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IN-VITRO AND *IN-VIVO* EVALUATION OF SUSTAINED-RELEASE SUPPOSITORIES CONTAINING THEOPHYLLINE MICROSPHERES

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The sustained release microspheres of theophylline were formulated using non-solvent addition technique. The in-vitro dissolution of the drug from the fabricated microspheres that having size ranges of 300-600, 600-800 and 800-1000 µm was tested. The release of theophylline was extended over 8 hrs and it was found that the drug release decreased non-significantly as the particle size increased ($p \geq 0.05$). Incorporating theophylline-containing microspheres into suppository formulation using polyethylene glycol base resulted in a slight increase in dissolution rate, but still in a sustained release pattern over 8 hrs. In-vivo study of the prepared suppositories on beagle dogs revealed that the peak of theophylline serum concentration C_{max} (mean±S.D) was 11.1+0.3 µg/mL. It was also found that $AUC_{(0-24hrs)}$ value averaged 154.7±20.3 µg-h/ml. The median peak time (T_{max}) was 3.0 hrs and MRT was 13 hrs indicating a sustained effect.

INTRODUCTION

Sustained release dosage forms are of increasing importance in drug therapy. These dosage forms are developed to give a slower rate of drug release which maintains drug levels at uniform therapeutic for an extended period. Sustained release dosage forms had many advantages such as reduction of the dose intervals, less adverse effects and improved the patient compliance[1]. The effective formulation that control drug release for the wanted duration and required release profile depends on many factors. Among these are the physical and chemical characteristics of the drug, the type of the polymer, ratio of polymer to drug, and the type of the plasticizer[2-8]. From last decade, much attention was focused on polymeric microcapsules and microspheres as drug delivery systems to modify and extend the drug release[9]. The formulation depends on the use of inert polymeric materials to coat the drug particles that allows the drug diffusion at a predictable and controlled rate in the release vehicle[10]. Several methods were applied to make polymeric microspheres as sustained release delivery systems for many drugs. Examples of these methods include: mechanical treatments (such as spray drying), physicochemical processes (solvent evaporation technique or phase separation method) and the non-solvent addition method[11-17].

Theophylline is one of the well-established drugs that used in the treatment of asthma. It has a narrow therapeutic index; with plasma concentrations of 5-20 µg/mL[18]. Extended release formulations of theophylline that can maintain more uniform serum drug concentrations with less fluctuation in peak-through levels could be useful. The objective of this work was to formulate extended release

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microspheres of the investigated drug theophylline, using ethylcellulose as a polymer for release-retardation, using the non-solvent addition method. Then the prepared microspheres were incorporated into suppositories dosage form followed by studying the *in-vitro* release and *in-vivo* absorption from the prepared suppositories.

MATERIALS AND METHODS

Materials

Theophylline (Theo) was purchased from Sigma Chemicals (St. Louis, MO, USA). Ethylcellulose (EC), with viscosity of approximate 14 cp for 5% solution in 80:20 toluene: ethanol by weight and 2.42 to 2.53 degree of substitution was supplied from Fluka Chemie AG (Switzerland). Petroleum ether, polyehelyne glycol 1540 and 4000 (PEG) and toluene were obtained from BDH Chemicals Ltd. (Poole, England). Diethylphthalate was purchased from Riedel-DE Haenag(Germany).

Methods

Preparation of theophylline loaded microspheres

Theophylline loaded Microspheres were prepared using the previously reported non-solvent addition method[19]. Microspheres composed of 1:1 w/w EC: Theo ratio was prepared. The pre calculated and weighted quantity of theophylline (2.5 g) was dispersed in fifty ml of toluene in which ethyl cellulose polymer (2.5 g) was previously dissolved, and the mixture subjected to stirring at 700 rpm for 15-minutes using paddle stirrer. Model Lightnin L. T52010, USA. Diethylphthalate (as plasticizer) was added to the EC polymeric solution in a concentration of 10% of EC content and stirred for additional 15 minutes. Then, one hundred ml petroleum ether was added drop wise to the mixture with continuous stirring for 2 hrs at room temperature (25°C). After decantation, the produced microspheres were thoroughly washed with fifty ml petroleum ether in three portions, to remove the excess toluene from the microspheres. The obtained microspheres were filtered off and then allowed to dry in the open air until complete drying. The dried microspheres were subjected to sieve analysis using set of sieves and three fractions (0.3 to< 0.6, 0.6 to< 0.8 and 0.8 to< 1 mm) were used for further studies.

Determination of drug content of the prepared microspheres

A weighed quantity of microspheres equivalent to 100 mg theophylline was transferred to a volumetric flask, 50 ml ethanol was added and the flask sonicated in a sonicator water path for 30 minutes to attain complete extraction of the drug. After Millipore filtration, theophylline concentration was spectrophotometrically assayed at λ_{max} of 272nm using spectrophotometer Philips Pu 8620, England, UK. Each experiment was carried out in triplicate. Theophylline content was calculated as a percentage of the drug theoretical content in the microspheres. Plain microspheres without drug, prepared and extracted in the same way, were used as reference blank.

Preparation of suppositories containing theophylline microspheres

Suppository bases were prepared using the composition of PEG 1540 and PEG 4000, in a ratio of 1:3 w/w, by the fusion method. Theophylline microspheres (0.3 to< 0.6 mm size) equivalent to 100 mg theophylline were added to the fused bases and dispersed by continues stirring for 10 min. The mixture was then transferred to suppository molds (capacity 2 g), that were immediately put in a refrigerator.

In-vitro release studies

Dissolution experiments were done using USP dissolution instrument 2, at 50 rpm (Caleva Ltd., Model 85T) connected to an automated monitoring system that composed of an IBM computer PK 8620 series and PU 8605/60 dissolution test software, Philips VIS/UV/NIR single beam eight cells spectrophotometer Model PU 8620, Epson FX 850 printer, and Watson-Marlow peristaltic pump. In each vessel, 0.9 liter phosphate buffer pH 7.4 was used as a dissolution medium. The temperature was kept at 37±0.5°C. A defined weight of the formulated microspheres equivalent to 100 mg of theophylline, or one suppository was put to each vessel. All the release experiment was done in triplicate and the absorbance was recorded automatically at

λ_{max} of 272 nm up to 8 hrs. The amount of drug released was computed as a function of time.

***In-vivo* study**

According to the approved protocol by the Institutional Review Board-Use and care of Animals at King Saud University for the *in-vivo* study, six male of beagle dogs (8–14 kg) were used for this study. The dogs were housed in separated cages at 25±1°C and 45–55% relative humidity with a 12 hrs light/dark cycle. All dogs were fasted overnight before the investigation. Water was available throughout the study period. The tested formulation was administered rectally to each dog. The dog's leg was shaved and blood samples were collected from a forefoot vein using cannula of an 18 gauge size. Serial 3 ml blood samples were taken from the tested animals just before the administration of the tested doses and at time intervals (0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, and 24 hrs) after rectal administration. Heparinized blood samples were centrifuged immediately for 15 min at 3500 rpm, and the plasma was collected in glass vials and kept frozen at -20°C until further analysis. The amount of theophylline in the plasma was investigated by the high-performance liquid chromatography method of Al Janobi *et al.*[20] as detailed below:

1- Theophylline plasma assay

An integrated high-performance liquid chromatography system (LC 2010C; Shimadzu Corporation, Kyoto, Japan) equipped with a column oven, a degasser, a UV detector, a quaternary pump (LC20AD), an auto-sampler (CIL20A) and a data analysis software was used to determine plasma theophylline concentrations. A C18 column (5 mm, 150 mm 4.6 mm, Waters Corporation, Milford, MA) at 25°C was used for separation of theophylline. A mixture of HPLC water/ acetonitrile (93:7, v/v) with a pH of 4.2 adjusted with glacial acetic acid (0.5 mL/L) was used as a mobile phase that pumped at a flow rate of 1.0 mL/ min. The wavelength of detection was set at λ_{max} of 272 nm.

2- Sample preparation

Samples were prepared by pipetting plasma samples (0.2 mL each) into micro-centrifuge tubes. After that, 0.1 mL of hydroxyethyl theophylline as internal standard (I.S.) working solution (250 µg/mL) was added and the blend was mixed by vortex for 30 s. Then, 0.7 mL of zinc sulfate solution (2%) was added for protein precipitation followed by vortex mixing for 1 min. The samples were then centrifuged at 3000 g for 15 min at 25°C. The clear supernatant was transferred into injector vials and a 50 µL aliquot was injected into the HPLC system. Standard stock solutions of theophylline (1 mg/mL) and I.S. (1 mg/mL) were made for calibration and control samples using methanol as a solvent. The internal standard (I.S) working solution (250 µg/mL) was prepared by diluting the stock solution with the mobile phase. The working solutions of theophylline and I.S. (0.2 mL) were added to drug-free plasma (9.6 mL) to obtain final concentrations of 0.1, 0.25, 0.5, 1.0, 2.5, 5.0, 10.0 and 25.0 µg/mL.

Statistical analysis

Software Graph Pad Prism5 (Graph Pad Software, La Jolla, USA) was used to analys the results by applying one-way ANOVA. The difference between formulations was considered to be significant if $p \leq 0.05$.

RESULTS AND DISCUSSION

One of the essential polymeric materials used in microspheres and microencapsulation preparations is the ethyl cellulose polymer[21-23]. This is because ethyl cellulose has advantages of its cheapness, good stability, high safety and easy of fabrication[16]. Different sizes (ranging from ≤300-1250 µm) of theophylline microspheres were successfully prepared. The results of drug content of the prepared microspheres showed that theophylline content was ranged from 95 to 102% of the theoretical content, representing high encapsulation efficiency. It was found that the total yield was not less than 70% in all formulations.

***In-vitro* release from the prepared microspheres**

Figure 1 demonstrates the cumulative percent released of theophylline from the microspheres batches (particle sizes 0.3 to< 0.6, 0.6 to< 0.8 and 0.8 to< 1 mm). The results presented that the release of theophylline from the microspheres of different batches was

prolonged over 8 hrs. It was evident from the release pattern that there was no significant difference (P> 0.05) between the batches of microsphere particle sizes of 0.3 to< 0.6 mm and those of size ranges 0.6 to< 0.8 mm. These results are similar with the previously published data by Ibrahim *et al*.[19] the release data of theophylline from the prepared microspheres were subjected to various kinetic models (zero order, first order and Higuchi diffusion models). The results are presented in Table 1. The results obtained showed that the drug release from the prepared microspheres followed Higuchi model as it showed the highest correlation coefficient.

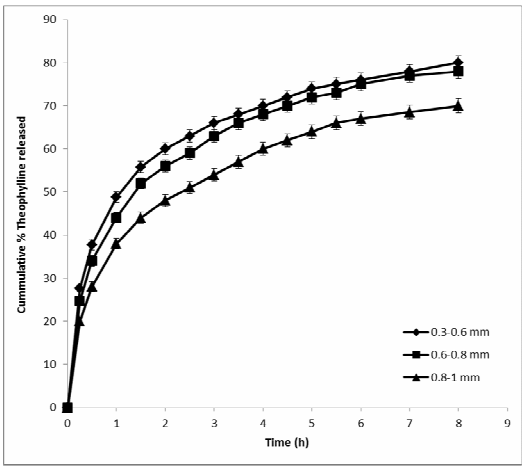

Fig. 1: Effect of particle size on the *in-vitro* release of theophylline from the prepared microspheres.

***In-vitro* release of theophylline from the suppositories containing theophylline microspheres**

The release pattern of theophylline from suppositories containing microspheres is displayed in figure 2. These results reveal that the release rate of theophylline from suppositories was initially comparable in the first hour to the microsphere, and then slightly increased in the following time intervals. The release reached 92% after 8 hrs. The slight increase in the drug release from theophylline microspheres incorporated in suppositories may be due to the enhancement effect of PEG.

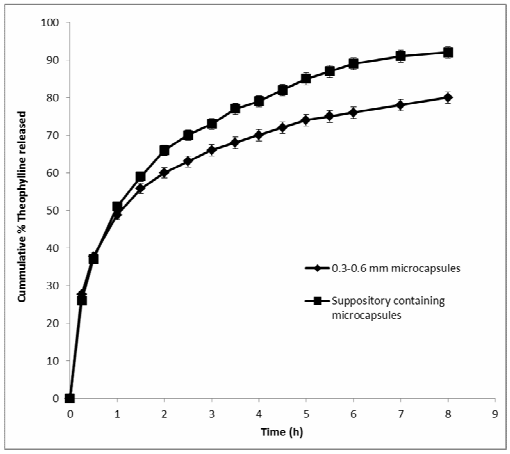

Fig. 2: *In-vitro* release of theophylline from the prepared microspheres and the microspheres containing-suppositories.

Table 1: Comparison of correlation coefficient (r) obtained from *in-vitro* release data of theophylline microspheres.

Release order	r value for different sizes of microspheres		
	0.3 to < 0.6 mm	0.6 to < 0.8 mm	0.8 to < 1 mm
Zero Order	0.841	0.858	0.864
First Order	0.940	0.936	0.941
Higuchi diffusion model	0.961	0.966	0.969

***In-vivo* study**

The therapeutic serum concentration of theophylline is optimum when it is ranged from 10-20 mg/mL[24&25] however it should not be considered as a rigid barrier; clinical decisions should never depend solely on the serum concentrations[26]. Several articles were available dealing with food effects on the pharmacokinetics of theophylline[27-30]. However, the present study, theophylline was rectally administered and the pharmacokinetic of its formulations was studied, so food effects are not essential. Figure 3 shows the mean theophylline plasma concentrations from the tested suppositories in beagle dogs after rectal administration. The results showed that the serum concentration peak of theophylline C_{max} (mean±S.D) was 11.1±0.3 µg/mL for the tested theophylline suppository as shown in table 2. It was also found that $AUC_{(0–24hrs)}$ value averaged 154.7±20.3 µg-h/ml and the median peak time T_{max} was 3.0 hrs. for theophylline suppositories (Table 2). In a previous study[31], after administration of 200 mg theophylline orally to beagle dogs, the maximum plasma theophylline concentration C_{max} (mean±S.D) was 16.4±0.7 µg/mL and the median peak time T_{max} was 2.1 hrs. Also, as previously reported, the median peak time T_{max} for pediatric regular theophylline PR (Minophylline suppositories), is within 30 minutes as a reported value for pediatric theophylline PR.[32]. Another published data[33] revealed that the theophylline pharma-cokinetics was evaluated in 24 healthy males after rectal administration of theophylline ethanoate (Minophylline 500 mg). The median peak time, T_{max} was 0.5 hr for theophylline rectal administration. However, in this study, the median peak time T_{max} was 3.0 hrs indicating a sustained effect.

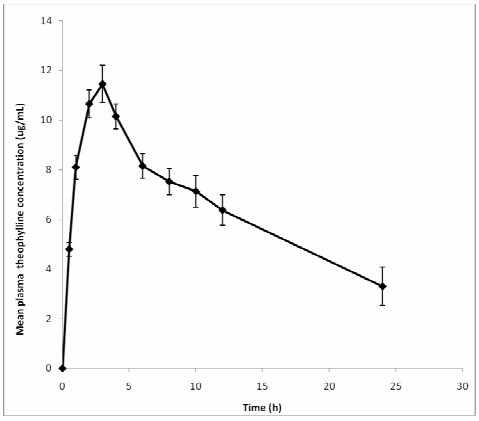

Fig. 3: Mean theophylline plasma concentration time curve after rectal administration of suppository contains microspheres equivalent to 100 mg theophylline (n=6).

Table 2: Pharmacokinetic parameters of sustained release theophylline suppositories (100mg) after rectal administration to beagle dogs (n= 6).

Parameter	Value
C_{max}	11.1± 0.30 µg/ml
T_{max}	3.0±0.2 hrs
$AUC_{(0-24)}$	154.7± 20.3 µg-h/ml
$AUC_{(24-end)}$	61.7± 8.8 µg-h/ml
MRT	13.1 hrs
K_{ab}	184.495 hr^{-1}
K_{el}	0.053446 hr^{-1}

Conclusion

From the present data, it was found that a good dissolution rate from theophylline microspheres was attained by preparing theophylline microspheres with a ratio of 1:1 ethyl cellulose: theophylline, of particle size ranging from 0.3 to< 1 mm, and containing 10% diethylphthalate as a plasticizer. The results showed that the release rate of theophylline from the prepared suppositories was initially comparable in the first hour to the microsphere, and then slightly increased in the following time intervals. Bioavailability of the prepared suppositories in beagle dogs showed median peak time T_{max} of 3.0 hrs and plasma drug concentration above 5 µg/ml for more than 12 hrs indicating a sustained effect.

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Disclosure

The authors report no conflicts of interest in this work.

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نشرة العلوم الصيدلية
جامعة أسيوط

التقييم الحيوي والمعملى للبوسات ممتدة المفعول محتوية على كريات دقيقة من الثيوفيلين

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تم تحضير كريات دقيقة تحتوى على عقار الثيوفلين باستخدام طريقة الاضافة لضد المذيب. وتم دراسة الاتاحة المعملية للعقار من الكريات المحضرة وذلك باستخدام كريات مختلفة الاحجام (٠،٣ الى ١ ملم). وقد وجد ان انطلاق عقار الثيوفلين قد امتد الى حوالى ثمانى ساعات مع وجود تاثير غير جوهرى لزيادة الانطلاق مع حجم الكريات الاقل. كما تم صياغة الكريات المحضرة من ٠،٣ الى ٠،٦ ملم فى صيغة تحاميل باستخدام البولى اثيلين جليكول كقاعدة. وبدراسة الانطلاق المعملى لعقار الثيوفلين من التحاميل المحضرة وجد انه قد امتد الى حوالى ثمانى ساعات مع زيادة غير جوهرية مقارنة بالكريات المحضرة. وعند دراسة امتصاص العقار من التحاميل المحضرة بعد اعطائها للكلاب عن طريق فتحة الشرج وجد ان تركيز العقار فى الدم كان ممتدا الى ٢٤ ساعة وبلغ اعلى تركيز لعقار الثيوفلين فى البلازما عند ٣ ساعات.