

Preparation and evaluation of a liquid sustained-release drug delivery system for theophylline using spray-drying technique

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Abstract

In recent years, great efforts have been devoted to the design of drug delivery systems. Many polymeric excipients have been studied in order to make drug release fit the desired profiles. The aim of this work was to design a theophylline oral suspension, as sustained release pharmaceutical preparation in order to decrease the plasma level fluctuations and adverse effects of theophylline. Microspheres were prepared by a spray-drying technique using theophylline and two polymers, ethyl cellulose and hydroxy propyl methyl cellulose phthalate (HPMCP) in different solvents and ratios of polymer to drug. The spray-dried microparticles were characterized in terms of shape and drug release. They were formulated in suspensions and evaluated by dissolution and stability studies. The type of polymer and spray dryer feed solution had a major impact on the *in vitro* performance and release of theophylline from microcapsules and suspensions. Only in the case of the microcapsules derived from HPMCP in acetone (as a solution feed) and ethyl cellulose in methylene chloride (as a suspension feed) in all of polymer to drug ratios, perfect spherical microcapsules with sustained release behavior were observed. Suspensions prepared from HPMCP microcapsules derived in acetone and ethyl cellulose microcapsules in methylene chloride met the requirements of USP for sustained release drug delivery systems. This report documents the suitability of these polymeric suspensions for encapsulated theophylline with a controlled release rate.

Keywords: Theophylline; Suspension; Sustained-Release; Microencapsulation; Spray-drying

INTRODUCTION

Much of the research efforts in developing novel drug delivery systems have focused on per oral sustained or controlled-release dosage forms. Among them multiple-unit dosage forms such as microparticles have become more popular because of their advantages over single-unit dosage forms. They may be spread out more uniformly in the gastrointestinal tract leading to more uniform drug absorption, reduced local irritation, and decreased retention of polymeric materials (1,2). They have been reported to be relatively unaffected by digestive tract activities, causing less variation in the results of

pharmacokinetic studies (3). Attention has been recently devoted to liquid sustained release preparations that are more palatable to pediatric and convenient to geriatric patients (1,4). A significant proportion of the populations including children and elderly have difficulty in swallowing solid oral dosage forms (2). This problem becomes more acute for the administration of sustained action dosage forms due to the increase in the volume of the delivery system. Formulating such systems as a suspension presents a novel means of circumventing the potential problems associated with the administration of such systems (5,6). Multiparticulate systems could also be formulated as liquid

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suspensions allowing ease of swallowing and flexibility in the dose adjustment for pediatric and geriatric patients (2). Many techniques for the preparation of microcapsules have been developed and reviewed (7). Spray drying is the transformation of liquid feed into a dried particulate form by spraying the feed into a hot drying gaseous medium (8). Different microcapsules for sustained release formulations have been prepared by this method (9-12). Spray drying is a one-step straight forward method for preparing microparticles and is preferable over other multi-step techniques such as solvent evaporation, solvent extraction and phase separation (9) and is less dependent on the solubility characteristics of the drug (11).

Theophylline is indicated for the treatment of the symptoms and reversible airflow obstruction associated with chronic asthma and other chronic lung diseases such as emphysema and chronic bronchitis (13). This drug has a short half-life and a narrow therapeutic range and as its absorption is prone to the effects of meals, the dosing management of the drug is difficult. Therefore, it has received a considerable amount of attention in sustained release formulation. Administration of sustained release suspension minimizes the plasma concentration fluctuations as well as the number of daily doses required. These advantages may also translate in avoiding toxic levels (3). The objective of this study was, therefore, to prepare sustained release suspension of theophylline microcapsules using ethyl cellulose and hydroxy propyl methyl cellulose phthalate (HPMCP) by spray-drying technique.

MATERIALS AND METHODS

Materials

The following materials were obtained from commercial sources. Ethyl cellulose (ethoxy content 46%, Aldrich, USA),

Acacia, ammonium hydroxide 25%, propyl paraben, Tween 80, Tween 20, PEG 6000, theophylline, methyl paraben, methylcellulose and HPMCP (Merck, Germany), cellulose acetate phthalate (Fluka, Switzerland), sorbitol syrup 70% and tragacanth (Modarres, Iran). All the other chemicals and solvents were of analytical grade.

Preparation of microcapsules

The drug was microencapsulated with the polymers by spray drying technique. The composition of feed solution or dispersed system is shown in Table 1. Two different methods were used to prepare the spray dryer feed. In the first method a solution of polymer and drug was utilized as feed solution. The polymer was first dissolved in appropriate solvent at room temperature and theophylline powder, in different weight ratios of drug to polymer, was then added to the solution and dissolved (Table 1 shows the details of feed solutions). In the second method, a dispersion of drug in polymer solution was employed as feed system. Polymer was dissolved in a solvent and finely-milled theophylline powder was then added into the polymer solution and uniformly dispersed (Table 1). The obtained liquid of the two methods were sprayed through the 0.5 mm nozzle of a spray-dryer (SD-O5, Labplant, England). The conditions of the spraying process for each preparation were: inlet air temperature 137 °C, outlet air temperature 75 °C, spray pressure 6 kg cm⁻² and feed rate always kept at 15ml/min. The spray-dried microparticles were harvested from the apparatus collector and kept under vacuum for 24 h, at room temperature.

To optimize conditions, the effect of different polymer to drug ratios (1:1, 2:1, 3:1) and different solvents on physical properties of microcapsules and their release behavior was evaluated. 1.5% PEG

6000 was used in either method as plasticizer.

Morphological studies of microcapsules

In order to demonstrate the formation of microcapsules and preliminary studies of their shape, spray-dried particles were studied using a simple optical microscope (HM-LUX3, Leitz, Germany). Samples of spray dried microspheres were selected randomly.

Drug content determination in microcapsules

The theophylline content of microcapsules was determined according to USP 23 (14). Briefly, a sample of microcapsules containing about 100 mg of drug was triturated with 20 ml of water, transferred to a 100 ml volumetric flask, 25 ml of 6 N ammonium hydroxide added, sonicated for 45 min, and cooled to room temperature. The mixture was then diluted with water to volume, and mixed. A portion of the mixture was filtered and the

first 20 ml of the filtrate was discarded. A portion of the filtrate was appropriately diluted with water and the absorbance of this solution and a standard solution of theophylline, similarly prepared at the wavelength of 273 nm with a suitable spectrophotometer using water as the blank was read and the quantity of theophylline in the microcapsules taken was determined.

Preparation of suspensions

Two suspension formulations were prepared as the medium of suspension (Table 2), either contains 100 mg/5ml theophylline (15).

Characterization of suspensions

- Rheology: The rheology of the suspensions was characterized using a Brookfield viscometer (Metler RM180) with measuring bob No. 2 and measuring tube No. 2.

Table 1. Formulation of feed solutions prepared for spray-drying

| Feed type | Polymer | Polymer to drug ratios | Solvent |
|--|--------------------------|------------------------|------------------------|
| Solution of both polymer and drug | Ethyl cellulose or HPMCP | 1:1, 2:1, 3:1 | Ethanol /water (80:20) |
| | Ethyl cellulose or HPMCP | 1:1, 2:1, 3:1 | Acetone |
| | Ethyl cellulose or HPMCP | 1:1, 2:1, 3:1 | Ammonium hydroxide |
| Dispersion of drug in polymer solution | Ethyl cellulose or HPMCP | 1:1, 2:1, 3:1 | Methylene chloride |

Table 2. Formulation details and composition of the medium of two suspensions

| Materials | Uses | Amount in suspensions | |
|---------------------------|------------------------------------|-----------------------|----------------|
| | | Suspension (1) | Suspension (2) |
| NF simple syrup | Sweetening agent | 1 part | 2 parts |
| Sorbitol syrup 70% | Sweetening agent | 1 part | 2 parts |
| Deionized distilled water | Vehicle | 3 parts | 1 part |
| Tragacanth | Suspending agent, Thickening agent | 0.6% | 0.6% |
| Tween 80 | Nonionic moisturizing agent | 0.02% | 0.02% |
| Methyl paraben | Preservative | 0.1% | 0.1% |
| Propyl Paraben | Preservative | 0.1% | 0.1% |

- Sedimentation volume: The sedimentation volume (F) was obtained based on the following equation: $F = \frac{V_1}{V_0}$, in

which, V_1 is the equilibrium volume of sediment and V_0 is the total volume of suspension. For equilibrium volume of sediment the sediment volume which remains unchanged for 3 weeks was considered (16,17).

- Degree of flocculation: Degree of flocculation (β) was estimated by the following equation: $\beta = \frac{F}{F_\infty}$, in which, F is

the sedimentation volume of the flocculated suspension, and F_∞ is the sedimentation volume of the suspension when deflocculated (16,17).

- Ease of redispersibility: For determination of ease of redispersibility (N), the number of shears required for redispersibility of a cylindrical glass graduate containing dispersed suspension, was considered (18).

- Freeze/thaw cycles: Inspection of physical and microscopic changes of suspensions undergoing sudden thermal changes was conducted. During this test suspensions were kept in a 40 °C oven for 24 h and then transferred to a 0 °C freezer for 24 h (19).

- Normal temperature fluctuation: Inspection of physical and microscopic changes of the suspension which occurred during a gradual decrease in temperature from 40 °C to -5 °C was also performed. For this purpose, suspensions were kept 24 h in each temperature (16).

- pH of suspensions: pH of suspensions was determined using a Rotring pH meter (5).

Drug release studies

The USP paddle method was used to determine the release of theophylline from microcapsules and suspensions according

to dissolution test No. 1 for sustained-release theophylline preparation using a dissolution tester (Pharma test, PTZWS3, Germany).

The dissolution medium was 900 ml of phosphate buffer (pH 4.5) maintained at 37 °C with a stirring rate of 75 rpm. At appropriate time intervals, 3 ml of samples was obtained and an equal volume of medium was added to maintain the volume constant. Samples were filtered, diluted, and analyzed for theophylline concentration at 273 nm in order to characterize the dissolution profiles.

Dissolution efficiency percentage after 8 h (DE₈%) was considered as a basis for comparison of the dissolution rates and was calculated based on the following equation:

$$DE \% = \frac{\int_0^t y \cdot dt}{ty_{100}} * 100$$

Basically, DE is the ratio of area under the dissolution profile time at a given time to the total area at the same time once the entire content is released (20).

Kinetic models

The goodness of fit of the release data was tested with the mathematical models as the following: First-order kinetic $\ln W = \ln W_0 - k_1 t$, Hixson-crowell's cube root of time $W^{1/3} = W_0^{1/3} - k_2 t$, and square-root of time $W = W_0 - kt^{1/2}$, where W is the amount of drug remaining to be released and W_0 is the initial amount of drug (21).

Statistical analysis

Student t-test was used to compare two means and one-way analysis of variance (ANOVA) was used to assess the differences between more than two means. P value of less than 0.05 was considered significant.

RESULTS

In order to study the effect of polymer type and feed solution on *in vitro* characteristics of the microcapsules, different polymers and solvents were used for preparation of microcapsules (Table 1). Microscopic studies showed that only in the case of the microcapsules derived from HPMCP in acetone (as a solution feed) and ethyl cellulose in methylene chloride (as a suspension feed) in all of polymer to drug ratios were perfect spherical microcapsules formed. Microscopic images of these two microcapsules are shown in Fig. 1. In other instances microparticles were not spherical and had a rough surface.

Encapsulation efficiency, calculated from actual drug contents were found to be $54.8 \pm 0.96\%$ ($n = 6$) for HPMCP microcapsules and $57.3 \pm 0.45\%$ ($n = 6$) for ethyl cellulose microcapsules. The dissolution profiles and $\%DE_8$ (Table 3) of microcapsules proved the results of microscopic studies. Only in the case of the microcapsules derived from HPMCP in

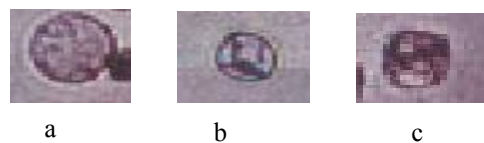


Fig. 1. a) HPMCP-theophylline (1:1) microcapsule, b) Ethyl cellulose-theophylline (1:1) microcapsules with drug protrusions on the surface, c) Encapsulated drug crystal produced with ethyl cellulose-theophylline (1:1).

acetone and ethyl cellulose in methylene chloride in all of polymer to drug ratios, sustained release behavior was observed. As indicated in Table 3, $\%DE_8$ for these two formulations were 54.5 % and 58.24%, respectively, which are significantly smaller than that of their mixture of spray-dried powder of drug and polymer which were 89.6% and 87.42%. Fig. 2 and Fig. 3 show the release profiles of HPMCP and ethyl cellulose microcapsules, respectively. This clearly indicates that the spray-dried particles of HPMCP in acetone and ethyl cellulose in methylene chloride at polymer to drug ratio of 1:1 are sustained in release

Table 3. $\%DE_8$ obtained for various microcapsules or suspensions

| Formulation | $\%DE_8$ | |
|--|----------|------|
| | Mean* | SD |
| Spray dried powder (ethyl cellulose-theophylline 1:1) | 87.42 | 0.10 |
| Spray dried powder (HPMCP-theophylline 1:1) | 89.62 | 0.25 |
| Microcapsules (ethyl cellulose-theophylline 1:1) | 58.24 | 0.19 |
| Microcapsules (HPMCP-theophylline 1:1) | 54.54 | 0.26 |
| Suspension 1 (ethyl cellulose-theophylline) | 62.17 | 0.10 |
| Suspension 1 (ethyl cellulose-theophylline) after 24 hr | 62.24 | 0.25 |
| Suspension 1 (ethyl cellulose-theophylline) after 1 week | 62.25 | 0.29 |
| Suspension 2 (ethyl cellulose-theophylline) | 61.48 | 0.12 |
| Suspension 2 (ethyl cellulose-theophylline) after 24 hr | 62.54 | 0.74 |
| Suspension 2 (ethyl cellulose-theophylline) after 1 week | 63.58 | 0.35 |
| Suspension 1 (HPMCP-theophylline) | 64.34 | 0.22 |
| Suspension 1 (HPMCP-theophylline) after 24 hr | 64.47 | 0.23 |
| Suspension 1 (HPMCP-theophylline) after 1 week | 64.53 | 0.47 |
| Suspension 2 (HPMCP-theophylline) | 63.66 | 0.68 |
| Suspension 2 (HPMCP-theophylline) after 24 hr | 64.74 | 0.46 |
| Suspension 2 (HPMCP-theophylline) after 1 week | 66.25 | 0.82 |

$\% DE_8$: Dissolution efficiency percent after 8 h.

*Mean of 6 measures.

Table 4. Values of correlation coefficients (R^2) and constants (K) for fitting of data to different kinetic models

| Formulation | First order | | Higuchi | | Hixon crowell | |
|---|-------------------|-------------------|-------------------|--------------------------|-------------------|--------------------|
| | R^2 | K (1/min) | R^2 | K ($\text{min}^{1/2}$) | R^2 | K (1/min) |
| Microspheres | | | | | | |
| Ethyl cellulose-theophylline (1:1) | 0.9991± 0.0077 | 0.0017± 0.0251 | 0.9958± 0.0236 | 2.3094± 0.8731 | 0.9112± 0.0061 | 0.0039± 0.02542 |
| HPMCP-theophylline (1:1) | 0.9941± 0.0073 | 0.0018± 0.0012 | 0.9832± 0.0441 | 2.136± 0.8562 | 0.8675± 0.0263 | 0.0054± 0.00001 |
| Suspensions | | | | | | |
| Ethyl cellulose-theophylline (suspension 1) | 0.9932± 0.0328 | 0.0036± 0.1853 | 0.9356± 0.0327 | 3.0001± 0.2429 | 0.9251± 0.0315 | 0.0149± 0.0121 |
| Ethyl cellulose-theophylline (suspension 2) | 0.9941± 0.0068 | 0.0039± 0.0061 | 0.9691± 0.0221 | 3.4102± 0.2821 | 0.9238± 0.0271 | 0.0125± 0.0004 |
| HPMCP-theophylline (suspension 1) | 0.9963± 0.0127 | 0.0054± 0.0008 | 0.9619± 0.0128 | 3.9131± 0.0071 | 0.886± 0.0213 | 0.0167± 0.0004 |
| HPMCP-theophylline (suspension 2) | 0.9981± 0.0161 | 0.0058± 0.0029 | 0.9889± 0.0038 | 4.1591± 0.0351 | 0.9596± 0.0047 | 0.0089± 0.00015 |

Values have been presented as mean \pm SD (n = 6).

behavior. In other formulations containing ethyl cellulose derived from ethanol/water, ammonium hydroxide solution or acetone or HPMCP derived from ethanol/water or ammonium hydroxide solution and HPMCP in methylene chloride suspension; drug was released very quickly within the first 20 min and did not show sustained-release manner (data not shown).

A representative release profile for HPMCP-theophylline spray-dried particles formed in methylene chloride is shown in Fig. 4. Although the release rate in formulation containing polymer to drug ratio of 3:1 is to some extent sustained and much slower than the other two formulations, however, the release rate is still faster than desired. The release profile of microparticles of ethyl cellulose-theophylline formed using acetone as dispersion medium is illustrated in Fig. 5. Increasing the polymer to drug ratio resulted in a decrease in dissolution rate, however, even with the highest ratio of polymer to drug being 3:1 the sustained release profile did not meet the objective of the study.

In order to obtain meaningful information for the release models, the drug release profiles were fitted to the 3

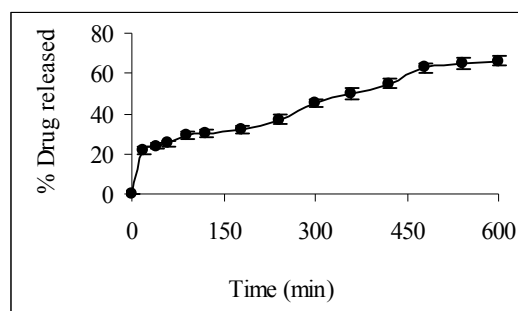


Fig. 2. Release profile of HPMCP-theophylline (1:1) microcapsules formed in acetone (n = 6). USP paddle method was used with 900 ml phosphate buffer (pH 4.5) at 37 °C and stirring rate of 75 rpm according to USP XXIII dissolution test, No. 1 for sustained release microcapsules.

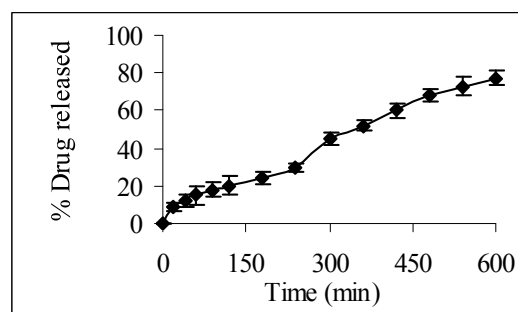


Fig. 3. Release profile of ethyl cellulose-theophylline (1:1) microcapsules formed in methylene chloride (n = 6). USP paddle method was used with 900 ml phosphate buffer (pH 4.5) at 37 °C and stirring rate of 75 rpm according to USP XXIII dissolution test, No. 1 for sustained release microcapsules.

different kinetic models and the goodness of the fit of the release data was tested. As shown in Table 4, although there is no significant difference between correlation coefficients of the three models, first order kinetic is the best fitted method for all the formulations.

Suspensions prepared from microcapsules also showed a sustained release which is in the acceptable range of USP. Fig. 6 and Fig.7 report the release profiles of suspensions prepared from HPMCP and ethyl cellulose microcapsules. No significant difference ($P>0.05$) was observed in %DE for suspension 1 of both polymers on first day and after 1 week which indicates the suspension stability. For suspension 2 of both polymers a significant difference observed 1 week after production ($P<0.05$), however both suspensions met the USP requirements 1 week after production.

During freeze/thaw cycles and normal temperature fluctuation tests for both suspensions, no changes in flocculation and crystallization were observed. Some of physical tests performed on suspensions are listed in Table 5 which indicates the suitability of the suspension properties. Both suspensions of two types of microcapsules had a thixotropic rheogram. Suspension 1 had more thixotropic property and less viscosity compared to suspension 2 (Fig. 8, Fig. 9).

DISCUSSION

The encapsulation method by spray-drying is simple and rapid, since spray-drying combines drying of feed solution and embedding of the drug into the polymeric network processes into a one-step operation (9). In order to optimize the production of microcapsules and the efficiency of the spray dryer, a suitable feed type must be used. It is useful to compare the type of product formed from a solution feed with a suspension feed. On

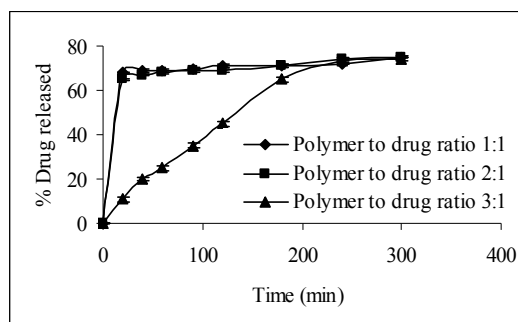


Fig. 4. Release profiles of HPMCP-theophylline spray-dried powder formed in methylene chloride ($n = 6$) in different ratios of polymer to drug. USP paddle method was used with 900 ml phosphate buffer (pH 4.5) at 37 °C and stirring rate of 75 rpm according to USP XXIII dissolution test, No. 1 for sustained release microcapsules.

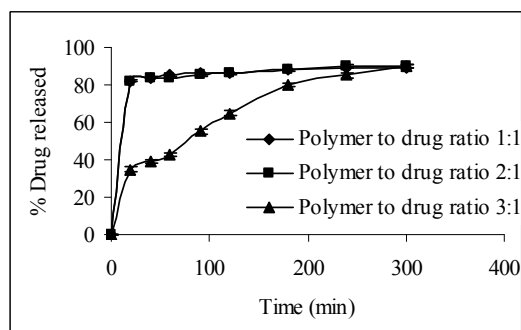


Fig. 5. Release profiles of ethyl cellulose-theophylline spray-dried particles formed in acetone ($n = 6$) in different ratios of polymer to drug. USP paddle method was used with 900 ml phosphate buffer (pH 4.5) at 37 °C and stirring rate of 75 rpm according to USP XXIII dissolution test, No. 1 for sustained release microcapsules.

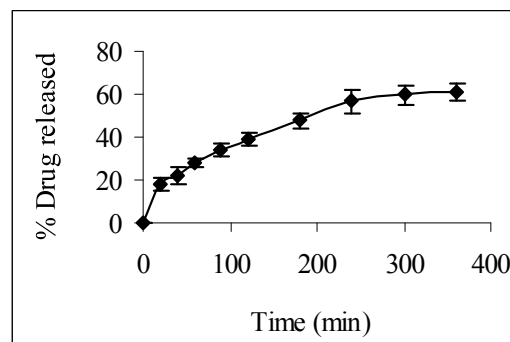


Fig. 6. Release profile of ethyl cellulose-theophylline (1:1) suspension ($n = 6$). USP paddle method was used with 900 ml phosphate buffer (pH 4.5) at 37 °C and stirring rate of 75 rpm according to USP XXIII dissolution test, No. 1 for sustained release microcapsules.

drying a droplet from a solution feed, the products formed could contain spray dried polymer or drug individually without coating, spray dried drug with a thin polymeric film or drug particles on the surface of the polymer (Fig. 10), while, with a suspension feed, for majority of the drug, the polymer forms an envelope around the drug and the dried products are microencapsulated drug crystals with smooth surfaces compared to solution feed spray dried products (Fig. 10) (22).

In our study for the first method, that is the solution feed, intact microcapsules with a smooth surface and smallest amount of drug crystals and rods on the surface of microcapsules only formed with the polymer HPMCP in acetone which can be attributed to the high viscosity and excellent adhesive properties of the polymer and quick evaporation of solvent (Fig. 1a) compared to ethanol/water or ammonium hydroxide solution of drug and polymers. The microcapsules obtained under this condition were spherical particles as shown in Fig. 1a. The mean diameter of spray-dried microspheres ranged from 5 to 10 microns. In other instances in the first method, microcapsules were not intact and particles yielded had rough surfaces. In the second method that is suspension feed, perfect spherical microcapsules with a smooth surface were formed when ethyl cellulose in methylene chloride used as the polymer (Fig. 1b and 1c). The spray dried drug particles coated with the spray dried polymer were obtained under these circumstances (Fig. 1c). Microparticles derived from HPMCP, in some cases, were not spherical and were broken with a rough surface. It had been found to be difficult to form smooth spherical particles by spray-drying technique due to the formation of fibers that are formed by insufficient forces present to break up the liquid into droplets during the spray-drying of the polymeric solution (23). The disadvantage of spray-

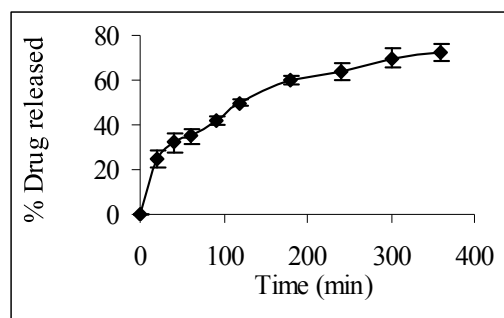


Fig. 7. Release profile of HPMCP-theophylline (1:1) suspension (n = 6). USP paddle method was used with 900 ml phosphate buffer (pH 4.5) at 37 °C and stirring rate of 75 rpm according to USP XXIII dissolution test, No. 1 for sustained release microcapsules.

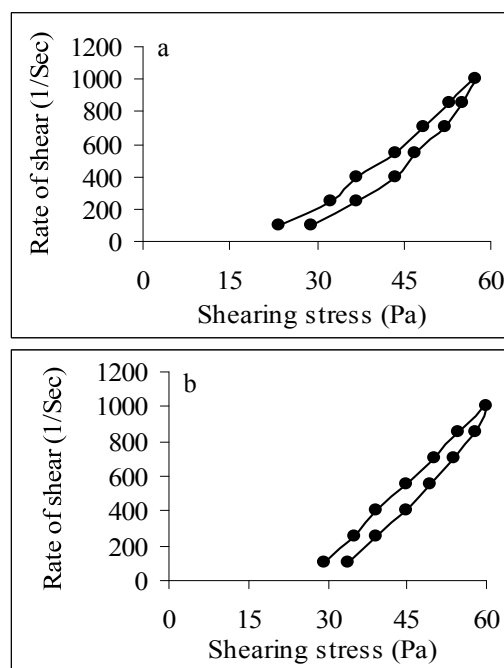


Fig. 8. Rheograms of suspension 1 of a) Ethyl cellulose-theophylline microcapsules, b) HPMCP-theophylline microcapsules. Rheology of the suspensions was characterized using a Brookfield viscometer (Metler RM180) with measuring bob No. 2 and measuring tube No. 2.

drying technique used in this study was the low yields which can be explained both by the relatively low volume of feed solution sprayed for the preparation of each batch of microspheres (100-200 ml) and by the structure of the spray dryer apparatus that is not equipped with a trap to recover the smaller and lighter particles which are

exhausted by the aspirator. Adhesion of the spray-dried powder onto the walls of drying chamber and cyclone collector is another problem associated with this technique. The use of a small amount of additives as talc or colloidal silica could reduce the adhesion phenomena. The use of these additives was avoided in the systems in order not to introduce another trivial variable to the method which could affect the characteristics of spray-dried particles and so, evaluating the effect of other parameters becomes more difficult. In samples of HPMCP-theophylline and ethyl cellulose-theophylline which yielded microspheres with sustained-release behavior about 50% of the particles had the diameter of 7 microns or more. The dissolution profiles of microcapsules proved the results of microscopic studies. Only in the case of the microcapsules derived from HPMCP in acetone and ethyl cellulose in methylene chloride in all of polymer to drug ratios, sustained release behavior was observed. As illustrated in Fig. 2 for HPMCP microcapsules up to 5 h only 40% of drug was released and it was increased to 60% after 10 h. The minimal burst release (about 20%) observed at the early stage of release profiles may be related to the broken microparticles or drug crystals not engulfed with polymer. This clearly indicates that the spray-dried particles of HPMCP at polymer to drug ratio of 1:1 are sustained in release behavior. These data show that microcapsule formation results in sustained release profile and therefore lower DE. For microcapsules of ethyl cellulose-theophylline in methylene chloride an appropriate sustained manner was observed (Fig. 3). The dispersion of drug in the solvent and polymer coating around the drug particles are effective factors in obtaining sustained release profiles (22). Increasing the polymer to drug ratio resulted in a decrease in dissolution rate but not as much that is necessary for sustain-

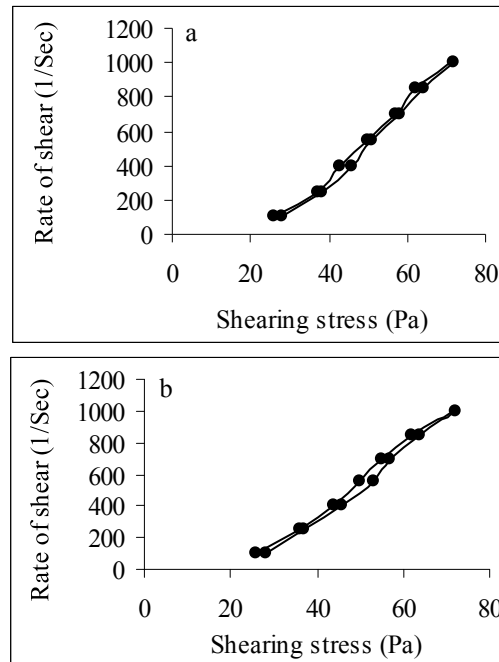


Fig. 9. Rheograms of suspension 2 of a) Ethyl cellulose-theophylline microcapsules, b) HPMCP-theophylline microcapsules. Rheology of the suspensions was characterized using a Brookfield viscometer (Metler RM180) with measuring bob No. 2 and measuring tube No. 2.

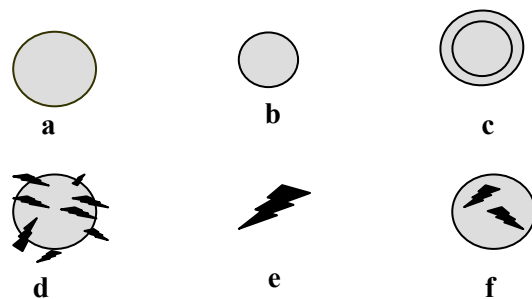


Fig. 10. Possible types of products obtained by spray drying a solution-feed (a-d) and a suspension-feed (a-f). a) Free spray dried polymer, b) Spray dried drug, c) Encapsulated spray dried drug, d) Polymer with drug protrusions on the surface, e) Free drug crystal, and f) Encapsulated drug crystal.

ing the drug release. Increasing polymer content may result in an increase in coating thickness surrounding the drug particles, thereby increasing the distance traveled by the drug through the coat. These findings are in agreement with Pamieri et al. study (12).

Two suspensions prepared from microcapsules had the desired

characteristics as suitable drug delivery systems for controlled delivery of theophylline. They showed a sustained release profile, suitable physical and performance properties which were determined by calculating N , F and β factors and a thixotropic rheogram that are features of suspension good performance. Both suspensions were stable under accelerated stability tests and met the requirements of USP in these circumstances.

In conclusion, the type of polymer and feed solution of the spray dryer had a major impact on the *in vitro* performance and release of theophylline from microcapsules and suspensions. The obtained suspensions met all the requirements and can be proposed as sustained release delivery systems for precise dosing of theophylline as sustained-release liquid formulation.

ACKNOWLEDGMENTS

This work has been supported by Research Council of Isfahan University of Medical Sciences.

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