

Time released theophylline for chronotherapeutic treatment of nocturnal asthma

Alhassan H. Aodah¹, Saleh Al-Suwayeh², Ehab I. Taha², Alaa Eldeen B.Yassin*²

*Corresponding author:

Alaa Eldeen B.Yassin

¹National Center for Biotechnology, King Abdulaziz City for Science and Technology (KACST), Riyadh, Saudi Arabia;

² Department of Pharmaceutics, College of Pharmacy, King Saud University, Riyadh 11451, Saudi Arabia.

Abstract

The aim of this work is designing and evaluation of chronotherapeutic dosage form of theophylline (TPH). Film coated tablets were formulated using an Eudragit S-100 based coating formula as time released system and optimized toward a prospective control of nocturnal asthma. Core tablets, containing 200 mg TPH, were formulated by wet granulation process. Different formulae F1, F2, F3 and F4 were prepared by film coating to percentage weight gain of 5%, 10%, 15%, and 20%, respectively. The in vitro release profiling test was done in variant pH media with certain order mimicking GIT media (pH 1.2, 6, 7.5 and 6.8). The in vivo performance of the optimum formula was compared with Avolen[®] SR, a marketed generic sustained release TPH tablets, in beagle dogs. The results clearly showed the criticality of film thickness in the performance of the coat and its function. F1 and F2 failed to protect TPH tablet in the acidic pH media, while both F3 and F7 showed lag time of release 4 and 5 hours, respectively. F4 exhibited only 52.9% cumulative drug release along the 9 hours dissolution period. The C_{max} values were found to be 5.49 ± 0.46 and 5.12 ± 0.85 $\mu\text{g/ml}$ for F3 and Avolen[®] SR, respectively, F3 showed higher mean plasma concentration than Avolen[®] SR from the period 1.5 till 5.5 hours post administration indicating high potential as chronotherapeutic treatment of nocturnal asthma.

Keywords: chronotherapy – nocturnal asthma – Eudragit S – Film coating – Beagle dogs.

Introduction

Chronotherapeutics refers to the clinical practice of harmonizing delivery of the drug in accordance with body's circadian rhythm including ailment states to create maximum benefit and minimizing harm [1]. Many diseases are affected by the biological rhythm and show circadian symptoms intensity. For example, gout and peptic ulcer attacks are most common at night [2, 3]. Acute pulmonary edema, congestive heart failure, and asthma worsen nocturnally [4, 5]. Signs of allergic rhinitis and rheumatoid arthritis are stronger overnight or in the morning at the time of waking [6-8]. Bleeding ulcers is more regular in the afternoon than in the morning [9]. However, Asthma would be the most familiar disease with the largest circadian variation that considered as a chronic condition. The activity of the lung exhibits a circadian rhythm with a maximum around 4 p.m. and a minimum around 4 a.m. In asthmatic patients, the intensity of variation in lung function is as much as 50% in a day. Bronchial reactivity generally follows the same circadian cycle in asthmatic patients [10].

Nocturnal asthma is any breathing difficulty during sleep time. It is associated with shortness of breath, coughing and wheezing [11]. Nocturnal asthma is associated with critical symptoms and urgent

need for proper medications. The most death accidents of asthmatic attacks happen between midnight and 8 a.m. at morning [12] In a survey of almost 8000 patients with varying degrees of asthma found that approximately 75% of asthmatics attacks happened once a week with symptoms, 64 % three times a week, and 39 % every night [13].

Controlling of nocturnal asthma is currently tried by either using of long- acting 2 agonists, bronchodilator like TPH [14] or inhaled anti-inflammatory systemic corticosteroids [15]. All current prolonged released mediations for asthma lack the ability to keep high plasma levels of the drug during the time of disease intensity, This may lead to leaving the patient unprotected against the worse events of nocturnal asthma. Thus, the development of a system with lag time period of absorption may be useful. When administered at bedtime would give high plasma levels in early morning hours at which maximum disease intensity occurs.

Systems designed for colon drug delivery can be utilized for the chronotherapy of diseases that exhibit circadian rhythms [16]. Colon drug delivery can be approached using polymers that only dissolve at high pH values, such as cellulose acetate phthalate (CAP), shellac and acrylic acid resins (Eudragits). Number of Eudragit polymers S or L or combinations have been investigated for colonic delivery system [17-19]. Combining the effect of film thickness with the solubility at pH higher than 7, coating with



Eudragit S100 proved successful in formulating time released pressure controlled colon delivery capsule [20].

TPH was selected in this study as one of the commonly indicated drugs in nocturnal asthma treatment. TPH is phosphodiesterase inhibitor and bronchodilator, in addition it stimulates ventilation by acting centrally on the nervous system [21].

In this project, a time released TPH colonic system was optimized by adjusting the film coat thickness using formula of Eudragit S-100 to the suitable *in vitro* release profile. The *in vitro* release profile was investigated in different pH media mimicking the GIT. The TPH plasma concentration profiles obtained after administration of the optimized system to Beagle dogs was compared with that obtained after the administration of Avolen® SR.

Materials and methods

Materials

Theophylline manufactured by Aarti Industries Limited, (Mumbai, India) was kindly provided as a gift from Riyadh Pharma pharmaceutical Industry, Riyadh, Theobromine: (BDH Chemicals Ltd, Poole, England). Eudragit® S-100 (Rohm Pharmaceuticals, Darmstadt, Germany) which was kindly provided as a gift from Riyadh Pharma pharmaceutical Industry, Riyadh, Saudi Arabia. Avicel PH 101 (FMC Corporation, UK), Crosscarmellose sodium (Rosewell industries, Ahmedabad, India), Tween 80 and ammonia (Merck, Schuchardt, Germany), triethyl Citrate (Jiangxi Dongtai Science and Technology Co. Ltd, China). Povidone K30, (Zhejiang Ouhua Chemical Imp, China), Magnesium Stearate (BDH Chemicals Ltd, Poole, England) were purchased through a local chemical trading company in Riyadh, Saudi Arabia. All other chemicals were commercially available products of analytical grade.

Methods

Preparation of theophylline core tablets

The core tablets were prepared by wet granulation method, using the formula containing 200 mg of TPH, 53 mg of Avicel PH 101, 10 mg of crosscarmellose sodium, 50 mg of povidone K30 and 2 mg of magnesium stearate. The lubricant was added and mixed with the prepared granules right before tablet compression using (10 stations) Rimek mini tablet press compression machine fitted with 9.5 mm plain standard concave punches for a tablet weight of 270 mg. The prepared tablets were evaluated for the uniformity of weight and thickness, mechanical properties (hardness and friability), and *in vitro* availability properties (disintegration and drug release profiling).

Film coating

The coating dispersion was prepared according to the method presented by Huyghebaert *et al.* [21] with minor modification. Briefly, Eudragit S-100 powder was dispersed in water to form

10%w/w dispersion. Amount of Ammonia solution (1M) equal to 5%w/w was added drop wise over five minutes under stirring. The formed milky latex was kept under continuous stirring over night. Weights equivalent to 6% w/w triethyl citrate and 2%w/w Tween 80 (33% aqueous solution) were added to the dispersion and stirred for 10 more minutes. The coating process was performed using Caliva Mini Coater/Drier 2 (Caleva Process Solutions Ltd, Dorset, U K). Different formulae F1, F2, F3 and F4 were prepared with different percentage weight gains of 5%, 10%, 15%, and 20% from the core tablet weight, respectively.

In vitro release

The release of TPH from different coated formulae was monitored using standard USP apparatus No. 2 (Paddle method). Three tablets from each formula were individually tested in variant pH media. The sequence of pH change was two hours at pH 1.2, followed by one hour period at pH 6, then another two hours at pH 7.5 and finally four hours at pH 6.8. The pH changes were commenced using HCl and trisodium phosphate dodecahydrate. The rotation speed was adjusted to 50 rpm±1 and the temperature was maintained at 37± 0.5°C. Samples of 5ml were withdrawn manually at appropriate time intervals (1, 2, 3, 3:15, 3:30, 3:45, 4, 4:30, 5, 5:30, 6, 6:30, 7, 8 and 9 hours) and replaced with fresh preheated (at 37 °C) dissolution medium. The amount of TPH released was determined spectrophotometrically at = 271 nm.

Comparative bioavailability study

The pharmacokinetic profile of TPH from 200 mg film coated tablets (F3) was compared with two thirds of a scored 300 mg Avolen® SR in six male Beagle dogs weighing 14- 16.8 kg. The dogs were allowed to fast over night prior to and 4 h after administration of each treatment; thereafter, they resumed a normal unrestricted diet. During the experimental period, dogs were placed in a normal cage without using a restrainer stand. Procedures involving animals were conducted in accordance with US guidelines as found in the NIH Guide for the Care and Use of Laboratory Animals (NIH Publication No. 18-23, 1985). Animals were maintained in accordance with the recommendations in King Saud University Guide for the Care and Use of Laboratory Animals, approved by Animal Care and Use Committee.

Study design

The two-way crossover design was applied with a washout period of two weeks between each phase. The dogs were divided into two groups, each contain three. Each group received one of the two treatments in each phase. The treatments were given by normal swallowing followed by 100 ml water. Five-ml blood samples were collected, in heparinized evacuated plastic tubes, at predetermined time interval. The plasma was immediately separated by aspiration after centrifugation at 4000 rpm for 5 minutes and frozen at -20 °C until the time of analysis.



Determination of TPH in plasma using HPLC assay method

The concentration of TPH in plasma was determined by the same procedures employed by Barakat *et al.* [20] which mainly based on the method introduced by Rogge *et al.* [22]. The principal of the method is based on plasma protein precipitation using methanol. The method showed sensitivity to concentration as low as 0.5 µg/ml. HPLC instrument (Waters 717 plus), with binary HPLC pump (Waters 15525) was used. The UV detector (Waters 2487) was set at wave length 280 nm. The same column and mobile phase used in the previous method were employed.

Certain volume of caffeine (internal standard) solution in methanol having a concentration of 17.6 µg/ml was added to 500 µl plasma then allowed to vortex for half minute and centrifuged at 14000 rpm for ten minutes. An aliquot of the clear supernatant was directly injected into HPLC auto injector in the time of preparation. The method was validated by preparation of standard calibration curves in blank Beagle dogs' plasma. These calibrations were subjected to the entire analytical procedure, so as to test the linearity, precision and accuracy of the method.

Pharmacokinetic analysis

The pharmacokinetic parameters were calculated from the determined TPH plasma concentrations obtained from each individual dog after different time intervals.

A plot of the mean plasma concentration versus time has been constructed for each of the two treatments. The maximum plasma concentration (C_{max} , µg/ml); and the corresponding time for the maximum plasma concentration (t_{max} , h) were directly determined for both treatments in each individual animal. The area under the plasma concentration-time curve (AUC) and the area under the first-moment curve, (AUMC), were calculated from 0 to infinity using a linear trapezoidal rule.

Statistical analysis

One way analysis of variance (ANOVA) using Dunnett multiple comparison test on computer program Graphpad Instat 3 was used. Differences were considered significant at p value equal or less than 0.05 ($p < 0.05$).

Results

In vitro evaluation

The core tablets complied with the requirements of the United States Pharmacopoeia with regard to the uniformity of weight and drug content. They showed excellent mechanical properties expressed by high hardness values and minimal percent friability. The mean disintegration time of this formula was 10.7 min.

The film coating process by Eudragit S was giving a uniform tablet building weight for each formula. All coated tablets were

met the requirement of B.P (2008), the average weight values were 283.6 ± 1.1 , 297.23 ± 0.7 , 310.67 ± 1.06 , and 324.18 ± 1.2 concerning those tablets of formula F1, F2, F3, and F4, respectively.

The prepared TPH tablets coated with different thicknesses of Eudragit S had acceptable limits of film thickness uniformity. The mean film thickness values were 0.095 ± 0.025 , 0.175 ± 0.031 , 0.275 ± 0.052 and 0.4 ± 0.061 mm for formulae F1, F2, F3 and F4, respectively.

The release study was carried out for nine hours. First two hours in pH 1.2 represented the average stomach residence time, while changing the medium pH to pH 6 for one hour was conducted to simulate the medium of the upper part of small intestine. The next successive two hours at pH 7.5 were intended to represent the middle and terminal intestinal medium, while adjusting the medium pH to pH 6.8 during the last four hours period aimed to simulate the colonic medium. Figure (1) shows the release profiles of TPH from the all the produced film coated tablet formulae. The results showed that F4 with only 5% coat gave 100% TPH release during the first hour in the acidic medium while F2 showed slightly more resistance with 91% release during the first two hours and complete release after three hours. F3 with 15% coat showed complete resistance to both the acidic medium and the upper small intestine medium with almost no release ($1.7 \pm 1.12\%$). After one hour in pH 7.5, the TPH release started to increase gradually and continued till it reached complete release after 7 hours from the beginning of the test. In the case of F4, with the highest coat thickness (20% weight gain), no release was seen till five hours from the beginning of the test. Then, the release was slowly and gradually increased reaching a maximum of only 52.9% of the labeled amount at the end of the test (9 hours).

It was found that a minimum film thickness of 0.275 mm is necessary for the protectivity of Eudragit S100 films against the acidic pH. F1 and F2 with film thicknesses of 0.095 and 0.175 mm, respectively, failed to protect TPH tablet in the acidic pH simulating the stomach medium. Increasing the thickness to 0.275 mm (F3, 15% weight gain) resulted in complete resistance to both the acidic medium and the upper intestinal medium (pH 6). The release showed almost one hour lag time in pH 7.5 then gradually increased reaching a value of 71% and continued in pH 6.8 (representing the colonic medium) for two more hours. Thus, complete dissolution occurred after 7 hours in different pH media. Higher film thickness (F4, with 20% weight gain) resulted in retention of the drug with 5 hours lag time including 2 hours at pH 7.5, in which Eudragit S100 is soluble. Thus, F3 achieved the best in vitro attributes as it showed a period of four hours with negligible amount released (less than 5%) and achieved a complete and gradual drug release profile in the following three hours. Accordingly, F3 was selected for the in vivo comparative study.

Pharmacokinetic analysis

As shown in Table (1), the C_{max} was found to be 5.12 ± 0.85 and 5.49 ± 0.46 ($\mu\text{g/ml}$) for Avolen[®] and F3, respectively. It is clear that F3 exhibited higher C_{max} value however the difference failed to be significant. These data of bioavailability study was in accord to that obtained by Rojanasthien *et al.* [25]. The secondary peaks which appeared in Figure (2) for both treatments, may be due to the possible enterohepatic circulation exhibited by TPH. The primary peak was the only considered in the calculation of the mean C_{max} values.

The average T_{max} values were found to be 2.92 ± 0.74 and 4.83 ± 1.86 (hr) for F3 and Avolen[®], respectively. Although F3 tablets formulation showed low value of T_{max} (2.92 hours) which indicated faster absorption of the drug from this formulation compared to that of Avolen[®] tablets, however, this difference was not statistically significant. It is clear that the T_{max} values showed high variation with very high RSD %. The $t_{1/2el}$ was 5.65 ± 1.64 and 7.72 ± 3.71 h for F3, and Avolen[®] respectively. The values of the MRT, which is the non-compartmental analogue of $t_{1/2el}$, were also parallel to those of $t_{1/2el}$ and all the differences failed to be significant.

The average AUC_0 was found to be 68.35 and 69.27 mg.h/l for F3 and Avolen[®] SR tablets, respectively. Thus, the percentage relative bioavailability of F3 was found to be 98.67% using Avolen[®] SR tablets as reference.

It is obvious that F3 exhibited much lower inter-subject variabilities compared with Avolen[®] SR. This can be directly concluded from the significantly higher magnitude of RSD% for Avolen[®] compared with F3 in all the pharmacokinetic parameters.

Discussion

The results revealed that film thickness is a critical factor for the performance of the coat and its function. There is minimum thickness which necessary for the protectivity of Eudragit S100 films against the acidic pH.

The release profile of F3 was in agreement with what Huyghebaert *et al.* [21] reported. They studied the effect of different pH (6.8, 7, 7.2, and 7.4) on the release from Eudragit S100 coated pellets at level of 15% weight gain following two hours in 0.1 N HCl. They found that fast release occurred only in media with pHs above 7.2 and 7.4. Similar results were reported by Alvarez-Fuentes *et al.* [25]. They developed a 27% Eudragit S100 coated matrix tablet composed of a mixture of different cellulose polymers. The *in vitro* release profile showed a lag time of 260 minutes followed by slow-release of the drug achieving 90% of release after 10 hours.

The release profile of F3 appears more suitable for the purpose of nocturnal asthma chronotherapy since it allows a reasonable lag time of release followed by controlled regular release pattern with complete dissolution after 7 hours. On the other hand, F4 showed retention of the drug with only 52.9% drug release after 9 hours.

The pharmacokinetic data of the tested F3 was found to be in good agreement with several reports in the literature [23; 26-28]. Similar bioavailability between F3 and Avolen[®] SR can be easily concluded relying on the existence of both the values of AUC_0 and C_{max} within the acceptance range of the FDA (80-125%).

The high pharmacokinetic variability among TPH slow-release formulation is extensively reported in literatures [29-31]. Hendeles *et al.* [32] reported that among 15 completely absorbed TPH slow-release formulations in USA, differences in rate of absorption may result in clinically important differences in serum concentration fluctuations.

Conclusions

The prepared coating formula containing Eudragit S100 was suitable and useful for producing elegant film coats up to high coat thicknesses. In addition, the optimized coating process conditions were useful in producing a reproducible tablet film-coating using the Caliva Mini Coater in a relatively short time. The resistivity of Eudragit S100 film coats to low pHs is highly affected by the film thickness. A threshold of film thickness equals to 0.275 mm is necessary for the resistance against acidic pH. The coat thickness should be optimized based on the required release profile. F3 is bioequivalent with the commercial slow release (Avolen[®] SR tablets).

The higher TPH plasma concentration achieved with F3 during the period from 1.5 to 5.5 h post administration can be considered a bench mark for such system for the chronotherapy of nocturnal asthma.

Authors' contributions

ABY has been initiated the research idea and constructed the main design. He also participated in the following experimental parts: evaluation of the tablets, film coating of the tablets and their *in vitro* evaluation, the comparative bioavailability study. He also participated in the analysis of the results. **ABY** has made intellectual revising of manuscript and approved the final version before submission.

AHA has conducted all the experimental work as part of his master thesis work. He has been extensively involved preparation of the first draft of the manuscript.

SA has extensively participated in the HPLC determination of theophylline in aqueous and in plasma. He also helped in the calculation of the pharmacokinetic parameters of theophylline in Beagle dogs. He participated in revising the manuscript.

EIT has also extensively helped in the performance of the drug analysis part and the statistical analysis of all the results. He did review the first draft of the manuscript and made important suggestions.



Acknowledgments

The authors extend their appreciation to the Deanship of Scientific Research at King Saud University for funding the work through the research group project No. RGP – VPP – 139.

The authors declare explicitly that they do not have any direct or indirect financial relation with any commercial identity mentioned in this manuscript and they don't have any conflict of interest whatsoever.

References

- [1]. Smolensky M, Labrecque G. Chronotherapeutics. *harmcaceutical News* 1997; 4: 10-16.
- [2]. Sydenham T, editor. *The Works of Thomas Sydenham MD*, Translated from the Latin by Lathan RG, vol. 2. London, England: The Sydenham Society; 1850. p 124.
- [3]. Moore J, Halberg F. Circadian rhythm of gastric acid secretion in active duodenal ulcer: chronobiological statistical characteristics and comparison of acid secretory and plasma gastrin patterns in healthy and post-vagotomy and pyloroplasty patients. *Chronobiol. Int.* 1987; 4: 101–110.
- [4]. Bateman J, Clark S. Sudden death in asthma. *Thorax*.1979; 34: 40–44.
- [5]. Cugini P, Di Palma L, Battisti P, Leone G, Materia E, Parenzi A, Romano M, Ferrera U, Moretti M. Ultradian, circadian and infradian periodicity of some cardiovascular emergencies. *Am. J. Cardiol.* 1990; 66: 240–243.
- [6]. Kowanko I, Knapp M, Pownall R, Swannell A. Domiciliary self measurement in rheumatoid arthritis and the demonstration of circadian rhythmicity. *Ann Rheum Dis.* 1982; 41: 453–455.
- [7]. Kelmanson I. Circadian variation of the frequency of sudden infant death syndrome and of sudden death from life-threatening conditions in infants. *Chronobiologia.* 1991; 18: 181–186.
- [8]. Smolensky M, Reinberg A, Labrecque G. Twenty-four hour pattern in symptom intensity of viral and allergic rhinitis: treatment implications. *J Allergy Clin Immunol.* 1995; 95: 1084–1096.
- [9]. Manfredini R, Gallerani M, Salmi R, Calò G, Pasin M, Bigoni M, Fersini C. Circadian variation in the time of onset of acute intestinal bleeding. *J Emerg Med.* 1994; 12: 5–9.
- [10]. Skloot G. Nocturnal asthma. *The Mount Sinai Journal of Medicine.* 2002; 69(3): 140-147.
- [11]. Neuenkirchen H, Wilkens J, Oellerich M, Sybrecht G. Nocturnal asthma: effect of a once per evening dose of sustained-release theophylline. *Eur J Respir Dis.* 1985; 66: 196–204.
- [12]. Robertson C, Rubinfeld A, Bowej G. Deaths from asthma in Victoria: a 12-month study. *Med J Austr.*1990; 152: 511- 517.
- [13]. Smolensky M. Chronobiology and chronotherapeutics: Applications to cardiovascular medicine. *Am J Hypertens.* 1996; 9: 11S-21S.
- [14]. D'Alonzo G, Smolensky M, Feldman S, Gianotti L, Emerson M, Staudinger H, Steinijan V. Twenty-four hour lung function in adult patients with asthma. Chronooptimized theophylline therapy once-daily dosing in the evening versus conventional twice-daily dosing. *Am Rev Respir Dis.* 1990; 142: 84–90.
- [15]. Reinberg A, Gervais P, Chaussade M, Fraboulet G, Duburque B. Circadian changes in effectiveness of corticosteroids in eight patients with allergic asthma. *J Allergy Clin Immunol.* 1983; 71: 425-433.
- [16]. Kinget R, Kalala W, Vervoort L, van denMooter G. Colonic drug targeting. *J Drug Target.* 1998; 6: 129-149.
- [17]. Dew M, Hughes P, Lee M, Evans B, Rhodes J. An oral preparation to release drugs in the human colon. *British Journal of Clinical Pharmacology.* 1982; 14: 405–408.
- [18]. Klotz U, Maier K, Fischer C, Bauer K. A new slow-release form of 5-amino salicylic acid for the oral treatment of inflammatory bowel disease: Biopharmaceutical and pharmaceutical characteristics. *Drug Res.* 1985; 35: 636-639.
- [19]. Touitou E, Rubinstein A. Targeted enteral delivery of insulin to rats. *Int J Pharm.* 1986; 30: 95-99.
- [20]. Barakat N, Al-Suwayeh S, Taha E, Yassin A. A new pressure-controlled colon delivery capsule for chronotherapeutic treatment of nocturnal asthma. 2011; 19(5): 365-372.
- [21]. Huyghebaert N, Vermeire N, Remon J. In vitro evaluation of coating polymers for enteric coating and human ileal targeting. *Int J of Pharm.* 2005; 298: 26-37.
- [22]. Rogge M, Solomon W, Sedman A, Welling P, Toothaker R, Wagner J. The theophylline-enoxacin interaction: I. Effect of enoxacin dose size on theophylline

- disposition. 1988; Clin Pharmacol Ther, 1988; 44: 579–587.
- [23]. Rojanasthien N, Kovjiriyapan K, Manorot M, Pothirat C. Comparative steady-state bioavailability of sustained-release theophylline preparations: Theo-Dur, Uni-Dur and Xanthium. Asian Pac J Allergy Immunol. 2001; 19(2): 69-78.
- [24]. Trevor A, Katzung B, Masters A, editors.. Pharmacology Examination and Board Review, 6th ed. North America: The McGraw-Hill Companies Inc.; 2002. P.187.
- [25]. Alvarez-Fuentes J, Fernández-Arévalo M, González-Rodríguez M, Cirri M, Mura P. Development of enteric-coated timed-release matrix tablets for colon targeting. J Drug Target. 2004; 12(9-10): 607- 612.
- [26]. DiLuccio R, Hussain M, Coffin-Beach D, Torosian G, Shefter E, Hurwitz A. Sustained-release oral delivery of theophylline by use of polyvinyl alcohol and polyvinyl alcohol-methyl acrylate polymers. J Pharm Sci. 1994; 83(1): 104-106.
- [27]. Tatsis G, Tsoukalas G, Peristerakis A, Filaditaki V, Orfanidou D, Anagnostou E. Bioavailability of a new sustained-release anhydrous theophylline product. J Int Med Res. 1996; 24(4): 331-339.
- [28]. Tulain U, Ur-Rahman N. Comparative bioavailability and in vitro in vivo correlation of two sustained release brands of theophylline tablets and pellets. Pak J Pharm Sci. 1996; 21(2):131-138.
- [29]. Weinberger M, Hendeles L, Bighley L. The relation of product formulation to absorption of oral theophylline. N Engl J Med. 1978; 299: 852-57.
- [30]. Weinberger M, Hendeles L, Wong L, Vaughan L. Relationship of formulation and dosing interval to fluctuation of serum theophylline concentration in children with chronic asthma. J Pediatr. 1981; 99: 145- 52.
- [31]. Hendeles L, Ifrate P, Weinberger M. A clinical and pharmacokinetic basis for the selection and use of slow release theophylline products. Clin Pharmacokinetic. 1984; 9: 95-135.
- [32]. Hendeles L, Massanari M, Weinbergen M. Update on the pharmacodynamic and pharmacokinetics of theophylline. Chest. 1985; 88: 103-111.



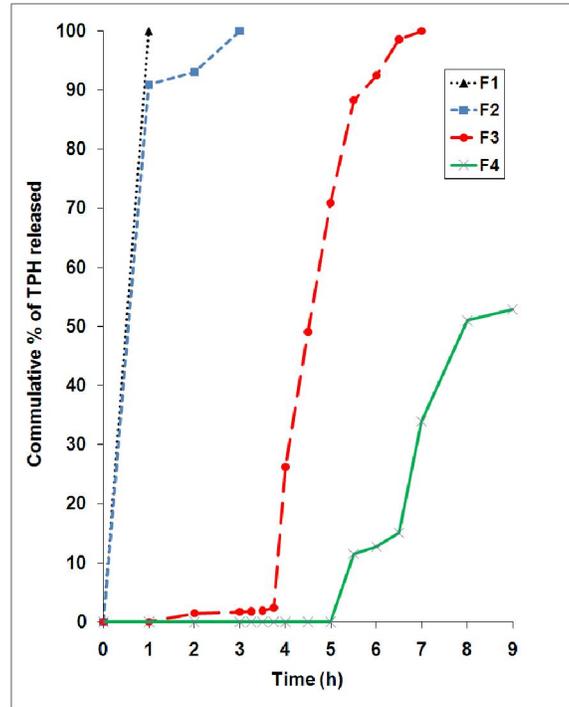


Figure 1: Release profiles of theophylline from tablets coated with different percentage of weight building of Eudragit S-100, (F1: 5%), (F2: 10%), (F3: 15%), (F4: 20%) in several pH media.

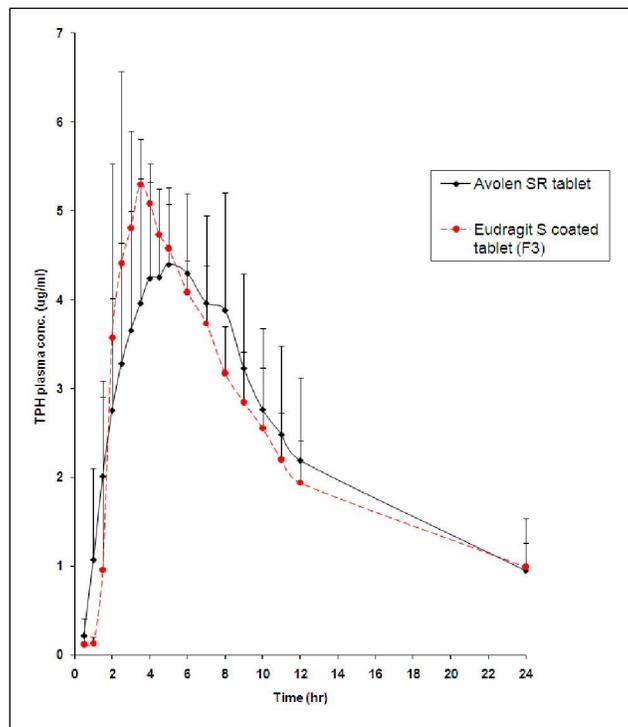


Figure 2: Mean plasma theophylline concentration after the administration of a single oral dose of Avolen® SR, and F3 (Eudragit S100 film-coated tablets).

