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IN VITRO DISSOLUTION PROFILE OF THEOPHYLLINE LOADED ETHYL CELLULOSE MICROSPHERES PREPARED BY EMULSIFICATION SOLVENT EVAPORATION

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Abstract

Theophylline was entrapped in ethyl cellulose microspheres by a water/oil/water emulsification-solvent evaporation method. Aqueous solution of drug was emulsified into a solution of ethyl cellulose in toluene, containing polyisobutylene as protective colloid, followed by emulsification of this primary emulsion into an external aqueous phase to form a water/oil/water emulsion. Microspheres was formed after solvent evaporation and precipitation of ethyl cellulose. *In vitro* dissolution profile and effect of polyisobutylene on it were studied.

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Introduction

Theophylline is widely used in the treatment of asthma and many other respiratory diseases. This drug is associated with a very narrow therapeutic range, 10 μg/ml to 20 μg/ml[1] and over 80 percent of individuals with serum levels from 20 to 29.9 μg/ml showed toxic symptoms[2]. Following oral administration to normal human subjects, the absorption half life was 0.27 ± 0.07 hrs and the elimination half life 6.19 ± 0.31 hrs[3]. It has also been reported that theophylline shows dose dependent kinetics at plasma concentrations encountered clinically[4]. The rapid absorption and elimination coupled with the small therapeutic range and undesirable side effects over the therapeutic range make frequent administration to maintain the blood level of the drug to obtain maximum beneficial effects.

Preparation of microspheres embodies a series of techniques for the entrapment of solids or liquids within polymer coats or matrices. Significant progress has been made in the preparation of microspheres with relatively narrow size distribution[5]. Principal methods developed to obtain highly uniform microspheres are based on step swelling polymerization[6], polymerization in the outer space where zero gravity forces exists[7], and polymerization in the presence of appropriate solvents and surfactants[8-11]. The choice of one particular method is primarily determined by the solubility characteristics of the drug and the polymer. One of the more recently developed techniques that first appeared in literature about a decade ago[12] is preparation of microspheres by emulsion solvent evaporation. The present method is modification of that one by the use of polyisobutylene and dextran T 70 to achieve better recovery and desired release profile of the microspheres. The objective of present investigation was to study the *in vitro* drug release profile of theophylline from microcapsules prepared with polyisobutylene as protective colloid, with a view to developing a controlled release dosage form of theophylline.

Experimental

Materials

Ethyl cellulose (BDH, England), degree of substitution 2.52 - 2.53, viscosity of a 5% solution in 80:20 toluene : alcohol at 25°C approx. 14 cP; Polyisobutylene (Aldrich Chemical Co., USA) MW 380,000, density 0.918 g/ml; Dextran T70 (Pharmacia Fine Chemicals, Sweden). Theophylline was received from Dey's Medical Stores (Mfg) Limited as gift; Toluene (E. Merck) analytical reagent grade. Double distilled water was used throughout the study.

Preparation of microspheres

An aqueous dispersion of theophylline (500 mg of drug in 5 ml of distilled water) was emulsified into a solution of ethyl cellulose containing varying percentages of polyisobutylene in toluene to form a W/O emulsion. The primary emulsion was then added to 1000 ml distilled water containing 5% w/w of Dextran T70, under stirring at 800 ± 20 r.p.m, at 25°C. Microspheres were collected by filtration after half an hour, rinsed several times with water and vacuum dried.

In vitro dissolution

Dissolution tests were carried out on all the batches using rotating basket method (USP apparatus I) in a 600 ml flask at a constant speed of 100± 5 r.p.m. Four hundered ml of freshly prepared simulated gastric fluid TS was used as the dissolution medium for the first 2 hours, then replaced by 400 ml of freshly prepared simulated intestinal fluid TS for an additional 4 hours. The dissolution basket was covered with 80 mesh nylon cloth to prevent escape of intact microspheres from the basket. Five ml samples were withdrawn at half hourly interval and replenished the same volume to maintain sink condition. The aliquots were suitably diluted and analysed in HITACHI UV-Vis spectrophotometer at 271 nm.

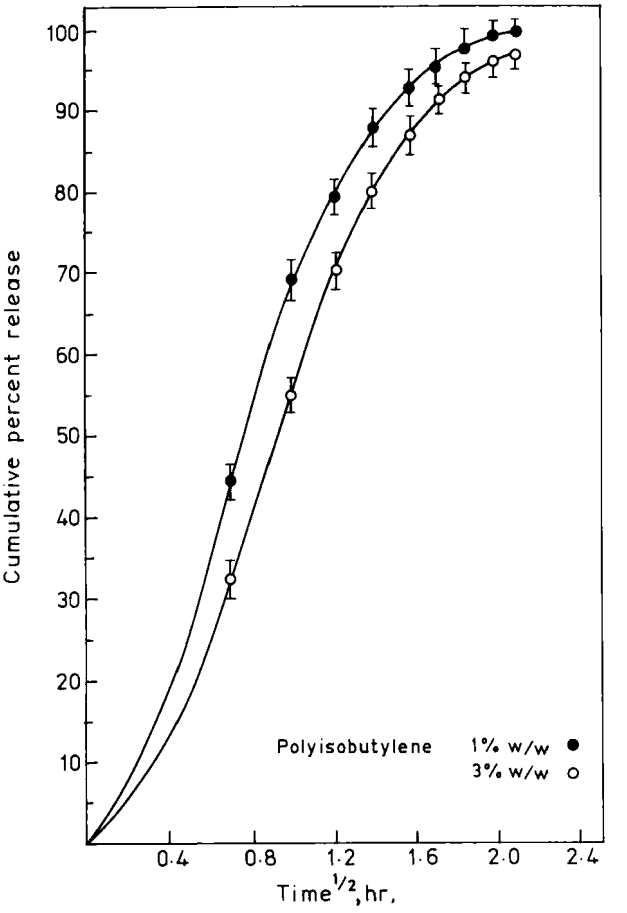

Figure 1 *In vitro* release profile of theophylline from microspheres

Results and Discussion

In order to achieve effective encapsulation or embedding, the drug solubility in the external phase has to be minimal to yield microspheres with satisfactory drug loading. Conventional solvent evaporation method could be used with water - insoluble drugs or with those drugs which has pH dependent solubility. Recently, Watts et al[13] described the selection criteria for disperse and continuous phase solvent. This particular method gives an opportunity to entrap water soluble drugs in microspheres without significant loss of drug in the external phase.

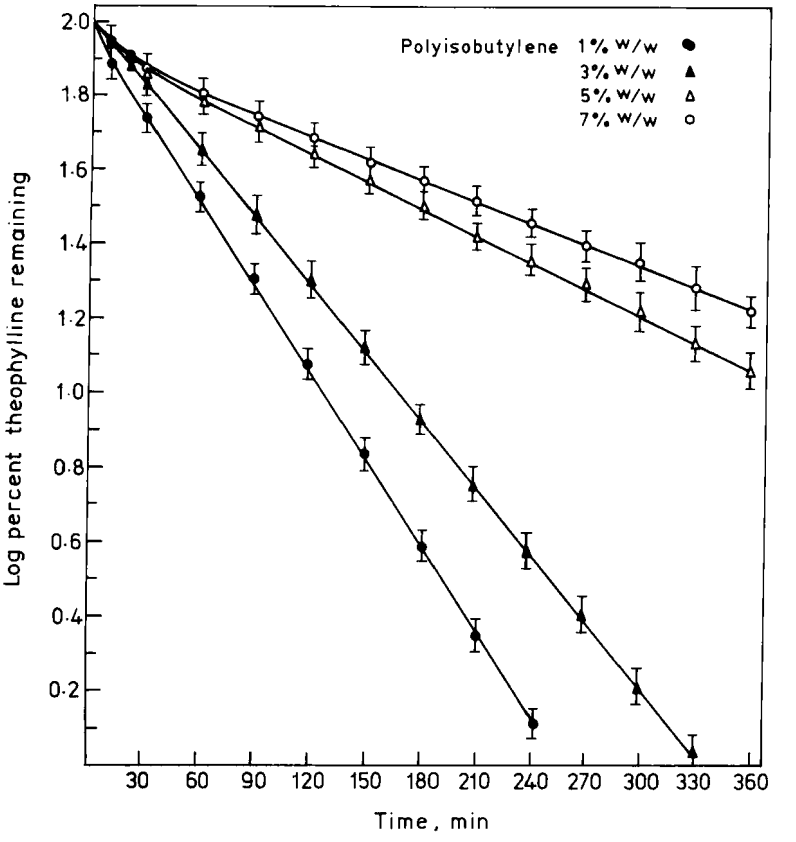

Figure 2 Effect of polyisobutylene concentration on drug release profile

Dissolution was conducted in simulated gastric and intestinal solutions in order to mimic more closely the physiological condition in the GI tract. Figure 1 demonstrates theophylline release from the microspheres and the effect of concentration of polyisobutylene on release profile, which were very smooth, continuous and unaffected by changes of pH and enzyme content of the dissolution media. This may be either due to similar solubility of theophylline in both the dissolution media or rigid matrix structure of microspheres. Figure 2 shows the effect of polyisobutylene concentration on the drug release profile when release profile was plotted in terms of log percent theophylline remaining vs time. It is evidenced that an optimum concentration of 5% w/w of

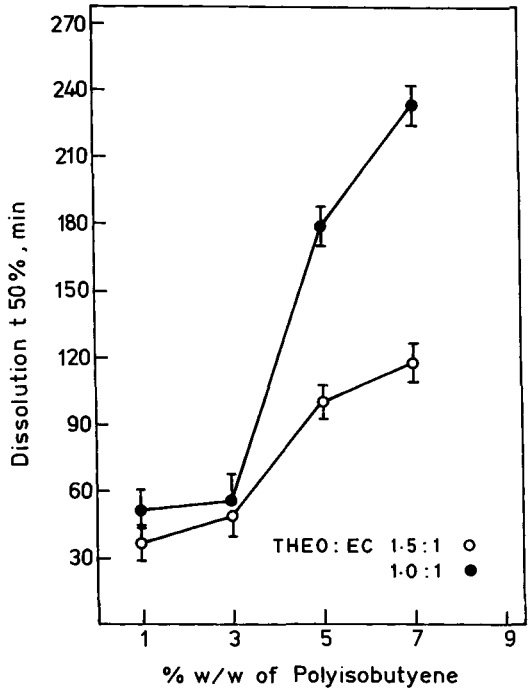

Figure 3 Effect of core - wall ratio on dissolution t 50% of microspheres

polyisobutylene gives satisfactory controlled release profile. Drug release profile was demonstrated to be matrix controlled apparent first order. Mechanism of drug release could be explained as the formation of a microsponge structure of the matrix followed by penetration of the liquid and activation of hydrodynamic pressure to cause the drug release.

Figure 3 shows the effect of core - wall ratio on dissolution t 50%. It is observed that at equal core and wall composition, prolonged dissolution was observed with increased concentration of polyisobutylene. It is expected that polyisobutylene modifies the surface characteristics of the microspheres and reduces the number of surface pores which give rise to formation of channels. Thus resulting in less porous surface area available for drug diffusion from the microspheres.

In conclusion, this modified method of emulsion solvent evaporation is simple and reproducible technique to produce microspheres with controlled drug releasing properties. The release of theophylline from the microsponge spheres follows apparent first order diffusion controlled dissolution. The release profile was significantly affected by added polyisobutylene and varying concentration of it.

Acknowledgement

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