

Preparation and Evaluation of Chitosan-Eudragit L 100 Polymer-based Sustained Release Tablet of Diclofenac Sodium

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Abstract

Objective: The objective of this investigation is to develop a sustained release matrix tablet by taking a mixture of chitosan (CS) and Eudragit L100 polymers and then to study the drug release pattern for a low solubility drug of diclofenac sodium (DS). **Materials and Methods:** The short biological half-life and frequent dosing make DS an ideal candidate for sustained release dosage forms. The tablets were prepared by direct compression method. All the batches were evaluated for thickness, weight variation, hardness, and drug content uniformity and *in vitro* drug release. **Results:** Fourier-transform infrared spectroscopy study was conducted to study any interaction between drug and ingredients. Hydrophilic matrix of CS alone could not control the diclofenac release effectively for 12 h whereas when combined with Eudragit L100 could slow down the release of drug and can be successfully employed for: formulating sustained-release matrix tablets. **Conclusion:** Fitting the data to Korsmeyer equation indicated that diffusion along with erosion could be the mechanism of drug release.

Key words: Chitosan, Eudragit L100, matrix tablets, release kinetics, swelling study

INTRODUCTION

Diclofenac sodium (DS) is a nonsteroidal anti-inflammatory drug, generally used to control pain in conditions such as menstrual pain, dysmenorrhea, and for the treatment of rheumatic arthritis. It has a short half-life (1.5–2.5 h) and conventional immediate-release DS tablets make the drug immediately available for absorption in the upper gastrointestinal (GI) tract resulting in local GI toxicity.^[1] The most common adverse effect of the DS is gastritis, peptic ulceration, and depression of renal function. The short biological half-life and frequent dosing make DS an ideal candidate for sustained release dosage forms.

Sustained delivery systems provide a mean to regulate the bioavailability of therapeutic agents by releasing the drug in predefined and prolonged manner.^[2] Various types of synthetic and natural polymers have been studied as drug carriers.^[3] Polymer-based hydrophilic matrix systems are widely used in oral sustained drug

delivery system due to their flexibility to provide a desirable drug release profile, economic benefits, simplicity of process development, and broad regulatory acceptance.^[4-6]

Chitosan (CS), a natural polymer obtained by alkaline deacetylation of chitin, is a nontoxic, biocompatible, and biodegradable polymer.^[7,8] It is widely used as a release controlling polymer in drug delivery but has limited capacity as retardant when used alone due to its easy disintegration characteristics at neutral pH. Among the available matrix-forming polymers, methacrylic resins (Eudragit®) appear particularly attractive due to high chemical stability, compatibility, and variability in physicochemical

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characteristics.^[9] Incorporation of pH-dependent soluble polymer into sustained-release delivery seems to be an obvious approach that provides the desired release over an extended period of time. Hence, in the present study, it was attempted to (a) use the combination of CS and Eudragit L100 as a matrix material to formulate sustained release tablet of diclofenac and (b) to evaluate the prepared tablets with respect to preformulation studies and *in vitro* drug release studies.

MATERIALS AND METHODS

Materials

Diclofenac was obtained as gift sample from Mylan Laboratories (Hyderabad, India). CS was procured from Research Lab Fine Chemicals (Mumbai, India), Eudragit L100 from Evonik Rohm GmbH (Germany) and Microcrystalline Cellulose from Loba Chemie Laboratory (Mumbai, India). All other ingredients used were of analytical grades.

Methods

Preparation of sustained release tablets

Preparation of tablets mainly comprises of blending of different ingredients, followed by direct compression method. All the excipients and drugs were passed through 80 mesh sieve before blending. The drug and all other excipients (except magnesium stearate) were firstly blended for at least 10 min. Magnesium stearate then was added and mixed for another 2 min. Compression was carried out in rotary press equipped with an 8 mm flat punch. Compression force was kept constant throughout the study. Hardness of all the tablets was adjusted to 40–80 N. Tablet weight was adjusted to around 250 mg. Tablets were prepared using drugs: Polymer ratios ranging from 1:0.5, 1:0.75, and 1:1 as shown in Table 1.

Evaluation parameters

Study of physical interaction between drug and polymer^[10]

Fourier-transform infrared (FTIR) spectroscopic studies
Infrared spectrum was taken by scanning the samples of pure

drug and the polymers individually over a wavenumber range of 4000–400 cm^{-1} using FTIR spectrophotometer (Shimadzu 8400S, Shimadzu, Japan). The change in spectra of the drug in the presence of polymer was investigated which indicates the physical interaction of drug molecule with the polymer.

Differential scanning calorimetric (DSC) studies

DSC measurements were performed using a Mettler TA 4000 apparatus equipped with a DSC 25 cell to evaluate the drug-excipient compatibility and to verify the absence of solid-state interactions. The thermal analysis was performed in a nitrogen atmosphere at a heating rate of 10°C/min over a temperature range of 30–300°C. Alumina was employed as the reference standard.

Post-compression assessment

Weight variation test of the tablets ($n = 20$) was carried out as per the official method and the results are expressed as mean values \pm standard deviation (SD). The hardness of the tablets ($n = 6$) was determined using Monsanto Hardness Tester. Tablet thickness and diameter ($n = 3$) were determined using an electronic digital caliper (ASAHI, India). Friability of the tablet ($n = 6$) was measured in a friability tester (EF-1W, Electrolab, Mumbai, India). Tablet disintegration time was tested using the disintegration test apparatus (Electrolab, Mumbai).^[11,12]

Determination of drug content

Amount of drug present in the formulation was determined as per pharmacopeial specification. Twenty tablets were weighed and powdered. Powder equivalent to 50 mg of DS was accurately weighed and it was taken in volumetric flask of 200 ml. It was shaken with 60 ml of methanol in volumetric flask and diluted to volume with methanol to 200 ml. About 5.0 ml of the solution was diluted to 100.0 ml with methanol and absorbance was measured at 285.0 nm.^[13-15]

In-vitro dissolution studies of sustained-release tablet formulations

To assess the potential of the CS and Eudragit L100 to be used in matrix sustained drug delivery systems. The *in-vitro* drug release tests were carried out using a dissolution apparatus USP apparatus-II Paddle method (Electrolab Tablet

Table 1: Composition of SR matrix tablets from Batch F1-F9

| Ingredient | Formulation code (in mg) | | | | | | | | |
|----------------------------|--------------------------|------|------|------|------|------|------|------|------|
| | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
| Diclofenac sodium | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |
| Chitosan | 50 | --- | 25 | 75 | --- | 37.5 | 100 | --- | 50 |
| Eudragit L100 | --- | 50 | 25 | --- | 75 | 37.5 | --- | 100 | 50 |
| Microcrystalline cellulose | 97.5 | 97.5 | 97.5 | 72.5 | 72.5 | 72.5 | 47.5 | 47.5 | 47.5 |
| Magnesium stearate | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 |

SR: Sustained release

Dissolution Tester–USP, Model No. TDT–06P) rotating at 50 rpm at $37 \pm 0.5^\circ\text{C}$. Aliquots of 10 ml were withdrawn at different time intervals (1, 2, 4, 6, 8, 10, and 12 h) and were replaced with equal amounts of fresh release medium. The amounts of DS released in the dissolution medium were determined spectrophotometrically at 285 nm using (Mode No. UV 2300, Techcomp). DS reported to shows a very marginal change in release pattern following the soaking in pH 1.2 (gastric acid).^[16] All the *in-vitro* studies were carried out in pH 6.8 phosphate buffer. Drug release studies were carried out in triplicate for each formulation tested and SDs were calculated.

Determination of release mechanism

The release kinetics of formulation was described by finding the best fit of the data. The results obtained were analyzed for probable release mechanism as, zero-order, first-order, Higuchi, and Hixson–Crowell models. To understand the drug release mechanism, Korsmeyer–Peppas model was applied. Korsmeyer RW. The criterion for selecting the most appropriate model was goodness of fit test.^[17]

Statistical analysis

The data were subjected to two ways analysis of variance followed by Bonferroni post-test for analyzing the statistical difference using the software GraphPad prism (San Diego, CA) and in all the cases $P < 0.001$ was considered as significant.

RESULTS AND DISCUSSION

Drug polymer compatibility studies

FTIR spectroscopic studies

The FT-IR spectra of pure diclofenac and its physical mixtures (1:1) with CS, Eudragit L100 as shown in Figure 1, revealed no considerable changes in IR peaks of DS indicating the absence of interaction between drug and polymer used.

DSC

The thermal curves of mixtures, obtained by simple blending corresponded to the superimposition of those of the single

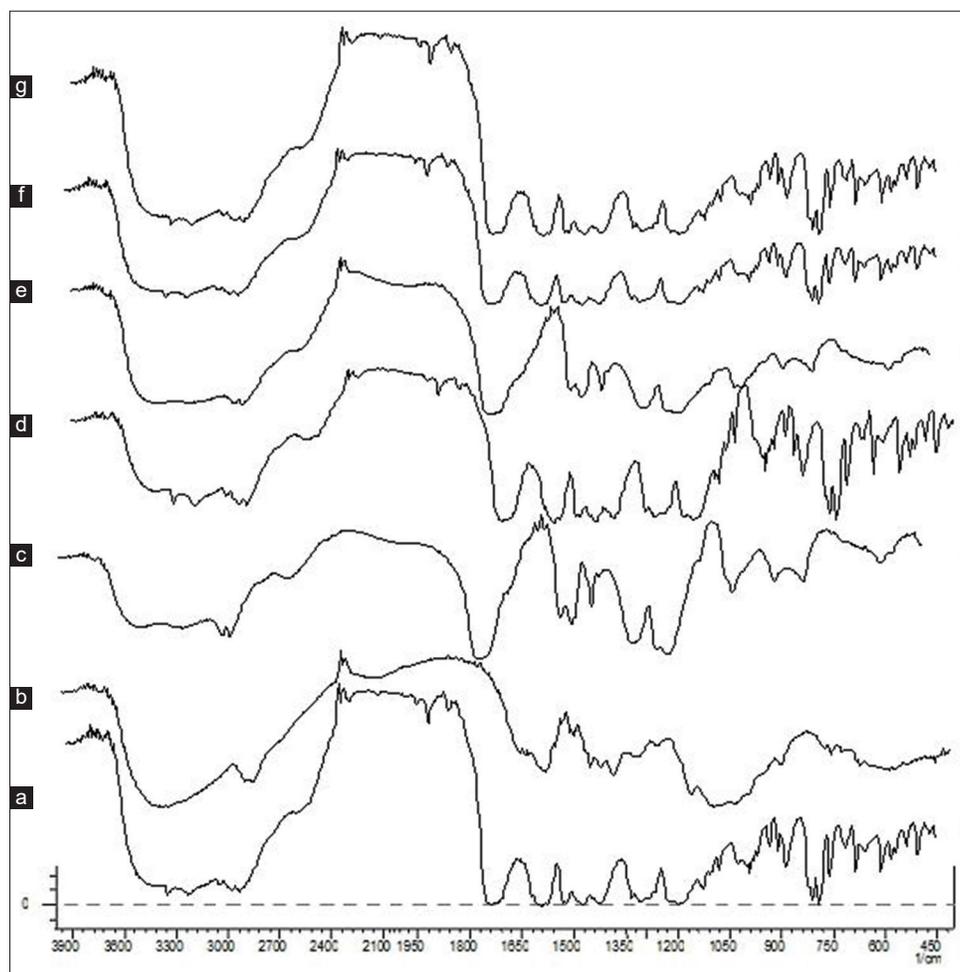


Figure 1: Fourier-transform infrared spectra of pure drug and polymers, (a) Diclofenac, (b) Chitosan, (c) Eudragit L100, (d) chitosan + diclofenac sodium, (e) Eudragit 100 L + diclofenac sodium, (f) chitosan + Eudragit L100, (g) chitosan + Eudragit L100 + diclofenac sodium

components, indicating the absence of solid-state interactions and allowing assessment of drug–polymers compatibility in all the examined formulations. Thus, no definite solid-solid interaction could be concluded examination of all the DSC thermograms. The DSC thermogram of pure DS, CS, and Eudragit L100 with their physical mixtures shown in Figure 2.

From DSC, the study it is indicated that there is no reaction between drug and polymers. The results of DSC studies also confirmed that there was no appreciable change in the melting endotherm which further supports the IR spectroscopy results. These results clearly indicate the usefulness of the utilized materials for preparation of sustained-release tablets.

Post-compression assessment of sustained-release tablets

The formulated tablets were evaluated for friability, hardness, thickness, weight variation, and drug content as per specifications given in pharmacopeias. The results are given in Table 2.

In determinations of tablet weights, all formulations weights were found to be within pharmacopeia limits. Friability value of all formulations and commercial tablets <1% indicates that tablet surfaces are strong enough to withstand mechanical shock or attrition during storage and transportation and until they are consumed. The average percentage deviation of all tablet formulations was found to be within the above limit,

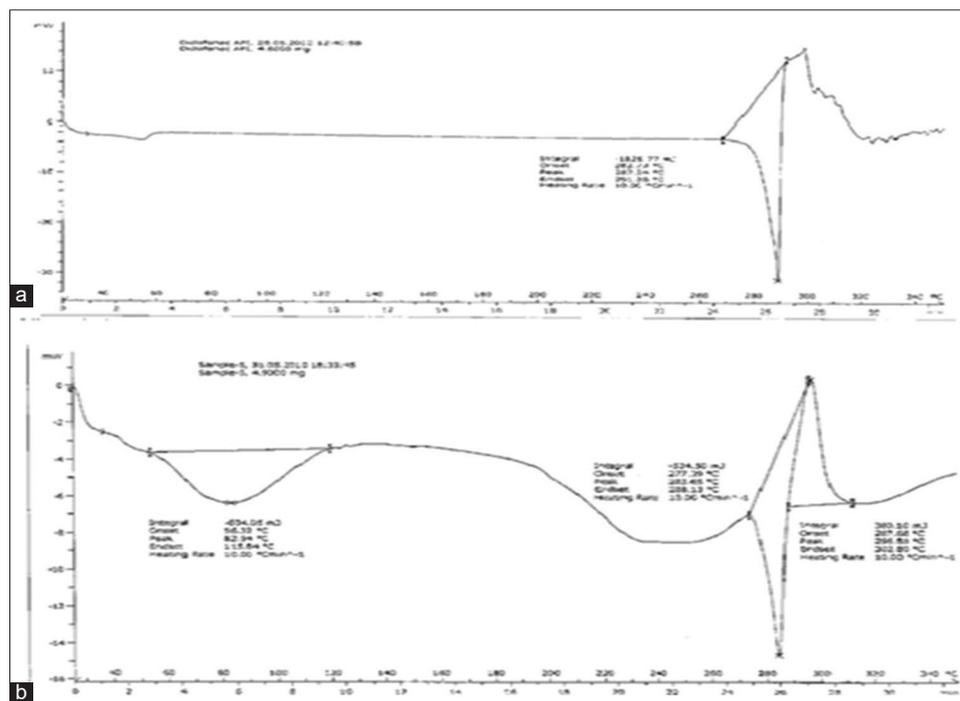


Figure 2: Differential scanning calorimetric thermogram of diclofenac sodium (a) and physical mixture of diclofenac with chitosan and Eudragit L100 (b)

Table 2: Post-compression assessment of batch F1-F9

| Formulation (%) | Friability* (%) | Hardness [†] (Kg/cm ²) | Thickness [†] (mm) | Weight variation (g) [#] | Drug content [#] |
|-----------------|-----------------|---|-----------------------------|-----------------------------------|---------------------------|
| F1 | 0.443±0.25 | 7.74±0.325 | 4.02±0.051 | 0.246±0.006 | 99.8±1.3 |
| F2 | 0.44±0.13 | 7.56±0.115 | 4.55±0.031 | 0.251±0.007 | 98.6±1.4 |
| F3 | 0.467±0.291 | 8.03±0.19 | 4.50±0.031 | 0.247±0.007 | 97.2±0.9 |
| F4 | 0.423±0.214 | 5.1±0.04 | 4.11±0.026 | 0.248±0.007 | 99.5±1.3 |
| F5 | 0.421±0.251 | 5.47±0.1 | 4.48±0.015 | 0.246±0.012 | 99.7±0.8 |
| F6 | 0.246±0.155 | 6.8±0.038 | 4.43±0.04 | 0.248±0.012 | 97.2±0.7 |
| F7 | 0.445±0.193 | 5.96±0.083 | 4.10±0.025 | 0.25±0.0077 | 99.8±1.7 |
| F8 | 0.488±0.136 | 4.54±0.123 | 4.61±0.053 | 0.25±0.0079 | 98.6±1.7 |
| F9 | 0.469±0.231 | 4.48±0.078 | 4.55±0.036 | 0.252±0.0059 | 97.2±1.5 |

Mean±SD, *n=3, [†]n=6, [#]n=20. SD: Standard deviation

as per official pharmacopeia requirements. The manufactured tablets showed low weight variations and a high degree of drug content uniformity among different batches of the tablets and drug content was more than 95%.

In vitro drug release from matrices

Release of DS from the matrices made up of CS with a different ratio revealed that batch F7 led to smaller drug release as compared to those with the batch F1 and F4. The significant differences ($P < 0.05$) in the release rate were observed between the tablets containing a different ratio of CS. As compared to CS, the release of DS from the matrices made up of Eudragit L100 with a different ratio showed more sustained effect. The batch F8 showed 31.87% release of drug in 12 h with good sustain effect as compared to batch F2 and F5. The significant differences ($P < 0.05$) in the

release rate were observed between the tablets containing a different ratio of Eudragit L100.

The results of dissolution studies of formulations F3, F6, and F9 comprise drug in combination with CS and Eudragit L100 (1:1). The physical mixture showed good sustained effect as compared to CS and Eudragit L100 alone. Batch F3, F6, and F9 showed 66.46%, 62.08%, and 39.71% release in 12 h, respectively. The significant difference in the release rate was observed between the tablets containing a different ratio of physical mixture. The results [Figure 3] of *in vitro* studies indicated that the rate and extent of drug release were decreased significantly ($P < 0.05$) with an increase in polymer concentration, which may be attributed to increase in the density of polymer matrix followed by increasing diffusional path length for drug molecules.

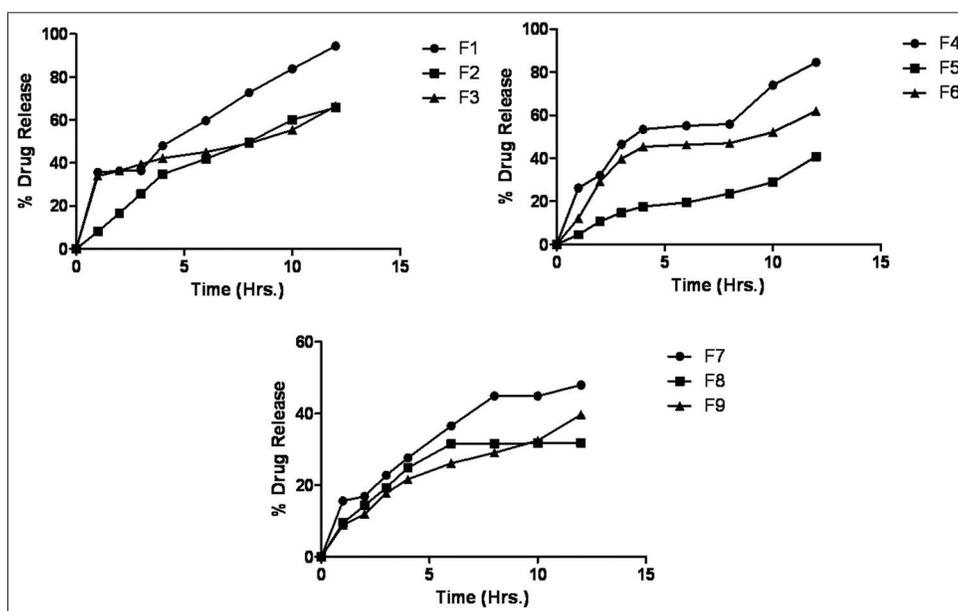


Figure 3: *In vitro* release profile of sustained-release tablet F1-F9

Table 3: Release kinetic study

| Batch | Zero order | | 1 st order | | Matrix | | Hix. crow | | Korsmeyer–Peppas | | |
|-------|------------|-------|-----------------------|---------|--------|--------|-----------|--------|------------------|-------|-------|
| | R | k | R | K | R | K | R | K | R | n | K |
| F1 | 0.88 | 8.32 | 0.975 | -0.1613 | 0.983 | 24.245 | 0.974 | -0.041 | 0.936 | 0.435 | 26.79 |
| F2 | 0.967 | 5.75 | 0.996 | -0.081 | 0.972 | 16.425 | 0.990 | -0.024 | 0.989 | 0.830 | 8.64 |
| F3 | 0.417 | 6.033 | 0.759 | -0.085 | 0.920 | 18.181 | 0.676 | -0.025 | 0.941 | 0.546 | 29.24 |
| F4 | 0.803 | 7.455 | 0.945 | -0.124 | 0.979 | 21.975 | 0.920 | -0.034 | 0.970 | 0.445 | 24.32 |
| F5 | 0.964 | 3.062 | 0.969 | -0.036 | 0.948 | 8.690 | 0.969 | -0.011 | 0.977 | 0.775 | 5.019 |
| F6 | 0.721 | 5.738 | 0.846 | -0.079 | 0.959 | 17.086 | 0.810 | -0.023 | 0.916 | 0.551 | 15.79 |
| F7 | 0.872 | 4.586 | 0.933 | -0.058 | 0.989 | 13.414 | 0.916 | -0.018 | 0.978 | 0.515 | 12.84 |
| F8 | 0.717 | 3.341 | 0.773 | -0.039 | 0.961 | 9.964 | 0.756 | -0.012 | 0.961 | 0.599 | 9.808 |
| F9 | 0.919 | 3.410 | 0.955 | -0.040 | 0.990 | 9.890 | 0.945 | -0.012 | 0.992 | 0.818 | 8.137 |

Determination of release kinetics and release mechanism

To describe the kinetics of drug release from matrix tablets, release data were analyzed according to different kinetic equations. The data were analyzed by the regression coefficient method and regression coefficient values (r^2) of all batches were shown in Table 3. On analyzing regression coefficient values of all batches, it was found that batch F1, F4, F6, F7, and F8 showed Higuchi's release kinetics. Batch F2 followed first order kinetics. Batch F3, F5, and F9 followed Korsmeyer–Peppas model.

To confirm the diffusion mechanism, the data were fitted into Korsmeyer–Peppas equation. An “ n ” value $0.5 < n < 1$ means an anomalous (non-Fickian) diffusion release model; $n < 0.5$ indicates Fickian diffusion, and $n > 1$ indicates a super case II transport relaxational release.^[18] The formulations showed good linearity with slope (n) between 0.526–0.565 which appears to indicate coupling of diffusion and erosion mechanisms so-called anomalous diffusion. Batch F1 and F4 followed Fickian diffusion ($n = 0.1–0.5$), while all the other batches showed non-Fickian ($n = 0.5–1$) as projected by Korsmeyer–Peppas equation.

CONCLUSION

In this study, we found a matrix tablet prepared by taking the mixture of CS and Eudragit L100 is responsible for extending drug release of DS. The drug release behavior was markedly influenced by the type and the amount of polymers used. When CS and Eudragit L100 were used as the only retarding polymer for DS tablet, a sustained drug release pattern was observed for 12 h only. Matrix tablets based on the combination of both the polymeric mixture gave a more sustained release pattern. The formulations showed good linearity which appears to indicate coupling of diffusion and erosion mechanisms so-called anomalous diffusion.

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