

**Design and In Vitro Evaluation of Chrono
Modulated Theophylline Tablets**

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ABSTRACT

The objective of this research work was to prepare a chrono modulated delivery system to meet chronopharmacological needs of asthma. In this study theophylline was selected as a model drug. To meet this objective we considered an initial lag phase of release for 3-5 hrs and later a rapid (surge) release phase. To achieve surge release a rapidly releasing core tablet of theophylline was developed by admixing theophylline with effervescent granules and super disintegrants. The lag phase in release was achieved by coating the EV core tablets with release retarding polymer EUDRAGIT RS-100 containing HPMC, further over coated with enteric polymer CAP. The results indicate that a rapidly releasing EV tablet of theophylline can be developed which when coated with the polymers a lag phase of 2 hrs was achievable followed by a surge release.

Key Words: Theophylline, Chrono Modulated Drug Delivery, Asthma.

INTRODUCTION

The role of circadian rhythms in the pathogenesis and treatment of asthma indicates that airway resistance increases progressively at night in asthmatic patients (Martin et al., 1998). Because bronco constriction and exacerbation of symptoms vary on circadian fashion, asthma is well suited for chronotherapy. Chronotherapy of asthma has been extensively studied (Arkinstall, 1988; Goldenheim et al., 1987). The symptoms of asthma worsen during midnight and early morning hours for such diseases, an initial lag phase of release for 3-5 hrs and later a rapid release have to be considered. With the documentation of nocturnal asthma, investigations have focused on effective therapies to treat nocturnal asthma. Previous studies have used various agents such as sustained released aminophylline (Barnes et al., 1982), slow-release salbutamol (Fairfax et al., 1980), and slow-release terbutaline (Postma et al., 1986). The major objective of chronopharmaceutics is to deliver the drug in higher concentrations during the time of greatest need and in lesser concentrations when the need is less to minimize unnecessary side effects. Examples of ChrDDS on the market include compounds such as theophylline (Uniphyll), famotidine (Pepcid), simvastatin (Zocor), COER-Verapamil (Covera-HS, Verelan PM), diltiazem (Cardizem LA) and propranolol (Inna Pran XL). Several chronopharmaceutical technologies are adopted to deal with chronotherapy issues. The key technologies include CONTIN®, OROS®, CODAS®, CEFORM®, DIFFUCAPS® AND TIMERx, etc (BI-Botti et al., 2004). We in this investigation aim at developing an oral delivery system with an initial lag phase (LP) by coating the tablet with release retarding polymers, followed by 'surge' release phase (SR). We propose to achieve 'surge' release by CO₂ gas pressure generated by effervescence composition, which normally contains an organic acid and bicarbonate. We intend to achieve 'surge' release tablets by effervescence triggered gas pressure and lag phase in release by coating the tablet with release retarding polymers.

EXPERIMENTAL**Materials**

Theophylline and sodium starch glycolate were gift sample from Dynamed Pharmaceuticals P.Ltd., Hyderabad. Eudragit RS-100 was a gift sample from Microlabs, Bangalore, Cellulose acetate phthalate(CAP) and Hydroxypropyl methyl cellulose 30 Cps (HPMC) were gift samples from

Dr. Reddy's Laboratories, Hyderabad. Polyvinyl pyrrolidone K30 (PVP) was a gift sample from Acto Pharmaceuticals, Wgl. all other chemicals were reagent grade.

Preparation of Theophylline Effervescent Tablets

Rapidly releasing theophylline effervescent tablets were prepared by using the formula shown in Table 1. Each tablet of average weight 300mg contains 100mg of theophylline.

Tablets were prepared by conventional non-aqueous wet granulation method using 5% PVP as binder in isoproponol. The tablet granulations were compressed into tablets to a hardness of 4 – 5.5 kg/cm² on a 16 station tablet machine

Table: 1 Formula of theophylline effervescent tablets

Theophylline	340G
Sodium bicarbonate	212G
Tartaric acid	112G
Citric acid	76G
Sodium starch glycolate	50G
Lactose	190G
Talc	10G
Magnesium stearate	10G

Estimation of Theophylline

An U.V. spectrophotometric method based on the measurement of absorption at 272 nm in a phosphate buffer of pH 7.4 was used for the estimation of theophylline. The method was validated for linearity, accuracy, precision and interference.

Evaluation of uncoated tablets

Hardness of the tablets was tested using a Monsanto hardness tester. Friability of the tablets was determined in a Roche friabilator. Theophylline content of the tablets was estimated by the spectrophotometric (Elico SL 159) method as described above. Disintegration time of the tablets was determined using a Thermonic tablet disintegration test machine using distilled water as fluid. Results are shown in Table 2.

Coating of effervescent tablets

Eudragit RS-100 (2, 4, 6, 8 %w/v) containing 10% PEG-400 as plasticizer was dissolved in dichloromethane. Similarly solutions containing RS-100 (6%) and HPMC in the proportions of 5, 7.5 and 10% of weight of polymer were prepared using dichloromethane and isopropanol (3:1) mixture. The coating solution of cellulose acetate phthalate (5% w/w) containing 10% castor oil as plasticizer was prepared by dissolving in acetone.

Tablets in lots of 300gm were either coated with plain Eudragit RS-100 or RS-100 containing varying amounts of HPMC till the tablets has gained weights upto 2, 4, 6 or 8% due to film deposit. Finally tablets coated with plain Eudragit or Eudragit + HPMC were further coated with CAP solution till they gained 5% weight due to film deposit. Various lots of tablets such as Eudragit, Eudragit + HPMC or Eudragit + HPMC over coated with CAP were cured by drying them at 50°C for overnight. In case of all coatings, always a tablet charge of 300gm was used. Coating solution was sprayed at a rate of 2ml/min and spray cycle was monitored with spraying for 10 seconds and non-spraying phase of 5 seconds, while coating pan was rotated at a speed of 25rpm and during entire coating period warm air (40°C ± 3) was continuously supplied.

Dissolution testing of tablets

Profiles of the tablets were obtained using USP dissolution test apparatus (Lab India 8 station) with a paddle stirrer. Tablet was placed in the dissolution vessel and stirrer was rotated at 100rpm. The dissolution of the tablets which are not enteric coated was carried out in 7.4 pH phosphate buffer medium. However for the enteric coated tablets dissolution for the first 3 hours was carried out using 1.12 pH buffer followed by phosphate buffer of 7.4. Samples (5 ml) were withdrawn at preset time intervals, filtered via 0.2μ membrane and filtered samples were analyzed for theophylline

using UV-spectrophotometer at 272 nm. The sample of dissolution fluid withdrawn at each time was replaced with fresh fluid. The dissolution experiments were conducted in triplicates.

RESULTS AND DISCUSSION

A rapidly releasing core tablet of theophylline was developed by admixing theophylline with effervescent granules and super disintegrants. The average values of theophylline content, hardness, friability and disintegration time were given in Table 2. The pattern of release of theophylline from such a tablet is shown in Fig.1 About 75% of theophylline is released in 15 minutes and 100% in 45 minutes.

Table 2 Characteristics of uncoated effervescent theophylline tablets

Assay of tablets (%)	Friability	D.T. in minutes	Weight in Variation	Hardness (Kg/cm. ²)
99.2	0.19	2.5 ± 0.6	0.18	4.5

These effervescent tablets of theophylline were coated with Eudragit RS 100. Such a coating retarded the release gradually with increase in the concentration RS-100 (Fig.2). Our earlier experimentation revealed superior impervious film forming tendency of RS-100 over RL-100. Hence RS-100 was chosen in these experiments. The applied films were highly impervious, and have not allowed 100% release even after 24 hours. To improvise the permeability characteristics of RS-100 films, we have incorporated HPMC in films to create hydration channels in the films. With increase in HPMC concentration in the film release improved dramatically and over 60-80% release was achieved within 4hours (Fig. 3).

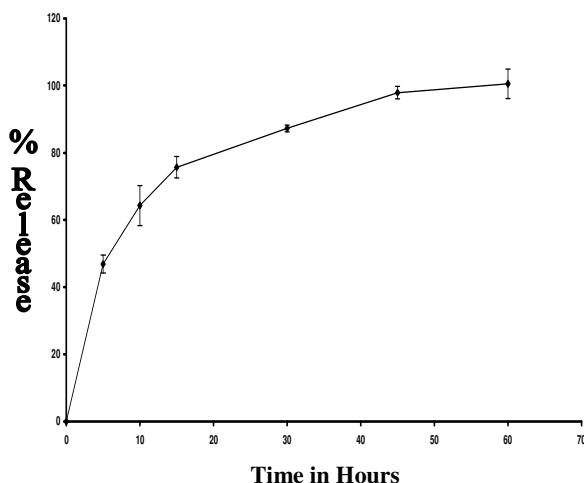


Fig 1: Release profile of effervescent theophylline tablet.

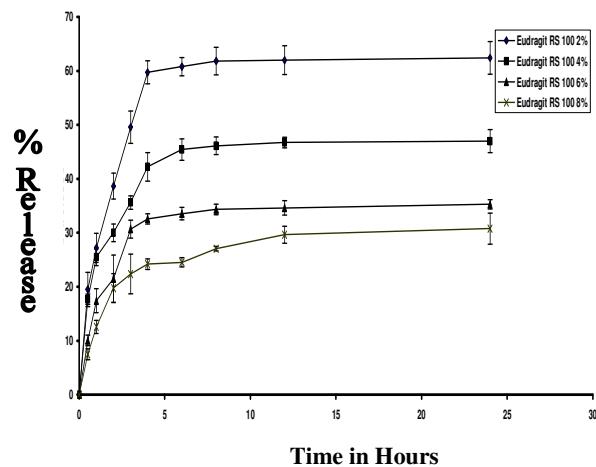


Fig 2: Release profiles of theophylline effervescent tablets on coating with various concentrations of Eudragit RS 100.

In accordance with chronotherapeutic model for nocturnal asthma, an initial lag phase of 3-4 hours is necessary where drug release should be minimal or absent. To achieve this, EV core tablets of theophylline were coated with films of Eudragit RS 100 with HPMC and were further coated with an enteric polymer (cellulose acetate phthalate). This coat has enabled us to achieve definite non-release lag phase for 2 hours. But irrespective of HPMC concentration, lag phase remained constant at 2 hours. However the post lag phase release rate of theophylline significantly differed with HPMC concentration in the films. The post lag phase release rate increased with increase in HPMC concentration. At 10% HPMC, about 80% of theophylline was released after lag phase, within 1½h. At 1h it was 60% (Fig.4).

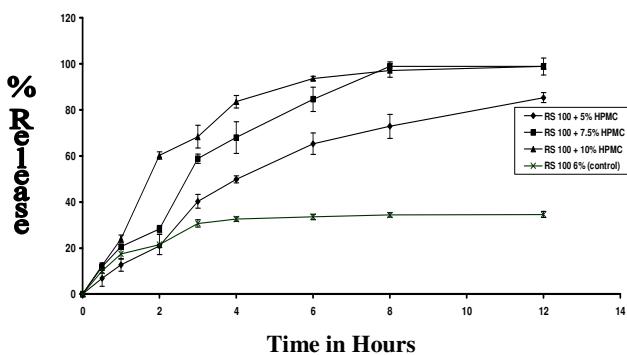


Fig 3 Release profiles of effervescent theophylline tablets on coating with 6% Eudragit RS 100 containing various concentrations of HPMC.

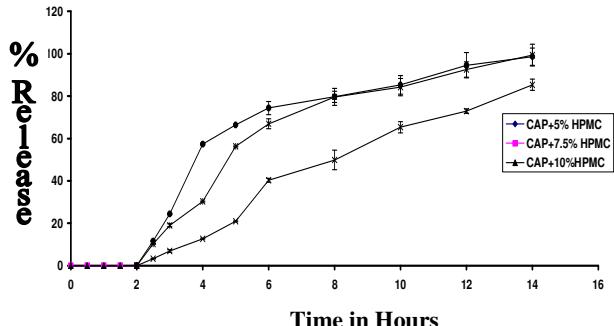


Fig 4: Release profiles of effervescent tablets primarily coated with RS 100 with different concentrations and finally over coated with CAP.

CONCLUSIONS

These results point out that 10% HPMC contained in Eudragit RS 100 films, if coated with CAP as an over coat one, gives rise to optimal lag phase of 2 hours and thereafter a 'surge' release of theophylline. Such a delivery system may be worth evaluating for chronotherapeutic intervention of nocturnal asthma.

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