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A study on the effects of different surfactants on Ethylcellulose microspheres

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Abstract: Purpose: To rationalize the use of surfactants by preparing Salbutamol sulphate microspheres using two types of surfactants, Tween 80 and Span 80 and study their effects on different characteristics of the microspheres.
Methods: Microspheres containing Salbutamol sulphate was prepared by emulsion solvent evaporation technique. Infrared Spectroscopy, Differential Scanning Colorimetry and X-Ray Diffraction Spectroscopy studies were carried out to study whether the surfactants have any impact on the physicochemical properties of the microspheres. Scanning Electron Microscopy was done to study the surface topography of the microspheres.
Results and conclusions: When Span 80 was used, the microspheres were smaller in size as compared to those obtained using Tween 80 while there was a higher release rate when Tween 80 was used.
Key words: Ethylcellulose microspheres, Span 80, Tween 80

INTRODUCTION

Microencapsulation has been used as one of the methods to deliver a drug in a controlled fashion. It provides a means to modify and retard the drug release. Several methods were developed for the preparation of microcapsules and emulsion solvent evaporation method is one of such methods and can be used to encapsulate both water soluble and water insoluble drugs. In microencapsulation by solvent evaporation method, surfactants play an important part in the final characteristics of the microcapsules. Tween 80 (polysorbate 80) and Span 80 (sorbitan monooleate) are two of the most commonly surfactants used interchangeably by different authors. The present study aims to rationalize their use by preparing Salbutamol sulphate microspheres using both types of surfactants and study their effects on different characteristics of the microspheres.

MATERIALS AND METHODS

Salbutamol sulphate IP (Ducbill drugs, Kolkatta, batch no. 20050340), ethylcellulose (22 cps grade determined at 80:20 Toluene:Ethanol, Wilson Brothers, Mumbai), Tween 80 (Rankem, New Delhi, batch no. R242K04), Span 80 (CDH, Mumbai, batch no. 02128), were obtained and all other chemicals and reagents used were of analytical grade.

Infrared Spectroscopy:

IR spectra of Salbutamol sulphate (pure drug and microspheres) were recorded using Perkin-Elmer model 883 IR-spectrophotometer between the ranges of 500 to 4000 cm^{-1}. The resultant spectra were then compared with standard reference (IP 1996) and observe for any type of deviation from the standard.

Differential Scanning Calorimeter Analysis (DSC):

DSC thermogram of the pure drugs and the microspheres were recorded with a differential scanning calorimeter (Universal V2.5H TA Instrument) from 20 to 550 ºC at a heating rate of 20 ºC/minute.

X-Ray Diffraction Spectroscopy (XRD):

X-Ray Diffraction Spectrum of the pure drug and microspheres were recorded with Phillips PW 1830 X-ray generator fixed with PW 1710 diffractometer (Phillips Industrial & Electro-acoustic Systems Division, Almelo, The Netherlands). The XRD was performed at the angle between 5-60 ° 2θ.

Preparation of microcapsules

The microspheres were prepared by emulsion solvent evaporation technique using the formulation as shown in Tables 1. In this method 900 mg of ethylcellulose was dissolved in 15 ml of acetone and a given amount of the drugs were dispersed in it to make different drug to polymer ratio of 1:2 and stirred for about 10 minutes. Then the polymer drug dispersion was poured into 50 ml of liquid paraffin (light) containing

varying concentrations of dispersing agents. The whole system was then stirred for about 4 hours at 900 RPM. After stirring process is over the liquid paraffin (light) was decanted off and the microcapsules formed were collected and washed with Cyclohexane to completely remove the remaining oil and dried at 50 ºC in Vacuum drier (NSW, India) for 6 hours and collected for further studies.

Particle size determination

The particle size of the microspheres was determined by microscopic method[1]. For each batch of the microspheres, 100 particles were counted and done in triplicate.

Drug entrapment efficiency:

The amount of Salbutamol sulphate present in the microsphere was determined by extraction in distilled water[2]. The solution was filtered and after suitable dilutions the content of Salbutamol sulphate was determined spectrophotometrically at 276 nm (U-2001, Hitachi).

$$\text{Drug entrapment efficency} = \frac{\text{Experimental drug content}}{\text{Theoretical drug content}} \times 100$$

In vitro drug release study:

The in-vitro release study of the microsphere was carried out using USP rotating basket method at 50 rpm at 37 ºC. Dissolution study was performed in Phosphate buffer pH 7.4 taking 900 ml for each study. 50 mg of the microsphere was taken and samples were taken at a predetermined time intervals up to 12 hours and Salbutamol sulphate content was determined by UV spectrophotometer at 276 nm.

Scanning Electron Microscopy (SEM):

Scanning electron microscopy was done to characterize surface topography of the microspheres. Photomicrograph of the microspheres before and after the release of drugs was taken (Hitachi S-3600N, Japan).

Release Kinetics:

Data obtained from in vitro release studies were fitted to various kinetic equations. The kinetic models used were:

(1) $Q_t = k_o t$ **(**zero-order equation)

(2) $ln\ Q_t = ln\ Q_0 - k_1 t$ **(**first-order equation)

(3) $Q_t = K\ .S.\ \sqrt{t} = k_H\ .\ \sqrt{t}$ **(**Higuchi eqn based on Fickian diffusion)

Where, Q is the amount of drug release in time t, Q_0 is the initial amount of drug in the microsphere, S is the surface area of the microcapsule and k_o , k_1 , and k_H are rate constant of zero order, first order and Higuchi rate equations respectively. In addition to these basic release models, there are several other models as well. One of them is Peppas and Korsenmeyer equation (power law).[3,4]

$M_t / M_\infty = k \cdot t^n$

Where M_t is the amount of drug release at time t and M_∞ is the amount release at time $t = \infty$, thus M_t / M_∞ is the fraction of drug released at time t, k is the kinetic constant, and *n* is the diffusion exponent.

RESULTS AND DISCUSSIONS

The physicochemical stability and compatibility studies performed through infrared spectroscopy (Figure 1), Differential Scanning Colorimetry and X-Ray Diffraction spectroscopy all shows that both types of surfactants do not cause any large shift or deviation in the spectra of the drugs when formulated into microspheres.

Scanning electron microscopy of drug-loaded ethylcellulose microspheres (Figure 2) shows that the microspheres posses a rough and rugged surface.

The mean particle size of the formulations was found to be in between 500 nm and 1400 nm. Two types of surfactants used have an influence on the particle size distribution of the microspheres (Figure 3). The hydrophobic surfactant Span 80 (Sorbitan monooleate, HLB 4.3) is found to produce smaller particle size microspheres compared to hydrophilic surfactant Tween 80 (Polyoxyethylene 20 sorbitan monooleate, HLB 14.9). Span 80 is oil soluble and produces a stable emulsion when the dispersion medium is oil. This may explain why smaller particle sizes are obtained with span 80. The concentration of surfactant/dispersing agents also affects the particle size. For both types of surfactants used, the higher concentration of surfactant resulted in production of smaller particle size. This is due to better stabilization of internal droplets with increase of surfactant concentration preventing coalescence. Also when more amount of surfactants are added, there is an accelerated dispersion of microcapsules in the microencapsulation system[5].

The entrapment efficiency was determined at phosphate buffer of pH 7.4. Higher percentage entrapment was found when the percentage of surfactant was increased from 0.2 % to 1 %. This is true in both types of surfactants used. Percent entrapment was found to be higher when Span 80 was used (Table 2).

The in-vitro release studies reveals that the rate and amount of drug release is increased, as the concentration of the surfactant is increased at constant polymer to drug ratio. This is due to the increase in wettability and better solvent penetration as the surfactant is increased. This effect is observed in both types of surfactants taken. Increase in surfactant concentration may also let to the increase in amount of drugs deposited at the surface. The type of surfactant taken also affects the in-vitro release behavior of the microspheres. Two types of surfactants Tween 80 and Span 80 are taken. In vitro release study in Phosphate buffer pH 7.4 shows that the rate of drug release was faster in case of hydrophilic surfactant Tween 80. This is due to the hydrophilic nature of the surfactant[7], also reported similar types of finding on ethylcellulose films. Microspheres prepared using Span 80 are expected to release the drugs faster than microspheres prepared using Tween 80 due to their

smaller particle size. But increase in surface area available for drug release is not effective enough as compared to hydrophilic nature of the microspheres to increase its release. But within the same type of surfactant, increase in surfactant concentration led to reduced particle size, increase surface area and increase drug release.

The in-vitro release data were fitted into various postulated kinetic models (Table 3). The release of Salbutamol sulphate from the microspheres exhibit diffusional characteristics and closely follows Higuchi Model and also highly correlated with first-order release model.

Results of experiments showed that the amount and types of surfactants have significant effects on the performance of the microspheres when microspheres are prepared by solvent evaporation method. Span 80 was found to produces good spherical microspheres but of smaller size compared to microspheres prepared using Tween 80. Drug release was found to be slower in case of microspheres prepared with Span 80. The rate of drug release can be describe by Higuchi equation and also closely related to firs-order equation (Figures 4(a) and 4(b)).

TABLE 1: FORMULATIONS OF SALBUTAMOL SULPHATE MICROSPHERES PREPARED WITH TWEEN 80

Formulations	A	B	C	D	E	F
Tween 80 %	0.2	0.6	1	-	-	-
Span 80 %	-	-	-	0.2	0.6	1

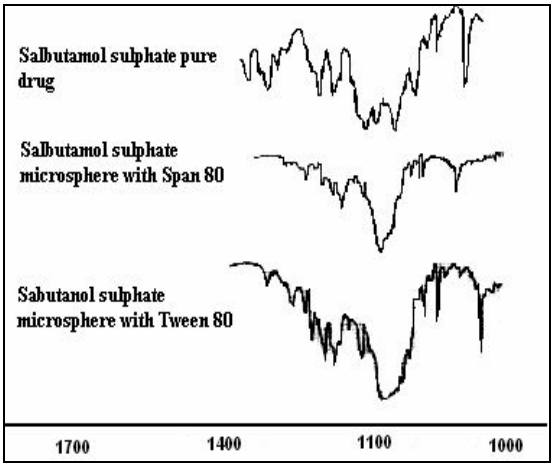
TABLE 2: PERCENTAGE ENTRAPMENT OF SALBUTAMOL SULPHATE

Formulation Codes	A	B	C	D	E	F
Percent Entrapped	80.98	81	83.98	84	94.9	90

TABLE 3: KINETIC TABLE FOR SALBUTAMOL SULPHATE MICROSPHERES

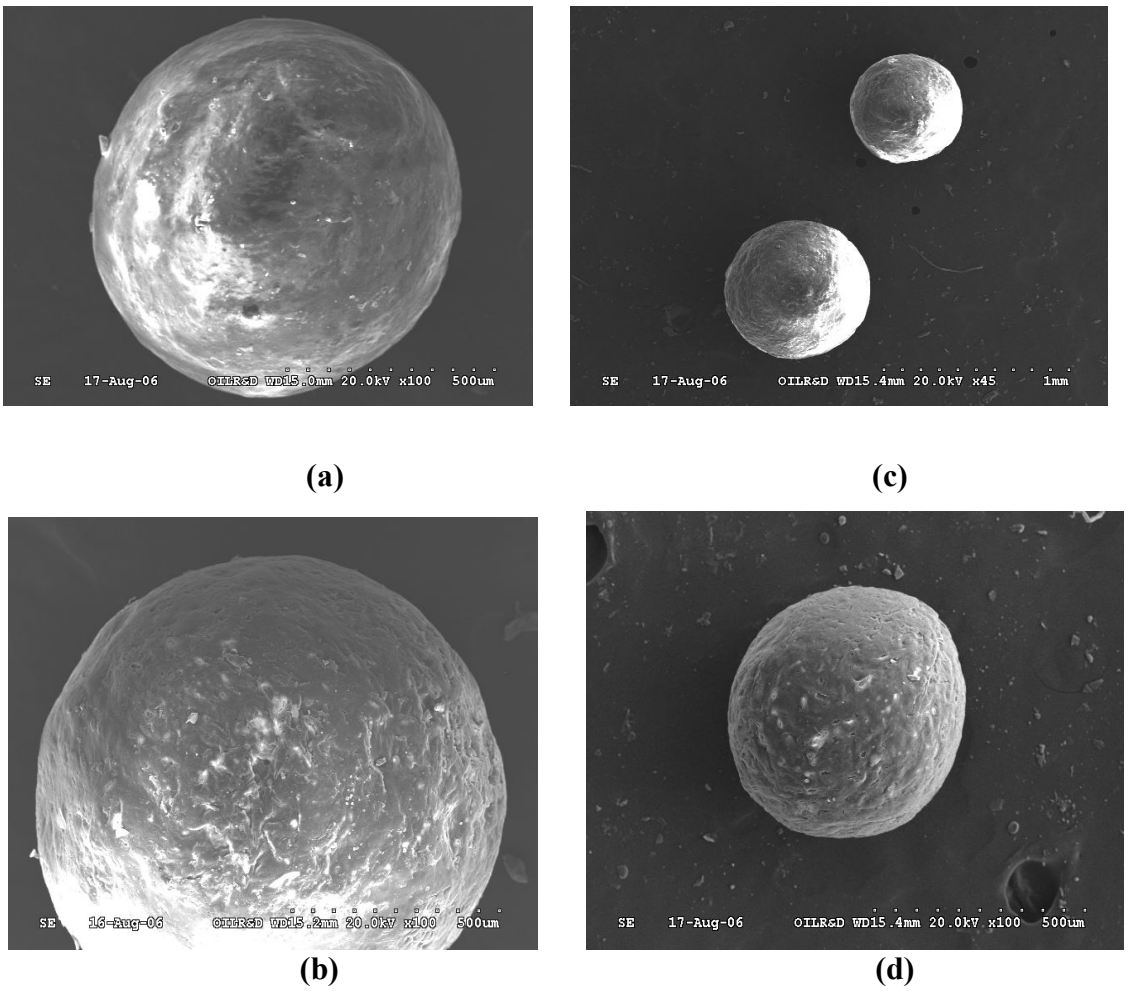
Formulation (Drug:Polymer)	Zero-Order	First-Order	Higuchi Model	Korsenmeyer-Peppas Model				
	r^2	K_o	r^2	K_1	r^2	K_h	r^2	n
F	0.8078	5.7496	0.9570	0.0589	0.9616	23.115	0.9979	0.2936
C	0.8403	5.0517	0.9705	0.068	0.9709	25.092	0.8678	0.3173

FIGURE 1:



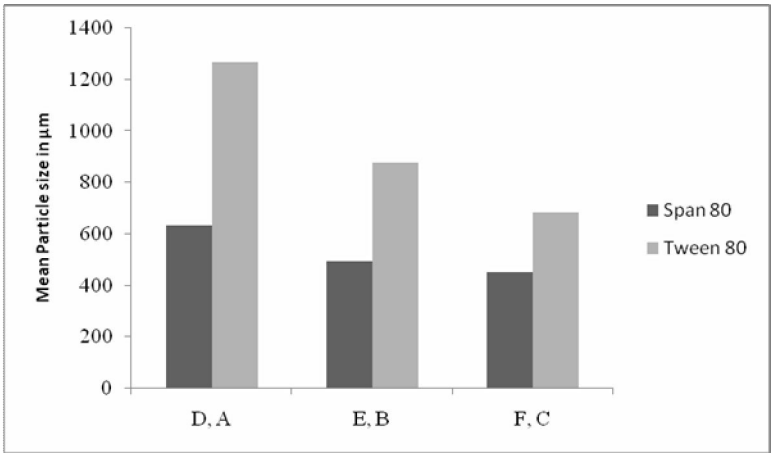
Infra red Spectra of the pure drug and microspheres prepared using Tween 80 and Span 80.

FIGURE 2:



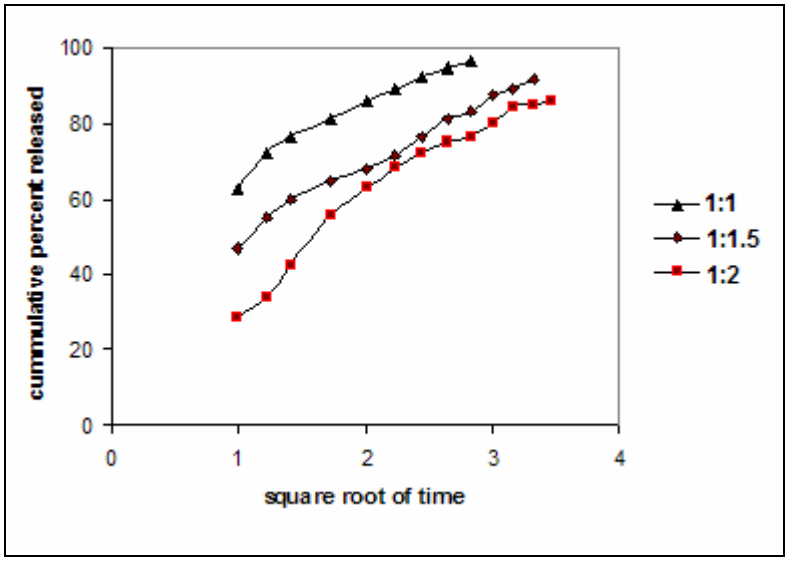
Scanning electron micrograph of Salbutamol sulphate microspheres (a) Tween 80 before drug release (b) Tween 80 after 12 hours drug release and its magnification (c) Span 80 before drug release (d) Span 80 after 12 hours drug release.

FIGURE 3:



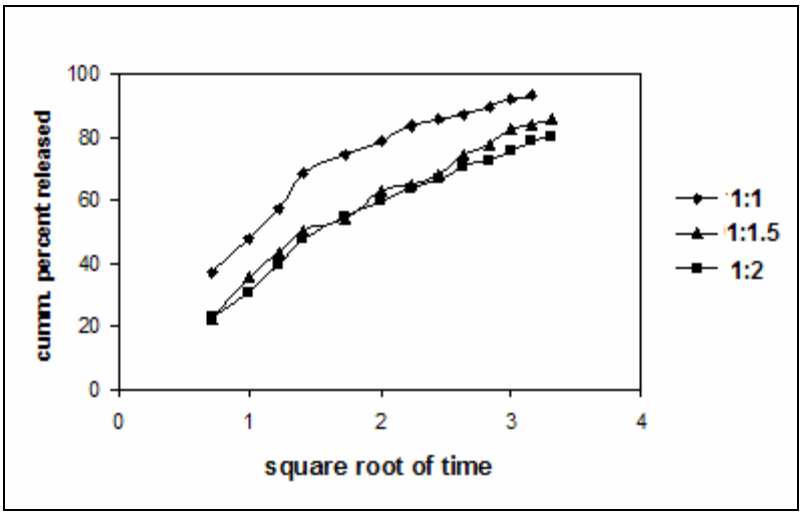
Comparison of mean particle size of the microspheres.

FIGURE 4 (a):



Higuchi plot (Tween 80)

FIGURE 4 (b):



Higuchi plot (Span 80)

Higuchi plot of Salbutamol sulphate from ethylcellulose microspheres of different drug to polymer ratio. Constant amount of(a) Tween 80 (1%) (b) Span 80 (1 %) was taken

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