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DEVELOPMENT AND COMPARATIVE EVALUATION OF THEOPHYLLINE LOADED EXTENDED RELEASE CAPSULE

Mehmet Ali Ege, Tamer Güneri

Ege University, Faculty of Pharmacy, Department of Pharmaceutical Technology, 35100, Izmir, Turkey

***Corresponding author e-mail:** mehmet.ali.ege@ege.edu.tr

Abstract

The aim of the present study was to develop a new theophylline hard gelatin capsule drug delivery formulation. The formulation have been prepared to enhance its dissolution which could provide better oral absorption of theophylline. Therefore, the effects of the component nature and their proportion in the release rate were investigated. Extended release capsules of theophylline were prepared by physical mixing using HPMC and cellulose acetate phthalate (CAP) at various drug-polymer ratios. Hydroxy propyl methyl cellulose (HPMC-E50) ratio was changed the release profile of theophyline. The optimum CAP % was selected as 75 % according to in vitro release studies. Flow properties of the F8 physical mixtures were evaluated by calculation of the Carr's index, angle of repose and Hausner ratio.The results of the study indicate that new extended release hard gelatin capsules can be promising alternative for the other oral formulations of theophylline.

Keywords: Theophylline, drug release, kinetic evaluation, hard gelatin capsule, stability

Introduction

It is now recognized that exacerbation frequency is an important outcome in chronic obstructive pulmonary disease (COPD) as patients prone to frequent exacerbations have impaired health status, reduced physical activity, increased lower airway bacterial colonization and a faster decline in lung function[1,2].COPD is a major cause of chronic morbidity and mortality throughout the world. Many people suffer from this disease for years and die prematurely of it or its complications [3]. Xanthines such as theophylline have been used in the treatment of respiratory diseases such as asthma and COPD since the 1930s although their popularity has declined due to the introduction of other classes of drugs, particularly the inhaled long acting b2-adrenoceptor agonists and glucocorticosteroids[4]. Theophylline is a good candidate to be encapsulated in slow-release capsules, since the treatment of obstructive chronic pulmonary disease and night crisis depend on keeping serious levels of the drug constant [5,6]. Theophylline (Figure 1) has been show to inhibit the activity of a cyclic 3', 5' nucleotide phosphodiesterase with a Ki of 100 mM and this activity has been suggested to contribute to its ability to promote suppressor cell activity in lymphocytes and its beneficial anti-inflammatory actions in patients with asthma and COPD [7-9].

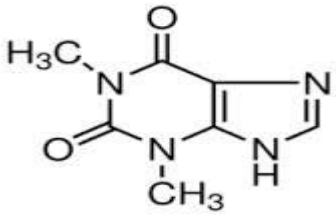

Figure 1: Molecular structure of theophylline

Oral route of administration has been received more attention in the pharmaceutical field and it is one of the most commonly-used routes for drug administration because of the more flexibility in the designing of dosage form than drug delivery design for other routes[10]. In addition, it's non-invasive nature and the fact that it avoids the pain and discomfort associated with injections, as well as eliminating contamination [11,12].

Solid dosage forms are important for oral administration because their stability is pretty good

their application is easy and they have a high-metering accuracy. Drug–polymer solid dispersion can improve the dissolution rate of drugs and lead to higher bioavailability [13]. In this way, a capsule formulation often is in the industry the first dosage form for early clinical studies. Furthermore, capsules improve drug stability because the content is tightly enclosed by the capsule shell and thus protected from oxygen, humidity and light [14,15].Moreover, hard gelatin capsules are effective containers for various of fill materials ranging from solids to semi-solids. Furthermore solubility and dissolution behavior of a drug is one of the key determinants of its oral bioability. In latest years, the number of poorly soluble drug candidates has improved enormously. The formulation of poorly soluble drugs for oral delivery offers a challenge to the formulation researchers[16]. Based on this information; USP has some restrictions on extended release theophylline preparations relating the *in vitro* drug release about time.

The purpose of the present study was to develop a new extended release capsules of theophylline for oral delivery treatment of COPD. Hard gelatin capsules were contained cellulose acetate phthalate (CAP) and hydroxy propyl methyl cellulose (HPMC-E50)in order to increase the theophylline oral bioavailability. The physico-chemical characterizations, in-vitro release of these formulations were evaluated.

MATERIALS AND METHODS

Materials

Theophylline anhydrous was supplied by Dolder, Switzerland.Cellulose acetate phthalate(CAP) was obtained Röhm Pharma,USA. Hydroxy propyl methyl cellulose (E50) was kindly donated by Colorcon, USA. All other chemicals and solvents were of analytical grade. Ultrapure water was obtained from Sartorius 61316 pro VF, Germany.

Preparation of Extended Release Capsules

Physical Mixture

A series of extended release capsules of theophylline were prepared fixed concentration of theophylline (10 g) and varying concentrations of HPMC (E50) were mixed and then CAP solution (CAP 15 %) was added and mixed.The mixture was dried at 50 °C in a oven. The same process was repeated 4 times to obtain 60% CAP concentration. The above procedure was repeated 5 times to obtain 75% CAP concentration and last repeated six times matrix granules to obtain 90% CAP concentration. The composition of the theophyline loaded capsules were shown in Table 1. Sieving the granules are combined in three different particle size in sieve systems separated.The resultant granules were passed through various sieves. The prepared mixtures were sealed and stored in desiccator until used for further studies. All samples, which were used in dissolution studies, were analysed for drug content. Before the dissolution studies, these powders were hand filled into zero-size hard gelatin capsules using capsule filling apparatus.

In vitro Drug Release Studies

In-vitro drug release experiments were performed over 12 h. The dissolution rates of the extended release capsules of theophyline were measured by using USP XXII apparatus I (rotating pallet). The system was held at body temperature (37 ± 2 °C) and stirred continuously with magnetic stirrer at 50 rpm. pH 1.2 gastric medium and artificial intestinal medium pH 6.8 solutions were used as the release media. Samples of 2 mL were withdrawn at specified time intervals and analyzed spectrophotometerically at 272 nm using Shimadzu 160-A spectrometer, the samples withdrawn were replaced by fresh buffer solution. The samples were collected at every hour until 12 hour. Each dissolution study was carried out in six times and mean values were calculated. Gastric medium consisted of 8.3 mL HCl (37%) in 1 L of ultrapure water. The pH value of the medium was checked and adjusted as pH 1.2 ± 0.05.Artificial intestinal medium consisted of KH_2PO4 (6.805 g), NaOH (0.896 g) in 1 L of ultrapure water. The pH value of the dissolution medium was checked and adjusted as pH 6.8 ± 0.05.

Determination of flow properties of the physical mixtures

Carr's index: A pre-weighed quantity of dry powder was diposed in a measured 10 mL cylinder. The apparent volume occupied by the powder was then detected before and after the application of 1250 taps to the cylinder using a tap density tester (Varian, Inc. USA).

Carr's index formulas are calculated according to [17,18].

$$Carr's\ index = \frac{Tapped\ density - bulk\ density}{Tapped\ density} x100 \quad \text{Eq. (1)}$$

Angle of repose: The angle of repose can be defined as the constant three dimensional angle measured relative to the horizontal base, assumed by a cone-like pile of material formed when the powder is passed through a funnel-like container [17,19-21].

Angle of repose of the powder material was calculated by using the formula Eq. (2)

$$\theta = \tan\frac{h}{r}$$ .....Eq. (2)

where, h = height of the pile, r = radius.

Hausner ratio: The process is to determine the unsettled apparent volume, V_0 and the final tap volume,
V_f, of the powder tapping the material until no further volume changes happen. The Hausner ratio was calculated accoding to Eq. (3) [17].

$$Hausner\ ratio = \frac{V_0}{V_f}$$ --------Eq. (3)

Kinetic evaluation and determination of release mechanism: Kinetic evaluations of theophylline release from formulations were estimated using a computer based kinetic programme [22]. Zero-order, First-order and Higuchi kinetic models were used for evaluation and determination of the release mechanism [23,24].

Determination of theophylline release from capsules were estimated Eq. (4) [25].
Mt / M∞ = Ktn--------Eq. (4)
M_t/M_∞; the fraction of drug released, t; released time, k; release rate constant and n is the release exponent. The n value is used to characterize different release mechanisms as given in Table 2[26].

Statistical Analysis: Statistical analysis were conducted by one-way ANOVA using target significance levels of 0.05 ($P<0.05$).

RESULTS AND DISCUSSION

Drug Release Studies

In vitro drug release was determined using the USP pallet method. Release profiles of the extended release capsules (F1-F9) containing theophyllinewere showed in Figure 2, Figure 3 and Figure 4. In the release studies theophylline capsules did not show a burst release in stomach environment for 4 h.

The additional HPMC (E-50) ratio change the release profile. Highest CAP ratio of formulations was determined to be better release than other formulations. In addition when CAP (%) was compared the optimum % was selected as 75 %. These findings suggest that formulation F8 capsule could be good candidates for oral sustained drug delivery systems, especially for poorly soluble drugs as theophylline. Lin et al. developed tablets containing cellulose acetate phthalate as an additive or enteric-coating material. The developed granules show release patterns that are sustained[27]. It can be concluded that CAP was most effective agent for slowed release of drugs. In addition CAP was used common for oral formulations [27,28].

Determination of flow properties of the physical mixtures: Flow properties of F8theophylline capsule formulation are shown in Table 3.The flow propertie of F8 formulation was determined optimum porosity, carr's index and hausner ratio for oral delivery of theophylline.

Kinetic evaluation: The mathematical parameters of F8 formulation were presented in Table 4. The model that gave higher 'r' value was considered as best fit model.According to the analysis of all mathematical models, it is clearly seen that Higuchi square-root of time model show obviously a better fit for theophylline capsules [29](Table 4). The release of theophylline followed Higuchi kinetics as its correlation coefficient (r=0.9979) predominated over zero-order kinetics (r=0.9846). The Higuchi square root equation describes that the rate of drug release from systems is related to the rate of drug diffusion [24,30]. This data confirms that the theophylline capsule formulations have been generated in a Higuchian diffusion fashion, which is statistically proven by the release curves in comparison with their correlation coefficients. The "n" value of F8 formulation has been found to be more than 1. This result indicates that the drug release from the polymer matrix formulations suggests super Case II transport, that is the mechanism of drug release has been administered by both diffusion and polymer relaxation [31].

CONCLUSION

In this study theophylline loaded capsules were successfully prepared by granulation, using HPMC (E-50) and CAP together. Taken together, in the present study, the effect of component nature and proportion on the release rate and mechanism were investigated for theophylline extended release capsules. HPMC (E-50) ratio was changed the release profile of theophyline. The highest CAP ratio of capsules was determined to be better release than other formulations. In addition when CAP (%) was compared the optimum % was selected as 75 %. F8 capsule could be good candidates for oral sustained drug delivery systems, especially for poorly soluble drugs as theophylline. The flow propertie of F8 formulation was determined optimum porosity, carr's index and hausner ratio for oral delivery of theophylline. Thus, the findings of this study revealed suitability of F8 to improve performance of the drug in the treatment of chronic obstructive pulmonary disease. The presented delivery system could provide a new promising strategy for sustained release.

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Declaration of Interest: The authors declare no conflict of interest in the research paper.

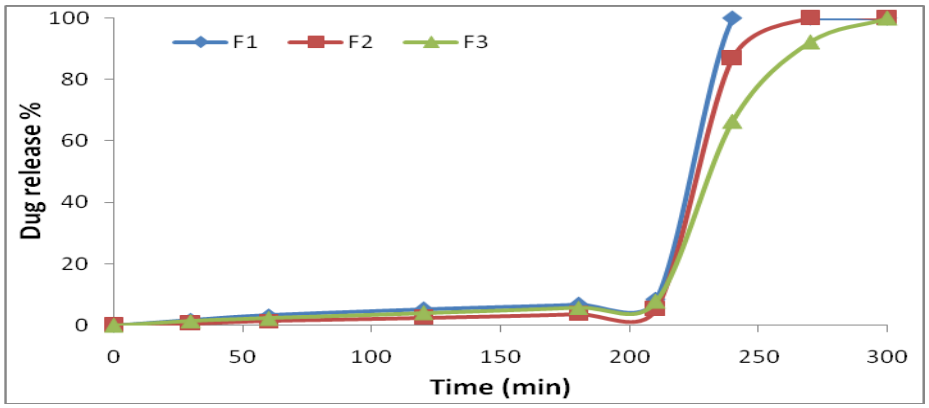

Figure 2: In vitro release of theophylline capsules (F1, F2 and F3)

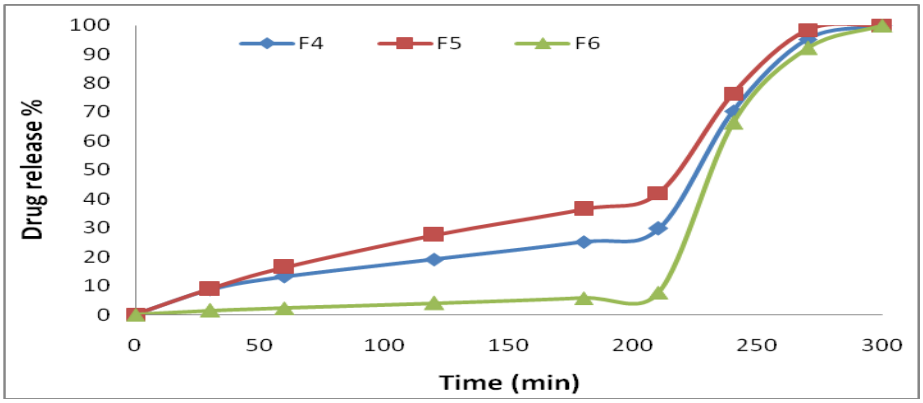

Figure 3: In vitro release of theophylline capsules (F4, F5 and F6)

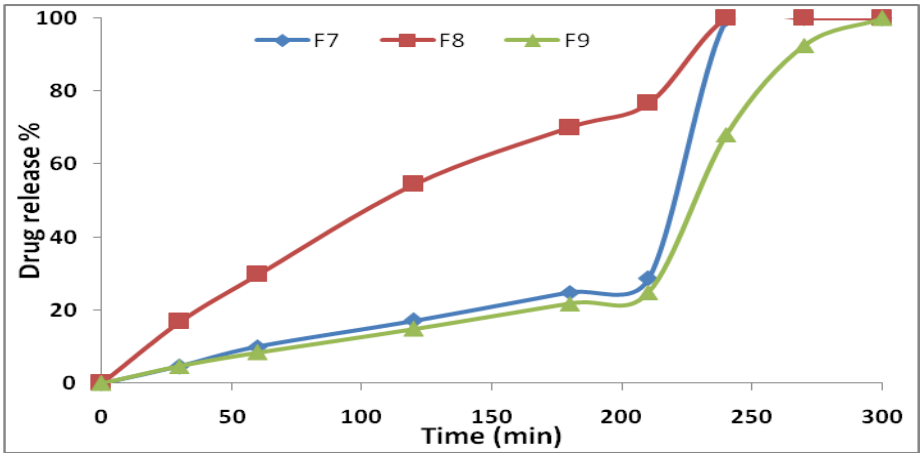

Figure 4: In vitro release of theophylline capsules (F7, F8 and F9)

Table 1: Capsule formulations of Theophylline

	Theophylline: HPMC ratio	CAP (%)	Theophylline (g)	HPMC E_{50} (g)
F1	**1:0**	60	10	0
F2		75	10	0
F3		90	10	0
F4	**1:0.25**	60	10	2.5
F5		75	10	2.5
F6		90	10	2.5
F7	**1:0.5**	60	10	5.0
F8		75	10	5.0
F9		90	10	5.0

Table 2: Diffusion exponent and solute release mechanism for cylindrical shape

Diffusion exponent (n)	Diffusion mechanism
0.45	Fickian diffusion
0.45 < n < 0.89	Anomalous (non-Fickian) diffusion
0.89	Case-II transport
n > 0.89	Super case-II transport

Table 3: Flow properties of extend release theophylline capsule (F8)

parameters	*F8capsule*
Porozity (g/ml)	1.042
Angle of Repose	17.89
Carr's Index	%9.288
Hausner Ratio	1.093

Table 4: Mathematical models of F8 capsule of theophylline obtained after fitting the drug release data.

Kinetic Model	First Order		Higuchi		Zero Order		Peppas	
parameters	**r2**	**K**	**r2**	**K**	**r2**	**K**	**r2**	**n**
F8	0.9974	6.6539	0.9979	5.5227	0.9846	496.219	0.7292	3.3455

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