



Formulation and evaluation of bi-layered floating tablets of Theophylline

N. Damodharan*, M. Mothilal, m.madhavi, P. Thejomayananthan

*Department of Pharmaceutics, SRM College of Pharmacy, SRM University,
Chennai, Tamilnadu*

Abstract

Bi-layered floating tablets of theophylline were developed using wet granulation technique. The current study aims at formulation and evaluation of bi-layered floating tablets of theophylline. The floating tablets of theophylline were formulated using polymers namely hydroxyl propyl methyl cellulose, sodium carboxy methyl cellulose, methyl cellulose and the tablets were evaluated. Two layered tablet formulations were designed with an immediately releasing layer consisting of theophylline with lactose as diluents and sustained release layer with slow releasing swellable matrix consisting of theophylline in hydroxyl propyl methyl cellulose, sodium carboxy methyl cellulose and methyl cellulose alone or in combination. The formulations were tested for drug release, floating time, floating lag time, drug content. Tablets formulated employing a combination of hydroxyl propyl methyl cellulose and methyl cellulose provide slow release of theophylline over a period of 9 hours and were found suitable for maintenance portion of bi-layered floating tablets. Theophylline release from these tablets was diffusion controlled and followed first order kinetics. The tablets exhibited good floating behavior in the stomach for 9 hours.

Key-Words Floating drug delivery system, theophylline, bi-layered, Hydroxy propyl methyl cellulose, Methyl cellulose

Introduction

The high cost involved in the development of a new drug molecule has diverted the pharmaceutical companies to investigate various strategies in the development of novel drug delivery systems[1]. Drug release from the drug delivery devices can be sustained up to 24 h for many drugs using current release technologies. However, issue in the development of oral SR dosage forms is to prolong the residence time of the dosage form in the stomach or upper gastro intestinal (GI) tract until the drug is released[2].

Several approaches are currently used to retain the dosage form in the stomach. These include, bio-adhesive systems[3], swelling and expanding systems[4],[5] floating systems[6, 7] and other delayed gastric emptying devices[8, 9]. The principle of floating preparation offers a simple and practical approach to achieve increasing gastric residence time for the dosage form and sustained drug release.

Theophylline is highly effective in the treatment of bronchial asthma and infant apnea. But their long term use is beset with nausea, diarrhea, increase in heart rate, arrhythmia, and CNS excitation. Several matrix based sustained release products of theophylline have been reported based on the use of hydrophilic polymers (HPMC, SCMC and MC)[10-18]. Because of short biological half-life, narrow therapeutic index and problems associated with gastro-intestinal disturbances, attempts have been made to develop sustained release products with prolonged clinical efficacy, reduced side-effects and dosing frequency. A few sustained release floating formulations of theophylline are also available commercially. In the present study, bi-layered floating tablets of theophylline were formulated employing HPMC, MC and SCMC. These materials are reported to have good floating behavior.

Materials and Methods

Theophylline was a gift sample obtained from Ajanta Pharmaceuticals, Mumbai. HPMC, SCMC and MC were purchased from Signet Pharma Agencies, Chennai. Sodium bi-carbonate, lactose and starch were purchased from ISP Agencies, Bangalore. MCC was purchased from FMC Pharma Agencies, Mumbai. All other ingredients were of analytical grade and used as received.

Preparation of bi-layered floating tablets of theophylline:

The drug theophylline and other additives were allowed through standard sieve number 100 separately. The immediate release granules were prepared by wet granulation method. Theophylline and other additives were mixed well by geometric dilution. To this, starch mucilage was allowed to add little by little until a coherent mass was obtained. This was passed through standard sieve number 20 to get wet granules. The wet granules were dried at 50°C in hot air oven. The dried granules were passed through sieve number 20 and the retained granules were passed through sieve number 85 to break the lumps and to remove fines respectively. 1% of the fines were added to the granules to be compressed. The sustained release granules were also prepared in the same way by wet granulation technique using starch mucilage 3% as binding agent. 1% of the fines were finally added to the granules to be compressed. To both portions of the granules, 1% of talc was added separately for lubricant and glidant action. Accurately weighed immediate release granules containing 100mg of anhydrous theophylline were poured in to the die to form the bottom layer. The sustained release granules equivalent to 200mg of anhydrous theophylline were also weighed accurately and this portion was poured over the bottom layer. Half inch or 13mm size round flat punches were used for compression. Compression of the prepared bi-layered floating tablets of theophylline were presented in [Table 1] and [Table 2] respectively.

Evaluation of bi-layered floating tablets of theophylline:

The fracture strength, which is defined as, the force required to break the tablet by radial compression, was measured with the tablet hardness tester[19]. Friability of the tablet was measured using Roche friability tester. The weight variation was evaluated for 10 tablets using an electronic balance.

Table 1: composition of immediate release layer

INGREDIENTS (mg)	F _I	F ₂	F ₃
Theophylline	100	100	100
Sodium Bi-carbonate	40	-	-
Lactose	10	40	40
Microcrystalline Cellulose	-	10	-
Starch	-	-	10
Starch Mucilage 3%	Q.S	Q.S	Q.S
TOTAL	150	150	150

Table 2: Composition of sustained release layer

INGREDIENTS (mg)	F _{1A}	F _{1B}	F _{1C}	F _{2A}	F _{2B}	F _{2C}	F _{3A}	F _{3B}
Theophylline	200	200	200	200	200	200	200	200
HPMC	200	400	600	100	200	300	-	300
SCMC	-	-	-	100	200	300	-	-
MC	-	-	-	-	-	-	600	300
Starch Mucilage 3%	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
TOTAL	400	600	800	400	600	800	800	800

For the measurement of in vitro disintegration time of immediate release layer, a modified dissolution apparatus (paddle type) was used. 1.2 hydrochloric acid buffer (900ml) maintained at 37°C and stirred with a paddle at 100 rpm was used as the disintegration fluid. A tablet was placed in the sinker and the disintegration time was determined at the point at which the immediate release layer of the tablet was disintegrated completely and passed through the screen of the sinker[20].

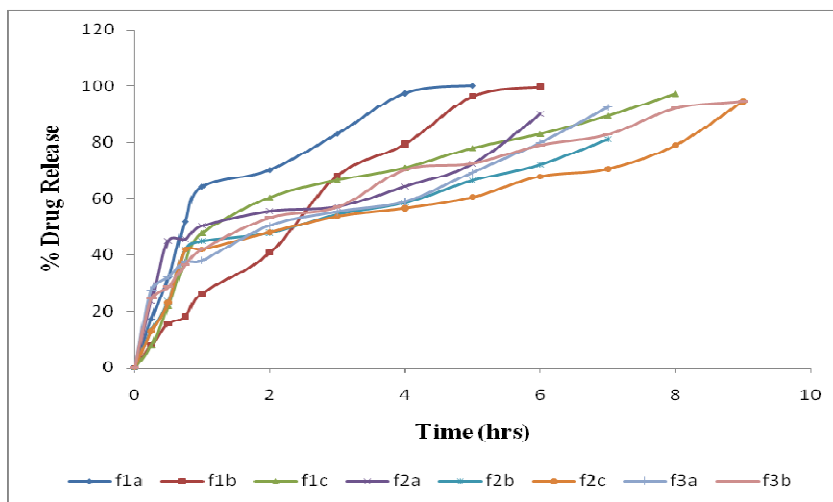
Drug content of the manufactured tablets of each batch was determined by weighing and finely grinding the tablet from each batch. Aliquot of this powder equivalent to 100mg of theophylline was accurately weighed and suitably extracted in 10ml of 0.1N NaOH. Shaken well for 5 minutes and diluted to 200ml 0.1N NaOH and set aside for 15 minutes and filtered through filter

paper, discarding first 20-30ml of the filtrate. 3ml of the filtrate was diluted to 200ml with 0.1N NaOH. The extinction was measured at 272nm using NaOH as blank.

The floating lag time is defined as, the time taken for the dosage form to emerge on to the surface of the medium. This is also known as buoyancy lag time (BLT). The duration of time by which the dosage forms constantly emerge on surface of the medium is called as total floating time (TFT). The buoyancy time and floating behavior were determined as a part of in vitro drug release study.

In vitro dissolution study of the theophylline tablets was performed using USP apparatus II (model TDT – 06 T, Electro tester, India) fitted with paddles (50 rpm). After the immediate release layer was disintegrated out, the tablet started floating in the dissolution fluid i.e., 0.1N hydrochloric acid buffer. The dissolution was continued till the tablet floats. Then, the dissolution medium was changed to pH 4.4 buffer. The dissolution was continued in the second dissolution fluid for two more hours after which, the same dosage form was transferred to the next dissolution medium pH 7.5 buffer. The dissolution was continued in the same dissolution fluid until the tablet is completely eroded and dissolved. At the pre-determined intervals, 1ml of sample was withdrawn, filtered through 0.45mm membrane filter and the volume was made up to 10ml with distilled water and assayed at 272nm using a Shimazu UV/Visible double beam spectrophotometer. Cumulative percentage drug release was calculated using an equation obtained from the calculation curve. The drug release profile is shown in [Figure-1].

Figure 1: Graph showing the comparative dissolution profile of all the formulations



The dissolution profile of all the batches was fitted to various models like zero-order, first-order[21], Higuchi[22], Hixon-crowel[23] and Korsmeyer and Peppas's[24],[25],[26] to ascertain kinetic modeling of drug release. The method of *Bamba et al*, was adopted for deciding the most appropriate model[27].

Three batches of best formulations were studied for the effect of storage under different conditions on the stability and release profiles of drug from the different formulations respectively. The tablets were sealed in air tight cellophane packets and were stored in different temperature conditions (temperature- 25°C, 30°C, 40°C and relative humidity- 60%, 65%,

and 75% respectively). The in-vitro release profile for each was studied as per the specification enlisted in previous sections and compared with its initial release profile.

Results and Discussion

Hardness, friability, weight variation, disintegration of first layer, drug content, buoyancy and floating time were found satisfactory [Table-3]. The manufactured tablets showed low weight variation and high degree of content uniformity.

Table 3: Evaluation of various physic-chemical parameters

Formulation	Hardness (kg/cm ²)	Wt. variation(gms)	Disintegration of 1 st layer (min)	Swelling thickness (cms)	Drug content (%)	Friability (%)	Buoyancy (min)	Floating time (hrs)
F _{1A}	8	0.5580	10	0.5	99.7	0.9	8	2
F _{1B}	10	0.7550	10	0.7	99.7	0.7	5	3
F _{1C}	11	0.9509	8	1.0	99.7	0.8	3	3
F _{2A}	10	0.5524	11	0.5	99.5	0.8	9	3
F _{2B}	11	0.7548	10	0.8	100.5	0.9	6	3
F _{2C}	11	0.9462	12	1.0	100.3	1.2	5	4
F _{3A}	8	0.9580	1	0.7	97.5	0.8	7	7
F _{3B}	9	0.9524	2	0.7	100.3	0.9	3	9

Theophylline, a xanthine derivative is practically insoluble in simulated gastric acid. Therefore, the dissolution studies were carried out first in the simulated gastric acid till the tablet floats on the medium. Then, the dissolution medium was changed to pH 4.4 phosphate buffer and the dissolution was continued for 2 hrs. Then finally, after 2 hrs, the dissolution medium was again changed to pH 7.2 phosphate buffer till the remaining period of study. This medium was considered as most suitable for as the drug was freely soluble at this pH and it also mimics the alkaline environment of small intestine. The selection of granulation technique for matrix tablet preparation was based on porosity that gave very slow release rates when compared with direct compression.

The drug release profile of all the batches of tablets exhibits three phases. First, fast releasing phase can be released by the release of drug from both immediate release layer and sustained release layer. Second phase up to a particular time indicates that the release is diffusion controlled through swollen matrix of hydrophilic materials. The third phase of sudden increase in the rate of drug release indicates the sinking of the tablet and erosion of the tablet which is the

reason for increased drug release. Then, the release of the drug is by both diffusion through the matrix and erosion of polymer. In formulation F_{3B}, the drug polymer ratio 1:3 (1 part of drug : 1.5 part of HPMC : 1.5 part of MC) tablets were found to float for a period of dissolution i.e., up to 9hrs and erosion starts after sinking of the tablet.

The drug release studies were used in order to assess the swelling character of the matrix polymer by drawing the Peppas's plot for the formulation F_{3B}. The slope value was calculated and was found to be 0.6254. The slope value for this formulation is in the range of 0.5-0.9. So that, the drug release may be controlled by the swelling of the polymer and it is anomalous diffusion.

The disintegration test was carried out for the tablet till the immediate release layer of the tablet disintegrates out. First layer of all the batches of tablets were found to disintegrate within 15 minutes. The disintegration of immediate release layer of the formulation F_{3A} (drug : MC) took only 1 minute to disintegrate which may be due to greater water withdrawing capacity of methyl cellulose and porosity of the tablet. The higher volume of water sucked in may have caused the disintegration of immediate release layer quickly.

The friability loss was found to be within the limits in all formulations except F_{2C}. As the amount of polymer in the tablet is increased, the friability of the tablet formulation was also found to increase. The hardness and drug content of the bi-layered floating tablets were found to be within limits specified (hardness 3-11 Kg/cm² and friability up to 1%). In the preparation of F_{2C} batch tablets, the quantity of the binding agent must be increased or the compression force must be augmented.

Out of three formulae developed for immediate release layer, only the CO₂ producing layer containing tablets with 1.2 buffer was found to float after disintegration of first layer. This may be due to trapping of CO₂ in the swollen pores of the second layer resulting in the floating of the whole tablet. From the present study, it was found that, as the polymer proportion increases, floating time also increases. Formulations containing methyl cellulose alone (F_{3A}) and combination of methyl cellulose and hydroxyl propyl methyl cellulose (F_{3B}) were found to have floating characters for a long period. All the batches of the tablets were found to pass weight variation test since, the tablets were compressed after manually pouring the accurately weighed portion of the granules. So, the chance of weight variation is greatly reduced.

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