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Effect of Surfactants on Morphology and Drug Release of Ethylcellulose Microspheres

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ABSTRACT

An emulsion-solvent evaporation technique was used to prepare microspheres of aceclofenac using ethyl cellulose as a carrier. The effect of change in the type and surfactant amount on the size and drug release from the microspheres was investigated. The surfactant concentration was found to be greatly affected the microsphere size distribution and dissolution. The mean diameter of the microspheres decreased exponentially as a function of surfactant concentration. The microsphere size distribution became narrower with increasing surfactant concentration. A clear correlation between the types of surfactant on mean diameter of the microspheres was found. Results have indicated that the incorporation of hydrophilic surfactant (tween-80) gave larger microspheres, where as incorporation of the hydrophobic surfactant (span-80) gave smaller microspheres and hydrophilic surfactant containing microspheres had higher drug release rate compared to hydrophobic surfactant containing microspheres.

INTRODUCTION

Drugs that are easily absorbed from the gastrointestinal tract (GIT) and which have a short half-life are eliminated quickly from the blood circulation, so they require frequent dosing. To avoid this drawback, the oral sustained release formulations have been developed with an attempt to release the drug slowly in the GIT and to maintain an effective drug concentration in the serum for longer period of time1.

Aceclofenac is a non-steroidal anti-inflammatory drug used extensively in the treatment of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis. Aceclofenac is newer derivative of diclofenac which is having less GIT complications, the short biological half-life (3-4 hours), so it requires multiple dosing for maintaining therapeutic effect throughout the day. To reduce the frequency of administration and to improve patient compliance, aceclofenac is suitable for making sustained release dosage form2.

Microencapsulation has been used as one of the method to deliver the drug in a controlled manner. It provides a means to modify and retard the drug release3. Due to their small particle size, they are widely distributed throughout the gastrointestinal tract and this potentially improves drug absorption and reduces side effects related to localized buildup of irritating drugs against the gastrointestinal mucosa4.

The solvent-evaporation method of microencapsulation involves the use of emulsification of a solution containing polymer and drug with an additional medium in which the drug and polymer cannot dissolve. Surface active agents play a significant role in microsphere formulation by emulsification. They have the properties of adsorbing to the interface and stabilizing the emulsion droplets by preventing their aggregation5.

The technique is relatively simple and has been used to prepare microsphere of a variety compounds using several different polymeric materials. There are several formulation and process parameters that, when modified during the manufacture of microsphere by solvent evaporation, may affect the properties of microspheres. The parameters in question includes the aqueous solubility of raw material or drug to be encapsulated, the type and concentration of the surfactant, the polymer/drug ratio, and the stirring rate used to agitate the emulsion system formed during the manufacturing process6

The object of the present study was, to prepare aceclofenac microspheres by the encapsulation of drug particles in ethyl cellulose and to investigate the effect of surfactants on morphology and the drug release from ethyl cellulose microspheres.

MATERIALS AND METHODS

Aceclofenac (Gift Sample from micro lab. Bangalore), ethyl cellulose, Tween 80, Span 80, Acetone, Petroleum ether, liquid paraffin (light) were obtained from Sd-fine. Chem Limited, Mumbai.

Preparation of microspheres

Emulsion solvent evaporation method was used for the preparation aceclofenac microspheres8. The drug to carrier ratios for different formulations was shown in Table 1. An accurately weighed quantity of aceclofenac and ethyl cellulose was dissolved in acetone at room temperature. This solution was introduced into 50 ml of liquid paraffin which containing various concentration of surfactant (i.e tween or span) and stirred continuously for 4 hours at 900 rpm using a mechanical stirrer equipped with four-blade "butterfly" propeller until acetone was completely evaporated. The resultant microcapsules were harvested by vacuum filtration after which they were washed four times with petroleum ether to remove all non-encapsulated drug and oil. Recovered microspheres were dried at 50oC for 6 hours9.

Table-I: Composition of ethyl cellulose microspheres with different concentration of surfactant

FORMULATION CODE	DRUG:POLYMER RATIO	SURFACTANT CONCENTRATION (%)	
		Tween 80	Span 80
T1	1:1	0.2	
T2		0.6	
T3		1.0	
S1			0.2
S2			0.6
S3			1.0

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T4	1:2	0.2	
T5		0.6	
T6		1.0	
S4			0.2
S5			0.6
S6			1.0
T7	1:3	0.2	
T8		0.6	
T9		1.0	
S7			0.2
S8			0.6
S9			1.0

EVALAUATION PARAMETERS:

Drug-Excipients Compatibility Studies

Infrared Spectroscopy: Infrared spectroscopy was conducted using a Shimadzu FTIR 8300 Spectrophotometer and the spectrum was recorded in the region of 4000 to 400 cm-1 10.

Differential Scanning Calorimetry: Differential scanning calorimetry was performed using DSC-60, Shimadzu, Japan. The samples were placed in a sealed aluminium pans, before heating under nitrogen flow (30 ml/min) at a scanning rate of 5oC/min from 25oC to 200oC. Empty aluminium pan was used as a reference. The heat flow as a function of temperature was measured for the drug and drug-polymer mixture. Duplicate determinations were carried out for each sample11.

Particle size determination

The particle size of the microspheres was measured by optical microscopic method. Dry microspheres (5 mg) were suspended in distilled water and ultrasonicated for 2 min. A drop of suspension was placed on a clean glass slide and microspheres were counted under stage ocular micrometer. A minimum of 100 microspheres was counted per batch.12.

Surface Morphology

Scanning electron microscopy is used to determine surface topography, texture and to examine the morphology. SEM was carried out by using (JSM 6380 A JOEL, Japan).The sample of SEM were prepared by lightly sprinkling the microspheres powder on a double adhesive tape which was stuck on aluminium stab. The stabs were then coated with gold to thickness about 300A using a sputter potter. The photographs were taken by SEM analyser13.

Determination of entrapment efficiency

Aceclofenac content in the microspheres was estimated by a UV-Spectrophotometer. Accurately weighed 50mg of microspheres were crushed in phosphate buffer pH 7.4. The solution was filtered, after suitable dilution, Aceclofenac content in the filtrate was analyzed at 275nm using Shimadzu 1700 UV-Visible spectrophotometer. The obtained absorbance was plotted on the standard curve to get the exact concentration of the entrapped drug. The percentage drug entrapment efficiency was determined using following equation14.

% Drug Entrapment Efficiency = [Actual drug content /Theoretical drug content] x 100.

In vitro drug release study

In vitro drug release studies were carried out by using dissolution apparatus USP XXII (Electrolab). Drug loaded microspheres equivalent to 100 mg of drug was introduced into the 900 ml of phosphate buffer pH 7.4±0.1. The medium was maintained at 37±0.5ºC at 100 rpm. Aliquots of 5ml were withdrawn at regular intervals for 12 hours and analyzed spectrophotometrically (UV 1700, Shimadzu, Japan) at 275nm. Three trials were carried out for all formulations in phosphate buffer pH 7.4±0.1. Sink condition was maintained throughout the study by replacing equal volume of fresh dissolution medium14.

Data Analysis of Release Studies:

Data obtained from *in vitro* release studies were fitted to various kinetic equations such as zero order, first order, Higuchi and Korsemeyer – Peppas to find out the kinetic and mechanism of drug release from the microspheres.

RESULT AND DISCUSSION

An attempt has been to modify the aceclofenac release from the microspheres, the formulations (Table 1) were prepared in which the increasing amounts of ethyl cellulose were added to the fixed amount of aceclofenac with different amount of surfactants as variables. Optimization and proper control of these variables were essential for the formation of discrete and spherical microspheres.

Drug-Excipients Compatibility Studies

A prerequisite for the successful preparation of dosage form is the compatibility between the polymer and the drug. IR spectral analysis for drug alone and in combination with other excipients was carried out. In the absence of any interaction, the IR spectrum of mixtures shows peak patterns corresponding to those of the individual components. In the event that interaction occurs, this is indicated in the IR spectrum of a mixture by the appearance of one or more new peaks or the disappearance of one or more peaks corresponding to those of the components.

The principal IR peaks of pure aceclofenac, pure ethyl cellulose and microspheres prepared from tween and span are shown in Fig.1to 4 respectively. There were no considerable changes in the IR peaks of mixture of drug and polymer when compared to pure aceclofenac. These observations indicated the absence of interaction between aceclofenac with excipients.

Fig. 1: FT:IR spectrum of Pure Aceclofenac

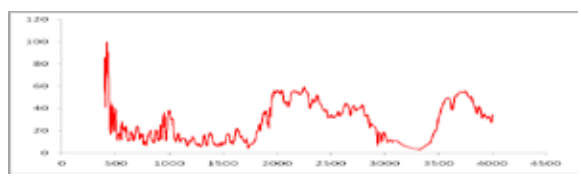


Fig. 2: FTIRIR spectrum of Ethyl Cellulose

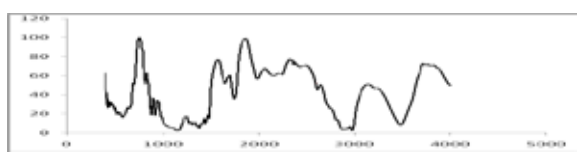


Fig.3: FT: IR spectrum of Ethyl Cellulose Tween80 microsphears

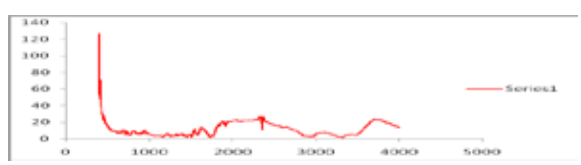
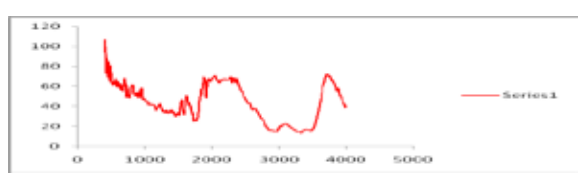


Fig.4: FT: IR spectrum of ethyl cellulose Span80 microsphears



The compatibility of pure aceclofenac in ethyl cellulose microspheres was evaluated through DSC analysis. The DSC curves of pure aceclofenac, aceclofenac loaded ethyl cellulose microspheres with tween 80 and span 80 are presented in Fig. 5, 7 and 8. It was evident from the DSC profile (Fig. 5) that pure aceclofenac exhibited a sharp endothermic peak at 155.54° C, which corresponds to the reported melting temperature of the drug. The same DSC profile (Fig. 7 and 8) of the drug appeared

at the temperature corresponding to its melting point in the aceclofenac loaded ethyl cellulose microspheres but with the loss of its sharp appearance. It appears that there may be significant reduction of drug crystallinity in the microspheres. The DSC study apparently revealed that the drug was compatible with the polymer and either drug decomposition or drug-polymer interactions not occurred in the freshly prepared microspheres.

Fig. 5: DSC Thermogram of Aceclofenac

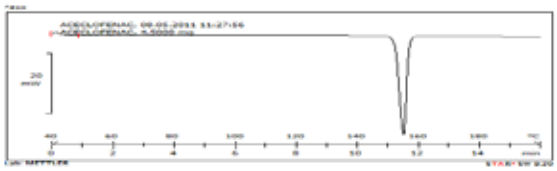


Fig. 6: DSC Thermogram of Ethyl Cellulose

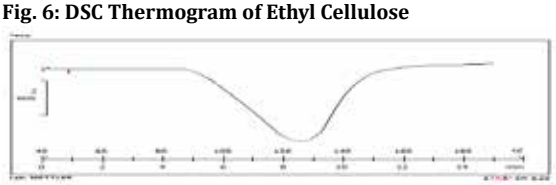


Fig.7: DSC Thermogram of ethyl cellulose Tween 80 microsphears

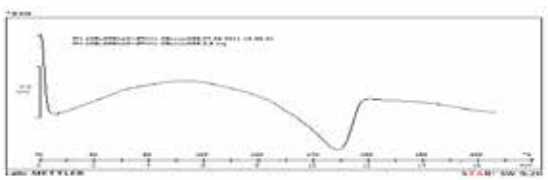
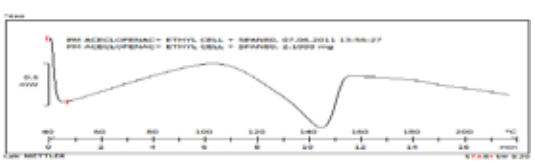


Fig.8: DSC Thermogram of ethyl cellulose Span80 microsphears

Particle size and size distribution



The mean particle size of the formulations were found to be in range of 300 µm to 600 µm for span and 700 to 1100 µm for tween as shown in fig.9, the mean particle size distribution was found to be affected by variables taken (type and concentrations of surfactants), both type of surfactants used have an influence on the particle size distribution of the microspheres (Fig. 9). The hydrophobic surfactant Span 80 (Sorbitan monooleate, HLB 4.3) produced 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 be the reason for smaller particle size with span 80. The concentration of surfactant/dispersing agents also affects the particle size. For both type of surfactants used, the higher concentration of surfactant resulted in production of smaller particle size. This may be due to better stabilization of internal droplets with increase of surfactant concentration preventing coalescence.

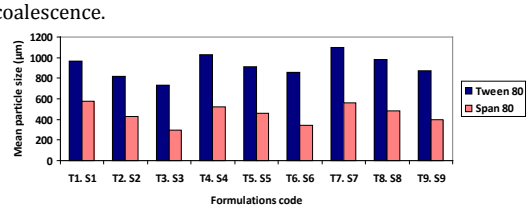


Fig.9: Histogram showing average particle size of ethyl cellulose microsphears

SEM study:

Results of SEM showed that ethyl cellulose microspheres of aceclofenac were predominantly spherical in shape with smooth surface. The porous nature and characteristics internal structure of the microspheres, a hollow cavity inside enclosed with the rigid shell constructed with drug and polymer was clearly evident as shown in fig no 10.

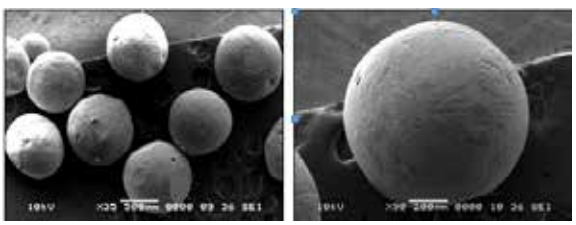


Fig.10: SEM PHOTOGRAPHS OF ETHYL CELLULOSE MICROSPHEARS CONTAINING ACECLOFENAC

Drug entrapment efficiency

The entrapment efficiency was determined in phosphate buffer of pH 7.4. Higher percentage entrapment was found when the percentage of surfactant was increased from 0.2 % to 1 %. In both surfactants, but among all the formulations the optimum drug entrapment efficiency was found in tween 80 (1%)

In vitro drug release

In-vitro release studies reveal that as the surfactant concentration was increased at constant polymer to drug ratio, the rate and amount of drug release was also increased. This may be due to the increase in wettability and better solvent penetration as the surfactant increased. This effect was observed in both types of surfactants taken. The type of surfactant taken also affects the in-vitro release behaviour of the microspheres (Fig. 11 and 12). Two types of surfactants Tween 80 and Span 80 were 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, microspheres prepared using Span 80 were expected to release the drug faster than microspheres prepared using Tween 80 due to their smaller particle size. But increased surface area available for drug release was not effective enough as compared to hydrophilic nature of the microspheres. But within the same type of surfactant, increase in surfactant concentration leads to reduced particle size, increase surface area and increase drug release.

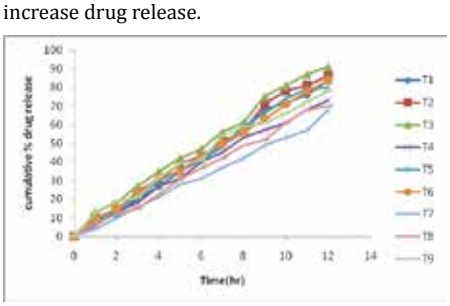


Fig. 11: In vitro dissolution profile of Tween 80 containing microspheres

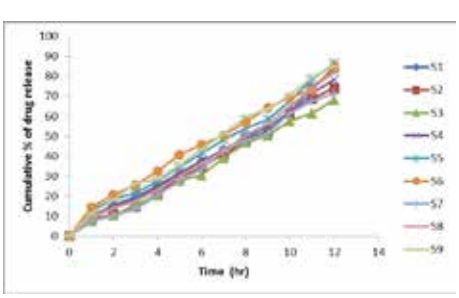


Fig. 12: In vitro dissolution profile of Span 80 containing microspheres

In order to obtain meaningful information, the drug release data's were fitted to different kinetic models and the best suitable release data was assessed. The release of aceclofenac from the microspheres exhibited diffusional characteristics and closely followed Higuchi model and also highly correlated with first order release kinetic.

CONCLUSION

Results of experiments revealed that the amount and types of surfactants have significant effects on the performance of the microspheres when microspheres were 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 was followed by Higuchi and also closely related to first-order kinetic.

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