Research Article

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FABRICATION AND CHARACTERIZATION OF DICLOFENAC SODIUM LOADED MICROCAPSULES

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ABSTRACT

Aim: In order to maintain the therapeutic concentrations of Diclofenac sodium, the physicochemical properties of drug, its short half-life and problems associated with gastrointestinal disturbances make it suitable candidate for preparation of controlled release microcapsules.

Method: Diclofenac sodium microcapsules were prepared with the polymer Ethyl Cellulose by emulsion solvent evaporation technique at various concentrations of 1:1, 2:3 & 2:1.

Results: SEM Photographs of samples revealed that all prepared microcapsules were spherical in shape and possessed smooth surface. The encapsulation efficiency was found to be in the range of 66.17 – 72.99%. The data obtained from *in-vitro* release profile of Diclofenac indicates that all the batches of microcapsules showed controlled and prolonged drug release and spread over an extended period of 10 hrs.

Conclusion: Diclofenac release from microcapsules followed zero order kinetics and diffusion controlled mechanism. From the *in-vitro* drug release profiles, it was also observed that the drug release from microcapsules was decreased with an increase in coat thickness in the microcapsules.

Keywords: Diclofenac Sodium, Ethyl cellulose, NSAID, microcapsules, extended period.

INTRODUCTION:

Diclofenac Sodium is a nonsteroidal Anti-inflammatory drug (NSAID) belongs to the group of aryl acetic acid derivative. It is widely used in treatment of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis. It possesses narrow therapeutic index due to its short biological half-life. It is eliminated from plasma compartments within few hours, so frequent administration is necessary to maintain its therapeutic concentration[1-3]. An ideal dosage regimen in the therapy of any disease is the one, which immediately attains the desired therapeutic concentration of drug in plasma (or at the site of action) and maintains it constant for the entire duration of treatment.

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This is possible through administration of conventional dosage form in a particular dose and at a particular frequency. The frequency of administration or a dosing interval of any drug depends upon the half-life or mean residence time and its therapeutic index [4].

An ideal controlled drug delivery system is the one, which delivers the drug at a predetermined rate, locally or systemically, for a specified period of time. Thus, unlike conventional immediate release systems, the rates of appearance of drug in the body with such a system are not controlled by absorption process. Following absorption of drug from such a system, there is no control over its fate. An ideal targeted drug delivery system is the one, which delivers the drug only to its site of action and not to non-target tissues. With this system, control over kinetics of drug release is difficult [5-6].

There are several terms used interchangeably viz. controlled release, sustained release, programmed release, prolonged release, timed release, slow release, extended release and other such dosage forms. However, controlled release will imply as defined earlier. It differs from sustained release systems, which simply prolonged the drug release, and hence the plasma drug levels for an extended period of time. Thus, the chief objective of most products should be controlled delivery to reduce dosing frequency to an extent that once daily is sufficient for therapeutic management through a uniform plasma concentration at steady-state [7].

Microencapsulation is a process by which very tiny droplets or particles of liquid or solid material are surrounded or coated with a continuous film of polymeric material, ranging in size from 1 to 1,000 microns. Microencapsulation is one of the most interesting fields in the area of drug delivery systems. It is an interdisciplinary field that requires knowledge of field of pure polymer science, familiarity in emulsion technology and an in-depth understanding of drug and protein stabilization. This is the technology devoted to entrapping solids, liquid or gases inside one or more polymeric coatings. This technique provides the means of converting liquids to solids, of altering colloidal and surface properties of providing environmental protection and of controlling the release characteristics or availability of coated materials [8-9].

MATERIALS AND METHODS:

The following materials were used: Diclofenac Sodium (Yarrow Chemical Pvt. Ltd., Mumbai), ethyl cellulose, chloroform, hydro chloric acid, sodium carboxy methylcellulose (S.D Fine chemicals, India). All the solvents and chemicals were used analytical grade satisfying Pharmacopoeial standards.

Preparation of Diclofenac microcapsules:

Microcapsules of Diclofenac sodium were prepared by emulsion solvent evaporation technique [10-14] by employing the chloroform as solvent and ethyl cellulose as a polymer with a core: coat ratio of 1:1, 2:3 and 2:1. The polymer (1, 1.5 and 0.5g) was dissolved in chloroform (25ml) to form a homogeneous polymer solution. Core material Diclofenac sodium was added to the polymer solution and mixed thoroughly. The resulting solution was then added in a thin stream to 100ml of 0.1N HCl containing 1%w/v sodium carboxy methylcellulose contained in a 250ml beaker while stirring at 600 rpm to emulsify the added droplets. A Remi medium duty laboratory stirrer with speedometer was used for stirring. Stirring was continued for 10 min to disperse the added mixture as fine droplets. The dispersion was transferred to a Buchner flask and stirring was continued with laboratory stirrer. The solvent was then removed by evaporation at room temperature to produce spherical microcapsules. The microcapsules were collected by decantation and washed with water. The product was then dried at 60^{o}C for 1 hour to get discrete microcapsules. The compositions of microcapsules of Diclofenac sodium were showed in table No.1.

% Practical Yield:

Percentage of practical yield[15] is calculated to know about percent yield or efficiency of any method, thus its help in selection of appropriate method of production. Microcapsules were collected and weighed to determine practical yield (PY) from the following equation.

$$PY\ (\%) = \frac{\text{Practical Mass (Microcapsules)}}{\text{Theoretical Mass (Drug + Polymer)}} X100$$

Particle size distribution:

Different sizes of microcapsules in a batch were separated by sieve analysis with respective standard sieves. The amount retained on different sieves was weighed. From the obtained data, weight percent retained on different sieves and average size[16] of microcapsules were calculated.

Shape and surface morphology:

The microcapsules were observed under a scanning electron microscope (JSM-T330A, JEOL). They were mounted directly onto the SEM sample stub using double-sided sticking tape and coated with gold film (thickness 200 nm) under reduced pres-sure (0.001 mm of Hg). SEM photograph of F1 & F2 loaded Diclofenac Sodium microcapsules were showed in figure 1 & 2.

Drug content:

Microcapsules equivalent to 50 mg of Diclofenac were weighed accurately and dissolved in the 10 ml of chloroform. The solution was filtered, diluted suitably and drug content[17] was analyzed at 285 nm by UV spectrophotometer. Each sample analyzed in triplicate.

Encapsulation Efficiency:

The encapsulation efficiency of microcapsules was calculated by using the formula:

$$EE\ (\%) = \frac{\text{Estimated drug content}}{\text{Theoretical drug content}} X100$$

***In-vitro* drug release studies:**

In-vitro release[18-20] profile for microcapsules were performed using USP XXII type 2 dissolution apparatus (TDP-06P, Electro lab, Mumbai, India). Sample equivalent to 100 mg of Diclofenac was added to 900 ml Phosphate buffer P^H 7.4 at 37± 0.5ºC and stirred at 50 rpm. The study was carried out up to 10 hr. The data obtained was subjected to kinetic treatment to obtain the order of release and release mechanism.

RESULTS AND DISCUSSION

Microcapsules of Diclofenac Sodium were prepared and evaluated for their use as controlled release drug delivery system. In the present work total three formulations were prepared and their complete composition is shown in Table No. 1.

The results of % practical yield studies are shown in Table No.2. Percent practical yield decreased as the amount of carrier/polymer added to each formulation increased. The % practical yield was found to be in the range of 62.84 to 80.85 %. The maximum % practical yield was found to be 80.85% in F-1. The average size of microcapsules in various batches was found to be 759.12 µm, 669.97 µm and 758.7 µm for F1, F2 and F3 respectively and showed in table 3. The prepared microcapsules sizes were increased with increasing polymer concentration due to a significant increase in the viscosity which leading to an increased aqueous droplet size leading to an increase in size of the microcapsules. The determination of shape and surface morphology was done by scanning electron microscope. As in figure No.1 and Figure No.2 shows the SEM photographs of Diclofenac microcapsules (F1&F2). SEM analysis of the samples revealed that all prepared microcapsules were almost spherical in shape and has a slightly smooth surface.

The Actual drug content and encapsulation efficiency of all three formulations are shown in the Table No.2. The low values of standard deviation (SD<0.3) indicate uniformity of drug content in each batch of microcapsule. The encapsulation efficiency ranges from 66.17 to 72.99% for formulation F-1 to F-3. The maximum EE was found to be 72.99% in F-3, which may be due to increase in core material in the microcapsules.

The release profile of an entrapped drug predicts how a delivery system might function and gives valuable insight into its *in-vivo* behaviour. The data obtained from *in-vitro* release profile of Diclofenac indicated that all the batches of microcapsules showed controlled and prolonged drug release and spread over an extended period of time. From the *in-vitro* drug release profiles, it was observed that the drug release from microcapsules was decreased with an increase in coat material in the microcapsules (F-2). The results obtained from *in-vitro* release studies were attempted to fit into various mathematical models as follows zero order, first order, higuchi matrix and peppas kinetics model.

Plots of zero order, first order, Higuchi matrix and Peppas are depicted in Figure 3 to 7. The regression coefficient (r) and 'n' values for formulations (F-1 toF-3) of zero order, first order, Higuchi matrix, and Peppas, and tabulated in table no.3. The regression coefficients for formulations F1 to F3 of zero order plots were found to be 0.9953, 0.9926 and 0.9968 respectively. The regression coefficients for formulations F1 to F3 of first order plot were found to be 0.9679, 0.9879 and 0.9859. These results indicated that zero order plots were not linear for all formulations and the first order plots were almost linear for all formulations. Figure 6 shows the graphical representation of cumulative percent drug released as a function of square root of time. This Higuchi's plot was almost linear with regression co-efficient values of 0.9812, 0.9852

and 0.9918 for formulations F1 to F3 showed in table no 4. The linearity suggests that the release of Diclofenac from microcapsules was diffusion controlled. Plot of log cumulative % drug released Vs. Log time (Peppas) is shown in Figure 6. Peppas – Korsmeyer Equation is gave, 'n' values for F1 to F3 were 0.922, 0.751 and 0.603 respectively and indicated that the release could follow Non-Fickian diffusion mechanism.

Table 1: Formulation plan of Diclofenac microcapsules

S. No	Batch Code	Composition	Ratio(Core: Coat)
1	F1	Diclofenac Sodium + Ethyl cellulose	1:1
2	F2	Diclofenac Sodium + Ethyl cellulose	2:3
3	F3	Diclofenac Sodium + Ethyl cellulose	2:1

Table 2: % practical yield, drug content & encapsulation efficiency of Diclofenac sodium microcapsules

Formulation	% Practical yield	Drug content (mg)	Encapsulation efficiency
F-1	80.85%	36.336 ± 0.221	72.60%
F-2	67.06%	33.088 ± 0.122	66.17%
F-3	62.84%	36.496 ± 0. 296	72.99%

Table 3: Particle size distribution profile of Diclofenac sodium microcapsules

Sieve No.	Percent Retained		
	F1	F2	F3
10/22 (1250 µ)	31.8%	21.05%	3.03%
22/44 (532.5 µ)	67.3%	73.78%	61.94%
44/52 (328.5 µ)	0.9%	5.11%	4.29%
52/60 (276.0 µ)	-	0.78%	0.72%

Table 4: Different release mechanisms as per diffusion coefficient

S. No	'n'	Mechanism
1	0.5	Fickian diffusion
2	0.5<n<1	Non-Fickian diffusion
3	1	Zero Order

Fig. 1: SEM Photograph of Diclofenac-loaded microcapsules (F-1)

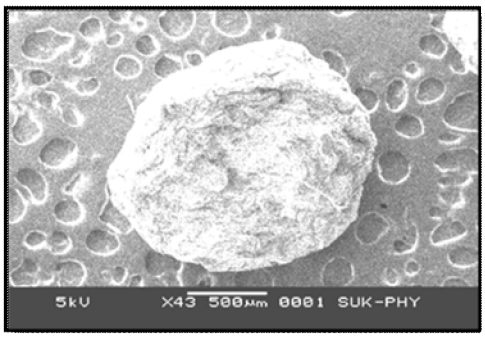

Fig. 2: SEM Photograph of Diclofenac-loaded microcapsules (F-2)

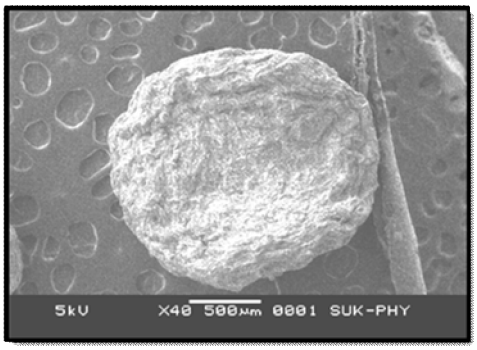

Fig.3: Comparative i*n-vitro* drug release profile of Diclofenac sodium microcapsules

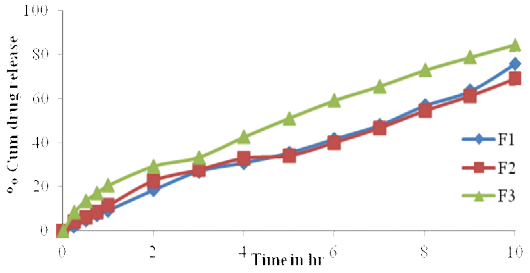

Fig. 4: Comparative zero order plot of Diclofenac sodium microcapsules

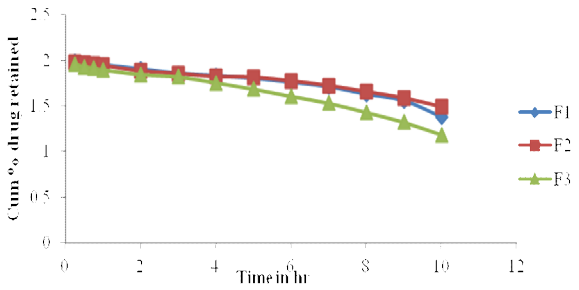

Fig. 5: Comparative first order plot of Diclofenac sodium microcapsules

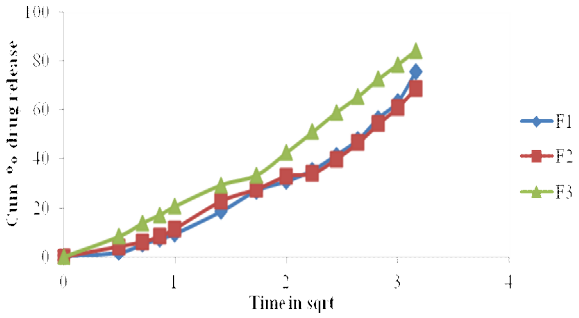

Fig. 6: Comparative Higuchi's plot of Diclofenac sodium microcapsules

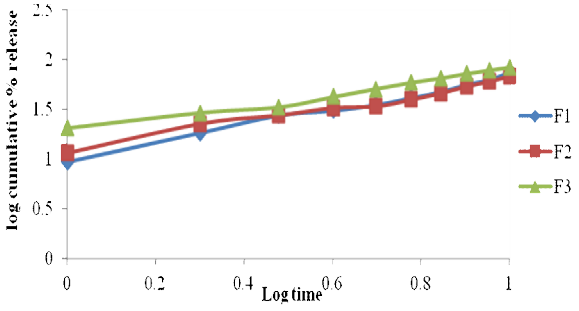

Fig. 7: Comparative peppas plot of Diclofenac sodium microcapsules

CONCLUSION:

From the experimental results, it can be concluded that the microcapsules of Diclofenac was successfully formulated by emulsion solvent evaporation method using ethyl cellulose in 1:1, 2:3 and 2:1 ratio. All the microcapsules prepared were found to be discrete, spherical and free flowing. Percent practical yield decreased as the amount of carrier/polymer added to each formulation increased (1:1 and 2:3 ratio of drug: carrier). SEM Photographs of samples revealed that all prepared microcapsules were almost spherical in shape and has a slightly smooth surface. The encapsulation efficiency ranges from 66.17 to 72.99% for formulation F-1 to F-3. The maximum EE was found to be 72.99% in F-3, which may be due to increase in core material in the microcapsules. The data obtained from *in-vitro* release profile of Diclofenac indicates that all the batches of microcapsules showed controlled and prolonged drug release and spread over an extended period of time. Cumulative percent drug released after 10 hours was 75.82%, 69.10% and 84.5% for F1, F2 and F3 respectively. From the *in-vitro* drug release profiles, it was observed that the drug release from microcapsules was decreased with an increase in coat material in the microcapsules (F-2). The release followed first order kinetics with 'r' greater than 0.967 for all formulations (F1-F3). It was observed that all the formulations F1 – F3 followed the Higuchi matrix suggesting drug release by diffusion. The 'n' value obtained from Peppas plot indicated that the all formulations F1–F3 followed Non-Fickian controlled release mechanism. Present work was a satisfactory preliminary study in formulating Diclofenac microcapsules by emulsion solvent evaporation method. An *in-vitro* & *in-vivo* correlation needs to be established to guarantee the efficacy and bioavailability of the formulation.

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