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To cite this article: Meena Rani, Rahul Surana, C. Sankar & B. Mishra (2004) Formulation and Biopharmaceutical Evaluation of Osmotic Matrix Tablets of Diclofenac Sodium, Drug Delivery, 11:4, 263-270, DOI: [10.1080/10717540490467393](https://doi.org/10.1080/10717540490467393)

To link to this article: <https://doi.org/10.1080/10717540490467393>



Published online: 19 Oct 2008.



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Formulation and Biopharmaceutical Evaluation of Osmotic Matrix Tablets of Diclofenac Sodium

Meena Rani, Rahul Surana, C. Sankar, and B. Mishra

Department of Pharmaceutics, Institute of Technology, Banaras Hindu University, Varanasi, India

The objective of our study was to prepare and evaluate osmotic matrix (OM) tablets of diclofenac sodium (DS). In vitro studies were done on USPXXIV dissolution apparatus II in different release medium. Surface characteristics of coating films and osmotic contribution of OM tablets also were studied. In vivo evaluation was carried out in 6 healthy human volunteers using HPLC method to assay plasma samples, and the results were compared with the performance of fabricated matrix and two commercial tablets of DS. Through in vitro drug release kinetics, using regression coefficient analysis and Peppas equation, different pharmacokinetic parameters and relative bioavailability were determined. OM tablets were found to provide more prolonged and controlled therapeutic plasma DS levels and also showed improved bioavailability in comparison to fabricated matrix and commercial tablets studied.

Keywords Bioavailability, Controlled Release, Diclofenac Sodium, Osmotic Matrix Tablets, Pharmacokinetic Parameters

Diclofenac sodium (DS), a nonsteroidal anti-inflammatory drug, is used in the treatment of rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis (Hui et al. 1998). Because of its short biological half-life and the hazards of adverse gastrointestinal (GI) reactions, the development of an oral sustained-release formulations of this drug is highly desirable (Garcia-Encina et al. 1995; Rani and Mishra 2001a and b), to achieve improved therapeutic effect with negligible side effects and improved patient compliance. Many efforts have been made toward achieving sustained-release formulations of DS (Nishihata 1987;

Liu et al. 1995; Hosny, Al-Helw, and Al-Dardiri 1997; Mishra, Panyam, and Sharma 1999; Rani et al. 2001a and b; Sajeev et al. 2002; Rani and Mishra 2001 a and b), especially matrix formulations. But the reliability of the drug dissolution rate in biological fluids from matrices, which are diffusion-controlled systems, is affected by the variability of pH and hydrodynamic conditions of the GI tract (Lee and Robinson 1987). When swellable matrices were coated with an impermeable film on one base and the lateral surface (leaving only the surface of the other side available for swelling and drug release), it led to development of osmotic matrix (OM) systems (Catellani et al. 1998). Their release kinetic behavior was found closer to linear (Bettini, Catellani, and Colombo 1996). Therefore, an effort was made in our study to prepare and evaluate OM tablets of DS to achieve much more prolonged and controlled delivery of DS for better therapeutic effect and patient compliance.

MATERIALS AND METHODS

Materials

DS was obtained as a gift sample from Win-Medicare Ltd., India. Commercial tablets of DS [Batches C10 (Voveran-SR[®] – 100 mg) and C11 (Voveran[®] – 2 × 50 mg conventional tablets)] were purchased from an Indian market. Hydroxypropyl methylcellulose (HPMC-K4M) and cellulose acetate (CA) were obtained from Dow Chemicals (France) and Thomas Baker (Chemicals) (India) respectively. Polyethylene glycol (PEG 400) and Triacetin were obtained from Glaxo Lab Ltd. and Loba Chemie in India, respectively. All other chemicals/reagents used were of analytical grade except those used in HPLC analysis were of HPLC grade.

Preparation of OM Tablets of DS

Swellable Matrix Tablets

Swellable matrix tablets (FM1) were prepared by direct compression technique using 33.3% w/w of DS, 66.7% w/w of polymer (HPMC), and 1.0% w/w of magnesium stearate, in each

Received 2 March 2004; accepted 16 March 2004.

The authors acknowledge University Grants Commission, New Delhi (India), for financial assistance. They also thank V.K. Arora and Tausif of Ranbaxy Research Laboratory, Gurgaon (India), for their help in providing facilities for the analysis of plasma samples on HPLC.

Address correspondence to Dr. B. Mishra, Reader in Pharmaceutics, Department of Pharmaceutics, Institute of Technology, Banaras Hindu University, Varanasi-221005 (U.P.), India. E-mail: bmishra@banaras.ernet.in; ranix002@umn.edu

tablet. All the ingredients were passed through sieve No. 85 (aperture size 180 μm , British Standard), 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 vacuum pump holding tablet from one side) on their base and lateral surface by carefully dipping them in an organic solution of film-forming polymer. The solution was prepared by dissolving 2, 5, or 6 gm of CA and different concentrations (0%, 5%, 33%, and 66% w/w of CA) of PEG 400 or Triacetin, as porogenic agents, in a mixture solvent (methylene chloride:ethyl acetate:cellosolve in 3:1:1 v/v) 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 $37 \pm 0.1^\circ\text{C}$ for 48 hr. The composition of all fabricated OM formulations are shown in Table 1. All fabricated formulations were evaluated for various physical parameters using standard methods. The film coatings were evaluated using scanning electron microscope (SEM)-Olympus polarizing microscope B \times 50P (model 840A) with SC35 camera, Japan.

In Vitro Studies

In vitro studies, in triplicate, were done on USPXXIV (USP 24, 2001) dissolution apparatus II in different release media [pH 7.4, distilled water (DW), 0.02M sodium chloride (SCL) in

TABLE 1

Composition of coating solutions used for partial coatings of different batches of fabricated osmotic matrix (OM) tablets of DS

Batch no.	Cellulose acetate		Triacetin (%) [*]	MC:EA:CV: (3:1:1) q.s. to- (ml)	Coating thickness (mm)
	(g)	(%) [*]			
FM1	—	—	—	—	—
OM1	2	—	—	100	0.08 ± 0.01
OM2	5	—	—	100	0.09 ± 0.01
OM3	6	—	—	100	0.10 ± 0.02
OM4	6	5	—	100	0.11 ± 0.01
OM5	6	33	—	100	0.11 ± 0.01
OM6	6	66	—	100	0.12 ± 0.01
OM7	6	—	33	100	0.12 ± 0.02

^{*}% w/w of cellulose acetate.

MC = methylene chloride; EA = ethyl acetate; CV = cellosolve; — = not present.

The tablet composition in all cases was DS = 100 mg; HPMC = 200 mg; magnesium stearate = 1% w/w.

DW, and 0.2M SCL in DW] maintained at $37 \pm 0.2^\circ\text{C}$ and at 100 rpm. Withdrawn samples were analyzed on Jasco UV/VIS Spectrophotometer (model 7800, Japan) at 275 nm. In vitro studies were conducted to investigate the effect of the following factors on DS release from different formulations of OM tablets:

- DS release from OM versus FM tablets.
- Effect of polymer concentration in coating film on DS release from OM tablets.
- Effect of the type and concentration of porogenic agents on DS release from OM tablets.
- Effect of osmotic contribution on DS release from OM tablets.
- Effect of pH of release medium on DS release from FM and OM tablets.

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

In Vivo Studies

In vivo studies were performed following standard protocols in 6 healthy human volunteers of either sex weighing 55–75 Kg and 24–29 years old in a crossover design. Volunteers agreed in writing to participate in the study after explanation of the experimental protocol. All subjects were in good health on the basis of their medical history and complete physical examination. The volunteers were neither smoking nor on any kind of medication before and during the experiment. The modified HPLC method (Giagoudakis and Markantonis 1998) was used to analyze plasma samples (stored frozen at -20°C until analysis) collected at different time intervals up to 24 hrs following oral administration of formulated tablets (FM and OM tablets) as well as two commercial tablets (C1 and C2) to human subjects. HPLC procedure was carried out our methods: Novapak C-18 column, 4 μm (150 \times 3.9 mm) (Shimadzu, Japan); 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; injection volume of 75 μl ; and a detection wavelength of 275 nm for detection in a Shimadzu UV detector.

The plasma drug concentrations versus time profiles and the calculated bioavailability and pharmacokinetic parameters for different formulations were compared.

Statistical Analysis of Data

Experimental results were expressed as mean \pm SD values. Student *t* test also 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 the official limits (data not shown).

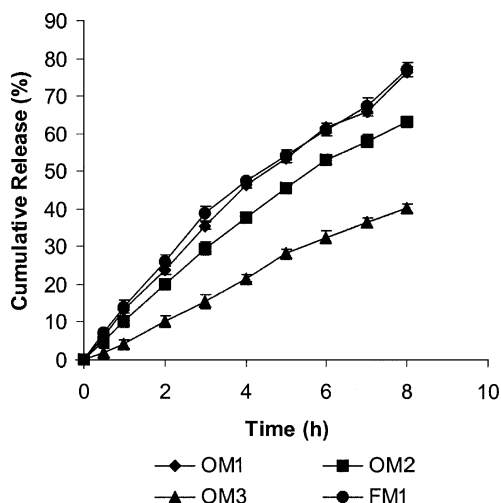


FIG. 1. In vitro release profiles showing the effect of different concentrations, 2% (OM1), 5% (OM2), and 6% (OM3) w/w, of CA in coating film on DS release from OM tablets in pH 7.4 buffer in comparison to uncoated matrix tablet (FM1). Error bars represent \pm S.D ($n = 3$).

DS Release from OM versus FM Tablets

The cumulative percent drug release versus time profiles shown in Figure 1 clearly indicate that all the fabricated OM tablets of DS showed more controlled and prolonged DS release compared with FM1 matrix tablets.

Polymer (CA) Concentration in Coating Film

We observed (Figure 1) that the increase in polymer (CA) concentration incorporated within coating film from 2% (OM1) to 5% (OM2) to 6% w/v (OM3) resulted in more prolonged and controlled drug release. The possible mechanism of controlled and prolonged drug release from OM tablets as compared with matrix (FM1) tablet is attributed to controlled diffusion of the drug through the swelled gel polymeric matrix available on one side only in OM tablets (having no porosigenic agents), where otherwise the coated membrane was present on base and lateral surface, as in OM1, OM2, and OM3. However, in FM1 matrix tablets drug diffusion occurred through swelled polymeric matrix available over all the sides of the matrix tablets and resulted in more drug release than OM tablets.

Type and Concentration of Porosigenic Agents

The drug release also was affected by the type of porosigenic agent used in coating films. The batch OM7 containing 33% Triacetin in coating solution exhibited a significantly ($p < .05$) decreased rate and extent of DS release compared with batch OM5 having 33% PEG 400 (Figure 2). This may be attributed to more hydrophilicity of PEG 400, which led to formation of more pores during dissolution resulting in higher DS release. This is evidenced by the SEM analyzed microphotographs shown in Figure 3(A–D). From SEM analysis, it was observed that be-

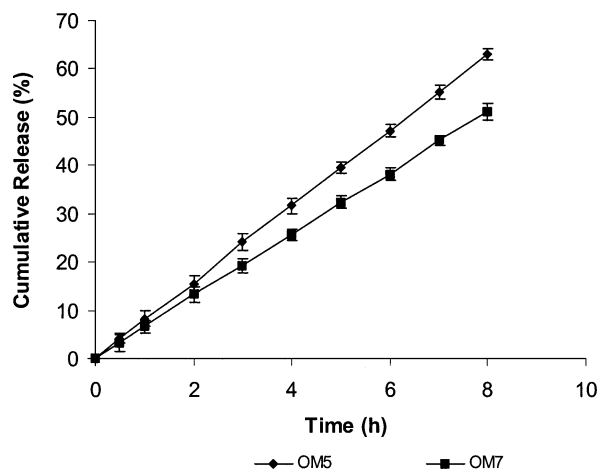


FIG. 2. In vitro release profiles showing the effect of porosigenic agents, 33% w/w PEG 400 (OM5) and 33% w/w Triacetin (OM7) used in coating, on DS release from OM tablets in pH 7.4 buffer. Error bars represent \pm S.D ($n = 3$).

fore dissolution, the surface of the coating film containing 33% Triacetin (OM7) was smoother than that containing 33% PEG 400 (OM5) which had nonuniform surface with shear marks. 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 (OM5) compared with those with Triacetin (OM7), possibly a result of more hydrophilic nature of PEG 400 than Triacetin.

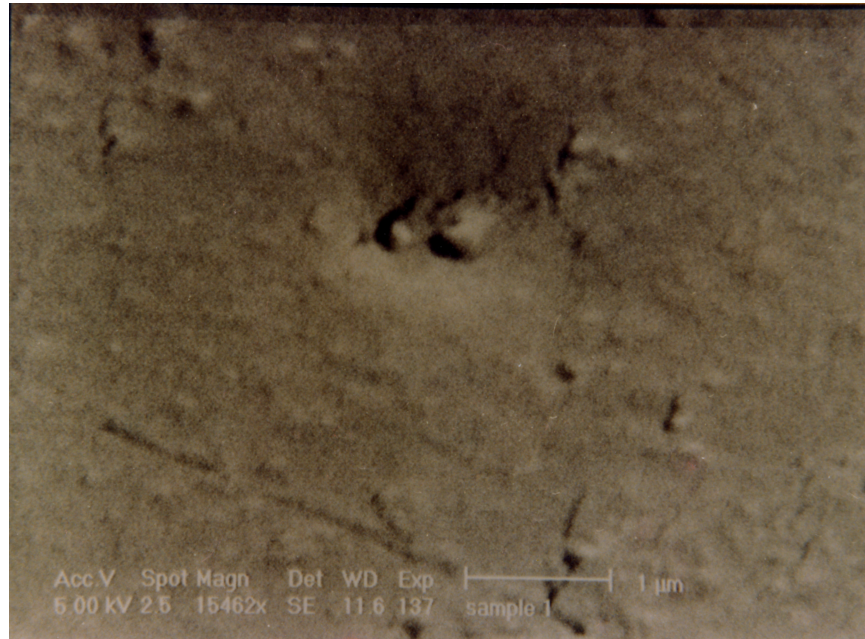
Further, it we observed (Figure 4) that with an increase in the concentration of porosigenic agent (PEG 400) in OM tablets (OM3 – 0%, OM4 – 5%, OM5 – 33%, and OM6 – 66% w/w PEG 400), a significant increase in rate and extent of drug release was found. The DS release profiles from all the OM tablets were much linear than the matrix (FM1) tablets. The presence of porosigenic agents in the coating film of OM tablets resulted in double control and more linearity of drug release: one by controlled drug diffusion through swelled gel polymeric matrix from one side of the tablets and the second by controlled drug permeation from the other side of the tablets where the micropores formed in the coating membrane due to dissolution of porosigenic agents (PEG 400 or Triacetin) in the release medium. With an increase in concentration of porosigenic agents (PEG 400) in the OM tablets (OM3, OM4, OM5, and OM6), subsequent increase in DS release was observed (Figure 4). It is attributed to formation of more micropores in the coating film.

Osmotic Contribution

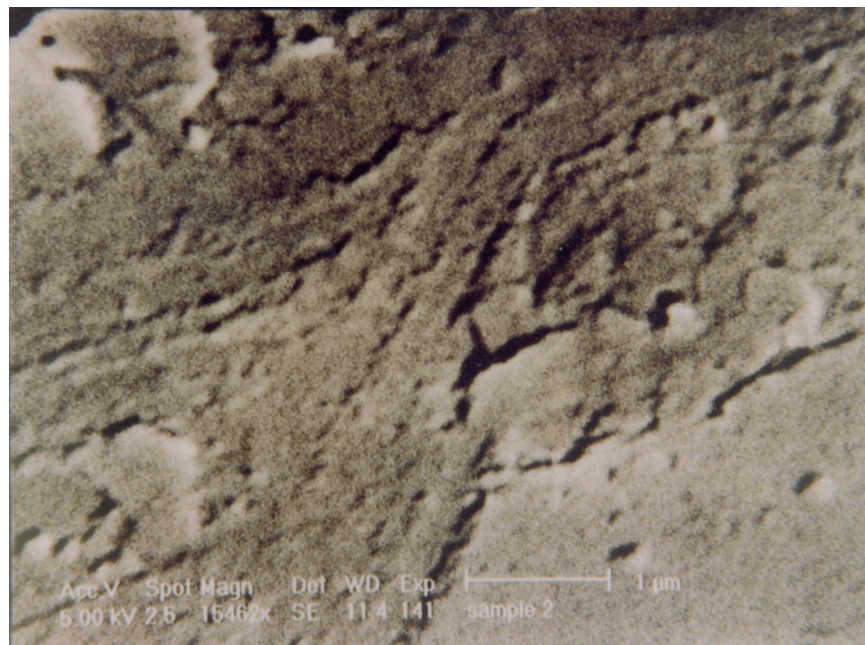
To study the osmotic contribution of osmotic matrix on DS release, the in vitro release investigations on OM3, OM4, OM5, and OM6 were done in release media with increasing osmolarity (0.02M SCL in DW and 0.2M SCL in DW). The in vitro drug release profiles shown in Figure 5 indicate that batch OM3, containing no porosigenic agent in coating film, and batch OM6,

containing highest amount (66% w/w) of PEG 400 as porosigenic agent in coating film, exhibited insignificant ($p > .05$) differences in rate and extent of drug release in release media of increasing osmolarity. This indicated no effects of increased osmotic pressure of release media on DS delivery from OM3 and OM6 tablets. Since OM3 did not contain any porosigenic agent,

drug release occurred by diffusion process through the gel formed around uncoated side of the tablet, without any osmotic contribution of the system. However, a greater amount of PEG 400 (water soluble porosigenic agent) resulted in formation of large numbers of micropores in the coating film during drug release study, and the drug release from batch OM6 was expected to be

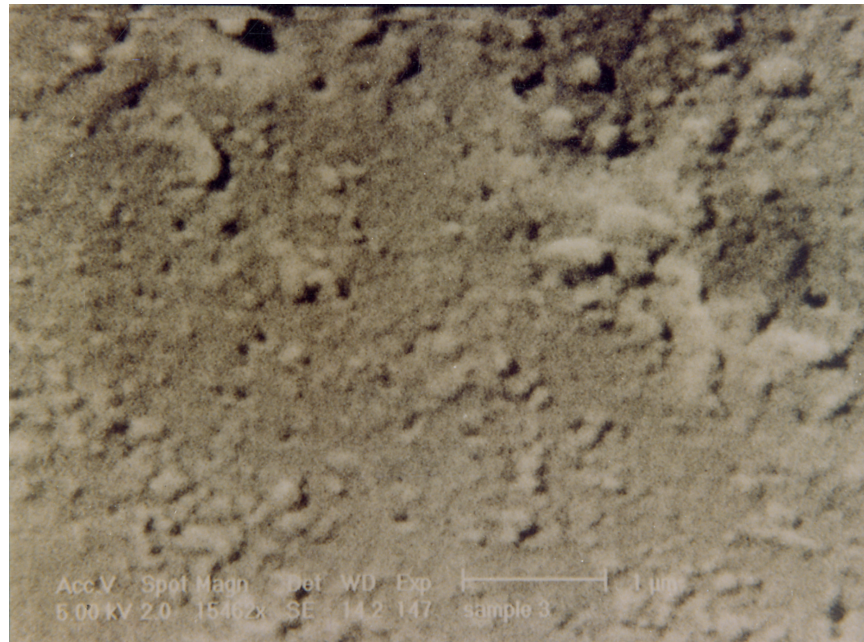


(A)

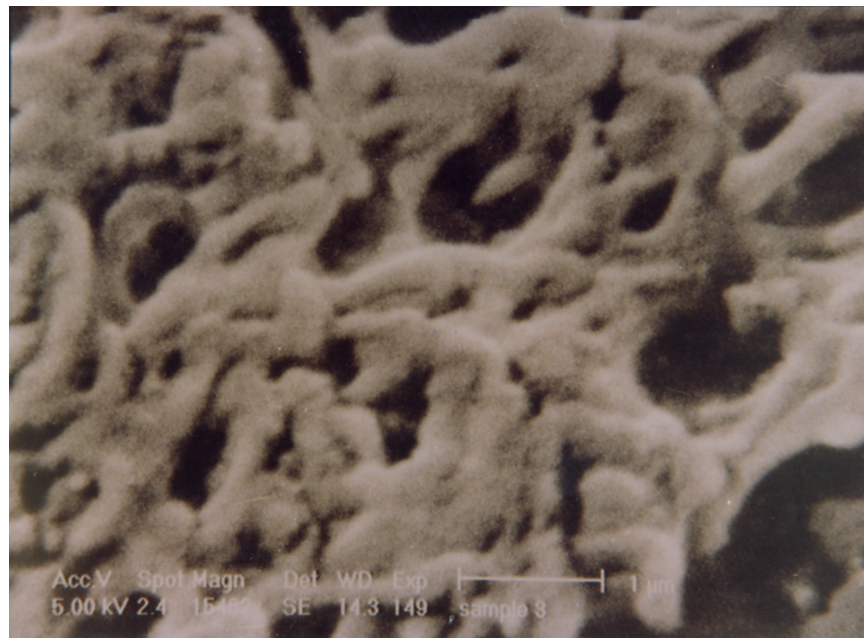


(B)

FIG. 3. SEM of the film coatings having Triacetin and PEG 400 before and after dissolution. (A) Triacetin and (B) PEG 400 before dissolution. (C) Triacetin and (D) PEG 400 after dissolution. (Continued)



(C)



(D)

FIG. 3. Continued.

controlled by the diffusion of drug through gel around uncoated part of the tablet and also by permeation through large numbers of micropores formed in the membrane without any osmotic contribution of the systems (Catellani et al. 1998). But, as shown in Figure 6, batches OM4 and OM5 exhibited a decrease in rate and 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 these two batches. This behavior was observed because the coating membrane in these two cases probably behaved as a semipermeable membrane with comparatively less microporous character than that in OM6 and thus resulted in osmotically controlled DS release from such systems.

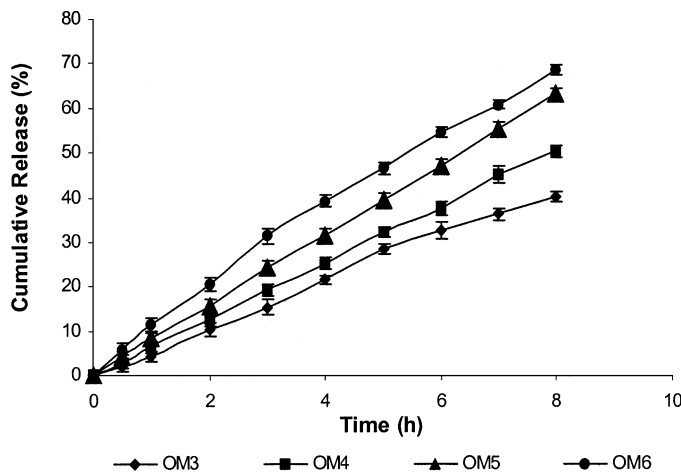


FIG. 4. In vitro release profiles showing the effect of different concentrations, 0%(OM3), 5% (OM4), 33% (OM5), and 66% w/w (OM6), of porogenic agent (PEG 400) used in coating on DS release from OM tablets in pH 7.4 buffer. Error bars represent \pm S.D ($n = 3$).

Effect Release Medium pH on DS Release

To further verify whether drug delivery from osmotically contributed systems remain independent of environmental pH, batches FM1 and OM5 were evaluated to study pH effect (effect of different release media) on DS release from them. We observed (Figure 7) that the matrix tablet FM1 exhibited significant difference in DS release in two different release media (pH 7.4 and DW) whereas osmotic matrix tablet (OM5) exhibited

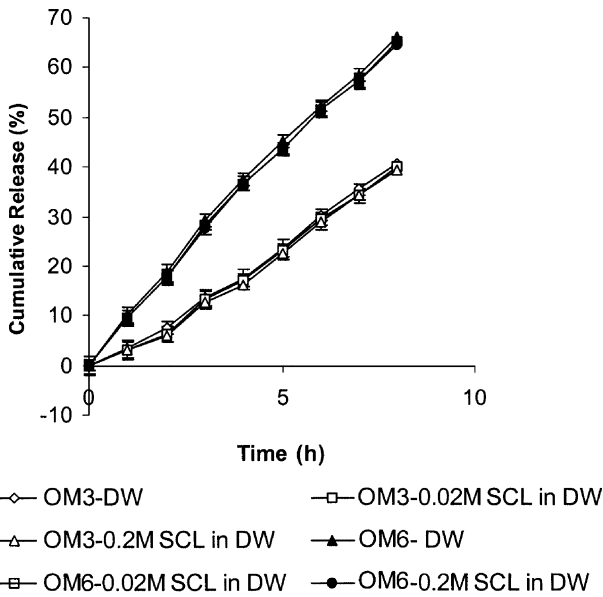


FIG. 5. In vitro release profiles showing the effect of osmolarity of release medium on DS release from OM3 and OM6 tablets. Error bars represent \pm S.D ($n = 3$).

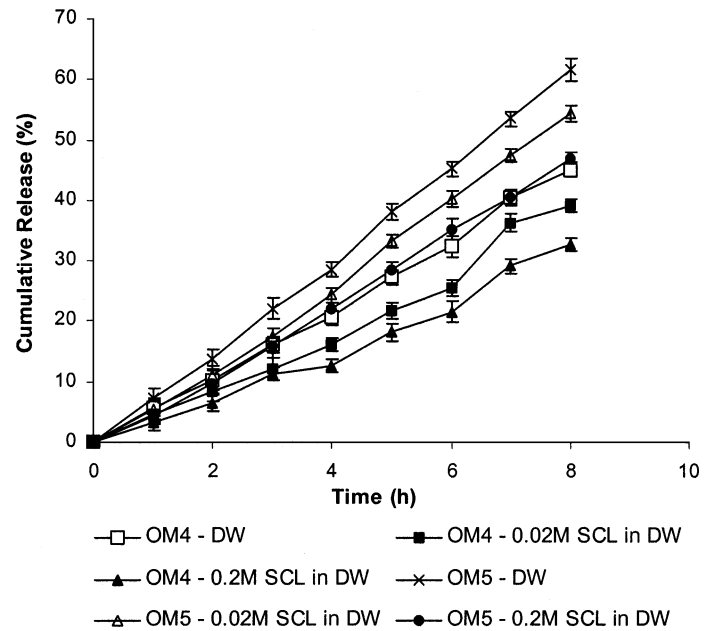


FIG. 6. In vitro release profiles showing the effect of osmolarity of release medium on DS release from OM4 and OM5 tablets. Error bars represent \pm S.D ($n = 3$).

no significant difference in DS release in these two release media. Thus, the results clearly suggest that variation of pH does not affect the DS release from OM tablets, compared with FM tablets.

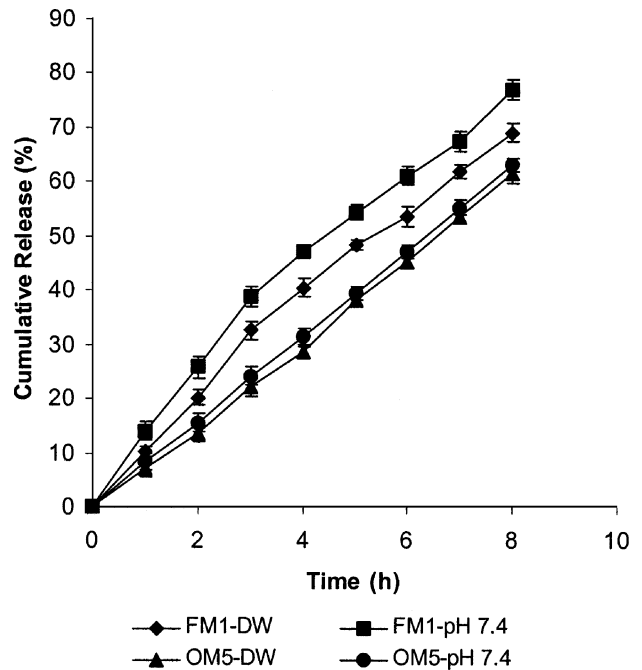


FIG. 7. In vitro release profiles showing the effect of two different release media on DS release from FM1 and OM5 tablets. Error bars represent \pm S.D ($n = 3$).

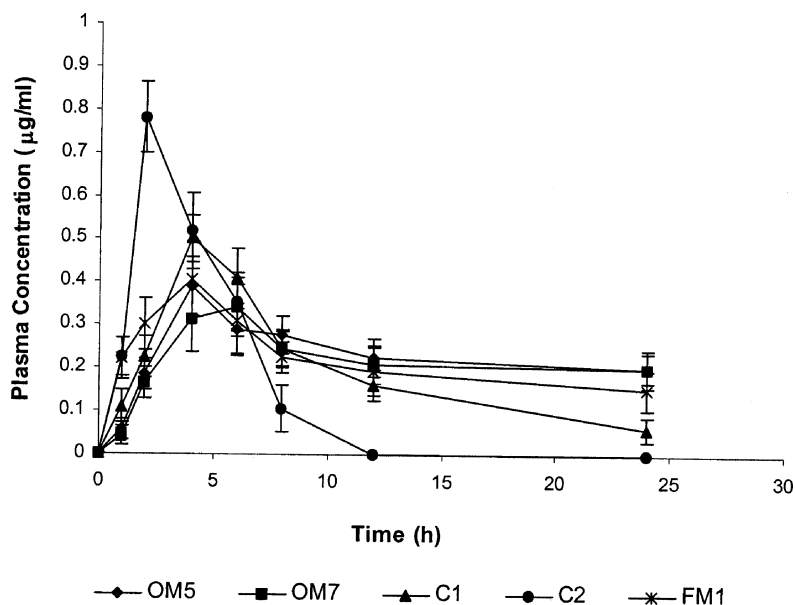


FIG. 8. Plasma profiles of DS following oral administration of fabricated OM5 and OM7 tablets and FM1 in comparison to commercial SR (C1) and conventional (C2) tablets to healthy human subjects. Error bars represent \pm S.D ($n = 6$).

In Vitro Drug Release Kinetics

The in vitro drug release kinetics and mechanisms from different batches of OM tablets and FM1 was studied by regression coefficient analysis (Sankar et al. 2001) and the Peppas equation (Ritger and Peppas 1987). Tables 2 and 3, show that all OM tablets exhibited drug release with zero-order kinetics, FM1 showed Higuchi kinetics of drug release, and more linearity was observed among OM tablets as determined by 'n' values using Peppas equation.

In Vivo Studies

From in vivo data (Table 4) and plasma profiles (Figure 8), it was observed that OM tablets provided more controlled and

prolonged plasma DS levels compared with commercial tablets. We found that the fabricated OM tablets exhibited lower C_{max} but within therapeutic range (Reiss et al. 1978) and higher T_{max} values than the commercial tablets (C1 and C2). This clearly indicate that the fabricated OM tablets evaluated in vivo were able to deliver DS within therapeutic range, slowly with more controlled rate and for a much longer duration. Significantly higher values of AUC_{0-24} , relative bioavailability, and mean residence time (MRT) of fabricated OM formulations in comparison to C1 and C2 further indicated the superiority of fabricated OM formulations over commercial SR (C1) and conventional (C2) tablets. Thus, the developed OM tablets of DS are expected to perform therapeutically better as a potential prolonged and controlled release dosage form.

TABLE 2

In vitro release kinetics (analyzed by regression coefficient method) of DS from different batches of OM tablets

Sample no.	Batch no.	Regression coefficient values (r)		
		Higuchi	Zero-order	First order
1	FM1	0.9869	0.9089	0.7969
2	OM1	0.9758	0.9958	0.8277
3	OM2	0.9766	0.9934	0.8392
4	OM3	0.9420	0.9968	0.9039
5	OM4	0.9564	0.9996	0.8886
6	OM5	0.9569	0.9999	0.8749
7	OM6	0.9750	0.9963	0.8400
8	OM7	0.9750	0.9999	0.8856

TABLE 3

In vitro release kinetics (analyzed by Peppas equation) of DS from different batches of OM tablets

Sample no.	Batch no.	k	n	r^2
1	FM1	0.036	1.23	0.9966
2	OM1	0.064	1.09	0.9983
3	OM2	0.830	1.08	0.9984
4	OM3	0.260	0.90	0.9968
5	OM4	0.190	0.94	0.9988
6	OM5	0.120	1.01	0.9997
7	OM6	0.067	1.10	0.9993
8	OM7	0.154	1.00	0.9998

TABLE 4
Bioavailability and pharmacokinetic parameters (mean \pm SD [$n = 6$]) for different fabricated and commercial tablets

Sample no.	Batch no.	Bioavailability and pharmacokinetic parameters					
		C_{\max} ($\mu\text{g/ml}$)	T_{\max} (hr)	AUC_{0-24} ($\mu\text{g}\cdot\text{hr/ml}$)	RB* (%)	RB** (%)	MRT (hr)
1	OM5	0.389 \pm 0.068	4.0 \pm 0.21	5.20 \pm 0.15	113.04	144.44	11.86
2	OM7	0.342 \pm 0.069	6.0 \pm 0.18	5.70 \pm 0.26	123.64	158.33	10.48
3	C1	0.501 \pm 0.054	4.0 \pm 0.46	4.61 \pm 0.28	100.00	128.19	8.63
4	C2	0.781 \pm 0.081	2.0 \pm 0.49	3.60 \pm 0.28	78.00	100.00	3.71
5	FM1	0.405 \pm 0.089	4.0 \pm 0.27	5.24 \pm 0.19	113.58	145.61	10.19

C_{\max} = maximum plasma concentration; T_{\max} = time to attain C_{\max} ; AUC = area under the curve; RB = relative bioavailability; RB* = with reference to C1 (Voveran-SR); RB** = with reference to C2 (Voveran-Conventional); MRT = mean residence time.

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