



RESEARCH ARTICLE

Modulated Release of Theophylline from Controlled Release Matrix Tablets

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ABSTRACT

The purpose of the present study was to design, development, formulation and evaluation controlled release matrix tablets for an antiasthmatic drug, Theophylline. Controlled release matrix tablets were prepared using different grades of Hydroxypropyl methylcellulose as matrix former and Povidone as binder. Preformulation study of drug shows that the drug has more solubility in 0.1N HCl hence it is difficult to control the drug release in gastric fluid. But a satisfactory formulation has been developed by using different grades of HPMC (Methocel K4M, Methocel K100 M, Methocel E-50 LV) for Theophylline to extend the drug release for more than 12 hours. The physicochemical compatibility of the drug with polymers was established through DSC spectroscopy. The study indicated that the drug have good compatibility with these polymers. The results of the stability studies suggested that the formulations may provide a minimum shelf life of 2 years.

KEYWORDS

Theophylline, Hydroxypropyl Methylcellulose, Povidone, Controlled Release

INTRODUCTION

Developing oral controlled release tablets for water soluble drugs with constant release rate has always been a challenge to the pharmaceutical technologist. Most of these water soluble drugs if not formulated properly, may readily release the drug at a faster rate and produce a toxic concentration of drug on oral administration. Hence it is a challenging task to formulate a suitable tablet dosage form for prolonged delivery of water soluble drugs.¹ The concentration of a drug in the blood fluctuates over successive doses of most conventional single unit oral dosage forms. The main reason for this is that the drug is released immediately after administration (i.e. burst release effect).

This causes the drug blood concentration to rise

quickly to a high value ("peak") followed by a sudden decrease to a very low level ("trough") as a result of drug elimination. One way of addressing this problem is by means of formulating dosage forms with sustained release profiles over a controlled period of time. The ideal drug delivery system would keep the drug blood plasma level constant over the entire treatment period after administration of a single dose.²

Theophylline is a bronchodilator agent; it mainly relaxes the smooth muscle of the bronchial airways and pulmonary blood vessels and reduces airway responsiveness to histamine, methacholine, adenosine, and allergen. It competitively inhibits type III and type IV phosphodiesterase (PDE), the enzyme responsible for breaking down cyclic AMP in smooth muscle cells, possibly resulting in bronchodilation and also binds to the adenosine receptor and blocks adenosine mediated

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bronchoconstriction.³ Once patient suffering from asthma they have to take medicine for the rest of their life. Asthma is a chronic disease and if dosing frequency of the medication or certain property of the medication is not proper (Like short half-life, low solubility etc.) than patient may have to suffer a lot.

Fast acting dosage forms leads to patient noncompliance and fluctuation in plasma concentration. To overcome this controlled release dosage form is better choice. It is desirable in the therapeutic and prophylactic treatment of diseases to provide the Theophylline in controlled release form. Controlled release dosage forms can increase patient compliance due to reduction in frequency of dosing. They may also reduce the severity and frequency of side effects as they typically maintain substantially constant plasma levels. Hence the current research work is carried out to develop pharmaceutical equivalent controlled release dosage form in comparison with innovator product.² The most commonly used method of modulating the drug release is to include it in a matrix system. Diffusion controlled polymeric matrix devices have been widely used as drug delivery systems owing to their flexibility to obtain a desirable drug release profile, less chance of dose dumping, cost effectiveness and broad regulatory acceptance. The controlled drug-delivery systems are useful to increase the retention time of the drug-delivery systems for more than conventional dosage forms.⁴

The aim of the present study was to formulate controlled release tablets of Theophylline. It is anticipated that it will provide smoother plasma levels compared with immediate release Bronchodilator formulations with minimized peak to trough variability over a 12 hrs period and could, therefore, be associated with a reduced risk of adverse effects and improved tolerability.

Sunil Reddy *et al.*, 2012; Formulated extend release tablets of metoprolol succinate using

HPMC, HPC, HEC, and further subjected for coating using blends of aqueous dispersion of a hydrophilic and hydrophobic polymer. The *in-vitro* dissolution study was carried out in pH 7.5. It is concluded that the release rate is inversely proportional to the concentration of matrix former in the core tablet and percent of coating thickness. The kinetic treatment illustrate that the optimized formulation HMC 5 followed zero order kinetics with diffusion mediated release exponent (n) 0.73 and having good stability as per ICH guidelines.⁵ S. Siddique *et al.*, 2010; Investigates that the objective of this investigation was to prepare sustained release capsule containing coated matrix granules of metoprolol tartrate and to study its *in-vitro* release and *in vivo* absorption. The design of dosage form was performed by choosing hydrophilic hydroxypropyl methyl cellulose (HPMC K100M) and hydrophobic ethyl cellulose (EC) polymers as matrix builders and Eudragit® RL/RS as coating polymers. Granules were prepared by composing drug with HPMC K100M, EC, dicalcium phosphate by wet granulation method with subsequent coating. The release mechanism of capsules followed Korsmeyer–Peppas model that indicated significant contribution of erosion effect of hydrophilic polymer.⁶ Keny *et al.*, 2009; have formulated once daily Minocycline hydrochloride controlled release matrix tablets using hydroxypropyl methylcellulose alone or in combination with ethyl cellulose and compared it with marketed product. Result suggested that drug release was obtained for 24 hrs whereas marketed product was found to extend the release only up to 14 hrs.⁷ Raja Sekharan *et al.*, 2009, Developed theophylline controlled release matrix tablets were prepared with guar gum in two ratios and with three different hardness of 5, 6, and 7 kg/cm². It was concluded that the polymer ratio and hardness plays a major role in drug release. As the polymer ratio and hardness of the tablets increased the drug release was prolonged.⁸

MATERIALS AND METHOD

Materials

Theophylline was gifted sample from Torrent Laboratories, India. Other materials used in the study such as hydroxyl propyl methylcellulose, Povidone, Lactose monohydrate, Magnesium Stearate purchased from Loba Chemie Laboratories Ltd., Goa, India were of Pharmacopoeia standard (USP/NF).

Determination of Pre-compression and Post-compression Parameters^{9,10}

Tap density of granules was determined by using tapped density tester (Electrolab, India). Bulk densities of granules, particle size distribution, percent compressibility (Carr's Index), Hausner's ratio, angle of repose, rate of granule's flow were determined by USP method. Frequency of size distribution and percent of fines in the dried granulation were determined by sieve analysis. The tablets were stored for at least 6 days at room temperature before characterization. Ten samples were chosen randomly for conducting each test. The thickness and diameter of the tablets were determined using a micrometer gauge (Mitutoyo, Japan). Friability of coated tablets was determined by Roche friabilator (Camp-bell Electronics, Mumbai).^{11,12}

Manufacture of Tablets

Theophylline anhydrous has a low bulk density and shows very poor flow properties. Hence, wet granulation technique was preferred as it improved the bulk density and made it easy to compress. As per the strategy, following trials were taken to develop Theophylline controlled-release tablets. Accurately weighed quantities of Theophylline (Anhydrous) USP, hypromellose and lactose monohydrate were sifted through sieve #40 and mixed using rapid mixer granulator. The binder solution was prepared by dissolving Povidone (K 30) in hydro alcoholic mixture using magnetic stirrer. The blend of step 1 was granulated with the prepared Povidone K 30 solution using rapid mixer granulator. The granulated wet mass was dried in rapid dryer at 50 °C. Drying was stopped when the LOD values of post drying samples (granules) were within $\pm 1.5\%$ to the preblended samples. The dried mass was sifted through sieve #20 and lubricated with magnesium stearate (previously sifted through sieve # 60) in Conta blender. The lubricated granules were compressed using 19.05 x 7.04 mm capsule shaped with break line and embossed with L108 on one side and plain on other side with total target weight of 945 mg on a suitable compression machine.

Table 1: Formula for formulation of Theophylline controlled release tablet (450 mg)

Formula	MT1	MT 2	MT 3	MT 4	MT 5	MT 6
API	450	450	450	450	450	450
HPC GXF	300	300	-	-	-	-
HPMC 4M	-	-	280	-	-	-
HPMC K-100 M	-	-	-	300	250	210
HPMCE-50 LV	-	-	-	-	-	-
Lactose monohydrate	150	150	170	150	200	240
Povidon K-30	40	40	40	40	40	40

Ethanol : P.W. (9:1)	NO	q. s.				
Magnesium Stearate	05	05	05	05	05	05
Total	945	945	945	945	945	945

Formula	MT 7	MT 8	MT 9	MT 10	MT 11	MT 12
API	450	450	450	450	450	450
HPC GXF	-	-	-	-	-	-
HPMC 4M	-	-	-	-	-	-
HPMC K-100 M	-	160	160	160	160	160
HPMCE-50 LV	210	50	60	70	80	90
Lactose monohydrate	240	240	230	220	210	200
Povidon K-30	40	40	40	40	40	40
Ethanol : P.W. (9:1)	q. s.	q. s.	q. s.	q. s.	q. s.	q.s.
Magnesium Stearate	05	05	05	05	05	05
Total	945	945	945	945	945	945

*NOTE: All the ingredients were taken in mg/tab

Study of *In- Vitro* Drug Release^{13,14,15}

The *in-vitro* dissolution studies were performed in USP- 30- type I dissolution apparatus operating at 50 rpm. The dissolution medium consisted of 0.1N hydrochloric acid for the first 2 hr (pH 1.2) and the phosphate buffer at pH 7.5 for the next 3 to 12 hr (900 ml) and the medium was maintained at 37°C ± 0.5°C. This was simulated with gastrointestinal pH in humans.

An aliquot (5 ml) was withdrawn at specific time intervals and replaced with the same volume of fresh medium at same temperature. The withdrawn sample was filtered through 0.45 µm filter paper. Its drug content was determined by UV-visible spectrophotometer (Shimadzu, Kyoto, Japan) at wave length of 280 nm. It was ascertained that none of the ingredients used in the matrix formulations interfered with the

assay. The release studies were conducted in triplicate.

Drug-Excipient Compatibility Studies

Drug excipient compatibility study was performed by mixing drug with polymer in equal proportion and the mixture was kept under accelerated stability condition (i.e. 40°C and 75±5% RH) for a period of 21 days in a glass vial. It was hermetically sealed with rubber stopper using molten carnauba wax. On the basis of result obtained the polymers are selected. Differential scanning calorimeter was also used for thermal analysis of drug and mixture of drug and excipients. The drug and excipients were passed through the sieve no. 40 and mixed in different ratio. The drug alone and mixture of drug and excipients was weighed directly in the pierced DSC aluminum pan and scanned at the temperature range of 150-350°C and at heating rate of 10°C/min. and nitrogen purging rate 50 ml/min. the thermogram obtained were observed for any interaction .

Effect of Storage on the Stability of Sustained Release Matrix Tablets

Stability studies were conducted on CR matrix tablets of the final batch (MT 11) to assess their chemical stability and therapeutic efficacy by examining their physical appearance, drug content and release characteristics. Hundred tablets were packed in a plastic bottle and placed in two humidity chambers where temperature was kept at 25°C with 60% relative humidity (RH) for 6 months and 40°C with 75 % RH for 3 months.

RESULTS DISCUSSION

Pre-Compression and Post-Compression Parameters

The granules were first prepared and characterized with respect to size distribution, % fines, bulk density, tapped density, Hausner ratio, Carr’s index, angle of repose, mass flow rate.¹⁶ Maximum weight (~80 ±2%) of granules for each batch had been retained by sieve no.20.and % fines was found very less. Smaller size granules (mesh size 30, 40 &60) fit well within inter particular gap of higher size

granules (mesh size 20) which ensure uniformity of weight. Mass flow rate of each batch was checked in triplicate and average value had been tabulated. It showed also uniformity within each batch. Values of Hausner ratio and Carr’s index were found within the ideal characteristics range. Bulk volume of granules of any capacity can be determined by bulk density. High bulk density ensures easy flow of granules. Angle of repose was less than 30° for all the batches of granules indicating satisfactory flow behavior.

The tablets of different batches were subjected to various evaluation tests, such as weight variation, friability, hardness, and content uniformity according to the procedure specified in USP 30. All the formulations have uniform thickness. The property of thickness is important for packaging purpose. The weight variation and friability were not more than 2% and 0.7%, respectively. Hardness of the tablets were found acceptable and uniform from batch to batch variation. Drug content was found uniform among different batches of the tablets, and the drug content was within 98-102 % which is within the prescribed limit. This showed low value of bulk density, low angle of repose, minimum friability and maximum MDT and good control on flow ability of its granules.^{17,18,19,20}

Table 2: Preformulation study of granules of final batch (MT 11)

Sr No.	Parameter	Result
1	Bulk Density	0.576± 0.02 gm/ml
2	Tapped Density	0.681±0.13 gm/ml
3	C.I (%)	17.3± 0.45
4	Hausner’s ratio	1.18±0.08
5	Angle of repose	21.9° ± 0.8

Study of *In-vitro* Drug Release from the Prepared Formulation

Initial batch MT1 and MT2 was taken in which matrix tablet of Theophylline was prepared with HPC (GXF), lactose monohydrate, povidone K-30, magnesium stearate by direct compression method. Here flow of powder blend was very poor therefore further, wet granulation technique was sought in order to enhance blend flow. Then batch MT3 and MT4 were formulated by wet granulation method. Here povidone K-30 was used as binder using ethanol:water (9:1) as solvent for granulation. Here good flow was obtained but high tablet erosion was observed without any swelling of polymer, and dissolution profile was too fast in initial 1-6 hrs and 77% drug release initially in 6 hours. Then batch MT4, MT5 and MT6 were prepared using HPMC K-100 M, lactose monohydrate and granulated with povidone K-30 solution using ethanol:water (9:1). Then batch MT8 to MT12 were prepared with reducing the level of HPMC E 50LV as tabulated in the Table No. 01. In formulation MT2 and MT6 more than 35% of the drug was released in 2 hours. So there are chances of dose dumping and is not acceptable for controlled release formulations. In formulations MT3, MT4, MT5, MT7, MT8 and MT9 the rate of drug release were initially very slow.

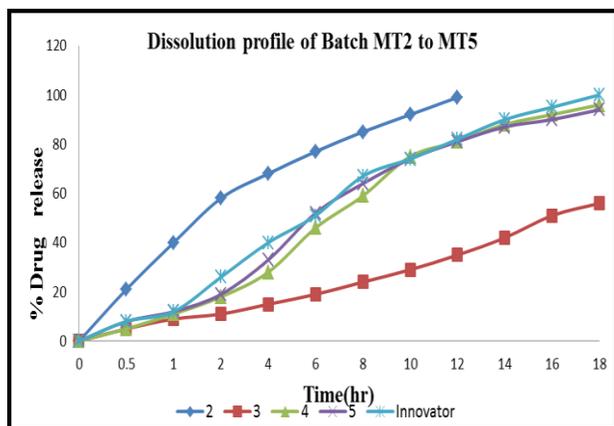


Figure 1: *In-vitro* Release Profile of Batch 02 to 05 in Comparison With Innovator

In formulations MT10, MT11, MT12 the rate of drug release followed Higuchi equation i.e about 20% drug was released in 2hours to reach

therapeutic level then these formulations controlled the drug release up to 18 hours. Availability of sufficient time for swelling and gelling might be the reason for decreased initial burst release. Out of there three formulations MT 11 was studied further for compatibility and stability study.

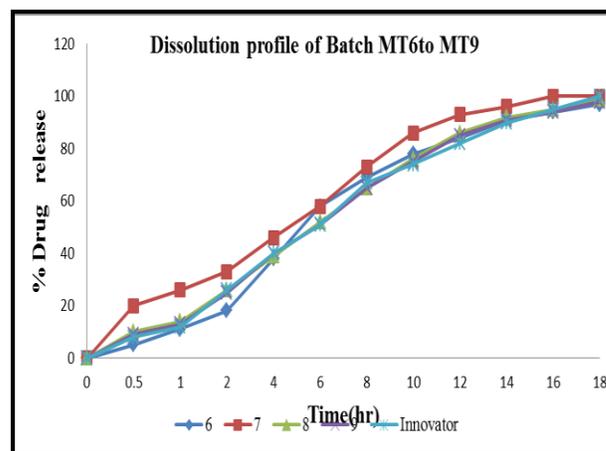


Figure 2: *In-vitro* Release Profile of Batch 06 to 09 in Comparison With Innovator

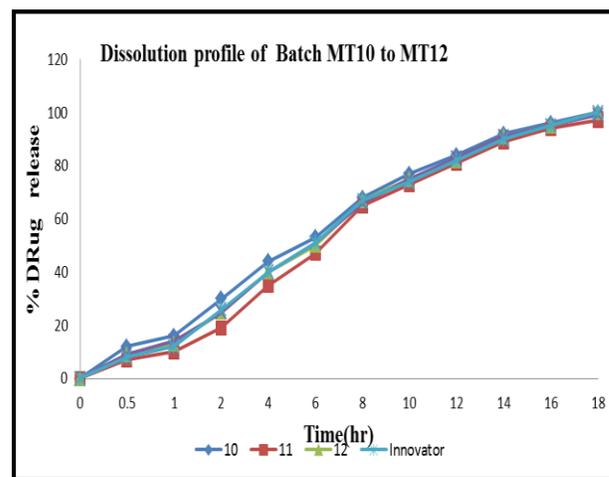


Figure 3: *In-vitro* Release Profile of Batch 10 to 12 Along With 09 After Stability in Comparison With Innovator

Drug-Excipients Compatibility Studies

No change in color, liquefaction or lumps formation and flow was observed after storing the powder mix at elevated temperature for 21 days. Comparison of DSC themograms of drug as well as in the presence of polymer gives an idea about the glass transition temperature of drug in the formulation and confirmed that there is no interaction between drug and excipients.

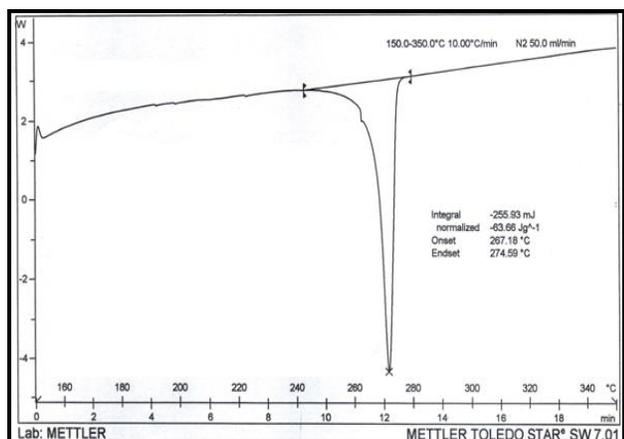


Figure 4: DSC of Drug + Excipients

Stability Studies

The formulations (MT 11) after storing at 25°C/60% RH and at 40°C/75% RH for 6 months showed no change in physical appearance or dissolution pattern. The results of the stability studies suggested that the formulations may provide a minimum shelf life of 2 years.^{21,22}

CONCLUSION

In conclusion, it can be postulated that HPMC has its effect on the release pattern of drug from matrices depending upon the grade and concentration. At the same time, type of diluents and method of preparation also affects the release of drug from the matrices which is true to the earlier findings. The release of drug from the combined matrices of different grades of HPMC follows the Higuchi equation, which means drug slowly diffuses through the gelatinous layer of the matrix.

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