Development and *in vitro* Evaluation of Theophylline Loaded Matrix Tablets Prepared with Direct Compression

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ABSTRACT
The objectives of the present study are to develop novel sustained release matrix tablets of theophylline and to evaluate release properties and kinetic behaviour of these tablets. The formulations have been prepared in order to improve their dissolution properties in terms of providing better oral absorption of theophylline. Therefore, the effects of the components’ nature and their proportion in the release rate were investigated. Theophylline loaded tablets were prepared with direct compression using Compritol® ATO 33 and Hydroxypropyl methylcellulose (HPMC E50) with different amounts and then they were evaluated for their *in vitro* drug release profiles. According the evaluation of drug release profiles, it has seen that Compritol® ATO 33 and HPMC E50 ratio changed the release profile of theophylline. The dissolution of tablets was determined by using USP XXIII dissolution testing apparatus II. Matrix tablets were carried out in pH 4.5 phosphate buffer, as dissolution medium, for 8 h. Te-3, Te-4 and Te-7 formulations ensure the criteria of The United States Pharmacopeia XXIII for theophylline extended release capsules (Test 2 criteria, apparatus II). The release data fitted to various mathematical models such as, zero order, first order, Higuchi, Hixson Crowell and Korsmeyer-Peppas for the evaluation of the kinetics and mechanism of the drug release. The release mechanism of matrix tablets followed first order release kinetics. The results of the study indicate that new matrix tablets can be promising alternative for the other oral formulations of theophylline.

Key words: Theophylline, Drug release, Kinetic evaluation, Tablet, Direct compression.

INTRODUCTION
Chronic obstructive pulmonary disease (COPD) has become an increasingly important cause of morbidity and mortality, pathological features of which are pulmonary inflammation and irreversible airflow obstruction. Furthermore, it is predicted that COPD will become the third most common cause of death and the fifth most common cause of disability in the world by the year 2020. COPD is characterized by airflow obstruction and various symptoms such as chronic cough, expectoration, exertional dyspnea and wheezing.

Although xanthines such as theophylline have been used in the treatment of respiratory diseases such as asthma and COPD since the 1930s, they declined in popularity due to the introduction of other classes of drugs, particularly the inhaled long acting b2-adrenoceptor agonists and glucocorticosteroids. Theophylline is a methylxanthine type of drug which is clinically used as bronchodilator generally in form of oral formulations. Due to its action as non-selective inhibitor of cyclic nucleotide phosphodiesterases causing relaxation of the airway smooth muscle cells, it is used for the treatment of asthma and COPD. In addition, theophylline (Figure 1) has shown inhibiting the activity of a cyclic 3’, 5’ nucleotide phosphodiesterase with a Ki of 100 mM and it has been suggested that this activity can contribute to its ability of promoting suppressor cell activity in lymphocytes and...
its beneficial anti-inflammatory actions in patients with asthma and COPD.7
Oral drug administration has been the predominant route for drug delivery for years. It is known as the most popular route of drug administration due to the fact that the gastrointestinal physiology offers more flexibility in designing dosage forms than most of the other routes.8,9 A major challenge for drug development is to produce harmless and effective drugs, therefore properties of drugs and the way in which they are delivered must be optimized.10 A controlled release drug delivery system delivers the drug locally or systemically at a predetermined rate for a specified period of time.11 The goal of such systems is to provide desirable delivery profiles that can achieve therapeutic plasma levels.8
Matrix type tablet formulations are prepared from either swellable hydrophilic polymers or non-swellable lipophilic excipients, like waxes and lipids. The use of lipid and wax matrix seems to have particular advantages due to their chemical inertness against other materials, better characterization of lipidic excipients and formulation versatility and the choices of different drug delivery systems provided by them.12 Recently, much attention has been paid to the usage of Gelucires as carriers in formulations of controlled-release drug delivery systems. In particular, Compritol or glyceryl behenate can be used as glyceride base for the preparation of controlled-release dosage forms.13
Theophylline is a methyl xanthine derivative with a narrow therapeutic index, in other words, there is a very close association among the plasma concentrations of this drug and its toxic and therapeutic effects.14 Thus the purpose of the present study was to develop new sustained release tablets of theophylline meeting the USP Drug Release Test 2 criteria for theophylline extended release capsules15 for oral delivery treatment of COPD. The other aim was to evaluate the drug release mechanisms of these tablets. For this purpose, tablets were prepared with Compritol (ATO 33) and hydroxypropyl methylcellulose (HPMC-E50) in order to improve performance of the drug in the treatment of chronic obstructive pulmonary disease. Moreover, the in vitro release patterns and kinetic evaluations of theophylline from the formulated tablets were studied over the sustained release period.

MATERIALS AND METHODS

Materials
Theophylline anhydrous was supplied by Dolder, Switzerland. Compritol (ATO 33) was a kind gift from Gattefosse, France. Aerosil was a kind gift from Mustafa Nevzat İlgaş San. A.S., Turkey. Avicel pH 102 was supplied by FMC Biopolymer, USA. HPMC-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 Matrix Tablets
Theophylline loaded tablets were prepared with direct compression. Composition of hydrophobic matrix is listed in Table 1. Tablets’ ingredients (theophylline, Compritol® ATO 33 and HPMC E50) were accurately weighed (Sartorius Basic, Germany) as mentioned in Table 1. These powders were then passed through 20 mesh sieve and homogeneously mixed. Then Avicel pH 102 was weighed and mixed into the powder. Finally aerosol was added and again mixed for 5 m so that particle surface was coated evenly by lubricant. Then the blend was compressed (2 ton roll pressure) into tablets using 8 mm diameter flat-faced punch.

In vitro Dissolution Studies
The procedure was determined for using USP XXIII dissolution testing apparatus II (paddle method). Release rate of all designed formulations were studied up to 8 h. at a paddle speed of 75 rpm, in 900 mL of pH 4.5 phosphate buffer solutions at 37 ± 0.5°C. The samples were passed through a 0.45-μm membrane filter and diluted to a suitable concentration with phosphate buffer. The theophylline concentration of each sample (n=6) was spectrophotometrically determined UV-VIS Spectrophotometer (Schmadowu 160-A-Japan).

Standard theophylline (20 mg) was accurately weighed and transferred into a 10 mL volumetric flask. It was dissolved properly and diluted up to the mark with phosphate buffer (pH 4.5). This solution was used as working standard solution. Suitable dilution was made from this solution. The absorbance of the solutions containing theophylline at 10 μg/ml was determined in the UV range 190-450 nm by using an appropriate blank. The λmax was found as 272 nm. At these wave-length maxima, calibration curve was drawn by plotting graph between absorbance and concentrations. As per the ICH guidelines, accuracy, precision and linearity of the calibration curve were determined.16,17 For linear response measurement, the least squares method was applied. The statistical analysis was calculated by ANOVA. Amounts of 10 and 30 μg/ml of theophylline standard solution were added into pre-analysed and 30 μg/ml samples and absorbance were measured and the recovery was calculated.
Kinetic evaluation and determination of release mechanism

Kinetic evaluations of theophylline release from matrix tablets were estimated using a computer based kinetic programme.\textsuperscript{18} Zero-order, firstorder, Higuchi, Hixson Crowell and Korsmeyer-Peppas kinetic models were used for the evaluation and determination of the release mechanism.\textsuperscript{19-22}

Statistical Analysis

Statistical analyses were conducted by one-way ANOVA using target significance levels of 0.05 (P<0.05).

RESULTS AND DISCUSSION

Recent pharmaceutical studies have focused on controlled drug delivery which has an advantage over conventional approaches. Adequate controlled plasma drug levels, reduced side effects, as well as better patient compliance are some of the benefits that these systems may offer.\textsuperscript{23} Thus matrix tablets were prepared in order to obtain controlled release of theophylline.

Tablet manufacturing by direct compression has steadily increased over the years. It offers advantages over the other preparation processes for tablets and provides high efficiency.\textsuperscript{24} This direct compression technique is more economic, reducing the cycle time and straightforward in terms of good manufacturing practice requirements.\textsuperscript{25} Therefore direct compression was selected as the preparation method for theophylline loaded matrix tablets. They were prepared successfully with direct compression technique. Compritol was selected as the tablet ingredient with glyceride base for matrix tablet preparation.

Different researches have highlighted the feasibility of using Compritol ATO as a lubricant or coating agent for oral solid dosage formulations. It has also been explored as a matrix-forming agent for controlling drug release. Moreover it has acceptable regulatory, common use and safety profiles for oral drug delivery.\textsuperscript{26-27} HPMC E-50, a semisynthetic derivative of cellulose, is a swellable and hydrophilic polymer. Some researchers have studied on the practice of HPMC as the retarding polymer to sustain the release of different drugs.\textsuperscript{28-30} In addition, it is very appropriate material to use in controlled release matrix tablets, as it is nontoxic and easy to handle.\textsuperscript{31-32}

The values of standard deviation and coefficient of variation were acceptably low. The percentage of recovery range from 99% to 101% was indicating the accuracy of method. From the proposed method, it was found that theophylline obeys linearity within the concentration range of 1-20 μg/ml. It was found that the % RSD is less than 2, which indicates that the method is highly reproducible. In addition, the correlation coefficient (r\textsuperscript{2}) of determination was found as 0.999 which is an indication of linearity.

In vitro release studies were carried out for all the formulations as per USP XXIII tablet dissolution tester employing rotating paddle at 75 rpm using 900 mL of pH 4.5 phosphate buffer medium for 8 h. Figure 2 shows the effect of polymer amount on theophylline release from the tablets (pH 4.5, 37°C) (n=4). The primary aim of the present study was to prepare controlled release-matrix tablets meeting the USP Drug Release Test 2 criteria for theophylline extended release capsules defined as follows: the range of dissolved theophylline is between 10-30% at 1 h, 30-55% at 2 h, 55-80% at 4 h and not less than 80% at 8 h.\textsuperscript{15} When the dissolution results for theophylline tablets were compared with USP XXIII Test 2 criteria, it was observed that theophylline was released too rapidly from Te-1 and Te-2
In addition, Te-5 and Te-6 tablets were released too slowly so these formulations met the upper criteria laid down in the USP (Figure 2). However, when the dissolution results for Te-3, Te-4 and Te-7 were compared to this criteria it was observed that the release profiles for these tablets almost met it (Figure 2). According to the results of the repeated ANOVA measurements, the percentages of drugs dissolved were not found to be significantly different for each time period or between formulations (p>0.005). When Compritol® ATO 33 and HPMC E-50 were used together for preparation matrix tablets; tablets including those excipients met the USP XXIII Test 2 criteria for theophylline extended release capsules. It can be seen clearly that, Compritol ATO 33, and HPMC E-50 ratio has changed the release profile of theophylline.

The drug release mechanism was determined by fitting the in vitro release profile in various release kinetic models and the values of release exponent (n), kinetic constant (K), residual value (Res) and regression coefficient ($r^2$) are shown in Table 2. Zero order, first order, Higuchi, Hixson Crowell and Korsmeyer-Peppas are the major models to identify the drug release from sustained release formulations and criteria of selecting the most appropriate model was based on the its goodness of fitting.\textsuperscript{14,33-36}

(Table 2) displays the release rate constants (K) calculated through the above-mentioned mathematical release models and the determination coefficient of the observed release data and the simulation profiles of the Te-3, Te-4 and Te-7 tablets. The release of theophylline followed first order kinetics as its correlation coefficient ($r^2$=0.9839-0.9986) pre-dominated over Higuchi, zero order and Hixson Crowell kinetics (Table 2). Therefore, predominant drug release mechanism is controlled release.

First order demonstrates time vs. log cumulative percentage drug remaining.\textsuperscript{33-36} In the present study, it was found that first order kinetics fitted to all formulations (Te-3, T-4 and Te-7). Two factors, however, diminish the applicability of first order equation to matrix systems. This model fails to explain the influence of swelling of...
the matrix upon hydration and gradual erosion of the matrix. Therefore, the in vitro release data were also fitted to the well-known exponential Korsmeyer-Peppas equation and value of release exponent (n) explains the release mechanism of the drug from the tablets. The observed ‘n’ values for release profiles of formulation Te-3, Te-4 and Te-7 were fall in between 0.6 and 0.7 indicated anomalous release behavior coupled with diffusion and erosion.

Hossain et al. have prepared indapamide loaded matrix tablet by direct compression method. The authors were evaluated the release mechanisms by zero order, Higuchi, first order and Korsmeyer-Peppas equations. They found that the drug release of indapamide loaded matrix tablet followed first order kinetic model ($r^2=0.99$) and they have determined ‘n’ values as ranging from 0.543 to 0.832 according to Korsmeyer-Peppas model.27 Similar to our study the release mechanism of Te-3, T-4 and Te-7 matrix tablets followed first order release kinetics and it was found that the release was a combination of diffusion and erosion. The values of $n (>0.5)$ indicated that the mechanism of drug release could be described as anomalous release mechanism, indicating a diffusion controlled drug release.39 In another study, Murtaza et al. have developed sustained release matrix tablets of tizanidine hydrochloride and they were investigated the dissolution data with kinetic models. They have reported that the release data of tizanidine hydrochloride tablets showed best fit to first order kinetics ($r^2=0.9963-0.9989$). In addition to this they have found that in case of Korsmeyer-Peppas, the developed tablets showed both diffusion and erosion ($n=0.513-0.597$).39

CONCLUSION

In this study theophylline loaded matrix tablets were successfully prepared by direct compression technique, using HPMC (E-50) and Compritol ATO 33. The effect of components’ nature and proportion on the release rate and mechanism were investigated for theophylline extended release tablets. When Compritol ATO 33 and HPMC E50 were used together for preparation matrix tablets, tablets met the USP XXIII Test 2 criteria XXIII for theophylline extended release capsules. Compritol ATO 33 and HPMC E-50 ratio has changed the release profile of theophylline. In the present study, it was found that first order kinetics was fitted to Te-3, Te-4 and Te-7. These tablets could be good candidates for oral sustained drug delivery systems, especially for poorly soluble drugs such as theophylline. Thus, the findings of this study revealed suitability of Te-3, Te-4 and Te-7 for improving the 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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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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PICTORIAL ABSTRACT

SUMMARY

- Theophylline loaded tablets were prepared with direct compression using Compritol® ATO 33 and Hydroxy propyl methyl cellulose (HPMC E50) with different amounts and evaluated for its in-vitro drug release.

- Te-3, Te-4 and Te-7 formulations showed compliance with The United States Pharmacopeia XXIII criteria for theophylline extended release capsules (Test 2 criteria, apparatus II).

- The release data were fitted to various mathematical models such as, zero order, first order, Higuchi, Hixone Crowell and Korsmeyer-Peppas for the evaluation of the kinetics and mechanism of the drug release.

- The results of the study indicate that new matrix tablets can be promising alternative for the other oral formulations of theophylline.

ABBREVIATIONS USED

COPD: Chronic obstructive pulmonary disease;
HPMC-E50: Hydroxy propyl methyl cellulose.

About Authors

Dr. Mehmet Ali Ege: Earned his Ph.D degrees in 2007 at the University of Ege, Faculty of Pharmacy, Department of Pharmaceutical Technology. He has several original research articles in various journals and several poster presentations in international and national congresses. Dr. Ege interested to solid dosage forms such as tablets and capsules for oral applications and in vitro release kinetic evaluations.
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Prof. H. Yesim Karasulu: Earned her Ph.D degrees at the University of Ege, Faculty of Pharmacy, Department of Pharmaceutical Technology. She was promoted to Associate Professor in 2006 and she was appointed as a Professor degree in 2011. Her main research interests are developing micro and nano particulate systems for oral applications, colloidal drug delivery systems such as microemulsions, SEDDS, in vitro release kinetics evaluation and cell culture studies.

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