FORMULATION AND EVALUATION OF ENTERIC COATED MICROCAPSULES OF DICLOFENAC SODIUM FOR MODIFIED RELEASE BY COMBINATION OF WET GRANULATION AND THERMAL CHANGE METHOD

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The purpose of the present work was to develop optimized novel enteric microcapsules containing diclofenac sodium, a non steroidal anti inflammatory drug (NSAID) used for rheumatoid arthritis, for improved delivery and to diminish its adverse effect after oral administration. The microcapsule was prepared by using different polymers and the enteric coating was provided by using an innovative technique combining wet granulation method and thermal change method. This work also investigated different levels of enteric polymers like cellulose acetate phthalate (CAP) (X_1) and ethyl cellulose (EC) (X_2) and the stirring speed during coating ethyl cellulose (X_3), by using 2^3 full factorial design. The dependent variables assessed were % yield (Y_1), Q8 (% drug released after 8 hour) (Y_2), n (Diffusion coefficient) (Y_3), DEE (Drug entrapment efficiency) (Y_4). The main effect and interaction terms were quantitatively evaluated using a mathematical model. The prepared microcapsules were evaluated for percentage drug dissolved, scanning electron microscopy, drug excipient interaction, angle of repose, particle size. Mean dissolution time (MDT) was used to compare dissolution patterns obtained. The results showed that X_1 and X_2 significantly affected the release properties.

Keywords: Diclofenac sodium, microcapsules, factorial design, wet granulation, thermal change method

INTRODUCTION

Diclofenac sodium, a potent non steroidal anti inflammatory drug with pronounced analgesic properties, is used in the long term treatment of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis. Its biological half life has been reported as 1–2 hour. However gastrointestinal side effects such as bleeding, ulceration or perforation of intestinal wall are commonly seen with diclofenac sodium administration (1). Due to short biological half life and associated adverse effects, it is considered as an ideal candidate for controlled drug delivery. Under ideal conditions, a sustained-release formulation maintains therapeutic blood level of a drug for a specific period of time. Oral controlled-release dosage forms have been developed and studied to restrict the delivery systems to specific regions of the gastrointestinal tract as well as to improve the pharmacological activity and to reduce toxic effects (2). Development of new drug molecule is expensive and time consuming. Improving safety, efficacy ratio of 'old' drugs has been attempted using different methods such as individualizing drug therapy, dose titration and therapeutic drug monitoring. Delivering drug at controlled rate, slow delivery, and in targeted fashion are other very attractive methods and have been pursued very vigorously. In the present work, an innovative method was employed to prepare dual coated enteric microcapsules of diclofenac sodium. Enteric-coated products are designed to remain intact in the stomach and then to release the active substance in the upper intestine (3). The enteric microcapsules were prepared by combining wet granulation and thermal change methods. Two polymers offered resistance for gastric erosion; enteric cellulose based polymer (CAP) and a water insoluble hydrophobic polymer, EC (4, 5). The drug was wet granulated using aqueous acacia mucilage with CAP and then coated with EC by thermal change method. The objective of the study was to develop optimized enteric microcapsules containing diclofenac sodium as model drug. Optimization with factorial designs and analysis of the response is a powerful, efficient and systematic tool that shortens the time required for the development of pharmaceutical dosage forms and improves research and development work (6). Independent formulation variables such as amount of CAP, amount of EC and stirring speed during coating were examined. The dependent variables assessed were % Yield (Y_1), Q8 (% drug released at 8 hour) (Y_2), n (Diffusion coefficient) (Y_3), DEE (Drug

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entrapment efficiency) (Y_4). Regression analysis was performed to validate the model by comparing the experimental results with the theoretical values of the responses.

MATERIALS AND METHODS

Diclofenac sodium was generously provided as gift sample by Emcure Pharmaceuticals Ltd., Pune. Cellulose acetate phthalate (CAP) & ethyl cellulose (EC), cyclohexane, were procured from Loba Chemicals, Mumbai. Other ingredients used were of analytical grade and procured from commercial source.

Experimental design

Factorial design is an experimental technique by which factors involved in a process can be identified and their relative importance assessed. It is thus a means of separating those factors that are important from those that are not and identifying the interactions, if any, between the factors chosen. Thus the construction of a factorial design involves the selection of parameters and the choice of responses.

Full factorial design is one of the best tools to study the effect of different variables on the quality determinant parameters of any formulation. Eight formulations were prepared according to a 2^3 factorial design employing the qualitative factors and levels shown in Tables 1 and 2.

Preparation of microcapsules:

Diclofenac microcapsules were prepared by using a simple but novel process that was designed by combining wet granulation with thermal change method. Diclofenac was mixed with CAP; the resulting mixture was granulated with 30% w/w aqueous acacia mucilage and dried at 50ºC. Dried granules of uniform size (No. 30/40) were further encapsulated with ethyl cellulose by thermal change method. The EC coating was done on drug – CAP core by using cyclohexane as solvent for EC and changing the temperature from 80ºC to room temperature with continuous stirring.

Evaluation of microcapsules:

Drug Content:

Drug content in each batch was determined by weighing 100mg of microcapsules and crushing them in a clean mortar. 50mg of the crushed microcapsules were transferred into (50ml) volumetric flask with 10ml methanol and 20ml of phosphate buffer pH 7.4 and then sonicated for 15 minutes. An aliquot was withdrawn, filtered through millipore filter and suitably diluted and assayed spectrophotometrically (UV – 1700, SHIMADZU CORPORATION, Japan) at 276nm, using the same medium as a blank. The percentage drug entrapment and yield were calculated as follows (7):

% Drug entrapment = [Practical drug content / Theoretical drug content] x 100

Scanning electron microscopy:

Surface morphology of the prepared microcapsule was studied by using Scanning Electron Microscope (SEM) (Jeol JSM – 6700F, Japan). The sample for SEM was prepared by lightly sprinkling the microcapsules on a double adhesive tape stuck to an aluminum stub. The stubs were then coated with gold and photomicrographs were taken.

Micromeritic properties:

Particle size distribution analysis was done by sieve method(8). Flowability of microcapsule was tested by angle of repose, it was determined according to the method reported by Abdelkader *et. al* (9).

Drug Excipient Interaction:

To determine any interaction between drug and polymer, Fourier Transform Infrared (FTIR) study was carried out. FTIR spectra were recorded on FTIR–8400S (SHIMADZU CORPORATION, Japan). Samples were compressed with Potassium bromide and transformed into disk. Disk was applied to the centre of the sample holding device and scanned between 4000–400cm^{-1} at a resolution of 4cm^{-1}. The IR scans were processed using IR Solution and represented as percentage Transmittance on a common scale.

***In vitro* release study:**

The drug release studies were carried out using the USP XXIII dissolution apparatus I (basket method; VDA – 8DR USP Standard, VEEGO, Kolkata, India). In the first step, the microcapsules were evaluated by dissolution testing in 900ml 0.1N HCl solution at 37ºC at a basket speed of 50 rpm. Accurately weighed sample containing the equivalent of about 100mg of diclofenac sodium were introduced in the dissolution medium. After 1 and 2 h, the samples were taken from the vessel, passed through a filter, assayed by

spectrophotometer (UV – 1700, SHIMADZU CORPORATION, Japan) at 276 nm. Sink conditions prevailed during the drug release studies. The initial volume of the dissolution fluid was maintained by adding fresh dissolution fluid after each withdrawal. In the second step, acidic medium was immediately replaced with the phosphate buffer (pH 7.4), then the dissolution testing was continued. Additional samples were taken in the same way as before at different time intervals and analyzed spectrophotometrically at 276 nm.

Mean Dissolution Time:

Mean dissolution time (MDT) is considered as a basis for comparison of the dissolution rates and was estimated by the following equation (9):

$$MDT_{\ in\,vitro} = \frac{\sum_{i=1}^{n} t_{mid}\,\Delta M}{\sum_{i=1}^{n} \Delta M}$$

where i is dissolution sample number, n is number of dissolution sample times, t_{mid} is time at the midpoint between times t_i and t_{i-1}, and ΔM is the amount of diclofenac sodium dissolved (μg) between times t_i and t_{i-1}.

Data Analysis

The results obtained were statistically validated using MS Excel (Microsoft) & Sigmaplot. The models were evaluated in terms of statistically significant coefficients and R^2 values. Contour plots were provided by the Sigmaplot software.

Table 1: Level of Investigated variables

Codes	Independent Variables		
	Amount of CAP (X_1) (mg)	Amount of EC (X_2) (mg)	Stirring speed during coating (X_3) (rpm)
–	50	100	1000
+	100	200	1500

CAP indicates Cellulose acetate phthalate; EC indicates Ethyl cellulose

Table 2: Composition of diclofenac sodium microcapsules as per 2^3 factorial designs

Combination	Formulation	Composition[a]		
		X_1	X_2	X_3
1	F1	-	-	-
A	F2	+	-	-
B	F3	-	+	-
AB	F4	+	+	-
C	F5	-	-	+
AC	F6	+	-	+
BC	F7	-	+	+
ABC	F8	+	+	+

[a] Factor at low level, -; Factor at high level, +

RESULT AND DISCUSSION

Diclofenac sodium is poorly soluble in gastric medium. As a result it possesses absorption problems in gastric medium. Hence an attempt was made to avoid the adverse reactions of diclofenac sodium. Diclofenac sodium is a NSAID and is presently considered as important drug for treatment of rheumatoid arthritis. Its successful treatment can be achieved by maintaining constant supply of drug. Multiple dose administration at intervals of 6 – 8 hours is difficult for a arthritic patient, which can lead to patient non compliance. Diclofenac sodium with all evident advantages has proved to be a suitable candidate for development of controlled release dosage form. In this study, the microcapsules were prepared by employing wet granulation and thermal change methods simultaneously. The method of preparation of these dual coated microcapsules is based on the simple idea that the mixture of CAP and drug is first converted into uniform granules

(to act as a core) employing wet granulation method and subsequently EC was coated using thermal change method which resulted in the formulation of dual coated microcapsules. The technique involved the principle of solvent evaporation. The compositions of formulations were varied as per factorial design and factor concentration of CAP and concentration of EC were considered to have an important effect on the release from the prepared microcapsules. The prepared microcapsules were subjected to various evaluations. Surface morphology, as shown in Fig 1 revealed that the prepared microcapsules were discrete and spherical in shape. Micromeritic analysis revealed that the mode of size distribution was normal in all batches with the range distribution of 414.14 ± 3.43 – 787.19 ± 3.25µm. Results of measurements of the angle of repose of the microcapsules are summarized in Table 3. The values in the range of 19.46 ± 2.13 – 27.02 ± 2.66 for all batches revealed that they have a good flow property (10) which is desired parameter for further processing. The drug content of diclofenac sodium was found to be in the range of 301.85 – 448.1mg. Fourier Transform Infrared (FTIR) spectra for the pure drug were recorded and compared with the FTIR spectra of the formulations for determining drug excipient interaction and shown in figure 4. Diclofenac sodium gives characteristic peaks at wave numbers 756, 775, 1286, 1308, 1504 and 1572 (11). FTIR studies revealed that there was no shift in peaks of the formulations containing diclofenac sodium and other excipients when compared to pure diclofenac sodium, indicating there was no interaction between diclofenac sodium and other polymers used. Release profiles from the 8 formulations according to 2^3 factorial designs are shown in Figs. 2 & 3. *In vitro* dissolution studies were carried out in two dissolution medium – 0.1N HCl solution for first two hours and then in phosphate buffer pH 7.4 for next 8 hours. It is clear from the figures that the formulation showed biphasic release of diclofenac sodium. Release of diclofenac sodium solution was lesser in 0.1N HCl. The design was evaluated for a factorial linear first order model:

$$Y = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + b_{12}X_1X_2 + b_{13}X_1X_3 + b_{23}X_2X_3$$

Coefficients with one factor indicate the effect of that particular factor, while the coefficients with more than one factor and those with second order terms represent the interaction between those factors and quadratic nature of the phenomena, respectively. Positive sign of the term indicates positive (additive) effect, while negative sign indicates negative (antagonistic) effect of the factor on the response (13). Two-dimensional contour plots are presented in Figs. 5–7, which are very useful to study the interaction effects of the factors on the responses. These types of plots are useful in study of the effects of two factors on the response at one time. All the relationships among the three variables are linear, although Figs. 5 and 6 exhibit a nearly non linear relationship of factor X1 with factors X2, in the form of curvilinear or non linear lines at the lowest and highest level of polymer concentration. At medium polymer concentrations these become linear.

Table 3: Responses for formulation (F1 – F8) by 2^3 factorial design

Batch code	Y_1 Yield (%)	Y_2 Diclofenac Sodium release after 8 hours, (%)	Y_3 Diffusion coefficient (n)	Y_4 Drug Entrapment Efficiency (DEE) (%)	Angle of repose (θ)	Average particle size (µm)	Dissolution efficiency (DE) (%)	Mean Dissolution Time (MDT)
F1	69.12	78.54	0.79	60.37±0.56	19.46±2.13	475.35±4.12	59.05	6.037
F2	75.50	69.97	1.27	82.18±1.43	24.06±3.22	682.21±3.17	54.79	6.169
F3	70.74	73.62	1.09	86.74±2.33	20.25±2.76	414.14±3.43	57.96	5.985
F4	82.90	60.12	1.42	89.62±4.21	24.99±4.10	702.16±2.14	53.31	6.208
F5	68.90	74.35	0.98	64.28±2.11	24.27±3.35	598.51±3.65	59.24	6.008
F6	76.08	70.13	1.20	62.41±3.76	23.02±3.26	640.74±4.09	51.56	5.521
F7	71.04	78.32	1.21	66.88±2.13	25.04±4.21	632.34±2.89	46.50	5.782
F8	83.88	59.17	1.25	83.19±1.25	27.02±2.66	787.19±3.25	46.25	6.386

Table 4: Regression coefficients for the responses

$Y_1 = 74.77 + 4.82X_1 + 2.37X_2$
$Y_2 = 70.53 – 5.68X_1 – 2.72X_2 – 2.48X_1X_2$
$Y_3 = 1.15 + 0.133X_1 + 0.09X_2$
$Y_4 = 74.46 + 4.89X_1 + 7.15X_2 – 5.27X_3$

Table 5: Analysis of Variance table for dependent variables from Full Factorial Design*

Source	df	Sum Square	Mean Square	F Value	Prob > F
Yield of the prepared microcapsules (%) $R^2 = 0.9311$					
X_1	1	185.86	185.86	54.42	0.0007
X_2	1	44.94	44.94	13.16	0.0151
Diclofenac Sodium release at 8 hours (%) $R^2 = 0.9476$					
X_1	1	258.10	258.10	50.89	0.0020
X_2	1	59.19	59.19	11.67	0.0269
X_1X_2	1	49.30	49.30	9.72	0.0356
Diffusion Coefficient (n) $R^2 = 0.7892$					
X_1	1	0.14	0.14	12.71	0.0161
X_2	1	0.068	0.068	6.01	0.0578
Drug Entrapment Efficiency (DEE) $R^2 = 0.8052$					
X_1	1	191.39	191.39	3.85	0.1213
X_2	1	408.84	408.84	8.22	0.0456
X_3	1	222.08	222.08	4.47	0.1021

* Prob > F less than 0.05 indicate model terms are significant

In the case of Y_2 (percentage of diclofenac release after 8 hours), coefficients b_1 and b_2 were found to be significant, with an interaction of b_{12}. In Table 4, we can see only negative coefficients. When the total polymer content to drug ratio was increased, diclofenac sodium release after 8 hours decreased.

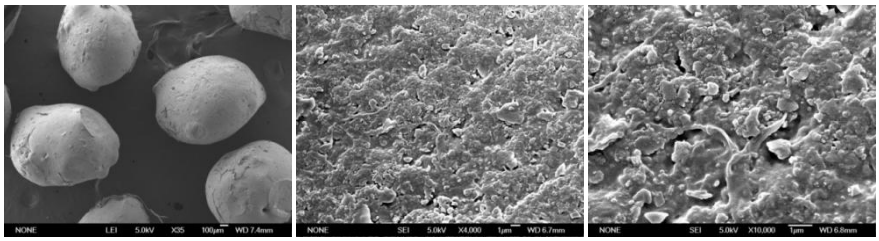

Figure 1. Scanning electron microscopy (SEM) of microcapsules

Conclusion

This article discussed a positive application of a computer optimization technique for the development of dual coated microcapsules in which the amount of polymer cellulose acetate phthalate (CAP) and ethyl cellulose (EC) did significantly affect the studied dependent variables. However, the stirring speed during preparation did not significantly affect the dependent variables. The dosage form can control the release, avoid dose dumping and extend the duration of action of a drug. This dosage form holds promise for *in vivo* studies, which can be extrapolated for the development of other delivery systems.

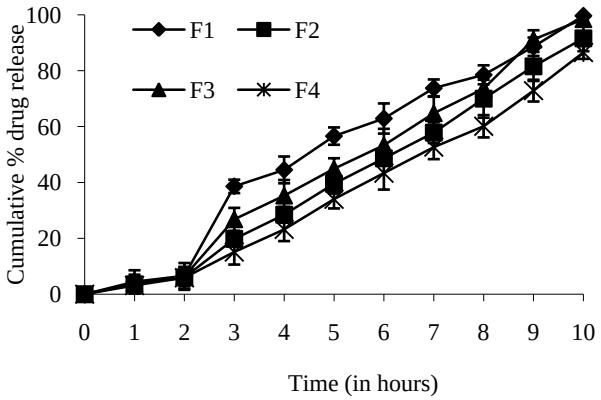

Figure 2. *In vitro* release profile (formulations F1 to F4)

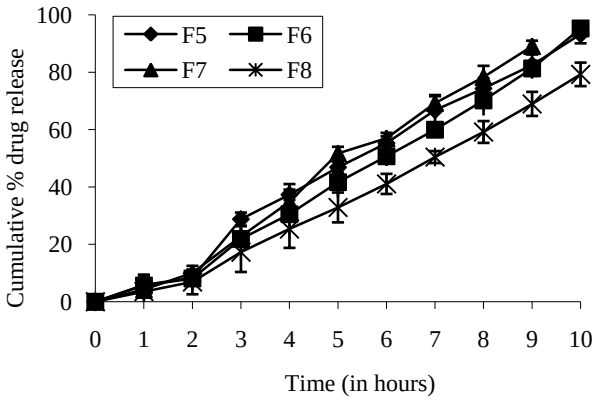

Figure 3. *In vitro* release profile (formulations F5 to F8)

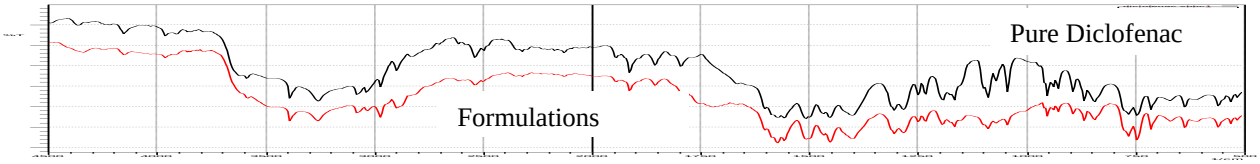

Figure 4. FTIR spectrum of pure diclofenac and formulation

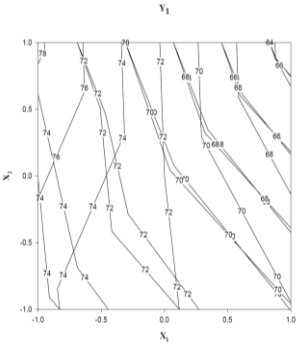

Figure 4: Counter plot showing the effect of amount of CAP (X_1) and amount of EC (X_2) on the yield of the microcapsules (Y_1)

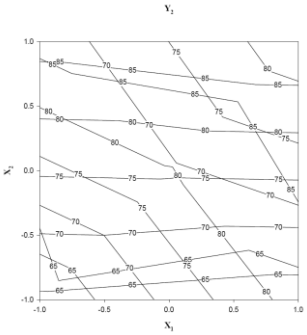

Figure 5: Counter plot showing the effect of amount of CAP (X_1) and amount of EC (X_2) on the percentage of diclofenac sodium at 8 hours (Y_2)

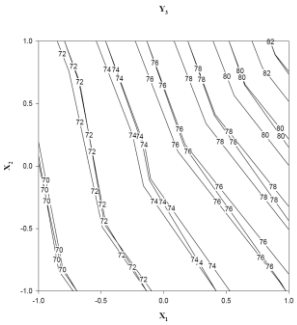

Figure 6: Coulter plot showing the effect of amount of CAP (X_1) and amount of EC (X_2) on the diffusion coefficient (n) (Y_3)

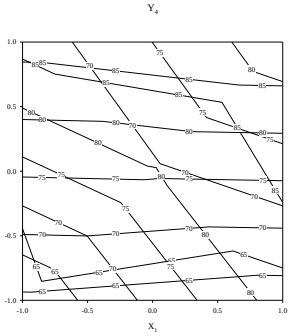

Figure 7: Counter plot showing the effect of amount of CAP (X_1) and amount of EC (X_2) on the Drug Entrapment Efficiency (Y_4)

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