

# Pharmaceutical Microencapsulation Technology for Development of Controlled Release Drug Delivery systems

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**Abstract**—This article demonstrated development of controlled release system of an NSAID drug, Diclofenac sodium employing different ratios of Ethyl cellulose. Diclofenac sodium and ethyl cellulose in different proportions were processed by microencapsulation based on phase separation technique to formulate microcapsules. The prepared microcapsules were then compressed into tablets to obtain controlled release oral formulations. In-vitro evaluation was performed by dissolution test of each preparation was conducted in 900 ml of phosphate buffer solution of pH 7.2 maintained at  $37 \pm 0.5$  °C and stirred at 50 rpm. At pre-determined time intervals (0, 0.5, 1.0, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 20 and 24 hrs). The drug concentration in the collected samples was determined by UV spectrophotometer at 276 nm. The physical characteristics of diclofenac sodium microcapsules were according to accepted range. These were off-white, free flowing and spherical in shape. The release profile of diclofenac sodium from microcapsules was found to be directly proportional to the proportion of ethylcellulose and coat thickness. The in-vitro release pattern showed that with ratio of 1:1 and 1:2 (drug: polymer), the percentage release of drug at first hour was 16.91 and 11.52 %, respectively as compared to 1:3 which is only 6.87 % with in this time. The release mechanism followed Higuchi model for its release pattern. Tablet Formulation (F2) of present study was found comparable in release profile the marketed brand Phlogin-SR, microcapsules showed an extended release beyond 24 h. Further, a good correlation was found between drug release and proportion of ethylcellulose in the microcapsules. Microencapsulation based on coacervation found as good technique to control release of diclofenac sodium for making the controlled release formulations.

**Keywords**—Diclofenac sodium, Microencapsulation technology, Ethylcellulose, In-Vitro Release Profile

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## I. INTRODUCTION

MICROENCAPSULATION technology has widely been used in many industrial applications, including graphics and food and agriculture. Application of micro particulate drug delivery system for pharmaceutical and medical problems has also been extensively studied. Microencapsulation technology allows protection of the drug from the environment, stabilization of sensitive drug substances, elimination of incompatibilities, or masking of unpleasant taste, Micro particles are particularly interesting for the development of controlled or prolonged release dosage forms. They play an important role as drug delivery system aiming at improved bioavailability of conventional drugs and minimizing side effects [12].

The term “microencapsulation” is used to designate a category of technologies used to entrap solids, liquids or gases inside a polymeric matrix or shell. In contrast to film coating techniques, particle formation occurs in a single step. Usually the drug substances are encapsulated in a biocompatible or biodegradable polymer forming particle with a diameter in range of 1 to 1000  $\mu\text{m}$ . For parenteral delivery system, the diameter of the particle should be less than 250  $\mu\text{m}$ , ideally less than 125  $\mu\text{m}$ , to allow injections with acceptable needle diameter ([5]; [2]; [12]).

Diclofenac sodium, (DFS, 2-(2, 6-Dichloranilino) Phenylacetic Acid, molecular formula  $\text{C}_{14}\text{H}_{11}\text{Cl}_2\text{NO}_2$ ) is an off-white crystalline solid employed for treating rheumatoid arthritis and related diseases. When orally administering DFS conventional formulation, it was difficult to achieve the desired clinical effect, because it elicited patients' non-compliance of administration in the early morning to coordinate the rhythm of rheumatoid arthritis, due to rapid absorption of the conventional formulation (Gang et al., 2004). Therefore, the present study was designed to formulate DFS using advanced pharmaceutical technology to make a suitable drug delivery system.

## II. EXPERIMENTAL

### A. Chemicals and Apparatus

Diclofenac sodium (DFS) was donated by Novartis Pharmaceuticals (Pakistan) Ltd. Ethylcellulose was taken as research donation from highnoon laboratories Lahore-Pakistan. Talc was purchased from Merck-Germany. Magnesium stearate was obtained from Fluka-Germany. Six vessels dissolution apparatus attached with auto sampler

(Pharma test-Germany), Magnetic Stirrer (Gallen Kamp-England) pH Meter (WTW pH 300-Germany) Ultrasonic Bath (Fisher Scientific FS 28 H-Germany), Electric Balance (Precisa, Japan).

#### B. Procedure for Preparation of DFS microcapsules by microencapsulation technology based on phase separation

Phase separation method based on thermal change was employed to formulate microcapsules of DFS using different concentrations of EC. Three formulations were developed in the ratios of (EC: DFS, (50: 50) in the ratio of 1:1 was designated as F1), (EC: DFS, (67: 33) in the ratio of 2:1 was designated as F2), (EC: DFS, 75:25 as F3). Weighed amount of EC was taken in a beaker then it was dissolved in cyclohexane (1gm EC in 20 ml of cyclohexane) heating up to 80 °C by using hot plate with magnetic stirrer. At this temperature EC makes a solution with cyclohexane. Finely pulverized DFS in quantities according to stated formulations was dispersed in the solution of EC in cyclohexane with vigorous stirring. Reducing the temperature while continuing vigorous stirring induced phase separation. The microcapsules obtained were washed with water and dried at 40 °C in oven (Mommert, Germany). These microcapsules were then passed through a sieve No.40. (USP) to separate the sizes of microcapsules.

#### C. Preparation of tablets from microcapsules

Sustained release tablets of DFS microcapsules (F1, F2 and F3) were prepared individually by blending the microcapsules passed through sieve No.40 with 1 % talc and 0.5 % magnesium stearate and direct compressing microcapsules by using single punch tablet machine (Emmy, Pakistan). Each tablet contains microcapsules equivalent to 200mg of DFS. To check the reproducibility of batches five batches were prepared at different time intervals.

#### D. Physical evaluation of tablets

In order to determine the uniformity of tablet weight, twenty tablets of each formulation were randomly collected and weighed using class A weight balance (Precisa, Japan) and their percentage variation was determined. Hardness of tablets was determined using automatic hardness tester (Curio, Pakistan). Ten tablets of each formulation were used and the average hardness value was calculated. The tablets of each formulation were also subjected to friability testing employing friabilator (Emmy, Pakistan). Twenty tablets were placed in the tumbling chamber and rotated precisely for 4 minutes at a speed of 25 rpm. The weight of twenty tablets prior to their placement in the chamber and at the end of the test was recorded. The percentage weight loss was then calculated. Triplicate measurements were conducted for each formulation.

#### E. Release pattern of the tablets

The in-vitro drug release profiles of DFS tablets were evaluated using USP apparatus II with auto sampler unit (Pharma Test, Germany). Dissolution test of each preparation

was conducted in 900 ml of phosphate buffer solution of pH 7.2 maintained at  $37 \pm 0.5^\circ\text{C}$  and stirred at 50 rpm. At pre-determined time intervals (0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 20 and 24 hours). An aliquot amount (5 ml) of dissolution media was with drawn by an automatic sampler unit. Samples were filtered automatically through milli-pore filter to remove suspended and insoluble tablet components. The volume of the dissolution medium was kept constant by replacing the sample volume with an equal volume of dissolution medium. The drug concentration in the collected samples was determined by UV spectrophotometer (Shimadzu, Japan) at 247 nm. Each formulation was run in sets of six tablets and the average percentage release over time was then calculated and plotted. Phlogin SR was used as reference in determining the percentage dissolution.

#### F. Reproducibility in different batches

To study batch reproducibility, five batches of each formulation were prepared and evaluated for drug loading and release profile of DFS.

### III. RESULTS AND DISCUSSION

#### A. Characteristics of microcapsules and their tablets

The microcapsules were white, free flowing and spherical in shape. Physical appearance, hardness, friability and weight variation of different tablet formulations were found to be satisfactory (Table 1). The study was designed to develop the microencapsulated formulation of 200 mg of DFS tablets. These tablets were then subjected to dissolution test to check the effect of polymer (EC) on the release pattern of DFS from microencapsulated tablets. Three formulations were developed and compared with Phlogin SR available in the market. The results of all the formulations and their comparisons are shown graphically in rectangular co-ordinate graph and on a semi logarithmic graph in Figures 1.

TABLE I  
PERCENT DRUG CONTENT, HARDNESS AND % WEIGHT LOSS IN FRIABILITY TEST OF VARIOUS FORMULATIONS

Formulations	Mean $\pm$ SEM values of DFS Microencapsulated tablets		
	Drug content (%)	Hardness (kg/cm <sup>2</sup> )	% wt. loss Friability
F 1 (1:1)	99.98 $\pm$ 0.12	7.18 $\pm$ 0.013	0.008 $\pm$ 0.0004
F 2 (1:2)	100.08 $\pm$ 0.14	7.13 $\pm$ 0.014	0.008 $\pm$ 0.0003
F 3 (1:3)	99.96 $\pm$ 0.19	67.09 $\pm$ 0.011	0.008 $\pm$ 0.0005

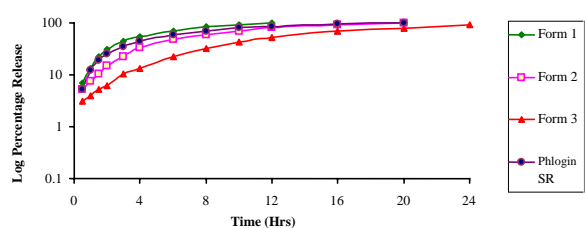


Fig. 1 percent release profile vs time of dfs microencapsulated tablets (f1, f2, f3) and phlogin-sr

### B. Formulation of Diclofenac sodium microencapsulated tablets

Microencapsulation is a process of particle coating employed extensively in pharmaceuticals to extend their release pattern as well as to enhance stability. Among various approaches of microencapsulation technology, coacervation/phase separation is a method to achieve the microencapsulated products. In this study three formulations were developed by using DFS and Ethylcellulose in various ratios (DFS: EC, 1:1, F1), (DFS: EC, 1:2, F2), (DFS: EC, 1:3, F3) using coacervation technique by thermal change. Different studies have been conducted to formulate the microcapsules by using coacervation technique [4], [10]. Among those studies, microencapsulation of Bacampicillin by using Ethylcellulose as a wall forming material and cyclohexane as solvent were performed by temperature change [4]. Microcapsules were also prepared from naproxen and Ethylcellulose by coacervation phase separation using polyisobutylenes as a coacervation-inducing agent. Using polyisobutylene at different concentrations, it was possible to regulate the release of naproxen during an in-vitro dissolution test from 60 to 90% [14]. In this study ethyl cellulose was employed as wall forming material on the basis that it provided a better release profile and produced microcapsules avoiding bursting affect and because of its biocompatibility, non biodegradability and availability in variety of grades that differ in their viscosity. Low viscosity grades have been utilized as wall forming materials because low viscosity grades are used for binding characteristics [7]. Many formulations of Ethylcellulose/drug ratios have been prepared to get optimum release of drug for a prolonged period of time. Many authors have developed Ethylcellulose microcapsules ([13]; [16]; [1]; [6]; [8]) with higher percentages of polymers to achieve the required sustained release effect. The above studies indicate the importance of EC to get a release over 12-24 h. The tablets prepared in this study were subjected to the physical tests and results of tests were analyzed by statistical methods and were within the specified limits (B.P. 2004). The weight variation of all the compressed tablets was also found well within the acceptable limits indicating uniform filling of the granules in the die of compression machine. All the formulations were weighed and weight variation was not more than  $\pm 1.5\%$ . The physical appearance, hardness and friability of all formulations were satisfactorily within the range. The hardness of the tablets was kept above  $5 \text{ Kg/cm}^2$  to

prevent the disintegration during the drug release. It was observed in earlier studies (Saha et al. 2001) that the Tablet hardness below a certain level significantly decreases the controlled release. In the present study, the release of drug from microencapsulated tablets was extended from 12 to 20 hours by increasing the ratio of Ethylcellulose (F1 to F2) and for F3 the release was extended beyond 24 hours that was 90%. The same results were reported in the previous studies [8]. The most probable mechanism of DFS release from ethyl cellulose microcapsules appeared to be diffusion of DFS from the insoluble porous microcapsules into the dissolution medium due to swelling of EC microcapsules.

### C. Comparison of release profile of three formulations (F1, F2, F3) and Phlogin-SR

The study was conducted with the aim to develop microcapsules for the prolonged delivery of DFS with different concentrations of ethyl cellulose, which was employed as wall forming material. The in-vitro release pattern showed that with ratio of 1:1 and 1:2 (drug: polymer), the percentage release of drug at first hour was 13.38% and 7.43 %, respectively as compared to 1:3 which is only 4% with in this time. The decrease in the release pattern was due to the increase in the concentration of Ethylcellulose. The decrease in release during initial timings was due to increase in the polymer ratio, which decreases the release rate of drug as earlier, studied (Saravanan et. al. 2003; [9]). In the ratio of formulation F1 (1:1) the release was 54% at 4 h whereas the formulation F2 (1:2) showed a release of 48% at 6h and the release rate for Formulation F3 (1:3) was 52% at 12 hrs showing a prolonged release pattern. The microcapsules prepared by Formulation F3 (1:3) achieved a 100% release of drug beyond 24 hrs, which proves that the drug release from microcapsules was increased gradually and slowly as the quantity of Ethylcellulose increased [11]. With high proportion of Ethylcellulose as in the case of Formulation F3 (1:3), release rate was very slow with respect to Formulation F2 (1:2) which releases the drug before 20 hrs. If the release of drug from microcapsules is from 18 to 21 hours, the Formulation may be considered as a sustained release product [11]. An increase in the ratio of Ethylcellulose in the microcapsules may reduce the diffusion of water molecules inside the polymer, thus reducing the extent of swelling of microcapsules, resulting in slower release of drug. Hence the presence of high percentage of Ethylcellulose in microcapsules resulted in a more hydrophobic character. At very high ratio of polymer, the capsules become impermeable to the dissolution medium and gave very slow release of drug as observed in the release profile of Formulation F3 (1:3). The above facts indicate that the reduction in drug release from the microcapsules may be due to a reduction in the diffusion of dissolution medium inside the microcapsules because of the hydrophobicity of Ethylcellulose in water. The In-Vitro dissolution of Phlogin SR (available in the market) was also performed and the results were compared with the microencapsulated DFS tablets. The release profile of Phlogin SR was found to be consistent with previous studies [9].

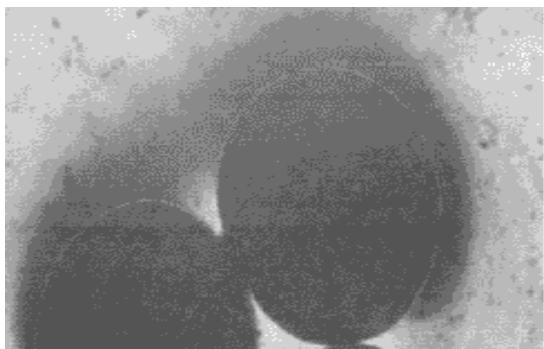


Fig. 2 (a): Microphotograph of DFS and EC Microcapsules (F2)

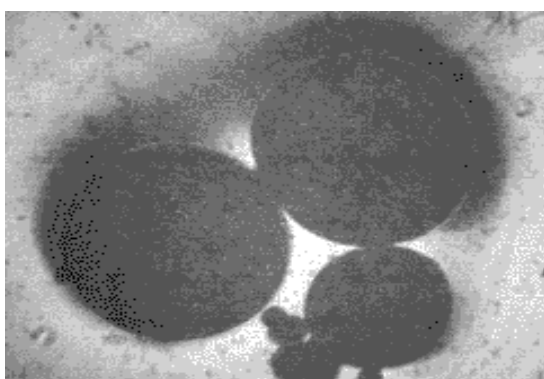


Fig. 2 (b): Microphotograph of DFS and EC Microcapsules (F3)

#### IV. CONCLUSION

Microencapsulation technology resulted in a drug delivery system conforming compendial requirements and retarding the release of DFS over an extended time period as tablets prepared in three Formulations (F1, F2, F3) showed increase in sustained effect as the ratio of Ethylcellulose was increased from (1:1, 1:2 and 1:3) and it was beyond 24 h. All In-vitro results of Formulation 2 (F2) showed comparable results with Phlogin SR as well as the data available in the previous studies.

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