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Investigations on Osmotic Matrix Tablets as Controlled Delivery Systems of Ketorolac Tromethamine

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Abstract

The study was done with an objective to achieve a potential sustained and controlled release oral delivery system of a drug, ketorolac tromethamine (KT). Osmotic matrix (OM) tablets, a hybrid system combining both matrix and reservoir properties, of KT were prepared by partially coating the swellable matrix tablets with cellulose acetate film and were evaluated for the physical characteristics and *in vitro* drug release. Formulation variables included the presence or absence of different types and concentrations of canalising agents in the coating film. The surface characteristics of the film were studied by SEM analysis. The drug release data were analysed by regression analysis and Peppas equation. The observation of the results indicated more linear and controlled drug release profiles from OM tablets being less dependent on hydrodynamic conditions of the dissolution medium, than from the matrix tablet. It was concluded that the osmotic effect of the partially permselective coated osmotic matrix systems contributed positively towards achieving more linear drug release profiles in comparison to swellable matrix tablet.

Keywords: Ketorolac tromethamine; NSAID; osmotic matrix tablets; controlled drug delivery.

Introduction

Swelling controlled release systems (Colombo *et al.*, 1992) are commonly used in development of oral sustained release dosage forms and the most preferred polymer is hydroxypropylmethylcellulose (HPMC). Whether the matrix releases drug via swelling control or erosion (or both), it is not possible always to achieve a zero-order release from such systems (Danckwerts, 1994). A possible means of altering the release kinetics from matrix systems is to alter the geometry of the matrix, otherwise it mostly follows Higuchi kinetics (Higuchi, 1962; Higuchi, 1963) and also gets affected by the environmental conditions of gastrointestinal tract (g.i.t).

Moreover, though osmotically controlled drug delivery systems are capable of combating these problems (Theeuwes, 1975; Ramadan and Tawashi, 1987; Jensen *et al.*, 1995), but defects in their membrane structure during coating can affect adversely and may result in loss of control over drug release (Bettini *et al.*, 1996). Thus, to avoid such problems, partial permselective coating of matrix systems with cellulose acetate had been worked out (Bettini

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et al., 1996; Catellani *et al.*, 1998), combining the properties of reservoir and matrix systems both, containing almost half portion of swellable core in impermeable cup, which resisted pressure of HPMC relaxation, and thus drug release kinetics is changed due to differences in the development of swollen releasing area. However, change in permeability of cup by addition of increasing amounts of water soluble polymer in the film, drug release kinetics may involve the osmotic contribution of the matrix systems also, in addition to drug delivery by polymer relaxation/diffusion mechanisms, which may contribute to more linearity of drug release profiles being independent on hydrodynamic conditions of the g.i.t.

KT is a non-steroidal agent with potent analgesic and moderate anti-inflammatory activity and is reported to produce high incidences of gastrointestinal side effects (Gordon *et al.*, 1995; Genc *et al.*, 1997) if administered as conventional dosage forms. Present investigation is, therefore, aimed with the development of sustained (SR) and controlled release (CR) product of KT as osmotic matrix (OM) tablets which is expected to reduce the various complications of this drug in addition to improvement of patient compliance due to reduced frequency of dosing. Moreover, the objective of the study also includes the investigations of the various mechanisms, specifically osmotic contribution, involved in overall drug delivery from OM systems. The release kinetics were studied using regression analysis (Sankar *et al.*, 2001) and Peppas equation (Peppas and Franson, 1983).

Materials and Methods

Materials: KT was obtained as a gift sample from Dr. Reddy's Laboratories (Hyderabad, India). HPMC and cellulose acetate (CA) from S.D. Fine Chemicals Ltd. (Mumbai); polyethyleneglycol 400 (PEG 400) from Glaxo Ltd. (Mumbai) and triacetin from Loba Chemie (Mumbai, India) were purchased. All other chemicals used were of analytical reagent grade.

Methods

Preparation of matrix tablets: Swellable matrix tablets (M) were prepared using KT and HPMC in 1:5 ratio (Table 1) and 1% w/w of magnesium stearate as a lubricant. The ingredients were passed through sieve No. 80, blended uniformly and compressed on a Manesty E_2 tabletting machine using 10 mm standard flat surface punch to obtain tablets of hardness 7.8 kg/cm^2. Each batch size of the tablets was 200 with individual tablet weighing around 120 mg.

Preparation of osmotic matrix tablets: The composition of OM tablets and coating solutions are shown in Table 1. The osmotic matrix tablets were prepared by partially coating one of the base and the lateral surface of the matrix tablets (prepared as above) using an aspirator (pipette connected to a vacuum pump that picks up the tablet from one side) by carefully dipping the tablet in coating solution. The dipped matrix was manually rotated till complete coating is achieved. While dipping the tablet the volume of the coating solution, the time for dipping and number of rotations were kept constant for all the batches in order to achieve uniform coating. Further, the solvent was evaporated at 30°C after 48 hours of the coating. PEG 400 and triacetin were used in the coating solution as canalising agents to modify the permeability of the coating membrane.

All the fabricated tablets were evaluated for thickness, weight variation, hardness and drug content uniformity as USP XXI monograph. Thickness of the coating membrane was determined with a screw gauge after peeling the membrane. Surface characteristics of the coating membrane recovered from the matrices before and after dissolution were studied at 5 kV by scanning electron microscopic (Model 840A, Olympus) analysis on samples mounted on metal stubs coated with silver to a thickness of 300-500 Å.

Table 1. Composition of different batches of KT matrix and osmotic matrix tablets

S. No.	Ingredients (quantity per tablet)	Batch No.					
		M	OM1	OM2	OM3	OM4	OM5
1.	KT (mg)	20	20	20	20	20	20
2.	HPMC (mg)	100	100	100	100	100	100
3.	Magnesium stearate (% w/w)	1	1	1	1	1	1
	Nature of coating	UC	PP	PP	PP	PP	PP
	Composition of coating solutions						
1.	Cellulose acetate (g)	-	6.6	6.6	6.6	6.6	6.6
2.	PEG 400 (% w/w)*	-	0	33	66	-	-
3.	Triacetin (% w/w)*	-	-	-	-	33	66
4.	MC:EA:CV (3:1:1) (ml) (quantity sufficient to)	-	100	100	100	100	100

MC - Methylene chloride; EA - Ethyl acetate; CV - Cellosolve (2-Ethoxy ethanol); PP - Partial permselective; UC - Uncoated; * % w/w in reference to CA; M - Matrix tablet; OM - Osmotic matrix tablets; - not present.

In vitro drug release study: All the fabricated matrix and OM tablets were evaluated *in vitro*, in triplicate, on an USP XXI dissolution apparatus II for 8 hours using 900 ml of distilled water maintained at 37 ± 0.1°C and stirred at 100 rpm. In order to investigate the effect of osmotic contribution on drug release kinetics, some of the *in vitro* evaluations were done in aqueous solution of either 0.05 M or 0.5 M sodium chloride. Some of the *in vitro* studies were also conducted in simulated gastric fluid (SGF) used as dissolution medium i.e., pH 1.2 for 2 hours followed by pH 6.8 for 6 hours, to investigate the environmental effect of g.i.t. on drug release kinetics from the OM tablets. Further to study the effect of gut motility on drug release, some *in vitro* studies in distilled water were done at a higher speed (150 rpm) of agitation of the dissolution medium. 5 ml samples withdrawn at different time intervals were analysed on a Jasco UV/VIS Spectrophotometer (model 7800) at 321 nm after suitable dilutions. In case of SGF, KT in the samples was analysed at 318 nm in pH 1.2 and at 321 nm in pH 6.8 media. The volume of withdrawn samples were always replaced with the same

volume of prewarmed (37 ± 0.1°C) fresh dissolution medium. Actual drug content in the samples was read from the respective calibration curves.

Results and Discussion

The variations in thickness, hardness, weight and drug content uniformity values for all the batches of fabricated tablets, shown in Table 2, were found within the official limits (in reference to average values of each parameter) (U.S.P., 1985). SEM analysis of the coating film recovered before and after dissolution was done to determine the surface characteristics and porosity. The observation of the photomicrographs indicated that the film containing triacetin (Fig. 1a) was smoother in surface than the film containing PEG 400 (Fig. 2a) showing non-uniform surface with shear marks. The same films when observed after dissolution exhibited more pores in film containing PEG 400 (Fig. 2b) than the film containing triacetin (Fig. 1b), and is attributed to PEG 400 being highly hydrophilic in nature dissolves easily in the dissolution medium and results in formation of more pores in the film than the film containing triacetin.

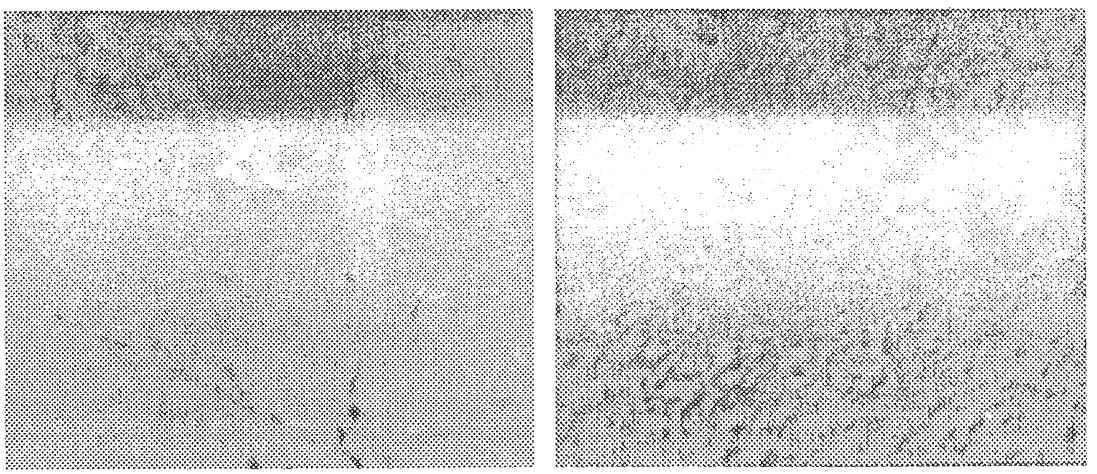
Table 2. Data (Mean ± S.D.) for different parameters studied on different batches of KT tablets

S. No.	Parameters Evaluated	Batch No.					
		M	OM1	OM2	OM3	OM4	OM5
1.	Hardness (kg/cm^2) (n = 10)	7.8 ± 0.45	7.8 ± 0.46	7.8 ± 0.46	7.8 ± 0.42	7.8 ± 0.44	7.8 ± 0.46
2.	Thickness before coating (mm) (n = 10)	2.38 ± 0.04	2.40 ± 0.03	2.39 ± 0.03	2.38 ± 0.04	2.38 ± 0.04	2.40 ± 0.03
3.	Weight variation (mg) (n = 20)	121.4 ± 2.60	122.0 ± 3.20	123.2 ± 1.20	121.2 ± 3.40	120.4 ± 1.40	122.5 ± 1.50
4.	Coating thickness (μm) (n = 10)	-	105 ± 0.12	108 ± 0.10	110 ± 0.20	100 ± 0.98	102 ± 0.40
5.	Percent drug content (%) (n = 10)	99.34 ± 1.82	101.79 ± 1.60	99.99 ± 2.10	99.40 ± 1.60	99.86 ± 0.96	99.69 ± 1.20

- Uncoated

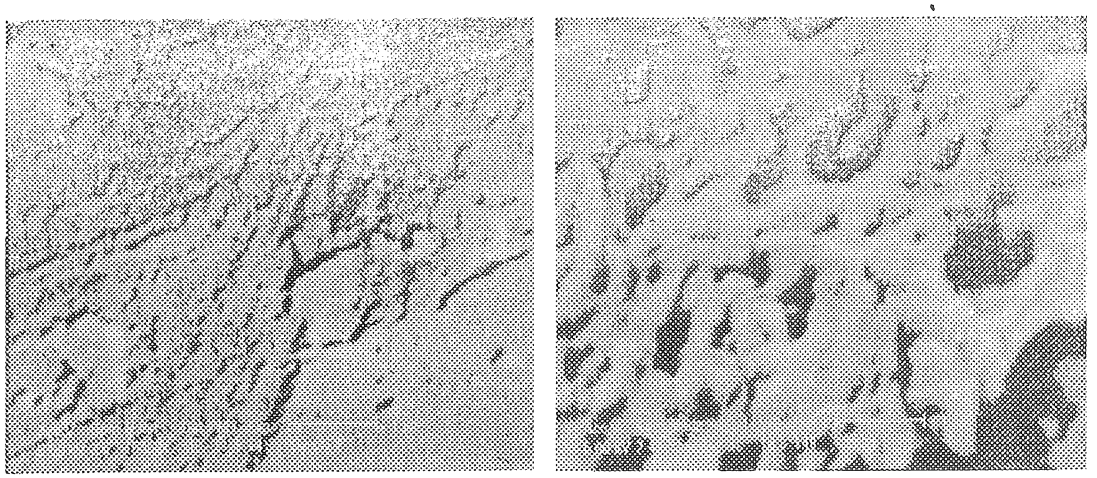
Drug release profiles of different batches of matrix and OM tablets are shown in Fig. 3. It has been observed that the OM tablets exhibited more linear drug release profiles than the matrix tablet (M). Further, the type of canalising agents and their percentage influenced the rate and extent of drug release to an appreciable extent. OM tablets containing PEG 400 in coating films (OM2 and OM3) provided higher rate and extent of drug release than the tablets containing triacetin in the film (OM4 and OM5). The change in drug release kinetics from the various OM tablets is attributed to the change in the permeability of the film forming cup

around half of the tablet due to presence of different types of canalising agents with varied amounts. The mechanisms governing drug release from OM tablets are attributed to drug diffusion (a) through uncoated gel layer (b) through the gel layer due to osmotic pressure inside the system and (c) through the pores of the film generated by the dissolution of PEG 400 and triacetin incorporated in the film. The third possible mechanism is evident from the observations that the OM tablets containing 66% PEG (OM3) provided higher rate and extent of drug release than the films containing 33% PEG (OM2) and no PEG (OM1). Similar results were also observed for the coating film containing triacetin.



(a) (b)

Fig. 1. Scanning electron photomicrographs of the film CA + 33% Triacetin before (a) and after (b) dissolution experiment.



(a) (b)

Fig. 2. Scanning electron photomicrographs of the film CA + 33% PEG 400 before (a) and after (b) dissolution experiment.

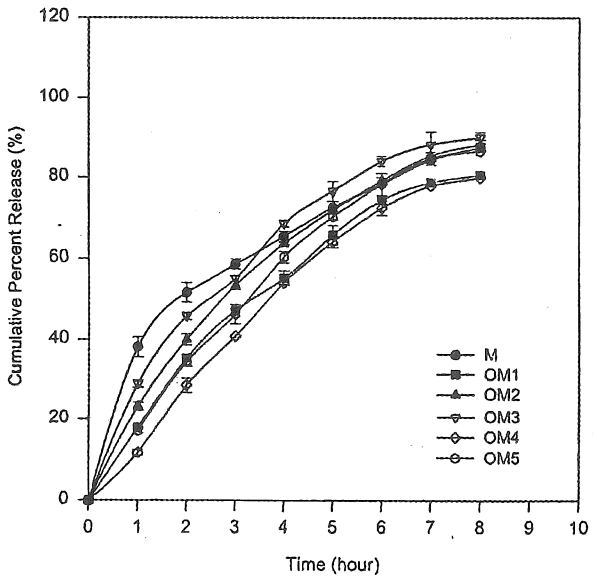


Fig. 3. *In-vitro* release profiles of KT from different batches of matrix and osmotic matrix tablets in distilled water. Bars represent ± S.D. (n = 3).

The effect of osmotic contribution on drug release kinetics was studied by carrying out dissolution experiments in aqueous sodium chloride solutions, whose osmolarity was varied by adding increasing amounts (0.05M and 0.5M) of sodium chloride in distilled water used as dissolution medium. The drug release profiles shown in Figs. 4-6 compare the kinetics of KT release in distilled water versus sodium chloride solutions from the OM tablets coated with partial permselective films using 0% (OM1), 33% (OM2) and 66% (OM3) w/w PEG 400. It was observed that batch OM3 having more permeable film (due to presence of 66% PEG 400) did not show any significant change in drug release profiles (Fig. 6) in dissolution media of variable osmolarity, and is attributed to least osmotic contribution of the system if the film is highly permeable (Catellani *et al.*, 1998). Batch OM1 with 0% canalising agent (PEG 400) having almost impermeable coating also showed (Fig. 4) negligible effect of osmolarity of the dissolution media on drug release. However batch OM2 containing 33% PEG 400 in the film, behaving as a semi-permeable membrane, showed (Fig. 5) significant decrease in drug release rates with an increase in the osmolarity of the dissolution media. This may be because of decrease in osmotic gradient across the tablet membrane when osmolarity of the media is increased by incorporation of sodium chloride. It may be argued that the decrease in drug release may be due to possible reduction of drug solubility in the medium and also due to polymer swelling reduction as a consequence of the increased ionic strength of the medium (Colombo *et al.*, 1985). But in one of our earlier solubility investigations of KT in different molar solutions of sodium chloride, it was found that there is negligible effect of different concentration of sodium chloride on KT solubility. Thus,

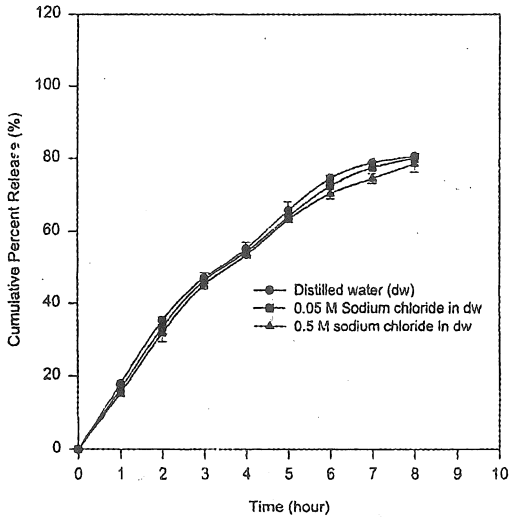


Fig. 4. *In-vitro* release profiles showing the effect of different osmolarity of dissolution medium on KT release from osmotic matrix tablet OM1. Bars represent ± S.D. (n = 3).

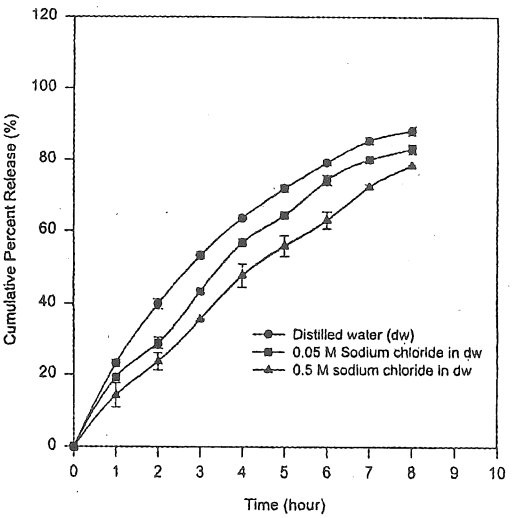


Fig. 5.*In-vitro* release profiles showing the effect of different osmolarity of dissolution medium on KT release from osmotic matrix tablet OM2. Bars represent ± S.D. (n = 3).

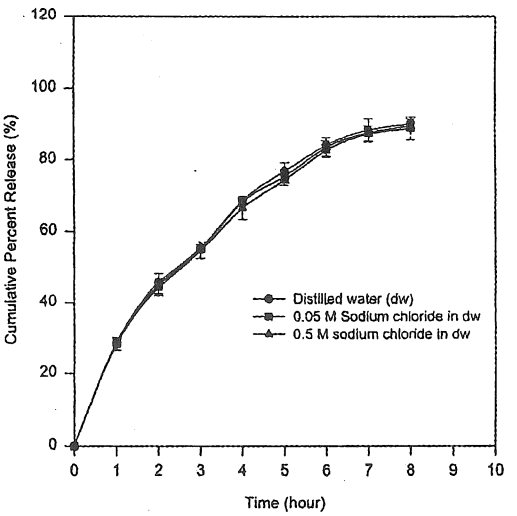


Fig. 6. *In-vitro* release profiles showing the effect of different osmolarity of dissolution medium on KT release from osmotic matrix tablet OM3. Bars represent ± S.D. (n = 3).

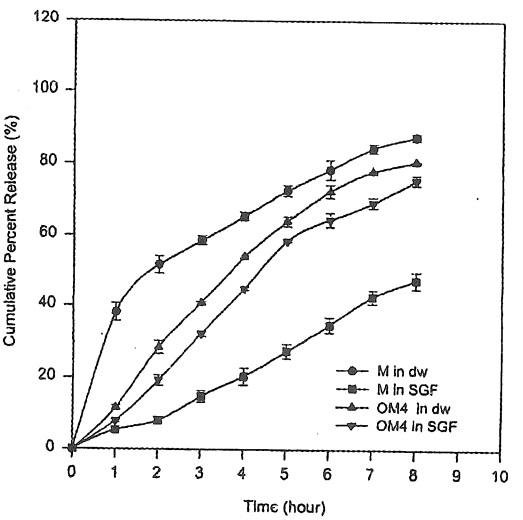


Fig. 7. *In-vitro* release profiles showing the effect of the type of dissolution medium on KT release from matrix (M) and osmotic matrix OM4 tablets. Bars represent ± S.D. (n = 3).dw is distilled water, SGF is simulated gastric fluid (pH 1.2 for first 2 hours and pH 6.8 for next 6 hours).

reduction of drug release observed in Fig. 5 in case of batch OM2 with semi-permeable cup was attributed mainly due to suppression of the osmotic contribution.

The drug release rates of diffusion controlled system in biological fluids is affected by variable pH and hydrodynamics conditions of g.i.t. (Lee and Robinson, 1987). In order to study the effect of pH conditions of g.i.t. on drug release kinetics, the drug release profiles for matrix (M) and OM tablet (OM4) in distilled water and SGF are compared in Fig. 7. The rate and extent of drug release from OM4 in distilled water and SGF were almost similar, whereas the matrix tablet exhibited large variation in drug release in distilled water than in SGF. Further, to investigate the effect of gut motility on drug release kinetics, release profiles for matrix tablet (M) were compared with OM tablet (OM2) at two different intensities of agitation (100 and 150 rpm) of dissolution media. Profiles shown in Fig. 8 clearly indicated the least effect of agitation on drug release from OM tablet than from the matrix tablet and is attributed to osmotic contribution to drug release from OM tablets. These observations clearly demonstrate the negligible effect of hydrodynamic conditions of g.i.t. on drug release kinetics from permselective membrane coated osmotic matrix tablets.

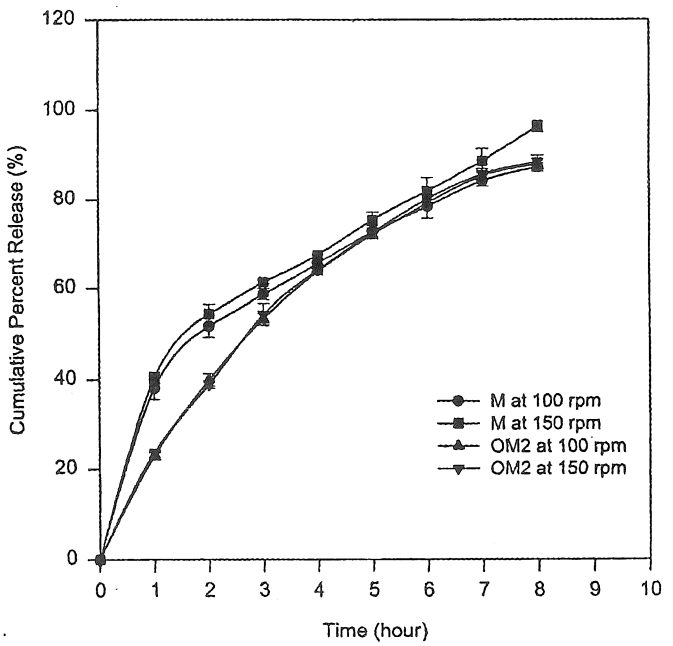


Fig. 8. *In-vitro* release profiles showing the effect of agitation intensity of dissolution medium on KT release from matrix (M) and osmotic matrix (OM2) tablets in distilled water. Bars represent ± S.D. (n = 3).

Based on the findings, it was concluded that partial permselective membrane coated formulations (OM tablets) led to improvement in linearity of drug release profiles as compared to matrix tablets. The drug delivery data analysed by regression analysis revealed

the Higuchi pattern of drug release from all the fabricated tablets (Table 3). However, n values (Table 3) calculated using Peppas equatio n ranged from 0.75 to 0.85 for OM tablets as compared to 0.68 for matrix tablet, indicating advancement towards zero-order drug delivery from the OM tablets. Further, it was concluded that the permselective semi-permeable cup behaved in part as osmotic system that led to least or negligible dependency of drug release on hydrodynamic conditions of the dissolution media and thus the gastrointestinal tract.

Table 3. Drug release kinetics for different batches of KT matrix and osmotic matrix tablets

S. No.	Batch No.	r values (by Regression Analysis)			Diffusional exponent n (by Peppas equation)*
		Higuchi	Zero order	First order	
1.	M	0.9951	0.9248	0.6874	0.68
2.	OM1	0.9896	0.9721	0.7036	0.80
3.	OM2	0.9946	0.9665	0.7547	0.78
4.	OM3	0.9958	0.9531	0.7307	0.75
5.	OM4	0.9845	0.9823	0.8205	0.85
6.	OM5	0.9850	0.9802	0.7899	0.82

*Peppas equation - $M_t/M_\infty = Kt^n$, where M_t/M_∞ = fractional drug release into the dissolution medium; K = constant incorporating properties of the macro-molecular polymeric system and the drug; n = diffusional exponent characterizing drug transport mechanism [$n \leq 0.5$ indicates quasi-Fickian diffusion, $n > 0.5$ anomalous non-Fickian diffusion, $n \approx 1$, zero order kinetics and $n > 1$; Pseudo-case-II transport mechanism].

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