PREPARATION AND IN VITRO EVALUATION OF SUSTAINED RELEASE TABLETS OF DICLOFENAC SODIUM

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ABSTRACT

Using Ethyl Cellulose (EC) as coat material, DFS was microencapsulated by a non aqueous phase-separation technique induced by nonsolvent addition and the resulting microcapsules were tabletted with an intention of extending the drug release profile. All the tablets prepared were of good quality, when tested for thickness, hardness, friability and drug content. *In vitro* Dissolution studies indicated that drug release from tablets followed zero order kinetics; the release could be extended up to 24 hours, and non-fickian diffusion was involved. The shelf life of selected Tablet formulation T-ECMC-4 was predicted to be 3.0 years.

KEY WORDS: Diclofenac Sodium, Ethyl cellulose, Coacervation, Phase separation, Microencapsulation.

1.INTRODUCTION

The rate of drug release from microcapsules may be manipulated by changing coat: core ratio, the polymer used as coating material, and the method of microencapsulation (Yazici,1996). Sustained release tablets made from individual coated particles have very different release characteristics than the original coated particles depending up on whether or not the tablets disintegrate to expose the majority of coated particles to the dissolution environment (Chang and Price,1988). Coacervation-phase separation (Gander,2007) is one way of microencapsulation. The benefits of administering diclofenac sodium (DFS) in a controlled release system have been established and demonstrated (Sajeev,2002). In the present work, DFS was microencapsulated with ethyl cellulose (EC) by organic phase separation induced by non solvent addition. Microcapsules with different coat: core ratios were prepared and were compressed into tablets to extend the drug release.

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2.MATERIALS AND METHODS

Materials

Diclofenac Sodium (gift sample from Amoli Organics, Ahmadabad), Ethylcellulose (EC) (BDH) (having an ethoxyl content of 47.5% weight and a viscosity of 22 cp in a 5 % concentration, by weight, in a 80: 20 toluene-ethanol solution at 25^0 C), Toluene (BDH) (109^0-112^0 C), Petroleum ether (Glaxo) (60^0-80^0 C), Talc I.P., and Magnesium stearate I.P. were used. All other chemicals and reagents used were of analytical grade.

Determination of Fractional Composition of Bulk Drug

It is commonly accepted that the technological properties of powders are determined predominantly by the parameters of major fractions (Emshanova,2007). For this reason, the fractional composition of DFS was also determined by sieve analysis.

Preparation of Microcapsules

DFS was microencapsulated with EC by coacervation-phase separation induced by a non-solvent addition method reported earlier (Al-omran,2002). Microcapsules were prepared at five coat: core ratios of 1:9 (ECMC-1), 1:4 (ECMC-2), 2:3 (ECMC-3), 3:2 (ECMC-4), and 3:1(ECMC-5).

Calculation of SR Dose of DFS

The dose of DFS required for initial and sustained delivery is calculated by considering its pharmacokinetic parameters (Adeyeye and Li,1990; www.pfizer.com).

Biological half life ($t_{1/2}$) = 2 h
First order elimination rate constant
$k = 0.693/t_{1/2} = 0.3465\ h^{-1}$
Time to reach peak plasma concentration T_p = 2 h
Volume of distribution V_D = 38.5 l
(for 70 kg body weight @ 550ml.kg^{-1})
Desired therapeutic concentration
(DTC) for 25 mg dose = 0.5 mg.l^{-1}
Time for which drug is to be released from extended dose T = 12 h

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Desired constant release rate k^o_r (zero order release)

$k^o_r = k \times V_D \times DTC$ (1)

$= 0.3465 \times 38.5 \times 0.5$

$= 6.67\ mg.h^{-1}$

$D_S = k^o_r \times 12$ (2)

$= 80.04$ mg

Amount of drug released from maintenance dose during release of initial dose (till peak plasma concentration achieved)

$= k^o_r \times T_p$ (3)

$= 6.67 \times 2 = 13.34$mg

$D_N^* = D_N - 13.34$

$= 25 - 13.34 = 11.66$ mg

$\backslash D_T = 11.66 + 80.04 = 91.70$ mg (equivalent to » 100 mg of diclofenac base, since, 1.074 mg of DFS is equivalent to 1.000 mg of diclofenac base) (Emami,2007).

Preparation of SR Tablets

Sustained release non-disintegrating tablets of DFS (T-ECMC-2, T-ECMC-3, T-ECMC-4, and T-ECMC-5) were prepared by direct compression of respective microcapsules separately. Each tablet contained microcapsules equivalent to 100 mg of DFS. The microcapsules were blended with 1% talc and 0.5% magnesium stearate and compressed into tablets on a Single Stroke Tabletting Machine (CMS-15-Cadmach Machinery Co. Pvt.Ltd., Mumbai) using 9 mm round and flat punches.

Evaluation of Tablets

Hardness and friability were evaluated using a Monsanto hardness tester and a Roche friabilator, respectively. Weight variation test was performed as per IP procedure (I.P.,2007). DFS content of the tablets was estimated at 276 nm in Shimadzu UV- 2550 UV/ Visible Spectrophotometer.

Release of DFS from microcapsules (equivalent to 100 mg of medicament) and from tablets was studied using USP Dissolution Type 2 apparatus. Distilled water was used as dissolution medium. The stirring speed was set at 50 rpm and at 37±0.5° C. During dissolution experiments of tablets, both dissolution vessel and the water bath used to warm the dissolution medium were covered, for the entire period of study, to minimize losses due to evaporation. A 2 ml sample of dissolution medium was withdrawn at different time intervals, suitably diluted and assayed at 276 nm for DFS. The percent of drug released at various was calculated and plotted against time. The dissolution studies were conducted in triplicate.

The kinetics and mechanism of drug release from tablets was fitted to the following equations (Zhang,2010).

$Q = Q_0 + k_0 t$	Zero order kinetics equation	(4)
$Ln\ Q = Ln\ Q_0 - k_1 t$	First order kinetics equation	(5)
$Q = k_H t^{1/2}$	Higuchi equation	(6)
$M_t/M\infty ?= k_P t^n$	Peppas Equation	(7)

If the n value is 0.5 or less, the release mechanism follows Fickian diffusion, and the values $0.5 < n < 1$ indicate a non-Fickian release (anomalous/zero order release). The drug release follows zero-order and case-II transport if the n value is 1. For the values of n higher than 1, the mechanism of drug release is regarded as super case-II transport. The criteria considered for selecting the best fit model were: the adjusted coefficient of determination ($R^2_{adjusted}$) and standard error of mean (SEM) (Costa and Sousa,2001).

To characterizing drug release curve, area under the release curve (AUC), mean residence time of the drug substance molecules in the dosage form (MRT), mean dissolution time (MDT), and dissolution efficiency up to 30 minutes (DE_{30}) were also calculated (Zhang,2010).

Further, data obtained from release rate studies was fitted for the following probability distributions using Anderson-Darling test statistic (De muth,2006) as the criterion: normal, log-normal, exponential, Weibull, logistic, and log logistic.

Shelf Life Prediction

For the purpose of shelf life prediction, the selected formulation (T-ECMC-4) was tested for potency (drug content) by testing at 0, 6, 12, and 18 months. The resultant data was subjected to linear regression and linear regression line was drawn with the potency data. The lower and upper 95% confidence lines were also graphed. The accepted definition of shelf life time is the x-axis coordinate for the intersection of the lower 95% confidence line with 90% drug activity (Guideline,1987).

3.RESULTS AND DISCUSSION

The fractional composition study of DFS used in the present investigation revealed the presence of particles in the size range of 10-50im upto 45% (Fig.1). This fraction was used in the present investigation.

Theoretical SR profile of DFS was worked out based on the pharmacokinetic parameters of the drug. As per the calculations, a SR preparation of DFS should contain a total dose of about 100 mg and the drug should be released at 6.67 $mg.h^{-1}$.

For microencapsulation with ethyl cellulose a non-aqueous phase separation method was employed. Five ratios of EC and DFS, namely, 1:9 (ECMC-1), 1:4 (ECMC-2), 2:3 (ECMC-3), 3:2 (ECMC-4), and 3:1(ECMC-5) were used to prepare microcapsules. The microcapsules were white, free flowing and spherical in shape.

A previous study (Amareshwar,2010) revealed that drug release from microcapsules was rapid. Hence, in order to extend the drug release from EC microcapsules (ECMC-2, ECMC-3, ECMC-4, and ECMC-5), tablets were made (T-ECMC-2, T-ECMC-3, T-ECMC-4, and T-ECMC-5 respectively). Because of low coat (EC) content, ECMC-1 was not compressed into tablets.

Release rate studies on these tablet formulations were conducted and compared to theoretical drug release profile. The results are shown in Fig.2. Tableting microcapsules resulted in the extension of release profile of the drug (Fig.2). Drug release depended on the proportion of EC and there is decrease in drug release with increase in EC proportion. The greatly reduced porosity and surface area, formation of a non-disintegrating matrix or an increase in tortuosity might be responsible for prolongation of the release of DFS from tablets compared to the original microcapsules. The tablets retained their shape and structure throughout the dissolution study period with very marginal erosion of the tablet matrix. It is clear from Fig.2 that the release profile of formulation T-ECMC-4 is closer to the theoretical SR profile of the drug.

From the data obtained from release rate studies of tablet formulations, Dissolution Efficiency upto 6 hours (DE_6), Mean Dissolution Time (MDT), Mean Residence Time (MRT), Area under the Release Curve (AUC), and T_{50} values were calculated and shown in Table 1. From Table 1 it is evident that, dissolution efficiency decreased from T- ECMC-2 to T-ECMC-5, mean dissolution time increased from T- ECMC-2 to T-ECMC-5, mean residence time increased from T-ECMC-2 to T- ECMC-5, AUC values increased from T- ECMC-2 to T- ECMC-5, and T_{50} values increased from T- ECMC-2 to T- ECMC-5. The reasons for these observations may be attributed to the differences in the proportion of EC in microcapsules as discussed in the above paragraph.

The drug release profile from tablet formulations prepared was analyzed by four kinetic models: zero order, first order, Higuchi, and Peppas models. It was observed that the drug release may be described by zero order kinetics. Since 'n' values in Peppas equation ranged from 0.6251to 8871 it may be concluded that drug release mechanism is of super case-II transport. Among the probability distributions verified, it was observed that normal distribution fitted well (based on high value of Anderson-Darling test statistic for normal distribution).

The pharmaco-technical properties of these tablets are shown in Table 2. Low standard deviation values in the percent drug content of the tablets prepared indicated uniformity of DFS content in each batch of tablets. Thickness uniformity was indicated by the low standard deviation values. Hardness of the tablets was found to be in the range of 6.2 to 6.5 $kg.cm^{-2}$ and was satisfactory. The percentage weight loss in the friability test was found to be less than 0.1%. The results of weight variation test on tablets are shown in stem-and-leaf display (Figs.3-6). These indicate that the tablets passed this test as per IP. Over all, the results indicated that all the tablet formulations prepared were of good pharmaco-technical properties.

For predicting shelf-life the graph between time (months) and potency (%) was plotted (Fig.7). It was found that the shelf life of T-ECMC-4 was 37.1427 months (~ 3.0 years) which is satisfactory.

4.CONCLUSIONS

DFS could be microencapsulated by non-aqueous phase separation method using ethyl cellulose - toluene - petroleum ether system. The microcapsules could be compressed into tablets. Tableting the microcapsules not only retarded drug release but also resulted in zero-order release. The mechanism of drug release was of non-fickian diffusion. Among the tablet formulations prepared, the release profile of formulation T-ECMC-4 is closer to the theoretical SR profile of the drug. The calculated shelf life of selected pellet formulation T-ECMC-4 was approximately 3 years.

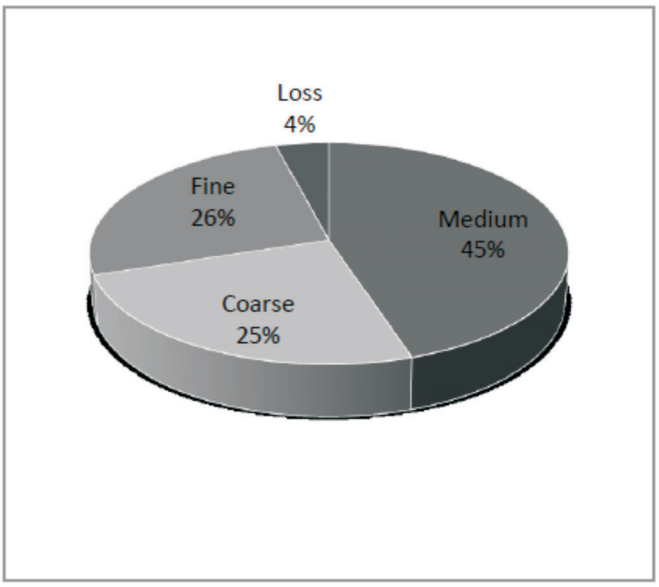

Fig.1. Particle Size Distribution of DFS Powder (Coarse, > 50µm; Medium, 10-50µm; Fine, < 10µm)

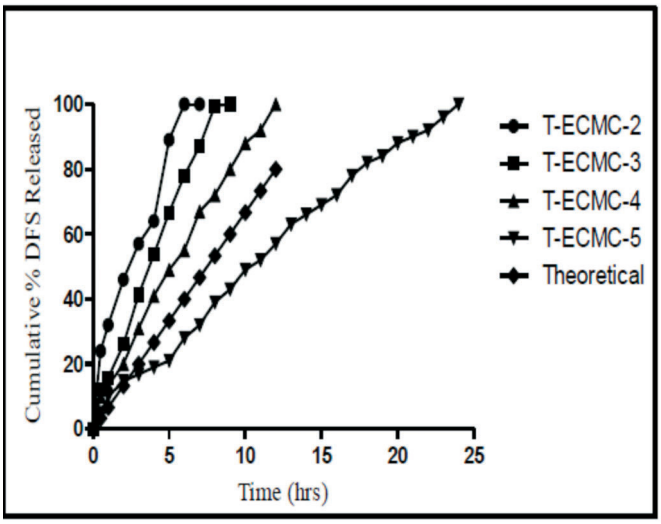

Fig.2. Release Rate Profiles of DFS from Tablets

T-ECMC-2- Weight Variation Test- Stem-and-Leaf Display

Leaf unit: 1

n	20
mean	170.1
median	169.5
std. dev.	1.55259
minimum	168
maximum	173

168	0 0
169	0 0 0 0 0 0 0 0
170	0 0
171	0 0 0 0
172	0 0
173	0 0

Fig.3. Results of Weight Variation Test on T-ECMC-2

T-ECMC-3-Weight Variation Test- Stem-and-Leaf Display

Leaf unit: 1

n	20
mean	210.9
median	210.5
std. dev.	2.40394
minimum	206
maximum	216

206	0
207	
208	0
209	0 0 0
210	0 0 0 0 0
211	0 0 0 0
212	0
213	0 0
214	0
215	0
216	0

Fig.4. Results of Weight Variation Test on T-ECMC-3

T-ECMC-5-Weight Variation Test- Stem-and-Leaf Display

Leaf unit: 10

n	20
mean	421.8
median	421
std. dev.	3.73603
minimum	417
maximum	429

41	7 7 8 8 9 9 9
42	0 0 1 1 1 2 4 5 6 6 6 8 9

Fig.6. Results of Weight Variation Test on T-ECMC-5

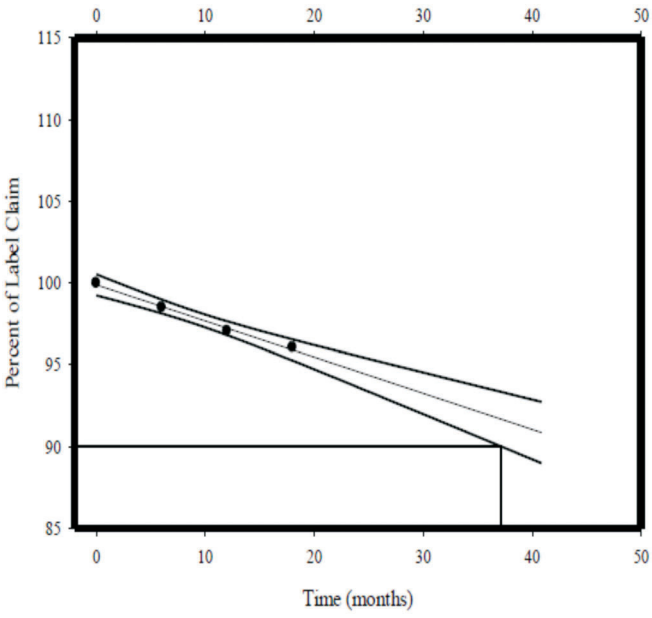

Fig.7. Shelf Life Prediction of T-ECMC-4

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