0.57	38.09 ± 1.09	31.3± 0.13	31.32 ± 0.38	58.62 ± 0.57	58.02 ± 1.05
6	45.72± 0.52	45.70 ± 1.02	35.96± 0.73	36.18 ± 0.88	65.35 ± 0.23	65.16 ±2.10
7	46.97 ± 0.53	46.16 ± 0.76	39.39± 0.94	39.14 ± 2.06	71.4± 0.81	72.04 ± 1.57
8	49.52 ± 1.27	49.18 ± 0.28	42.32± 0.13	42.33 ± 0.40	73.91 ± 0.92	72.94 ± 0.37
9	52.11 ± 1.29	52.62 ± 2.04	45.34± 0.72	44.94 ± 1.30	74.34 ± 0.13	74.93 ± 1.40
10	56.11 ± 1.04	56.46 ± 1.82	48.35 ± 1.10	48.32 ± 0.95	75.26 ± 0.24	75.00 ± 1.36
11	59.96 ± 0.29	59.37 ± 0.92	51.23± 0.92	51.58 ± 1.06	76.54 ± 2.03	76.28 ± 0.95
12	64.46 ± 0.15	64.12 ± 1.03	54.3 2± 0.30	53.95 ± 1.87	77.35 ± 1.14	77.43 ± 0.48
24	87.79 ± 0.53	87.7 8± 0.56	77.00 ± 0.60	76.93 ± 0.39	79.88 ± 0.87	79.89 ± 1.62
Similarity factor (f_2)	82.4		54.54		37.13	

All values are mean ±SD of three determinations

   The drug release pattern of the optimized formulations during the accelerated stability study was comparable to the marketed product in terms of similarity factor.

   The prepared Tablets exhibited satisfactory physicochemical characteristics. All the prepared batches showed good *in vitro* buoyancy. The tablets swelled readily during *in vitro* buoyancy studies. It was observed that the tablet remained buoyant for 24hrs.The tablets with HPMCK4 and HPMCK100 were floated for longer duration and had more matrix integrity as compared to formulations containing HPMC 15cps.

   All the Formulations were compared with marketed sustained release tablet (TheoSR200mg).Optimized formulations were selected based on the similarity factor determination. The Drug release of optimized formulation follows the Higuchi kinetic model,   and mechanism is found to be non-Fickian/anomalous according to Krosmeyer–Peppas. Formulations with

   HPMCk100M & HPMCK4M showed better control of drug release and the drug release was similar to that of marketed product.   The drug release pattern of Formulations with HPMC15cps was not similar to marketed product. X-ray pictures showed in vivo nature of the tablet at different time intervals and it was observed that total buoyancy time was able to delay the gastric emptying of Theophylline floating tablet. Developed optimized formulations were found to be stable after 3 months of storage at accelerated   stability conditions based on temperature and humidity.

   For Drugs with narrow absorption window in the gastrointestinal tract, Gastro retentive drug delivery systems help in maintenance of constant therapeutic levels for prolonged periods and produce therapeutic efficacy and thereby reduce the total dose of administration.

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