

## Preparation and In Vitro Evaluation of a Microballoon Delivery System for Theophylline

Maryam Kouchak\* and Ali Badrian

*Department of Pharmaceutics, School of Pharmacy, Ahwaz Jundishapur University of Medical Sciences, Ahwaz, Iran.*

---

### Abstract

A multiple-unit oral floating system was prepared using the emulsification-solvent diffusion method to prolong the gastric emptying time of theophylline. For this purpose, theophylline, ethyl cellulose and dibutyl phthalate were dissolved in an ethanol/dichloromethane mixture, added to 0.1 M HCl containing NaCl (20%) or saturated theophylline and/or different concentrations of polysorbate 80 and polyvinyl alcohol. The mixture was stirred at different speeds for 3 h. The resulting microspheres were separated from the solution by filtration. Physical characteristics, including the shape and size distribution, floating capability, drug loading and drug release of the resulting theophylline microspheres were investigated.

The prepared microspheres tended to float over the simulated gastric medium for over 12 h. Addition of NaCl (20%) to the aqueous phase increased the drug loading of microballoons. The mean geometric diameter of microspheres decreased, as the stirring speed rate or the polysorbate 80 concentration were increased. Microballoons prepared at higher stirring rates released their drug content faster. Also, it is concluded that particle size and floating capability of microballoons could be adjusted by altering the stirring rate during microencapsulation.

**Keywords:** Floating drug delivery systems; Microballoons; Emulsion-solvent diffusion; Hollow microspheres.

---

### Introduction

Floating drug delivery systems offer a good protection against early and random gastric emptying of non-digestible forms (1). These systems remain buoyant on the gastric content for extended periods of time because of their low densities compared to that of the gastric fluid (2). Floating dosage forms can be classified as single- and multiple-unit system (3).

For conventional oral sustained or prolonged-release dosage forms, multiple units are more advantageous than single units because

they disperse widely and uniformly along the gastrointestinal tract and could lessen intra- and inter-subject variability. For gastric-retentive systems, multiple units may have the advantage of avoiding all- or nothing emptying, and increase the probability that some of the dosage form will remain in the stomach (3). Approaches devising multiple unit floating systems include multiple unit HBS (3), polycarbonate microspheres (4), alginate beads (5-7), charged ion exchange resins with bicarbonate (8-11), air compartment multiple unit systems (7), coated granules with a dual effervescent layer (3, 12) and emulsion-solvent diffusion (3, 13-16). At present, hollow microspheres are considered to be one of the most promising buoyant systems, because

---

\* Corresponding author:

E-mail: koochekm@yahoo.com

they combine the advantages of multiple unit systems and good floating properties (17). These systems are also called "microballoons" due to their low-density core (14, 16, 18). Generally, techniques used to prepare hollow microspheres involve simple solvent evaporation or solvent diffusion/evaporation methods. Polycarbonate, Eudragit S<sup>®</sup>, cellulose acetate, calcium alginate, agar and low methoxylated pectin are commonly used as polymers. Buoyancy and drug release are dependent on the quantity of polymer, the plasticizer-polymer ratio and the solvent used (19, 20).

In this study, an emulsion-solvent diffusion/evaporation technique was used to prepare a floating controlled-release system for theophylline and the influence of several factors on various physical characteristics, including the particle size, drug loading, dissolution and floating properties of the resulting microspheres, were investigated.

Theophylline is a bronchodilator used in the treatment of asthma (21). So far different kinds of floating dosage forms have been prepared for theophylline. Atyabi et al. developed the ion-exchange resin beads loaded with theophylline and bicarbonate, coated with a semipermeable membrane (8). Carbon dioxide was released on contact with the acidic gastric juice. Studies in human volunteers, using gamma-scintigraphy, showed a prolonged residence time for beads (9). Stithit et al. used a novel emulsion-solvent evaporation process to obtain microspheres containing theophylline. The drug-polymer (cellulose acetate butyrate and Eudragit RL<sup>®</sup>100 [1:1]) dispersions are pressurized under CO<sub>2</sub>, which dissolves within them and forms bubbles upon the release of the pressure, giving microspheres with round cavities enclosed in the dispersed drug polymer droplets. They float for more than 24 h in pH 1.2 and 7.5 buffers (22). Streubel et al. developed foam-based floating microparticles consisting of polypropylene foam powder, drug (chlorpheniramine maleate, diltiazem HCl, theophylline or verapamil HCl) and polymer (Eudragit RL<sup>®</sup> or polymethyl methacrylate). They were prepared by soaking the microporous foam carrier with an organic solution of drug and polymer, followed by subsequent drying. The mixture was poured into an organic

liquid (ethanol or methylene chloride), forming a suspension. The polypropylene foam particles acted like microsponges, absorbing the organic liquid, and becoming free-flowing, low-density microparticles following solvent evaporation. Good in vitro buoyancy was observed in most cases and a broad variety of drug release patterns could be achieved by varying drug loading and the type of polymer used, with more than 77% or 98% of particles remain floated for at least 8 h depending on the polymer type (Eudragit RS<sup>®</sup> or polymethyl methacrylate, respectively) and initial drug loading of the system (10% or 23%) (23). Chitosan microcapsules containing theophylline and sodium carboxymethyl cellulose prepared by using an emulsion-phase separation method. The acetic acid and sodium carboxymethyl cellulose concentrations played an important role in controlling the floating property of the microcapsules (24).

Limited investigations have been conducted on the preparation of floating microparticulate systems based on the emulsion-solvent diffusion/evaporation technique (3, 13-16). The major problem with the o/w emulsification technique is the low encapsulation efficiency of moderately water-soluble drugs such as theophylline, caffeine and salicylic acid. In cases like this, the drug can diffuse from the organic dispersed phase into the aqueous continuous phase, which results in poor entrapment (21). The choice of theophylline, as the model drug, is based on: (i) the biopharmaceutics classification system, since it is classified as a Class I drug that has a high solubility as well as a high permeability (25); and (ii) the fact that it is a targeted drug for sustained delivery (20, 22). The aim of this study was to devise this technique in order to prepare microballoons with a high theophylline encapsulation efficacy, as a water-soluble drug model.

## Experimental

### Materials

Materials were obtained from commercial sources: ethylcellulose 100 cps (Dow Chemicals), theophylline anhydrous, polyvinyl alcohol (PVA), dichloromethane, polysorbate 80 and dibutyl phthalate (Merck, Germany).

## Methods

### Preparation of microspheres

For preparation of the base formula, theophylline (200 mg), ethyl cellulose (200 mg) and dibutylphthalate (40 mg) were dissolved in a mixture of dichloromethane and ethanol 96% (3: 7). The solution was added to 100 ml 0.1 M hydrochloric acid (as an aqueous solution) and stirred for 3 h at 600 rpm. The resulting microspheres (formula F) were separated from the solution by filtration.

In order to find an appropriate formulation, various aqueous media using PVA, NaCl and polysorbate 80 at concentrations outlined in table 1 within a constant base of 0.1 M HCl, were prepared and investigated. Formulas D<sub>1</sub>, D<sub>2</sub> and D<sub>3</sub>, which had a similar composition to A<sub>2</sub>, were prepared at different stirring rates of 500, 700 and 800 rpm, respectively (Table 1). Each formulation was prepared three times.

### Solubility of theophylline in different concentrations of NaCl

One gram theophylline was added to 100 ml 0.1 M HCl containing 0, 5, 10, 15

and 20% (w/w) NaCl and stirred for 3 h at room temperature. The resulting mixtures were filtered through 0.45- $\mu$ m membrane filters and the concentration of theophylline within the filtrate solutions was assayed spectrophotometrically at 270 nm.

### Characterization of the microspheres

#### Floating ability

Floating behavior of the prepared microspheres was studied in a 0.1 M HCl solution containing 0.02% polysorbate 80. The solution was stirred at 100 rpm for 12 h and the buoyant beads counted every hour.

#### Size and shape

Size distribution of the prepared microspheres was measured by the sieve analysis method. The logarithm of the particle size was plotted against the percentage of cumulative frequency on a probability scale and the logarithm of the geometric mean diameter, which is the particle size equivalent to 50%, on the probability scale was obtained (18).

**Table 1.** The type and amount of ingredients present within the aqueous medium, as well as the stirring rate of various formulations.

Formulation	PVA (%)	NaCl (%)	Polysorbate80 (%)	Theophylline	Stirring rate (rpm)
F	-	-	-	-	600
V <sub>1</sub>	0.5	-	-	-	600
V <sub>2</sub>	2	-	-	-	600
V <sub>3</sub>	5	-	-	-	600
M <sub>1</sub>	-	-	-	Saturated	600
M <sub>2</sub>	0.5	-	-	Saturated	600
M <sub>3</sub>	2	-	-	Saturated	600
M <sub>4</sub>	5	-	-	Saturated	600
A <sub>1</sub>	-	20	-	-	600
A <sub>2</sub>	-	20	0.2	-	600
A <sub>3</sub>	-	20	0.5	-	600
A <sub>4</sub>	-	20	1	-	600
D <sub>1</sub>	-	20	0.2	-	500
D <sub>2</sub>	-	20	0.2	-	700
D <sub>3</sub>	-	20	0.2	-	800

For morphological examination, the microspheres were sputtered with platinum and viewed under a scanning electron microscope.

#### Drug loading

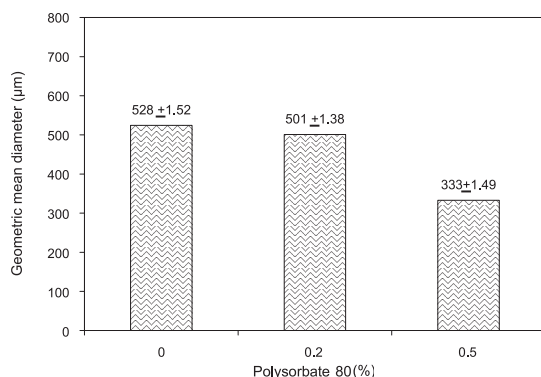
To assess the drug loading, specific amounts of microballoons were dissolved in small volume of ethanol and added to a large amount of water. The precipitated ethyl cellulose was filtered and the remaining solution analyzed spectrophotometrically at 271 nm.

#### Drug release

Drug release from 100 mg of microballoons was studied using a USP dissolution apparatus I, containing 900 ml of 0.1 M HCl (pH 1), preheated and maintained at  $37 \pm 0.5^\circ\text{C}$ . The basket was rotated at a speed of  $50 \pm 2$  rpm. Samples were removed periodically for 24 h, followed by the replacement of an equal volume of the test medium and analyzed at 270 nm after dilution.

#### Assay for NaCl in microspheres

To calculate the NaCl content of formulations A<sub>2</sub> and D<sub>3</sub>, 50 mg samples were dispersed in 10 ml distilled water and stirred at 100 rpm for 48 h. microballoons were filtered and the concentration of NaCl within the filtrate solution was determined using a solution containing 0.1 N AgNO<sub>3</sub> in 100 ml glacial acetic acid, 75 ml methanol and 0.5 ml eosin Y TS (19).



**Figure 1.** Effect of polysorbate 80 concentration present within the external phase on the particle size (n=3, mean ± SD).

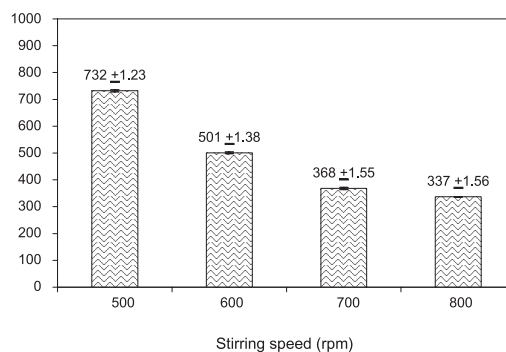
## Results and Discussion

#### Particle size and shape

With application of 0.1 M HCl alone as the aqueous external phase of the emulsion (formula F), spherical microballoons were obtained. In the presence of PVA, with or without saturated theophylline (V-series and M-series), no microspheres were produced. The applicable range of PVA (as an emulsifier) for the preparation of microspheres, using the o/w emulsion-solvent evaporation technique, in terms of various utilized drugs and polymers is very different (28). The levels used in this work resulted in the preparation of an aqueous colloidal dispersion of ethyl cellulose after evaporation of dichloromethane and ethanol.

When using a solution containing 20% NaCl in 0.1 M HCl, formation of microballoons was practicable (formula A<sub>1</sub>).

Presence of a low amount of polysorbate 80 (0.2%) accompanied with 20% NaCl in 0.1 M HCl improved the shape uniformity of microspheres. As can be seen in figure 1, the increase in the level of polysorbate 80 within the external phase led to a decrease in the particle size of microspheres, such that no microspheres were formed at the concentration of 1% (A<sub>4</sub>). This was due to a fall in surface tension of the solution and enhancement of drug and polymer solubilization within the medium. The mean particle size of microspheres decreased, as the stirring speed increased (Figure 2). Statistical analysis of data, using ANOVA (single factor),



**Figure 2.** Effect of stirring rate on the particle size distribution of microspheres (n=3, mean ± SD).



**Table 4.** The NaCl content of microspheres (n=3, mean ± SD).

Formulation	NaCl (%)
A <sub>2</sub>	14.4 ± 0.4
D <sub>3</sub>	14.8 ± 0.8

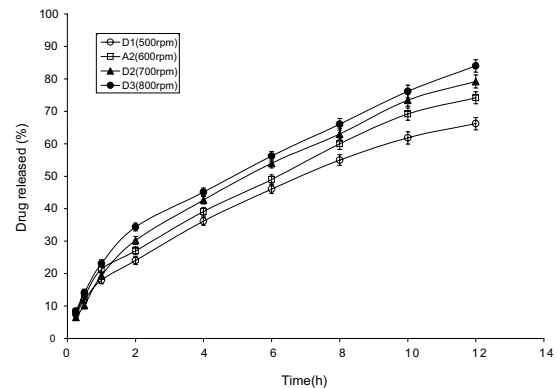
This reduces solvent loss, thereby reducing the polymer precipitation rate, and thus allowing an increased loss of drug from the microspheres being formed, before an adequate polymeric diffusion barrier could be formed (21).

*NaCl content*

Table 4 shows the NaCl content of A<sub>2</sub> and D<sub>3</sub> formulations. Concerning the therapeutic dose of theophylline, only a little amount of NaCl exists in each dose of microballoons and this will not be harmful for the user.

*Drug release*

Figure 4 compares theophylline release profiles of microballoons prepared at different stirring rates. Increasing the speed caused a faster drug release. One explanation for this phenomenon could be the reduction of particle size at higher speeds. The release rate will increase with a decrease in particle size, as a result of the increase in surface area (21). A linear relationship between the geometric mean diameter and the time for 50% of encapsulated drug to be released ( $t_{50\%}$ ) was found in this study (figure 5). Analogous results have also been observed by Suzuki et al (31) and Pongpaibul et al. (31, 32). In all formulations, the initial release of theophylline was relatively fast, showing a burst effect in the first 1-2 h. This is attributed to the release of the drug from the surface of microballoons, as the drug might have migrated to the surface along with alcohol during the solvent diffusion and with water during the drying



**Figure 4.** Effect of the stirring rate on the rate of drug release (n=3, mean ± SD).

process (21). For studying the kinetics of drug release, dissolution data were fitted to different kinetics models including the zero-order ( $M_t/M_\infty$  versus t), first-order ( $-\ln(1-M_t/M_\infty)$  versus t), and square root of time ( $M_t/M_\infty$  versus  $\sqrt{t}$ ) using linear and nonlinear regression. The ratio of  $M_t/M_\infty$  represents the fraction of drug released at time t. Square regression coefficient ( $R^2$ ) and F-statistic were calculated for each model (Table 5). As could be expected for granular matrix systems, all formulations followed a square root of time kinetics.

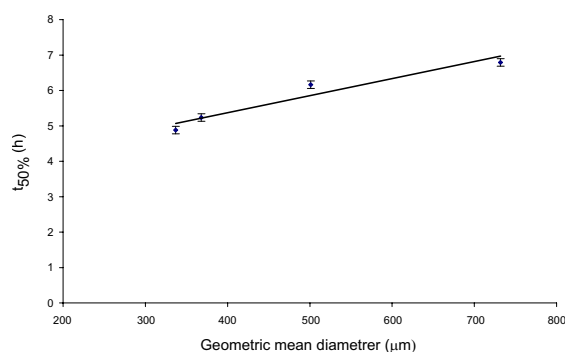
**Conclusion**

The present study reports the development of a novel multiple-unit floating dosage form for theophylline based on an o/w emulsion-solvent diffusion/evaporation method, using 100 cps ethylcellulose. This method has been applied for the preparation of microballoons system with other polymers and drugs (13-18).

Hollow theophylline microspheres were formed by preparing a solution of ethanol/dichloromethane containing the drug and polymer. On pouring into 0.1M HCl solution

**Table 5.** Goodness of fitting indices of drug release data with different kinetics models.

Kinetics model		A2	D1	D2	D3
Zero-order	R <sup>2</sup>	0.9920	0.9963	0.9959	0.9878
	F-statistic	869.1	1863	1697	565
First-order	R <sup>2</sup>	0.9789	0.9629	0.9645	0.9703
	F-statistic	324.3	181.7	190.4	229.1
Square root of time	R <sup>2</sup>	0.9955	0.9982	0.9987	0.9972
	F-statistic	1535	3796	5455	2465



**Figure 5.** Relationship between particle size and 50% of drug to be released ( $t_{50\%}$ ) ( $n=3$ , mean  $\pm$  SD).

containing 20% NaCl, an emulsion containing the dispersed polymer/drug/solvent particles, was formed, via a coacervation-type process. From this ethanol (a solvent for the polymer) was rapidly diffused, precipitating polymer at the surface of the droplet to give a hard-shelled particle enclosing the drug dissolved in the dichloromethane. At this point, a gas phase of dichloromethane was generated within the particle, which diffused through the shell.

In such a process, both drug and polymer should be insoluble in water. The problem existing with a low encapsulation efficiency of theophylline as a water-soluble drug was resolved by the use of NaCl. The presence of salt within the microencapsulation medium decreased the solubility of theophylline and the increased encapsulation efficiency. Polysorbate 80 (0.2%), as an emulsifier, accelerated the formation of droplets and stabilized them in the external phase. Particle size, floating capability and drug release of microballoons could be adjusted by altering the stirring rate during microencapsulation.

## References

- (1) Singh BN and Kim KH. Floating drug delivery systems: An approach to oral controlled drug delivery via gastric retention. *J. Control. Release* (2000) 63: 235-59
- (2) Moës AJ. Gastroretentive dosage forms. *Crit. Rev. Ther. Drug Carrier Syst.* (1993) 10: 143-95
- (3) Fell JT and Collet JH. Prolonged gastric retention using floating dosage forms. *Pharm. Technol.* (2000) 3: 82-9
- (4) Thanoo BC, Sunny MC and Jayakrishnan A. Oral sustained release drug delivery systems using polycarbonate microspheres capable of floating on gastric fluid. *J. Pharm. Pharmacol.* (1993) 45: 21-4
- (5) Whitehead L, Fell JT, Collett JH, Sharma HL and Smith AM. Floating dosage forms: an *in vivo* study demonstrating prolonged gastric retention. *J. Control. Release* (1998) 55: 3-12
- (6) Whitehead L, Fell JT and Collett JH. Development of a gastroretentive dosage form. *Eur. J. Pharm. Sci.* (1996) 4: S182
- (7) Iannuccell, V Coppi G, Bernabe MT and Cameroni R. Air compartment multiple-unit system for prolonged gastric residence. Part I. Formulation study. *Int. J. Pharm.* (1998) 174: 47-62
- (8) Atyabi F, Sharma HL, Mohammad HAH and Fell JT. Controlled drug release from coated floating ion exchange resin beads. *J. Control. Release* (1996) 42: 25-8
- (9) Atyabi F, Sharma HL, Mohammad HAH and Fell J T. *In vivo* evaluation of a novel gastric retentive formulation based on ion exchange resins. *J. Control. Release* (1996) 42: 105-13
- (10) Atyabi F and Kouchak M. *In vitro* evaluation of a new buoyant system for oral application. *Daru* (1999) 7: 26-30
- (11) Kouchak M and Atyabi F. Ion-exchange, an approach to prepare an oral floating drug delivery system for diclofenac. *Iranian J. Pharm. Res.* (2004) 2: 93-7
- (12) Ichikawa M, Watanabe S and Miyake Y. A new multiple-unit oral floating dosage system, I: preparation and *in vitro* evaluation of floating and sustained-release characteristics. *J. Pharm. Sci.* (1991) 80: 1062-6
- (13) Kawashima Y, Niwa T, Takeuchi H, Hino T and Ito Y. Preparation of multiple unit hollow microsphere (microballoons) with acrylic resin containing tranilast and their drug release characteristics (*in vitro*) and floating behavior (*in vivo*). *J. Control. Release* (1991) 16: 279-90
- (14) Kawashima Y, Niwa T, Takeuchi H, Hino T and Ito Y. Hollow microspheres for use as a floating controlled drug delivery system in the stomach. *J. Pharm. Sci.* (1992) 81: 135-40
- (15) Soppimath KS, Kulkarni AR and Aminabhavi TM. Development of hollow microspheres as floating controlled-release systems for cardiovascular drugs: preparation and release characteristics. *Drug Dev. Ind. Pharm.* (2001) 27: 507-15
- (16) Sato Y, Kawashima Y, Takeuchi H and Yamamoto H. *In vitro* and *in vivo* evaluation of riboflavin-containing microballoons for a floating controlled drug delivery system in healthy humans. *Int. J. Pharm.* (2004) 275: 97-107
- (17) Mitra SB. Sustained-release oral medicinal delivery device. *US patent 4451260* (1984) 29
- (18) Jayanthi G, Jayaswal SB and Srivastava AK. Formulation and evaluation of terfenadine microballoons for oral controlled release. *Pharmazie* (1995) 50: 769-70
- (19) Reddy LH and Murthy RS. Floating dosage systems in drug delivery. *Crit. Rev. Ther. Drug Carr. Syst.* (2002) 19: 553-85
- (20) Bardonnnet PL, Faivre V, Pugh WJ, Piffaretti JC and Falson F. Gastroretentive dosage forms: overview and special case of *Helicobacter pylori*. *J. Control. Release*,

- in press*.(2006) 111: 1-18
- (21) Watts PJ, Davies MC and Melia CD. Microencapsulation using emulsification/solvent evaporation. *Crit. Rev. Ther. Drug Carrier Syst.* (1990) 7: 235-58
- (22) Stithit S, Chen W and Price JC. Development and characterization of buoyant theophylline microspheres with near zero order release kinetics. *J. Microencapsul.* (1998) 15: 725-37
- (23) Lindenberg M, Kopp S and Dressman JB. Classification of orally administered drugs on the World Health Organization model list of essential medicines according to the biopharmaceutics classification system. *Eur. J. Pharm. Biopharm.* (2004) 58: 265-78
- (24) Lin SY and Lin PC. Effect of acid type, acetic acid and sodium carboxymethyl cellulose concentrations on the formation, micromeretics, dissolution and floating properties of theophylline chitosan microcapsules. *Chem. Pharm. Bull.* (1992) 40: 2491-7
- (25) Sweetman SC. (Ed.) *Martindale, the Complete Drug Reference*. 34<sup>th</sup> ed. Churchill Livingstone, Pharmaceutical Press, London. (2005) 798, 806
- (26) Martin A, Butamante P and Chun AHC. *Physical Pharmacy*, 4<sup>th</sup> ed. Lea & Febiger Philadelphia (1993) 427-28
- (27) United State Pharmacopoeia convention, *USP26/NF21*, *the United State Pharmacopoeia-National formulary*. The Convention, Washington, D.C. (2003) 1690-1
- (28) Hincle A A and Calis S. Microsphere preparation by solvent evaporation method. In: Donald L. (ed.) *Handbook of Pharmaceutical Controlled Release Technology*. Marcel Dekker, New York (2000) 329-43
- (29) Garcia-Contreras L, Abu-Izza K and Robbert LD. Biodegradable cisplatin microspheres for direct brain injection: preparation and characterization. *Pharm. Dev. Technol.* (1997) 2: 53-65
- (30) Jalil R and Nixon JR. Microencapsulation using poly (L-lactic acid). I: Microcapsule properties affected by the preparative techniques. *J. Microencap.* (1989) 6: 473-84
- (31) Suzuki K and Price JC. Microencapsulation and dissolution properties of a neuroleptic in a biodegradable polymer, poly (d, l-lactide). *J. Pharm. Sci.* (1985) 74: 21-9
- (32) Pongpaibul Y, Price JC and Whithworth CW. Preparation and evaluation of controlled release indometacin microspheres. *Drug Dev. Ind. Pharm.* (1984) 10: 1597-602

---

This article is available online at <http://www.ijpr-online.com>

---