



Osmotically controlled Diclofenac sodium tablets: membrane and osmogens effects

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ABSTRACT

The present investigation was aimed with the design and evaluation of osmotic controlled tablets (OCT) of Diclofenac sodium (DS). Different batches of OCT were prepared using variables like different osmogen, osmopolymer, different types of coating membrane with three variable thickness, and orifices of two different diameters. All the fabricated tablets were evaluated for various physical parameters and in vitro drug release characteristics studied on USP XXIV dissolution apparatus II in distilled water (DW). In addition to effect of different stirring conditions of release medium, the effect of above formulation variables were studied on drug release performance of OCT. The drug release from OCT were found to be dependent on the type and the thickness of coating membrane, various types of osmogens and osmopolymer, and were independent of orifice size and agitation intensities of release medium. All the fabricated formulations showed prolonged and controlled DS release as compared to commercial tablets studied.

Keywords: Osmotic controlled tablets, Controlled release, Diclofenac sodium, Osmotic pump.

INTRODUCTION

Diclofenac sodium (DS), a substituted phenyl-acetic acid derivative, is a non-steroidal anti-inflammatory drug (NSAID) widely used in the management of many inflammatory conditions [1, 2]. In addition to its anti-inflammatory effect, DS has analgesic and antipyretic action also [3 – 5]. But because of its short biological half-life and hazards of adverse GI reactions [6], the development of oral sustained release formulations of this drug is highly desirable [7], in order to achieve improved therapeutic efficacy and patient compliance. The use of controlled release technology in the formulation of pharmaceutical products has become increasingly important in the last few years [8]. Among controlled-release devices, osmotically driven systems hold a prominent place because of their reliability and their ability to deliver the drug at predetermined zero-order rates for prolonged periods [9 – 12]. Many efforts have been made towards achieving sustained release formulations of DS [13 – 19]. In one of our earlier investigations [16],

evaluation of commercially available SR tablets of DS from Indian market has revealed out a large variation in their rate and extent of drug (DS) release. So, in a direction towards achieving improved, controlled and prolonged release of DS, osmotic controlled tablets of DS have been developed in the present study and a comparative evaluation has been done with commercial conventional and SR tablets.

MATERIALS AND METHODS

DS was obtained as a gift sample from Win Medicare Ltd. Ethylcellulose (EC), Cellulose acetate (39.8 % acetylation) (CA) and Microcrystalline cellulose (MCC) were obtained from Alkem Laboratories Ltd ; Thomas Baker Chemicals Ltd; and S.D.Fine Chem. Ltd. respectively. Polyethylene glycol (PEG 400) and Polyvinylpyrrolidone (PVP) were procured from Glaxo Lab.Ltd. and Loba Chemie, respectively . All other chemicals / reagents used were of analytical grades from Indian markets. Commercial tablets of DS [conventional (Voveran ®-50 mg) (batch code MT1) and sustained release (Voveran ®-SR 100 mg) (batch code MT2) tablets (both from Novartis Pharm. Ltd) were obtained from Indian market.

Preparation of Osmotic Controlled Tablets of DS

Preparation of the core tablets

Accurately weighed quantity of ingredients for OCT mentioned in Table 1 was passed through sieve No. 85. All the ingredients except lubricant (magnesium stearate), glidant (talc) and binder (PVP) were manually blended homogeneously in a mortar through geometric dilution. The mixture was wetted with 10 % w/v aqueous solution of PVP, granulated through sieve No. 18 (aperture size 1000 µm, U. S. Standard) and dried in a hot air oven at 60 °C for sufficient time (3 to 4 hours) so that the moisture content of the granules reached 2 – 4 % level.

Table 1. Formulae for different osmotic pumps

| Formula ingredients (mg/tablet) | Batch code | | | | | | | | | |
|---------------------------------|------------|------|------|------|------|------|------|-----------------|-----------------|------|
| | I | Ia | Ib | Ic | II | III | IV | V | VI | VII |
| DS | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |
| Sodium chloride | 300 | 300 | 300 | 300 | - | 200 | 200 | 300 | 300 | 300 |
| Potassium chloride | - | - | - | - | 300 | - | - | - | - | - |
| Sodium bicarbonate | - | - | - | - | - | 200 | - | - | - | - |
| Potassium carbonate | - | - | - | - | - | - | 200 | - | - | - |
| Pectin | - | - | - | - | - | - | - | - | - | 40 |
| MCC | 163 | 163 | 163 | 163 | 163 | 63 | 63 | 163 | 163 | 123 |
| SLS | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 |
| Talc | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| Magnesium stearate | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| PVP | q.s | q.s | q.s | q.s | q.s | q.s | q.s | q.s | q.s | q.s |
| Coating membrane type | SP | SP | SP | SP | SP | SP | SP | MP ¹ | MP ² | SP |
| Coat thickness (µm ± S.D) | 20±2 | 20±2 | 30±2 | 40±2 | 20±2 | 20±2 | 20±2 | 20±2 | 20±2 | 20±2 |
| Orifice diameter (mm) | 0.32 | 0.50 | 0.32 | 0.32 | 0.32 | 0.32 | 0.32 | ND | ND | 0.32 |

MCC – Microcrystalline cellulose PVP – Polyvinyl pyrrolidone (as 10 % w/v solution in ethanol) ; S –Sodium lauryl sulphate SP-Semipermeable membrane; MP¹-Microporous membrane with 10 %PEG 400 as plasticizer; MP² - Microporous membrane with 20 % PEG 400 as plasticizer; ND- Not Drilled; - Not present.

The dried granules were passed through sieve No. 26 (aperture size 710 µm, U. S. Standard) and blended with talc and magnesium stearate. The homogeneous blend was then compressed into tablets (each around 600 mg) on Manesty E2 tableting machine using 12 mm standard deep

concave punches. The compression force was adjusted to give the tablets with hardness approximately 7 kg/cm² on a Monsanto tablet hardness tester (Campbell Electronics, India).

Coating of the core tablets

Core tablets were film coated either with a semi permeable membrane using coating solution I {2 % (w/v) cellulose acetate (CA) dissolved in acetone having castor oil (20 % w/w of total solid CA) as plasticizer} or microporous membrane using either coating solution II {2 % (w/v) cellulose acetate (CA) dissolved in acetone having PEG 400 (10 % w/w of total solid CA) as plasticizer} or coating solution III {2 % (w/v) cellulose acetate (CA) dissolved in acetone having PEG 400 (20 % w/w of total solid CA) as plasticizer} in a conventional laboratory model, stainless steel, 10 cm pear-shaped, baffled coating pan. The manual coating procedure [12] used was based on intermittent spraying and drying technique. An orifice (0.32 or 0.5 mm diameter) through the membrane was made by a micro drill on one side of each tablet [12]. Micro porous coated tablets were not micro drilled.

Evaluations

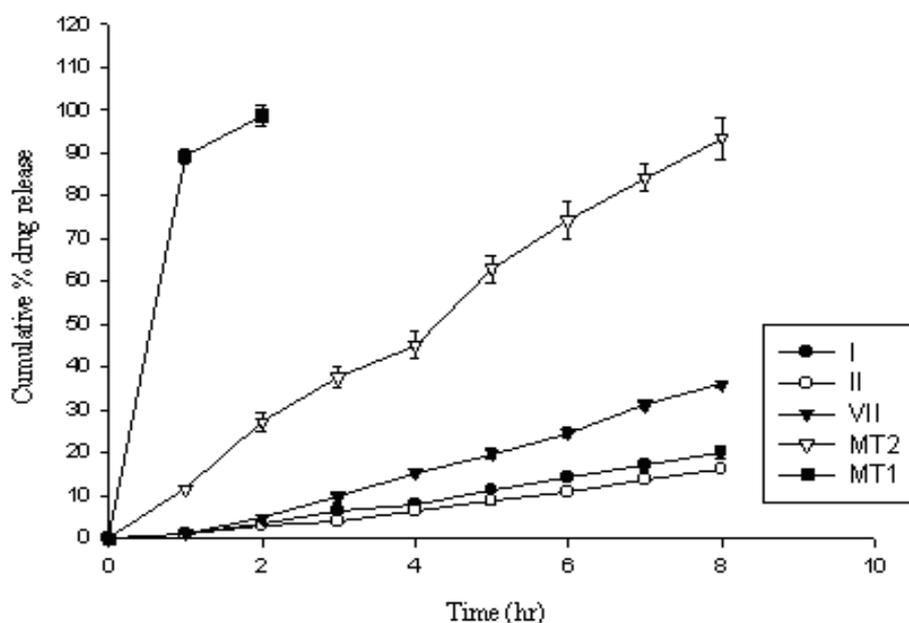
All the fabricated tablets were evaluated for various physical parameters (hardness, thickness, weight variation and drug content uniformity) using standard methods. Coat thickness and orifice diameter were measured by earlier reported method [12]. *In vitro* studies for 8 hours, in triplicate, were done on USP XXIV dissolution apparatus II in distilled water (DW) maintained at 37 ± 0.2 °C temperature and 50 rpm of stirring. Withdrawn samples were analyzed on Jasco UV/VIS Spectrophotometer (model 7800, Japan) at 275 nm. To study the effect of agitation intensity, drug release study was also performed at relatively high agitation intensity of 100 rpm. Effect of formulation variables (different types and amount of osmogen with or without osmopolymer, coating membrane type, and orifice size and membrane thickness) on drug release characteristics were also studied.

RESULTS AND DISCUSSION

The various physical parameters (hardness, thickness, weight variation and drug content uniformity) evaluated for all fabricated formulations were found within official limits. The coating membrane thickness and orifice diameter for different OCT are shown in Table 1.

All the prepared OCT have shown one hour delayed (Figs. 1 - 5) drug release, which may be attributed to time elapsed for imbibition of osmotic core with the release medium. After one hour, almost all the batches exhibited linear and controlled drug release profiles (Figs.1 -5). The smaller amount of drug delivered per unit time with controlled rate from OCT (was compared to larger amount of drug delivered within one hour from conventional oral tablet MT1, Fig.1) at the absorption site is expected to minimize the local as well as systemic side effects of DS. Drug release from marketed SR (MT2) tablet (Fig.1) was also faster when compared to fabricated OCT, which gave much controlled & prolonged drug release. The effect of same amount of two different osmogens {sodium chloride, batch I, and potassium chloride, batch II} and the effect of extra added osmopolymer (pectin, batch VII) on DS release profiles from OCT are shown in Fig.1. Sodium chloride based OCT exhibited little higher rate and extent of drug release than potassium chloride based tablets. However, on addition of pectin in sodium chloride based tablets a significant increase in rate and extent of drug release was observed. This is attributed to additional push offered by swelled osmopolymer (pectin in the core) on drug delivery through orifice.

Fig.1. Effect of different osmogen and osmopolymer on *in vitro* drug release from OCT and their comparison with marketed products. The vertical bars show the S.D. (n = 3)



To enhance the rate and extent of drug release, osmogens with higher osmotic pressure could be incorporated in the drug core. Therefore, effect of incorporation of dual osmotic agents (sodium chloride along with either sodium carbonate, batch III or potassium carbonate, batch IV) in drug core was studied on drug release characteristics from OCT. Drug release profiles shown in Fig.2 indicated higher rate and extent of drug release from batch III and batch IV than batch I, having single osmogen. Higher drug release from batches III and IV is attributed to higher osmotic pressure in drug core due to presence of dual osmogen. Apart from their osmogen properties, sodium carbonate and potassium carbonate provided alkaline environment in the core, causing easy dissolution and faster delivery of DS. Furthermore, DS being more soluble in alkaline pH and least soluble (or insoluble) in acidic pH, DS may precipitate in gastric medium after delivery through orifice. Precipitated drug may accumulate around the orifice and the exterior wall of the membrane and therefore may hinder in constant drug release. However, bicarbonate or carbonate present in the OCT tablets react with the acidic medium after delivery, generate carbon dioxide gas which can clear the orifice and the exterior wall of the membrane and thus result in unhindered and constant drug delivery. Comparatively, potassium carbonate based OCT (batch IV) gave more drug release than sodium bicarbonate based OCT (batch III) (Fig.2).

In order to study the effect of membrane type on drug release, OCT were prepared using semipermeable (Batch I) and microporous (Batch V & VI) membranes. *In vitro* drug release observed (Fig.3) was in the following order VI > V > I. The microporous membrane coated batches provided more drug release due to formation of many micropores in the membrane after dissolution of PEG 400 by the release medium and these pores allowed more drug to diffuse through them. PEG 400 (20 %) containing batch (VI) exhibited much higher rate and extent of drug release than PEG 10 % containing batch (V) (Fig.3).

Fig.2. Effect of different dual osmogen on *in vitro* drug release from OCT. The vertical bars show the S.D. (n = 3)

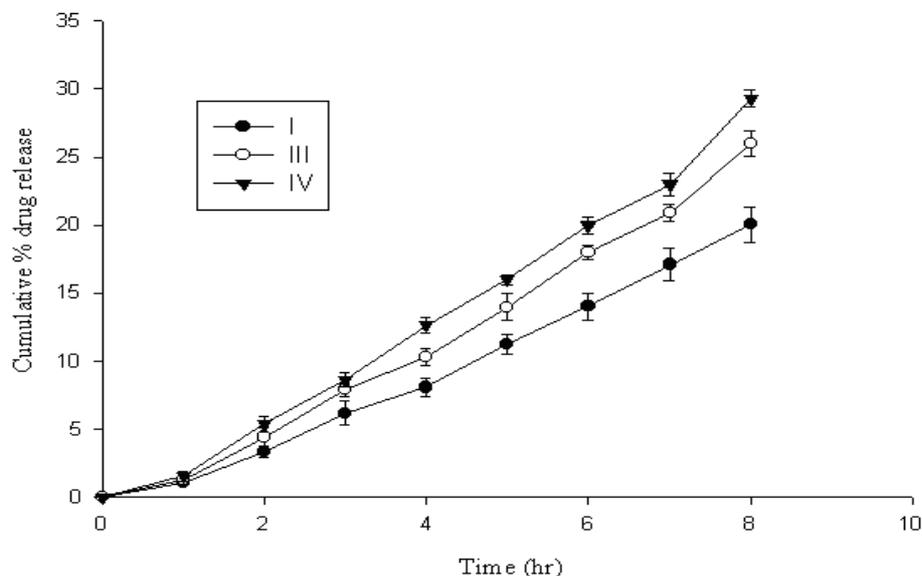
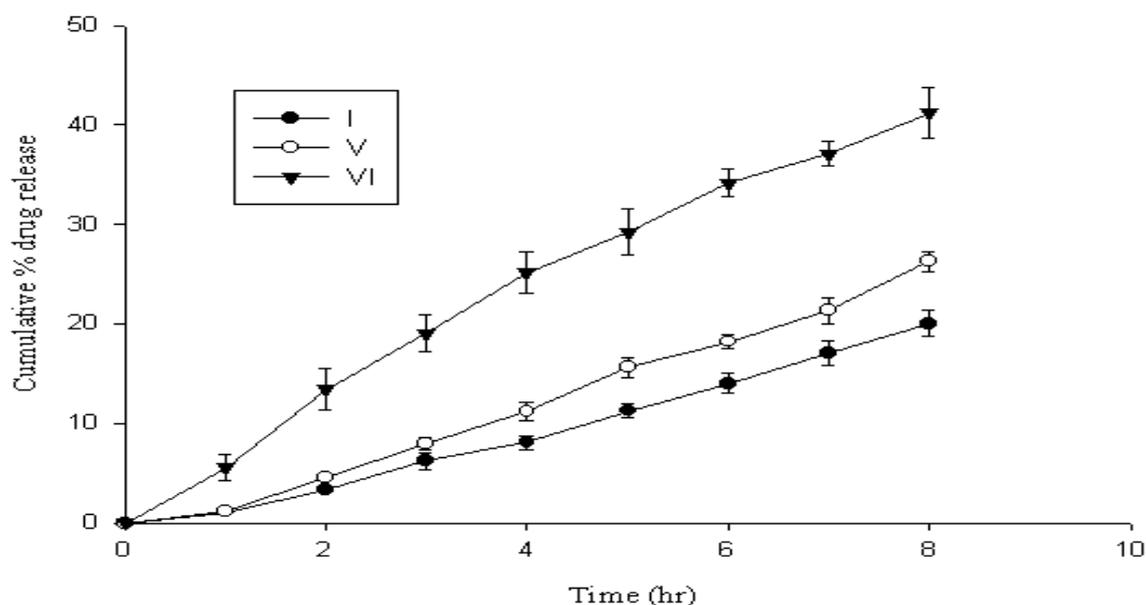


Fig.3. Effect of semi-permeable versus microporous membrane on *in vitro* drug release from OCT. The vertical bars show the S.D. (n = 3)



Effect of coating membrane thickness and orifice size on *in vitro* drug release profiles are shown in Fig.4. It was observed that the rate and extent of drug release decreased with increasing membrane thickness ($I > I_b > I_c$) but at the same time different orifice sizes of membrane (batch I – 0.32 mm, batch Ia – 0.5 mm) did not show any significant ($P > 0.05$) difference in the rate and extent of drug release.

Further the effect of agitational intensity on the drug release from batch I was investigated (Fig.5). It was observed that the agitation intensity of 50 and 100 rpm of dissolution medium had no significant effect ($P > 0.05$) on the rate and extent of DS release from OCT.

Fig.4. Effect of membrane thickness and orifice size on *in vitro* drug release from OCT. The vertical bars show the S.D. (n = 3)

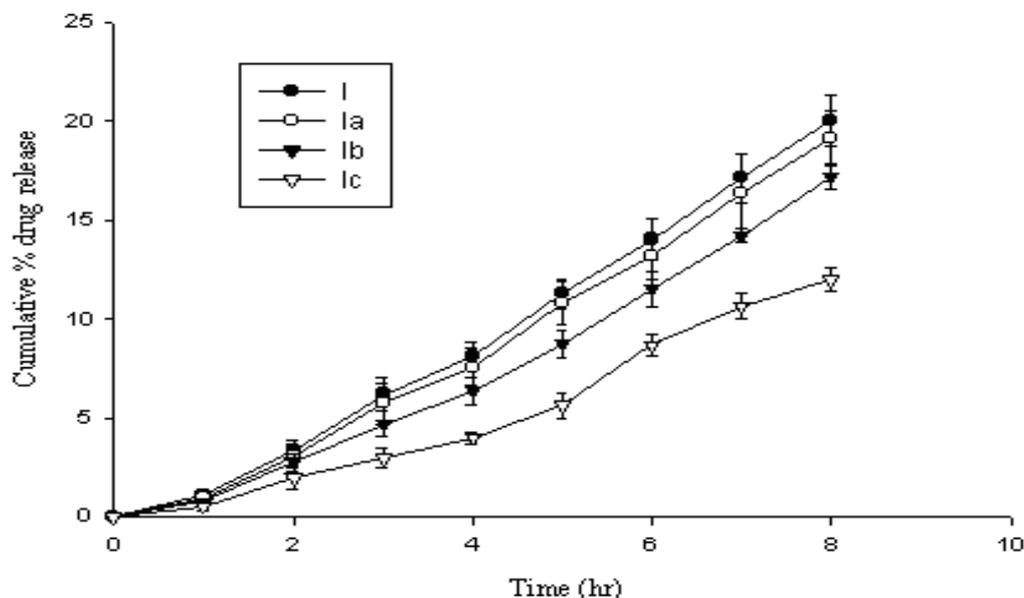
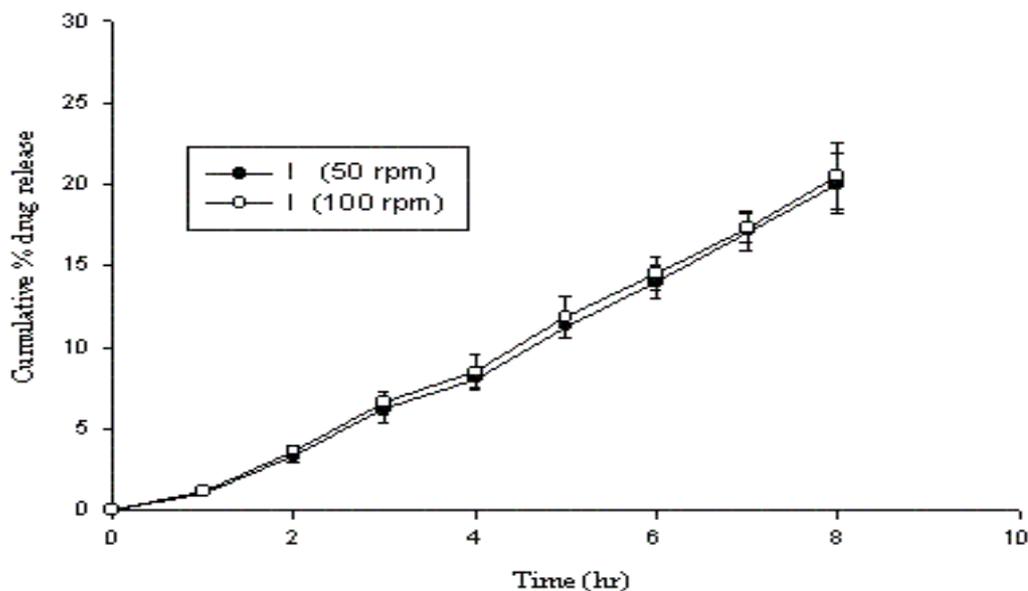


Fig.5. Effect of agitation intensity on *in vitro* drug release. The vertical bars show the S.D. (n = 3)



CONCLUSION

It was concluded that optimization of formulation variables, especially the type of osmogen and its quantity and type of coating membrane with specific thickness, are the key parameters to design and develop osmotic tablets for controlled and prolonged delivery of diclofenac sodium with improved therapeutic potential.

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