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Optimization of Theophylline Delayed Release Dosage Form Using D-Optimal Experimental Design

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ABSRACT

The aim of this study was to prepare a solid dosage form able to release theophylline after a maximum delayed time and at a maximum cumulative amount in 12 hours. To achieve this goal a blend of two polymers with different properties was used along with talc powder and utilizing D-expert statistical software package. The polymer blend consists of Eudragit NE 30D and Eudragit RL 30D-55. Solid precipitates composed from polymer blend and talc powder and containing a fixed amount of theophylline were prepared using spray dryer. The prepared solid precipitates were compressed into tablets and the dissolution profile of each formulation was investigated. Delayed time was observed in term of time required to release 10 % of the labeled theophylline. Delay time was ranged from 2.14 to 4.1 hour while, percent of theophylline released in 12 hours ranged from 84.06 to 97.94 %. After that optimization was performed to prepare a dosage form with a desired properties in term of maximum delayed time and maximum percent theophylline released in 12 hours. The optimized solid precipitates as generated from the statistical software package was formulated and investigated. The optimized formulation was able to delay the time of theophylline release to 3.24 hour and release 93.64 % of the incorporated theophylline in 12 hours. Solid dispersion technique in conjunction with statistical design was shown to be very efficient for the optimization of both the delayed time and cumulative amount of drug released in 12 hours.

Keywords: D-Optimal experimental design, optimization, Theophylline, Delayed release

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INTRODUCTION

Chronic bronchial asthma disease, shows distinct daily fluctuations that are in conformity with the sleep activity cycles or circadian rhythms[1-5]. Dethlefsen and Repges[6], for example, reported a sharp increase in the incidence of asthmatic attacks at the early morning hours, with a peak occurring at 04:00 am. Therefore, a therapeutic scheme that gives attention to diurnal variation in the occurrence of asthmatic symptoms is expected to be more effective. Drug delivery systems that tailor drug release to the circadian pattern of diseases are often referred to as sigmoidal,or delayed release dosage forms[7]. Delayed release dosage forms can be classified into site-specific and time controlled systems. Drug release from site-specific systems relies on the gastrointestinal environment such as pH and/or presence of enzymes which prompt drug release. On the other hand, drug release from a time-controlled system, such as a single or multiple unit osmotic pumps, is influenced by the system itself[8-11].These systems, however, require complicated process to be prepared[12].Therefore, attempts were made to prepare simpler sigmoidally released tablet dosage forms by incorporating materials with unique properties that allow for a distinct drug release pattern. One such attempt is demonstrated in the present study. Theophylline is a prescription drug with a long history as an asthma medication. As one of the first long-term bronchodilators, it has been used to treat respiratory disorders such as bronchitis and chronic obstructive pulmonary disease (COPD). In recent years, theophylline had fallen out of favor with some physicians because of concerns about the danger of toxicity from having too much of the drug in the bloodstream. However, new discoveries about the medication's effects on inflammation and immune function related to asthma have renewed interest in theophylline[13]. Theophylline is available in a variety of dosage forms. While extended-release forms of the medication have made it some-what easier to ensure a constant drug plasma level, a treatment based on theophylline controlled-release dosage form would not be optimal[14]. Eudragit® NE-30D: this is available as 30% w/w total solids, neutral ester latex dispersion[15] prepared by emulsion polymerization of monomers. It consists of ethyl acrylate and methyl methacrylate polymers in the ratio of 2:1 and has a molecular weight of 8 x 10^5. Water-insoluble films produced from this latex swell in water and show a medium degree of permeability. The minimum film-forming temperature (MFT) is around 5°C, therefore; a soft flexible film can be formed at room temperature without any plasticizer. This latex is used for sustained release granulation. Eudragit® L-30D-55: this polymer has a molecular weight of 2.5 x 10^5. It is a 30% w/w latex dispersion[15] of methacrylic acid and ethyl acrylate (1:1) prepared by emulsion polymerization. A spray dried form is available as a

redispersible powder under the trade name Eudragit® L-100 55. Films from these dispersions are relatively harder and require plasticization. Due to the presence of carboxylic group, the solubility of Eudragit® L-30D-55 ispH dependent i.e. pH > 5.5. Thus, it isused as gastro-resistant entero-soluble coatings. The Eudragit® polymers have interesting miscibility properties. The mixing of aqueous dispersions isrequired to improve processing, better film properties, and also to optimize drug release. The determination of the best possible composition of a set of conditions that results in an optimally performing product or process is often the main challenge of the pharmaceutical investigator. Determining such a set of conditions is an enormous task practically, optimization can be considered as a search for the result that is satisfactory and at the same time the best possible within a limited study field. Ideally, optimization can be accomplished by the use of expert knowledge or statistical experimental designs. Often, pharmaceutical systems are complex enough to require statistical design-based optimization. Optimization has been extensively used in pharmaceutical product development[16-18], especially in the process of developing a delivery system. The objectives of the present work was to develop a pharmaceutical dosage form that will be able to release theophylline after a delay time of no or minimum amount of the drug. To achieve this goal: i) solid co-precipitate containing polymers with different properties in different ratios along with talc powder was prepared with theophylline and formulated into tablets, ii) characterize the prepared tablets in term of dissolution properties, and iii) optimize the co-precipitate in order to get a tablet formulation with the maximum response.

MATERIALS AND METHOD

The aqueous dispersions of Eudragit® NE 30D [poly(ethylacrylate, methyl methacrylate), and Eudragit® L 30D-55 [poly(methacrylic acid, ethyl acrylate) were obtained from Evonic Industries (Piscataway, NJ). Talc was purchased from Spectrum Quality Products (Gardena, CA). Theophylline was provided from BASF Corp. (Mount Olive, NJ, USA). Sodium hydroxide and sodium tribasic phosphate were purchased from Sigma Chemical Co. (St. Louis, MO). Hydrochloric acid was purchased from EMD Chemicals Inc. (Gibbstown, NJ). Water used in this study was purified by water purification system, Direct-Q5, millipore (USA). All chemicals were used as supplied without further modification. A 14-run, three-factor, two-level D-Optimal mixture design was employed in this study to construct polynomial models in the form:

$$Y = A_o + A_1X_1 + A_2X_2 + A_3X_3 + A_4X_1X_2 + A_5X_2X_3 + A_6X_1X_3 + A_7X_1^2 + A_8X_2^2 + A_9X_3^2 + E$$

where

A_1-A_0 are the coefficients of the respective variables and their interaction terms, and E is an error term. These models were used to describe the effect of three formulation ingredients: Eudragit NE 30D (X_1), Eudragit RL 30D-55 (X_2), and Talc powder (X_3) on the dissolution behavior of the solid precipitates prepared into tablets dosage forms. A summary of the dependent and independent variables that were evaluated in this study and the constraints that were placed on the responses are given in Table 1. The range of each factor was chosen based on preliminary studies. To generate these empirical models, an experimental design was created using the Design-Expert software (v. 5.07; State-Ease, Inc., Minneapolis, MN). In this design (Table 2), 14 different ternary-blends were suggested based on the constrains and limits given in Table 1. These design points represented factorial points (high and low level from the constraints on each factor), centers of edges (points midway between adjacent factorial points), constrains plane centroid points, axial check points, and an overall center point. A schematic representation of the design is given in Figure 1.

Preparation of solid precipitates

The calculated aqueous dispersions of Eudragit® L 30D-55) and Eudragit® NE 30D were diluted with an equal volume of purified water. Eudragit® NE 30D: L 30D-55 dispersions were then blended at different ratios as shown in Table 2. Talc powder was homogenized with a suitable amount of water and added to the polymer blend. Theophylline 2.5 gm was dissolved and added to the polymer mixture. The solid contents for all runs was fixed to be 14.5 gm. The mixture was stirred for 1 hour and fed to spray dryer SD 1500 Lab Spray Dryer (Shanghai Triowin Tech. Co., Ltd, China).

Preparation of tablets

Solid precipitates obtained from spay dryer were compressed into tablets using TA.XT Plus texture analyzer (Texture Technologies Corp., Scarsdale, NY/Stable Micro Systems, Godalming, Surrey, UK). Actually 400 mg of each solid precipitates was filled into the die and compressed at 14 Kg. A representative force-time profile of a tablet compression obtained from texture analyzeris shown in Figure 2.

Dissolution study of solid precipitate tablets

Dissolution studies on a fixed weight of 0.4 g of the solid precipitates that will be compressed into tablets will be performed in triplicates using a USP type II (paddle) dissolution apparatus (UV-vis 6800, Jenway, UK). Dissolution studies were performed in 750mL of 0.1N HCl for 2 hr and then the pH was adjusted to 6.8 by adding 250mL of 0.2M sodium tribasic phosphate solution. A 0.1N HCl was prepared by adding 8.3mL of concentrated (36.5–38%) HCl to sufficient amount of purified water to make 1000 mL. During dissolution studies the medium was maintained at 37 °C

and agitated at 75 rpm. Samples (5 mL) were withdrawn at predetermined time intervals, filtered and analyzed spectro-photometrically at 275 nm. From the result, the cumulative percent of drug released was determined and plotted as a function of time.

Content uniformity

To determine the content of theophylline in the solid precipitates, an accurately weighed sample (0.4 g), from each run, will be ground and transferred to a 500mL volumetric flask containing purified water. The flask will be sonicated for 30 min and then stored at ambient temperature. After 24 hours of storage, the aqueous dispersion will be filtered and analyzed spectrophotometrically at 275 nm (UV-vis 6800, Jenway, UK). All assays will be carried out in triplicates and the mean value was reported.

RESULTS AND DISCUSSION

Dissolution study of solid precipitates tablets

Dissolution study of the 14 solid precipitates that compressed into tablets were performed in a steep function dissolution media using USP type II (paddle) dissolution apparatus. Dissolution profiles of the prepared solid precipitates tablets are shown in Figures 3 and 4.

Experimental design

A 14-run, three-factor, two-level D-optimal design was utilized in this study to correlate the effect of the level of Eudragit NE 30D (X_1), Eudragit RL 30D-55 (X_2), and Talc powder (X_3) on the dissolution behavior of solid precipitates tablets. The independent and dependent variables that were examined in this study are listed in Table 1. The composition of the 14 runs and the response that was investigated in this study, time to 10 % theophylline release, and percent released in 12 hours are given in Table 2. Data generated for the response were analyzed using the Design-Expert software. The probability value (α) for determination of statistical significance was set at 0.05, which indicates that a "hypothesis" theory would be rejected if the calculated *p*-value was less than 0.05 in favor of an alternative theory. The first step toward an optimal statistical analysis was to select the model that best (1) describes and (2) fits the data. Therefore, results were analyzed by the sequential model comparison test. Results of the sequential model comparison, which indicate whether a model could describe a response, and the lack of fit for each model are given in Table 3. As seen from the table, the linear model was statistically significant for both Y_1 and Y_2 responses ($p < 0.0001$ and $p = 0.0002$ respectively), which indicates that the model adequately describes the responses (time to 10 % release and percent drug releases in 12 hours). Statistical significance, however, was not improved by adding either quadratic or cubic terms. The lack of fit test was

subsequently performed to further demonstrate the suitability of a given model. Lack-of-fit test, which was calculated based on the residual sum of squares, diagnoses whether a model adequately fits the data. As seen in Table 3, large *p* values of the linear model ($p > 0.2379$) for Y_1 and 0.0441 for Y_2 indicates that the linear models adequately fits the data.

$Y_1 = 4.325\ X_1 + 1.656\ X_2 + 1.811\ X_3$.

$Y_2 = 83.5703\ X_1 + 100.2851\ X_2 + 94.2811\ X_3$.

A more elaborate discussion of the effect of study factors is given in the following sections.

Effect of study factors on Y_1

The effect Eudragit NE 30D (X_1), Eudragit RL 30D-55 (X_2), and Talc powder (X_3) on the dissolution behavior of solid precipitates compressed into tablets was investigated by measuring the absorbance of the released theophylline at λ max 275 nm. A contour plots showing the effect of X_1, X_2 and X_3 on the percent theophylline released is given in Figure 5. As seen from the Figure, an increase in the amount of X_1, X_2 and X_3 led to an increase in time to 10 % theophylline release (Y_1). However, the increase caused by X_2 is less than the other factors as seen from the coefficient in the linear model. These findings could be explained on the basis of the physic-chemical properties of polymers used. EudragitNE is water insoluble polymer used in preparation of controlled release dosage forms. Increase amount of Eudragit NE means less drug will diffuse to outside the blend and this lead to increase the time to 10 % theophylline release. On the other hand Eudragit RL is a polymer used in preparation of enteric coated dosage forms because it is insoluble in acid medium but it dissolves in alkaline medium. In acid medium it represents as intact polymer which retards the diffusion of drug to outside the blend and consequently increase the time to 10 % theophylline release. The third ingredient used in this study was talc powder which is water insoluble materials and used to facilitate processing in spray dryer. Increase the amount of talc powder resulted in increasing time to 10 % theophylline release because it is acting as a building blocks, in early stage of dissolution it blocks the opening so that the drug will not diffuse from the interior of the matrix system.

Effect of study factors on Y_2

The effect Eudragit NE 30D (X_1), Eudragit RL 30D-55 (X_2), and Talc powder (X_3) on the percent theophylline released in 12 hours is presented in the contour plot of Figure 6. As seen from the Figure, an increase in the amount of X_1, X_2 and X_3 led to an increase in the percent theophylline released in 12 hours (Y_2). However, the increase caused by X_2 is more than the other factors as seen from the coefficient in the linear model. This finding could be attributed to the ability of Eudragit RL (X_2) to dissolve in alkaline medium, therefore dissolution of Eudragit RL when the

pH reached 6.8 loosen the structure of the tablet and created more pores through which theophylline diffused to outside and consequently increase the percent theophylline released in 12 hours. In this stage, the adsorbed theophylline on the surface of talc powder during preparation of solid precipitates resulted in increased dissolution and diffusion of theophylline to outside the tablet and this explains the effect of talc powder in increasing the percent theophylline released in 12 hours. On the other hand the increasing effect of Eudragit NE (X_1) on the percent drug released in 12 hours is unpredicted but could be attributed to failure of the polymer to form a continuous membrane around the theophylline particles.

Optimization of solid dispersion formulation

After generating the linear equation relating the dependent and independent variables, the amount of each ingredient ($X_1 - X_3$) was optimized to give maximum time to 10 % drug release and maximum percent drug release in 12 hours. Based on the linear model and constraint, an optimal solid dispersion formulation was suggested by the statistical package. The suggested solid dispersion composition was a binary blend of Eudragit NE (1.73 gm), Eudragit RL(1.27 gm), and no talc powder with a maximum predicted time to 10 % theophylline release 3.19 hour and percent drug released in 12 hours 90.65. To validate the optimization process, a new solid dispersion was prepared based on the proposed composition and compressed into tablet using the same force of compression then tested for dissolution. Dissolution profile of the optimized formulation is shown in Figure 7. The optimized formulation as described from the statistical package had a time to 10 % theophylline release equal to 3.24 hour and 93.64 % theophylline released in 12 hour. The data illustrates a close agreement between the dissolution profile of the optimized formulation and that described by the statistical package.

Table 1: Independent and dependent variables of the D-Optimal mixture design (3-factor, 2-level design).

Independent variables	**Low level**	**High level**	
X_1 = Eudragit NE 30D (g)	0.50	2.00	
X_2 = Eudragit L 30D-55 (g)	0.50	2.00	
X_3 = Talc powder (g)	0.00	0.50	
Constrains on response			
Dependent variable	Lower limit	Upper limit	Goal
Y_1 = 10% release time	2.14	4.10	Maximum
Y_2 = percent released in 12 hours	84.06	97.94	Maximum

Table 2: Composition of the three-component blend in each of the 14-runs of the D-Optimal mixture design and responses.

Run	Eudragit NE gm	Eudragit RL gm	Talc powder gm	Time to 10 % release	Percent drug released
1	0.50	0.50	2.00	2.33	93.87
2	0.50	2.50	0.00	2.17	96.94
3	1.83	0.83	0.33	3.15	88.58
4	0.83	0.83	1.33	2.16	93.25
5	0.50	2.50	0.00	2.14	97.94
6	1.50	0.50	1.00	3.13	90.21
7	1.50	1.50	0.00	3.20	96.59
8	0.83	1.83	0.33	2.20	91.87
9	0.50	1.50	1.00	2.23	94.39
10	1.50	0.50	1.00	3.01	91.21
11	2.50	0.50	0.00	3.75	84.06
12	1.17	1.17	0.67	2.63	93.93
13	0.50	0.50	2.00	2.31	92.87
14	2.50	0.50	0.00	4.10	86.06

Table 3. Sequential model comparison and the corresponding lack-of-fit tests for Y_1 and Y_2

Type of model	Sequential comparison		Lack of fit	
	p Value		*p* Value	
	Y_1	Y_2	Y_1	Y_2
Linear	< 0.0001	0.0002	0.2379	0.0441
Quadratic	0.5326	0.1896	0.1804	0.539
Special cubic	0.0744	0.3686	0.3053	0.045
Cubic	0.8852	0.2433	0.0975	0.0328

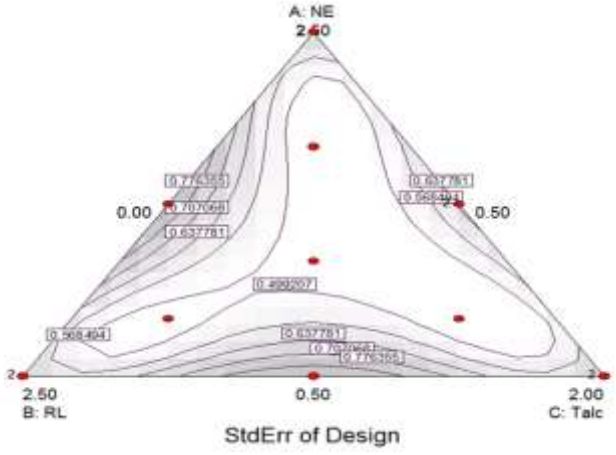

Figure1: Standard error plot and a schematic representation of the three-component D-Optimal mixture design with each corner of the triangle corresponding to one component. Dots represent the location of each design points (the 14 runs of the experimental design) within the design space. Dots with a (2) indicate that the point was replicated. Numbers in the boxes are the predicted variance at design point

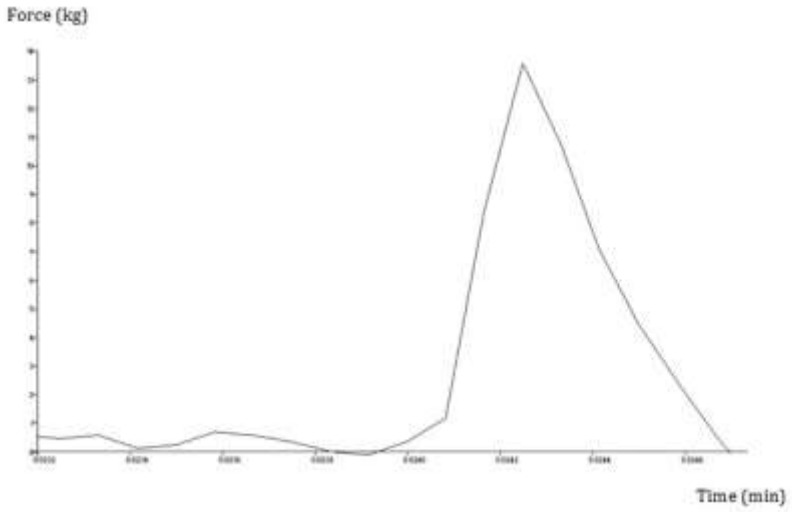

Figure 2: A representative force-time profile of a tablet compression obtained from texture analyzer

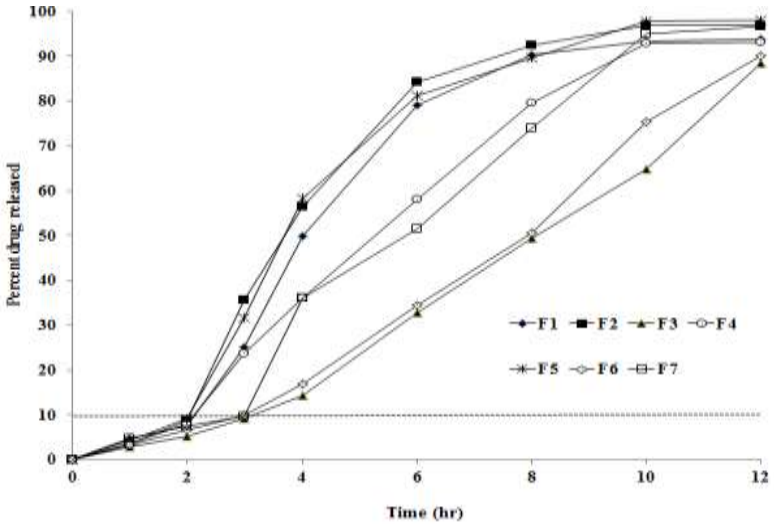

Figure 3: Dissolution profiles of different solid precipitates tablets

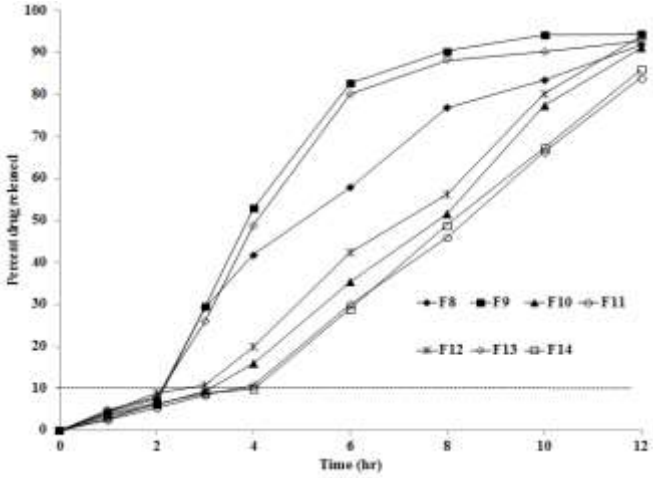

Figure 4: Dissolution profiles of different solid precipitates tablets

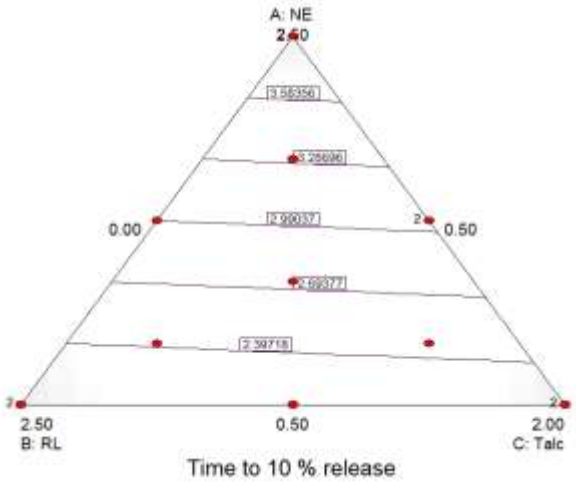

Figure 5: A contour plots showing the effect of X_1, X_2 and X_3 on the time to 10 % theophylline release.

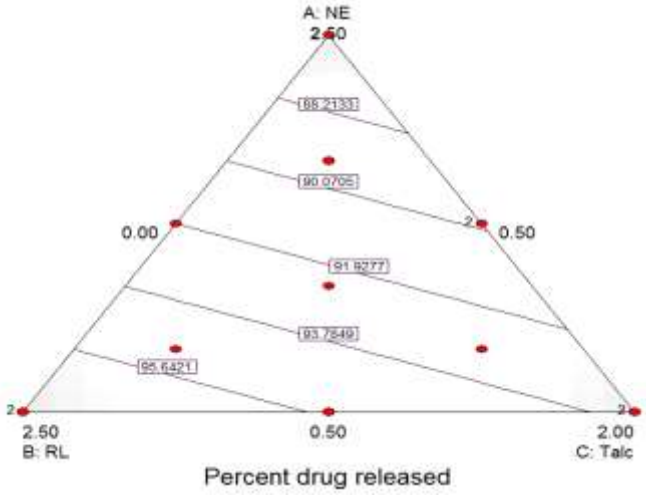

Figure 6: A contour plots showing the effect of X_1, X_2 and X_3 on the percent of theophylline released in 12 hours.

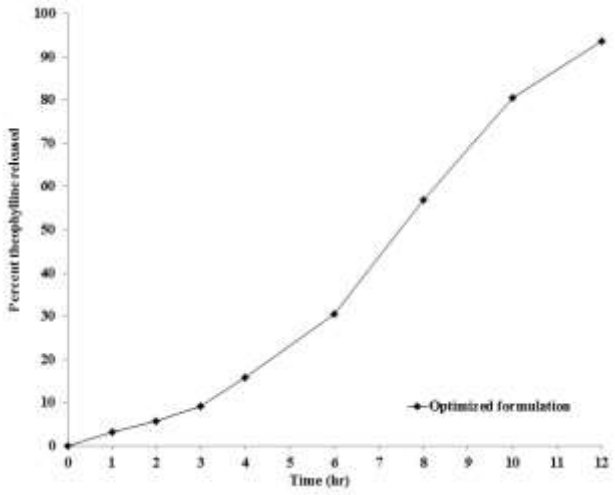

Figure 7: Dissolution profile of optimized formulation

CONCLUSION

Solid dispersion prepared from theophylline and a binary blend composed from polymers with different physico-chemical properties and compressed into tablets could be a useful technique to delay the time of theophylline release in an attempt to prepare a dosage that is able to release the drug in accordance with circadian rhythm. In this study for example, a D-optimal design was proven efficient in optimizing both the delay time and percent released of theophylline in 12 hours. The delay time was maximized to 3.24 hours while the percent of theophylline released in 12 hours was maximized to 93.64 % of the incorporated amount.

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