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Preparation and Evaluation of Ethyl Cellulose Microspheres Containing Diclofenac Sodium by Novel W/O/O Emulsion Method

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Abstract

The aim of present study was to formulate and evaluate microencapsulated controlled release preparations of a highly water/soluble drug, Diclofenac Sodium by (water in oil) in oil emulsion technique. Ethylcellulose, a biocompatible polymer is used as the retardant material. Various processing and formulation parameters such as drug/polymer ratio, volume and concentration of processing medium were optimized to maximize the entrapment efficiency. The release of DFS from ethyl cellulose microsphere was compared and possible release mechanism proposed by fitting in to different kinetic models. Microspheres were prepared by water in oil in oil emulsion technique using dichloromethane/ethanol solvent system. Span 80 was used as the dispersing agent and n-hexane was added to harden the microspheres. The prepared microspheres were characterized for their particle size and drug loading and drug release. The in-vitro release studies were carried out in phosphate buffer at pH 7.4. The prepared microspheres were white, free flowing and spherical in shape. The drug-loaded microspheres showed 51.2% of entrapment and release was extended up to 10 h. The in vitro drug release from the microspheres was affected by drug/polymer ratio. The best/fit release kinetics was achieved with Higuchi plot followed by zero order and first order. The release of DFS was influenced by altering the drug to polymer ratio and the drug release was found to be diffusion controlled.

Key words: *Diclofenac Sodium, Ethylcellulose, entrapment efficiency, w/o/o emulsion, release kinetics.*

INTRODUCTION

The use of Non-Steroidal Anti-Inflammatory drugs (NSAIDs) began over 100 years ago with the introduction of salicylic acid for the treatment of rheumatic diseases. During the past 30 years, there has been a substantial increase in the number of clinically available NSAIDs. They annually account for 70 million prescriptions and 30 billion over-the-counter (OTC) medications sold in the United States alone [1]. NSAIDs are amongst the most commonly prescribed medications in the world owing to their efficacy as anti-inflammatory, anti-thrombotic, anti-pyretic, and analgesic agents. However, numerous case-control, and post-marketing surveillance studies have revealed that NSAIDs are associated with extensive side effects, the most prevalent being GI disturbances [2]. These adverse effects are dose-dependent, and in many cases severe enough to pose the risk of ulcer perforation, upper gastrointestinal bleeding, and death, limiting the use of NSAID therapy.

Several approaches have been experimented in order to solve such problems. Among them, the development of innovative pharmaceutical dosage forms, which can transport active therapeutic molecules to specific target sites in the body and/or can be able to control the drug release rate are most promising. Such delivery systems can modify the drug bioavailability profile without altering the structure of the moiety being transported. Important examples of these modern dosage forms are microcapsules/microspheres [3].

Microspheres can be described as small particles (in 1-1000 micrometer size range) for use as carriers of drugs and other therapeutic agents. The term microspheres describe a monolithic spherical structure with the drug or therapeutic agent distributed throughout the matrix either as a molecular dispersion or as a dispersion of particles [4]. They can also be defined as a structure made up of continuous phase of one or more miscible polymers in which the particulate drug is dispersed at the macroscopic or molecular level. Microspheres provide constant and prolonged therapeutic effect, reduced the GI toxic effects and dosing frequency and thereby improve the patient compliance. They could be injected in to the body due to the spherical shape and smaller

size. Better drug utilization will improve the bioavailability and reduce the incidence or intensity of adverse effects. Microsphere morphology allows a controllable variability in degradation and drug release.

Although number of polymers can be used, natural or semi-synthetic polysaccharides, such as celullose derivatives, play an important role in microencapsulation processes [4]. For example, Ethylcelullose (EC) a biocompatible and water insoluble polymer that has been used in the preparation of coated and matrix tablets [5, 6], micro and nano capsules [7, 8], beads [9] and other coated solid pharmaceutical dosage forms [10, 11].

In present work EC is selected as the retardant material for DFS. EC, used as an encapsulating material is extensively studied by many researchers for the controlled release of DFS. The microspheres prepared using emulsion/solvent evaporation method shown only 4.33%entrapmentefficiency (Marcelo A. BACCARIN et.al.,). The purpose of the present work was to prepare and evaluate oral controlled release microparticulate drug delivery system of DFS using ethylcellulose by w/o/o double emulsion solvent diffusion method with high entrapment capacity and extended release.

MATERIALS AND METHODS

Materials

Diclofenac Sodium, Ethylcellulose (25 cps viscosity), Dichloromethane, Ethanol, Light Liquid Paraffin, Span-80, and n-Hexane (s.d. fine chemicals, Mumbai) were obtained from commercial sources. All the other reagents used were of analytical grade.

METHODS

Preparation of Microspheres

Microspheres were prepared by the w/o/o double emulsion solvent diffusion method [12]. Weighed amounts of Diclofenac Sodium and ethyl cellulose were dissolved in 8 ml of solvent mixture containing dichloromethane and ethanol (1:1). The initial w/o emulsion was formed by adding 2 ml of deionized water to the drug-polymer solution with constant stirring at 500 rpm for 5 min. The resultant w/o primary emulsion was then slowly added to light liquid paraffin containing Span 80 (0.5% w/v) as a surfactant with constant stirring for 1 hour. The resulting microspheres were separated by decantation, freed from liquid paraffin by repeated washing with n-hexane and finally air dried over a period of 12 h.

CHARACTERIZATION OF MICROSPHERES

Drug entrapment efficiency

A weighed quantity of microspheres were crushed into powder and added to 100 ml phosphate buffer (pH 7.4). The resulting mixture was kept under magnetic stirrer for 2 h. The solution was then filtered through Whatmann filter paper. One milliliter of this stock solution was diluted using phosphate buffer (pH 7.4) and analyzed spectrophotometrically for DFS content at 276 nm. The drug entrapment efficiency was determined using the relationship:

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

Size and Size distribution

The particle size of microspheres was determined using an optical microscopy method. Approximately 100 microspheres were counted using calibrated microscope.

In-vitro drug release study

The in-vitro release study of the microsphere was carried out using USP rotating basket method. A weighed quantity of the microspheres was introduced into the basket, the dissolution chamber was filled with 900 ml of phosphate buffer of pH 7.4 and the whole system was stirred at 75 rpm and maintained at constant temperature (37 ± 1°C). At specific time intervals, 5 ml of the sample were withdrawn and replaced by an equal volume of fresh pre-warmed dissolution medium. After suitable dilution, the samples were analyzed at 276 nm using UV-Visible spectrophotometer (Elico Ltd.).

Release kinetics

Data obtained from in-vitro release studies were fitted to various kinetic equations to find out the mechanism of drug release from the ethyl cellulose microsphere. The kinetic models used were [13]:

$Q_t = K_0 . t$ (zero-order equation)

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

$Q_t = K_h .t^{1/2}$ (Higuchi equation based on Fickian diffusion)

where Q_t is the amount of drug release in time t, Q_0 is the initial amount of drug in the microsphere, and k_0 , k_1 , and k_H are rate constants of zero order, first order and Higuchi equations, respectively. In addition to these basic release models, there are several other models as well. One of them is Korsenmeyer-Peppas equation (power law) [14].

$Mt / M\infty = k \cdot t^n$

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 which can be used to characterize both mechanism for both solvent penetration and drug release. Determining the correlation coefficient assessed fitness of the data into various kinetic models. The rate constants for respective models were also calculated from slope.

RESULTS AND DISCUSSION

The present study, attempt was made to encapsulate DFS with sufficiently high entrapment efficiency by w/o/o double emulsion solvent diffusion method using a non-aqueous processing medium. In the study by Marcelo A et al., EC microspheres were prepared by an emulsion/solvent evaporation method, using water as non solvent. According to them the highest entrapment efficiency was 4.33% when a 1:1 drug to polymer ratio was used. Dicolfenac Sodium, due to its hydrophilicity is likely to preferentially partition out into the aqueous medium, leading to low entrapment efficiency, when encapsulated using aqueous phase as the processing medium [14]. The process of solvent removal as well as the washing steps contributes to the drug partition from the matrix into the water.

Preparation of Microspheres

The primary requirement of this method to obtain microspheres is that the selected solvent system for polymer be immiscible with non-aqueous processing medium [15]. When Ethanol alone is used as a solvent along with oil as the processing medium, it does not ensure the formation of primary emulsion of the aqueous phase in the polymer solution. Immediately on mixing, the water miscibility of Ethanol brought about the precipitation of the polymer (ethyl cellulose). Hence, a non-polar solvent, namely dichloromethane was included with ethanol to decrease the polarity of the polymer solution. The optimal proportion of dichloromethane and Ethanol was found to be 1:1, which enabled emulsion formation and yielded good free flowing microspheres. Here ethyl cellulose itself acts as a surfactant and stabilizes the w/o primary emulsion. Secondary emulsion is stabilized by adding oil soluble surfactant Span-80.

Drug entrapment efficiency

The effects of various process and formulation parameters on the drug entrapment efficiency of microspheres are shown in Table 1. The highest (51%) entrapment efficiency was achieved with polymer-drug ratio (1:1) and further increase in polymer-drug ratio from1:1 to 1:2 and 1:3 shown decrease in encapsulation efficiency of DFS. As the concentration of polymer increased the viscosity of the polymer solution increased resulting in the formation of larger polymer/solvent droplets. The larger particles takes much time for hardening, allowing time for drug diffusion out of the particles, which tends to decrease encapsulation efficiency.

The polymer-drug ratio that shows the optimum drug encapsulation is kept constant and effect of other parameters on encapsulation efficiency was studied. Entrapment efficiency

was decreased with increased concentration of secondary surfactant. This may be due to the fact that the increase in surfactant concentration proportionally increases miscibility of ethanol with light liquid paraffin (processing medium), which may increase the extraction of DFS into the processing medium.

The volume of processing medium also significantly influenced the entrapment efficiency of the drug-loaded microspheres (Table 1). As the volume of processing medium was increased from 50 ml to 100 ml and to 150 ml, the entrapment efficiency was decreased respectively. The reason may be the higher amount of drug extraction into the processing medium, resulting in lower entrapment efficiency.

Particle Size

The average particle size of all the formulations were in the range of 60-80 microns and particle size was slightly increased with increase in concentration of the polymer. The increase in viscosity of polymer solution with increase in polymer concentration produced larger particles in higher polymer formulations.

Drug Release studies

In Vitro release of DFS from ethylcellulose microspheres exhibited initial burst effect, which was due to the presence of drug particles on the surface of the microspheres. The initial burst effect may be attributed as a desired effect to ensure initial therapeutic plasma concentrations of drug. The release profiles are illustrated in Figure 1.

Table 1. Effect of various parameters on entrapment efficiency

Formulation Code	Drug/Polymer ratio	Volume of Processing Medium(ml)	Concentration of Processing Medium(%w/v)	Entrapment Efficiency (%)
F1	1:1	50	0.5	51.2±0.53
F2	1:2	50	0.5	42.8±1.14
F3	1:3	50	0.5	36.7±0.82
F1a	1:1	50	1.0	41.1±0.64
F1b	1:1	50	2.0	28.6±1.89
F1c	1:1	100	0.5	44.4±0.65
F1d	1:1	150	0.5	38.6±093

Fig 1. In Vitro release profile of DFS Microspheres

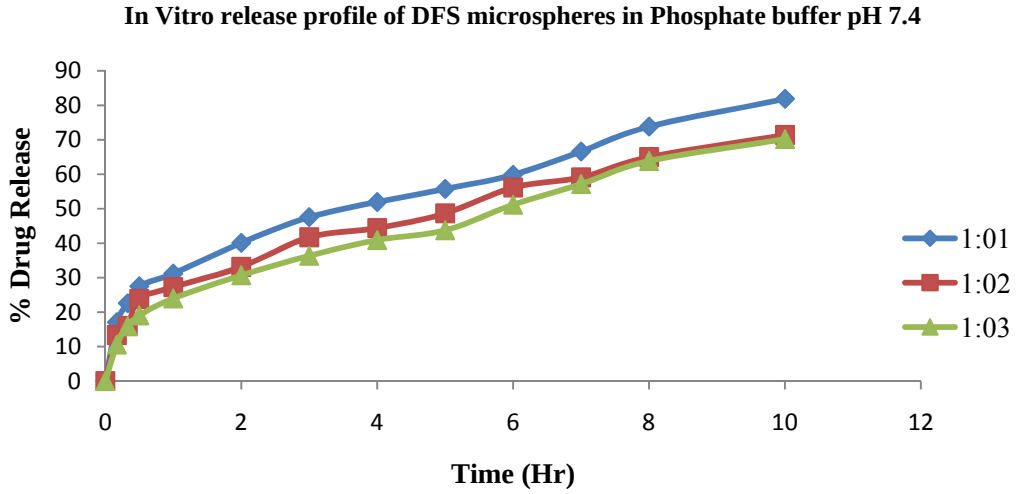

Table 2. Correlation coefficients the drug release data from kinetic mathematical models.

Formulation	*Kinetic Models*						
	Zero order		*First order*		*Higuchi model*		*Korsemeyer-Peppas model*
	R^2	K_0	R^2	K_1	R^2	K_h	n
F1	0.969	2.97	0.864	0.138	0.990	2.754	0.36
F2	0.962	1.278	0.837	0.149	0.991	1.344	0.39
F3	0.978	0.796	0.855	0.166	0.985	1.026	0.43

R^2 is the coefficient of correlation; K_0, K_1 and K_h are the release rate constants for zero-order, first-order and Higuchi model, respectively and n is the release exponent of Korsmeyer-Peppas model.

The drug release was decreased with increase in concentration of the polymer as increase in the polymer solution viscosity has produced microspheres with reduced porosity due to the thickening of the polymer wall. It is understood that higher polymer concentration results in a longer diffusional path length, so drug release is extended. The thick polymeric barrier slows the entry of surrounding dissolution medium in to the microspheres and hence less quantity of drug leaches out from the polymer matrices of the microspheres exhibiting extended release.

Release kinetics

The release mechanism of DFS from various formulations was successfully determined by comparing their respective correlation coefficient. The best fit with the highest correlation coefficient was found in Higuchi, zero-order and followed by first-order kinetics as given in (Table 2). It revealed that the drug release from ethyl cellulose microspheres was diffusion controlled. The data obtained were also put in Korsemeyer-Peppas model in order to find out n value, which describes the drug release mechanism. The n value of microspheres of different drug to polymer ratio was ranged between 0.36 -0.43, indicating that the mechanism of the drug release was diffusion controlled (Fickian Diffusion).

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