Comparative In Vitro and In Vivo Evaluation of Matrix, Osmotic Matrix, and Osmotic Pump Tablets for Controlled Delivery of Diclofenac Sodium

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ABSTRACT

The aim of this investigation was preparation and comparative evaluation of fabricated matrix (FM), osmotic matrix (OM), and osmotic pump (OP) tablets for controlled delivery of diclofenac sodium (DS). All formulations were evaluated for various physical parameters, and in vitro studies were performed on USP 24 dissolution apparatus II in pH 7.4 buffer and distilled water. In vivo studies were performed in 6 healthy human volunteers; the drug was assayed in plasma using HPLC, and results were compared with the performance of 2 commercial tablets of DS. Various pharmacokinetic parameters (ie, C_{max}, T_{max}, area under the curve [AUC_{0-24}], and mean residence time) and relative bioavailability were compared. All fabricated formulations showed more prolonged and controlled DS release compared with commercial tablets studied. The OM and OP tablets, however, performed better than the matrix tablets. The rate and extent of drug release from FM1 matrix tablets (single polymer) was significantly different from that of FM2 (admixed polymers). Type of porosigenic agents and osmogens also influenced the drug release. Analysis of in vitro data by regression coefficient analysis revealed zero-order release kinetics for OM and OP tablets, while FM tablets exhibited Higuchi kinetics. In vivo results indicated prolonged blood levels with delayed peak and improved bioavailability for fabricated tablets compared to commercial tablets. It was concluded that the osmotic matrix and osmotic pump tablets could provide more prolonged, controlled, and gastrointestinal environmental-independent DS release that may result in an improved therapeutic efficacy and patient compliance.

KEYWORDS: Matrix tablets, osmotic matrix tablets, osmotic pump tablets, controlled release, diclofenac sodium

INTRODUCTION

Diclofenac sodium (DS) is a substituted phenyl-acetic acid derivative; widely used in the management of many inflammatory conditions.[1] It also has analgesic and antipyretic actions.[2] But because of its short biological half-life and hazards of adverse gastrointestinal (GI) reactions,[3] the development of oral sustained-release formulations of this drug is highly desirable,[4] 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 past few years,[5-11] and many efforts have been made toward achieving sustained-release (SR) formulations of DS.[12-17] In one of our earlier investigations,[14] evaluation of commercially available SR tablets of DS from the Indian market revealed a large variation in their rate and extent of DS release. So, in an effort to achieve improved, controlled- and prolonged-release of DS, various formulations of DS have been prepared in the present study including fabricated matrix (FM) tablets using single polymer and admixed polymers,[18] osmotic matrix (OM) tablets,[19] and osmotic pump (OP) tablets.[20,21] A comparative evaluation has been made among all these formulations and with commercial tablets.

MATERIALS AND METHODS

Materials

DS was obtained as a gift sample from Win Medicare Ltd, Modipuram, Uttar Pradesh, India. Hydroxypropyl methyl cellulose (HPMC-K4M), ethylcellulose (EC), cellulose acetate (CA), and microcrystalline cellulose (MCC) were obtained from Dow Chemicals, France; Alkem Laboratories, Taloja, India; Thomas Baker (Chemicals) Ltd, Mumbai, India and S. D. Fine Chemicals Ltd, Mumbai, India, respectively. While polyethylene glycol (PEG 400) and Triacetin were procured from Glaxo Laboratories Ltd, Mumbai and Loba Chemie, Mumbai respectively, in India. All other chemicals/reagents used were of analytical grade except those used in high-performance liquid chromatography (HPLC) analysis, which were of HPLC grade. Commercial tablets of DS (batches C1 [Voveran-SR] and C2 [Voveran-2X50 mg conventional tablet]), each containing 100 mg of drug, were obtained from the Indian market.

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Table 1. Composition of Fabricated Matrix, Osmotic Matrix, and Osmotic Pump Tablets Containing 100 mg Diclofenac Sodium and 1% Magnesium Stearate*

		Batch No.					
No.	**Ingredients**	**FM1**	**FM2**	**OM1**	**OM2**	**OP1**	**OP2**
1	HPMC (mg)	200	100	200	200	-	-
2	EC (mg)	-	100	-	-	-	-
3	Potassium chloride (mg)	-	-	-	-	60	40
4	Potassium bicarbonate (mg)	-	-	-	-	-	25
5	MCC (mg)	-	-	-	-	122	117
6	SLS (mg)	-	-	-	-	12	12
7	Talc (mg)	-	-	-	-	3	3

*FM indicates fabricated matrix; OM, osmotic matrix; OP, osmotic pump; HPMC, hydroxypropyl methyl cellulose; EC, ethyl cellulose; MCC, microcrystalline cellulose; SLS, sodium lauryl sulfate; and a hyphen indicates not present. The formula for coating solutions for OM and OP tablets are given in the text in methods of preparation section.

Methods

Preparation of Fabricated Matrix Tablets of Diclofenac Sodium (Using Direct Compression Technique)

All the ingredients mentioned in Table 1 for batch FM1 and FM2 tablets were passed through sieve no. 85 (aperture size 180 µm, British Pharmacopeia Standard) and blended manually in a mortar uniformly through geometric dilution. The homogeneous blend was then compressed into tablets of 300-mg weight on a Manesty E2 tableting machine (England, UK) using 10-mm standard flat surface punches. Compression force was adjusted to provide Monsanto hardness of ~7 kg/cm^2.

Preparation of Osmotic Matrix Tablets of Diclofenac Sodium

Preparation of Swellable Matrix Tablets

Swellable matrix tablets were prepared by direct compression technique using 33.3% wt/wt of DS, 66.7% wt/wt of polymer (HPMC), and 1.0% wt/wt of magnesium stearate in each tablet. All the ingredients were passed through sieve no. 85, blended uniformly, and compressed on a Manesty E2 tableting machine using 10-mm deep concave punches at a pressure that gave Monsanto hardness of ~8 kg/cm^2.

Partial Coating of Matrix Tablets

The matrix tablets were partially coated using an aspirator (pipette connected with a vacuum pump holding the tablet from 1 side) on their base and lateral surfaces by carefully dipping them in an organic solution of film-forming polymer. This was prepared by dissolving 6 g of cellulose acetate (CA) and 33% (wt/wt concentration of CA) of PEG 400 (batch OM1) or Triacetin (batch OM2) as porosigenic agents, in a mixture solvent (methylene chloride:cellosolve:ethyl acetate in 3:1:1 vol/vol) with volume made up to 100 mL. The dipping volume and time, including time of rotation, remained constant until complete film coating was achieved, and solvent evaporation was allowed at 37°C ± 0.1°C for ~48 hours. The composition of fabricated OM formulations is shown in Table 1. The film coatings were evaluated using scanning electron microscope (SEM)-Olympus polarizing microscope B × 50P (model 840A) with SC35 camera (Tokyo, Japan).

Preparation of Osmotic Pump Tablets of Diclofenac Sodium

Preparation of the Core Tablets

An accurately weighed quantity of ingredients for OP tablets described in Table 1 were passed through sieve no. 85. All the ingredients except lubricant (magnesium stearate), glidant (talc), and binder (polyvinyl pyrrolidone [PVP]) were manually blended homogeneously in a mortar through geometric dilution. The mixture was wetted with 10% wt/vol aqueous solution of PVP, granulated through sieve no. 18 (aperture size 1000 µm, United States Pharmacopeia (USP) Standard) and dried in a hot air oven at 60°C for sufficient time (3 to 4 hours) to allow the moisture content of the granules to reach the 2% to 4% level. The dried granules were passed through sieve no. 26 (aperture size 710 µm, *USP* standard) and blended with talc and magnesium stearate. The homogeneous blend was then compressed into tablets (300 mg each) on a Manesty E2 tableting machine using 10-mm standard deep concave punches. The compression force was adjusted to give the tablets a hardness of ~7 kg/cm^2 on a Monsanto tablet hardness tester (Campbell Electronics, Mumbai, India).

Coating of the Core Tablets

Core tablets were film coated with a semipermeable membrane of 2% (wt/vol) CA in acetone having castor oil (20% wt/wt of total solid CA) as plasticizer using a conventional laboratory model, stainless steel, 10-cm pear-shaped, baffled coating pan. The manual coating procedure[22] used was based on an intermittent spraying and drying technique. An orifice (500-µm diameter) through the membrane was made by a microdrill on 1 side of each tablet.[22]

All fabricated formulations were evaluated for various physical parameters (ie, hardness, thickness, friability, drug content uniformity, and size and coating thickness, wherever applicable) using standard methods.

Solubility Studies

Before performing drug release studies from fabricated formulations in different release media (ie, distilled water [DW], pH 7.4, different concentrations of sodium chloride solution), the DS solubility was evaluated in all of these release media (data not shown); also the effect of different osmogens on solubility of DS was determined at 37°C (data not shown). The common ion effect, which can hinder DS solubility in the presence of salt solution containing the same ion, was also taken into consideration. The evaluation of DS solubility in various concentrations of NaCl solution (0, 10, 20, 40, 80, and so on to 410 mg/mL) at 37°C was performed in order to choose a safe molar concentration of NaCl (to study osmotic effect among formulations) that can be used without affecting DS solubility owing to common ion effect. Thus, for our present study, a concentration of NaCl was chosen that showed negligible effect on DS solubility. However, at higher concentrations of NaCl, the common ion effect was observed to affect DS solubility to a great extent; these concentrations were not used in our studies.

In Vitro Evaluation

In vitro studies, in triplicate, were done on USP 24[23] dissolution apparatus II in different release media (pH 7.4, DW, 0.02 M NaCl in DW and 0.2 M NaCl in DW) maintained at 37°C ± 0.2°C and 100 rpm stirring. Withdrawn samples were analyzed on a Jasco UV/VIS spectrophotometer (model 7800, Tokyo, Japan) at 275 nm.

In vitro studies were conducted to investigate the effect of the following factors on DS release from different formulations:

1. Effect of admixed polymers (FM tablets)
2. Effect of presence of porosigenic agents (OM tablets)
3. Effect of type of porosigenic agents (OM tablets)
4. Effect of osmogen (OP tablets)
5. Effect of osmotic contribution (OM and OP tablets)
6. Effect of pH of release medium (FM, OM, and OP tablets)

In vitro drug release kinetics were also studied for different formulations.

In Vivo Studies

In vivo studies were performed following standard protocols in 6 healthy human volunteers of either sex weighing 55 to 75 kg and 24 to 29 years old in a cross-over design in accordance with all applicable regulations. Informed consent was obtained from volunteers after the nature and possible consequences of the studies were explained. All the subjects were in good health on the basis of their medical history and complete physical examination. The volunteers did not smoke and were not on any kind of medication before or during the experiment. The modified HPLC method[24] was used to analyze human plasma samples (stored frozen at –20°C until analysis) at different time intervals up to 24 hours following oral administration of formulated tablets (ie, FM, OM, and OP tablets) and 2 commercial tablets (C1 and C2) to human subjects. HPLC assay was performed using (1) Novapak C-18, 4 μm (150 × 3.9 mm) (Shimadzu, Tokyo, Japan) column, (2) a mixture of 40 volumes of acetonitrile and 60 volumes of 0.025 M ammonium acetate solution as the isocratic elution mobile phase with a flow rate of 1 mL/min, and (3) injection volume of 75 μL; samples were detected at a wavelength of 275 nm in a UV detector (Shimadzu).

The plasma profiles, calculated bioavailability, and pharmacokinetic parameters were compared for the different formulations.

Statistical Analysis of Data

Experimental results were expressed as mean ± SD values. Student *t* test (paired and 1-sided) was performed to determine the level of significance. Difference was considered to be statistically significant at $P < .05$ and nonsignificant at $P > .05$.

Results and Discussion

The various physical parameters evaluated for all fabricated formulations were found within official[23] limits (data not shown).

In Vitro Studies

From the in vitro release profiles (Figure 1), it was observed that all fabricated formulations (ie, FM, OM, and OP tablets) of DS showed more controlled and prolonged DS release as compared with commercial SR (C1) and conventional (C2) tablets studied. Out of all fabricated formulations, OP tablets showed the most prolonging effect on DS release compared with OM, followed by FM tablets. This may be owing to a constant rate of slow and controlled DS delivery from OP tablets.

Effect of Admixed Polymers Among Fabricated Matrix Tablets

It was observed that batch FM2 tablets (containing HPMC and EC both) showed (see Figure 1) more prolonging effect compared with commercial tablets but exhibited more DS release in comparison to FM1 tablets having HPMC alone

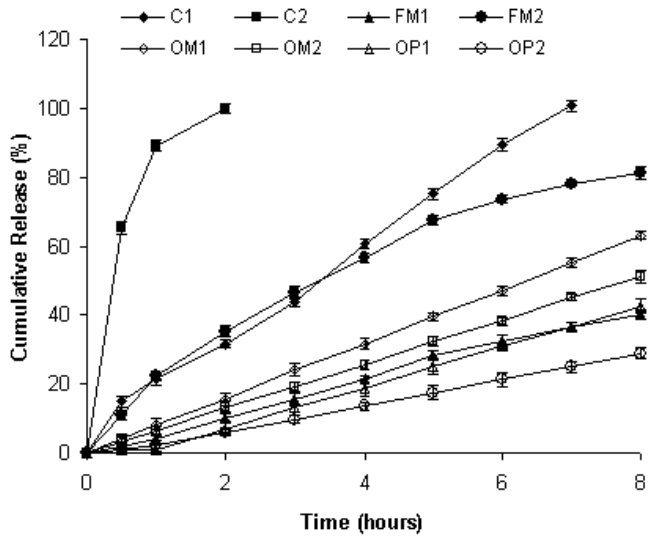

Figure 1. In vitro release profiles showing DS release from various fabricated (FM, OM, and OP) and commercial (C1 and C2) tablets in pH 7.4 buffer medium. Bars represent ± SD (n = 3).

(Table 1). This result was owing to weak interaction between hydrophilic (HPMC) and hydrophobic (EC) polymers in FM2 tablets in comparison to strong cohesive forces among hydrophilic (HPMC) polymeric molecules in FM1 tablets. This finding clearly indicates that the DS release from matrix tablets containing admixed polymers depends on the nature and composition of interacting polymers incorporated within the matrix tablets.[15]

Effect of Presence of Porosigenic Agents on Diclofenac Sodium Release From Osmotic Matrix Tablets

Marginally increased and controlled DS release from OM than from FM1 tablets (Figure 1) was observed owing to the presence of porosigenic agents (PEG 400 or Triacetin) within coatings of OM (OM1 and OM2) tablets. More controlled drug release from OM tablets was attributed to dual control of drug release among OM tablets (ie, controlled diffusion of drug through the swelled polymeric matrix and the controlled permeation of drug through coating membrane having micropores owing to the presence of porosigenic agent) as compared with FM1 tablet, wherein drug release is controlled only by diffusion through swelled polymeric matrix.

Effect of Type of Porosigenic Agents on Diclofenac Sodium Release From Osmotic Matrix Tablets

The DS release from OM tablets was also found to be affected by the type of porosigenic agent used in the coating films. A higher rate and extent of DS release was observed (Figure 1) from batch OM1 tablets incorporating PEG 400 as a porosigenic agent within coating compared with batch OM2 tablets, which had Triacetin. This result occurred owing to the more

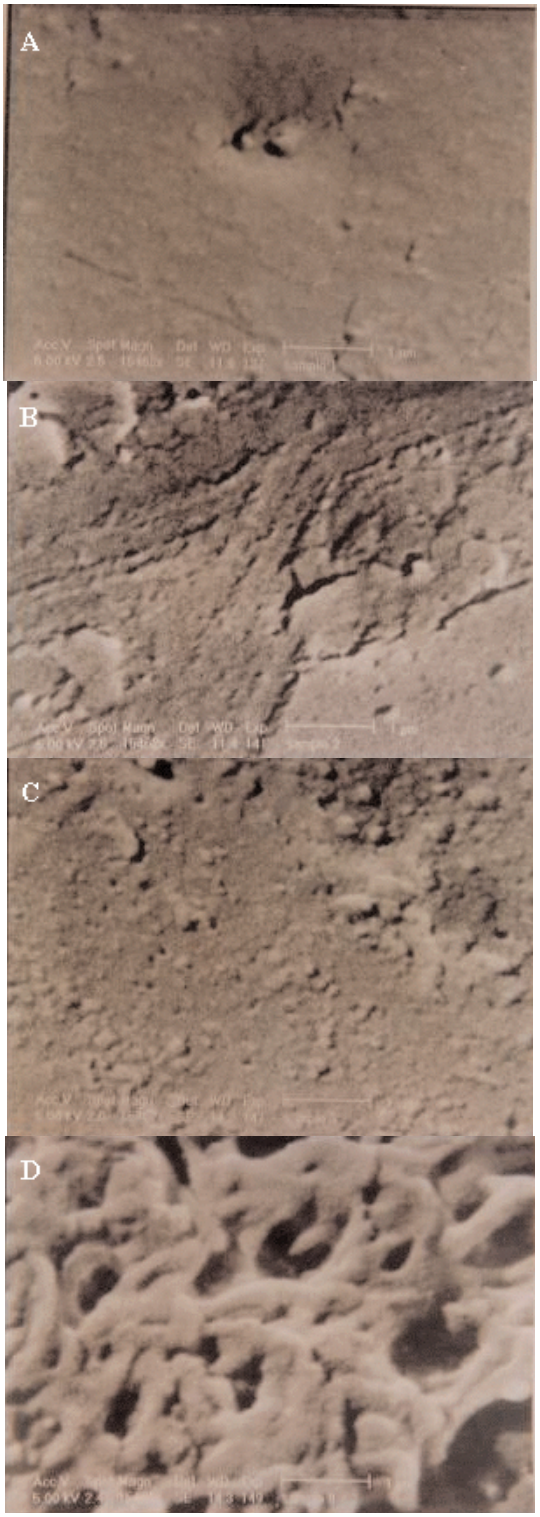

Figure 2. SEM of the film coatings among OM tablets having PEG 400 (OM1) and Triacetin (OM2) as porosigenic agents (A) Triacetin and (B) PEG 400, before dissolution; (C) Triacetin and (D) PEG 400, after dissolution.

hydrophilic nature of PEG 400 causing more pore formation in the coating film compared with Triacetin, which was evidenced by the SEM analysis (Figure 2A-D) of the coating membrane. It was observed that before dissolution, the surface of the coating film containing 33% PEG 400 (OM1) was nonuniform with shear marks compared with that containing

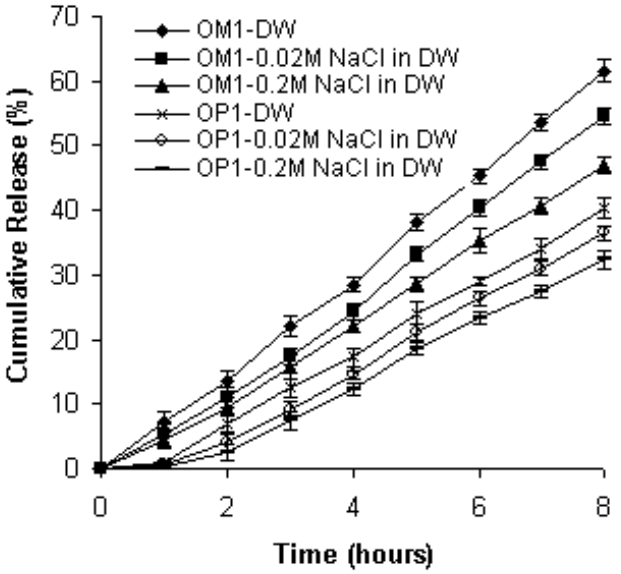

Figure 3. In vitro release profiles showing the effect of different osmolarity of release medium on DS release from OM1 and OP1 tablets. Bars represent ± SD (n = 3).

33% Triacetin (OM2), which had smoother surface. After the dissolution, the coating films lost their integrity, and the pores were clearly evident. More pores were observed in coating films with PEG 400 (OM1) as compared with that with Triacetin (OM2), which was possibly a result of more hydrophilic nature of PEG 400 compared with Triacetin.

Diclofenac Sodium Release From Osmotic Pump Tablets—Osmogen Effect

Both OP tablets exhibited highly controlled and prolonged drug release. The OP tablet (OP1) containing potassium chloride only (as osmogen) exhibited (see Figure 1) more DS release than OP2 containing less potassium chloride than OP1 but having potassium carbonate in addition.

Effect of Osmotic Contribution on Diclofenac Sodium Release From Osmotic Matrix and Osmotic Pump Tablets

To investigate the effect of osmotic contribution on DS release from OM and OP tablets, studies were conducted in DW and in aqueous solutions of different osmolarity. It was observed (Figure 3) that batch OM1 exhibited a decrease in extent of DS release with an increase in the osmolarity of the release medium, indicating that osmotic contribution also played a role in drug release from OM tablets. Similarly, decreased DS release was observed from OP1 tablets (see Figure 3) also in the medium with increased osmolarity, which indicated that DS release from OP tablets was also osmotically controlled. One-hour delayed drug release from OP tablets was attributed to time elapsed for imbibition of the osmotic core with the release medium.

Table 2. Data Showing In Vitro Release Kinetics (Analyzed by Regression Coefficient Method) of Diclofenac Sodium From Different Batches of Fabricated Matrix, Osmotic Matrix, and Osmotic Pump Tablets*

		Regression Coefficient Values (*r*)	
No.	**Batch No.**	**Zero-Order**	**Higuchi**
1	FM1	0.9807	0.9869
2	FM2	0.9738	0.9922
3	OM1	0.9999	0.9569
4	OM2	0.9999	0.9570
5	OP1	0.9999	0.9911
6	OP2	0.9999	0.9902

*FM indicates fabricated matrix; OM, osmotic matrix; and OP, osmotic pump.

Effect of pH of Release Medium on Diclofenac Sodium Release From Fabricated Matrix, Osmotic Matrix, and Osmotic Pump Tablets

To further verify whether drug delivery from osmotically contributed systems remains independent of environmental pH, batches of FM1, OM1, and OP1 were evaluated for the effect of pH on DS release. It was observed (not shown in the present study) that except for FM1, no significant difference was observed in DS release from OM and OP tablets in different release media (pH 7.4 and DW). Such results clearly suggest that variation of pH does not affect the DS release from OM and OP tablets compared with FM tablets.

In Vitro Drug Release Kinetics Evaluation

The in vitro release kinetics data (see Table 2) obtained using regression coefficient analysis[25] demonstrated that matrix tablets (FM1 and FM2) showed Higuchi kinetics, whereas OM (OM1 and OM2) and OP (OP1 and OP2) tablets showed zero-order kinetics.

In Vivo Studies

From the results of in vivo studies, which were determined by evaluating bioavailability and pharmacokinetic data (see Table 3) from plasma profiles obtained (see Figures 4 and 5) using 6 healthy volunteers, it was observed that the fabricated formulations (FM, OM, and OP) gave more prolonged and controlled plasma drug level profiles compared with commercial tablets (C1 and C2) studied.

Further, it was observed that OM and OP tablets exhibited lower C_{max} but within therapeutic range[26] and higher T_{max} values than FM and commercial (C1 and C2) tablets, which clearly indicates that the fabricated OM and OP tablets were able to deliver drug slowly but for a longer duration with a more controlled rate, thereby avoiding the possibility of plasma drug concentration exceeding the maximum safe concen-

Table 3. Bioavailability and Pharmacokinetic Data for Different Fabricated and Commercial Tablets*

No.	Batch No.	Bioavailability and Pharmacokinetic Parameters					
		C_{max} (µg/mL)	T_{max} (hours)	AUC_{0-24} (µg·h/mL)	RB† (%)	RB‡ (%)	MRT (hours)
1	FM1	0.405 ± 0.089	4.0 ± 0.27	5.24 ± 0.19	113.58	145.61	10.19
2	FM2	0.408 ± 0.075	4.0 ± 0.34	5.29 ± 0.18	114.66	147.00	9.41
3	OM1	0.389 ± 0.68	4.0 ± 0.21	5.20 ± 0.15	113.04	144.44	11.86
4	OM2	0.342 ± 0.069	6.0 ± 0.18	5.70 ± 0.26	123.64	158.33	10.48
5	OP1	0.331 ± 0.060	6.0 ± 0.24	4.98 ± 0.12	108.02	138.33	13.34
6	OP2	0.310 ± 0.061	6.0 ± 0.28	5.35 ± 0.22	116.14	148.88	14.84
7	C1	0.501 ± 0.054	4.0 ± 0.46	4.61 ± 0.28	100.00	128.19	8.63
8	C2	0.781 ± 0.081	2.0 ± 0.49	3.60 ± 0.28	78.00	100.00	3.71

*AUC indicates area under the curve; RB, relative bioavailability; MRT, mean residence time; FM, fabricated matrix; OM, osmotic matrix; OP, osmotic pump; C, commercial preparation. All data are mean ± SD (n = 6).

†RB - in reference to C1 (Voveran - sustained release).

‡RB - in reference to C2 (Voveran - conventional).

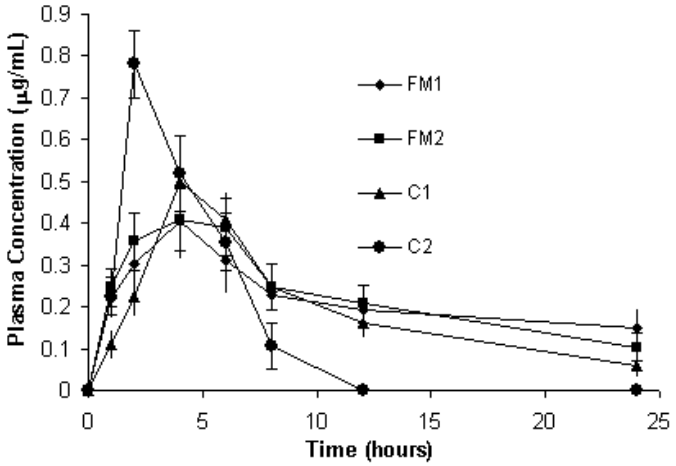

Figure 4. Plasma profiles of DS following oral administration of FM tablets in comparison to commercial (C1 and C2) tablets to healthy human subjects. Bars represent ± SD (n = 6).

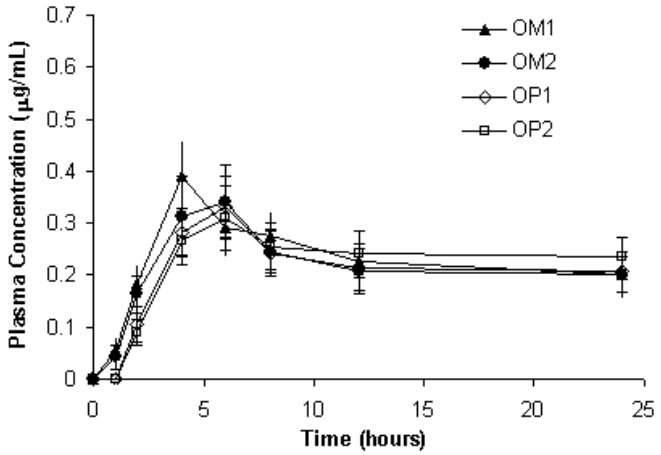

Figure 5. Plasma profiles of DS following oral administration of OM and OP tablets to healthy human subjects. Bars represent ± SD (n = 6).

tration (MSC) of therapeutic range. Significantly ($P < .05$) higher values of AUC_{0-24}, relative bioavailability, and mean residence time of fabricated OM (OM1 and OM2), OP (OP1 and OP2), and FM (FM1 and FM2) formulations in comparison to commercial tablets further indicate superiority of these fabricated formulations over commercial tablets (C1 and C2) studied.

Conclusion

Thus, OM and OP tablets could provide more prolonged, controlled, and pH-independent DS release and are expected to perform therapeutically better with improved patient compliance.

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