

**FORMULATION DEVELOPMENT AND EVALUATION OF MR MULTI UNIT
OSMOTIC SYSTEM OF DICLOFENAC****R. Sunitha*¹, S. Madhavi Latha², M. Sowjanya³ and J. Vasavi⁴**¹A.M.Reddy Memorial College of Pharmacy,Narasaraopet, Guntur (Dt), Andhra Pradesh, India.²Aditya College of pharmacy, Surampalem, Andhra Pradesh.^{3,4}Malineni Perumallu Educational Society's Group Of Institutions,Guntur, Andhra Pradesh.***Corresponding Author: R. Sunitha**

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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 porogenic 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**

Oral drug delivery is the most preferred and convenient choice as the oral route provides maximum active surface area among all drug delivery system for administration of various drugs.^[1] In conventional oral drug delivery systems, there is little or no control over release of the drug and effective concentration at the target site can be achieved by irregular administration of excessive doses.

This kind of dosing pattern result is fluctuation in therapeutic plasma concentrations, leading to marked side effects in some cases. Moreover, the rate and extent of absorption of drug from conventional dosage forms may vary greatly depending on factors such as presence of excipients, physicochemical properties of the drug, various physiological factors such as presence or absence of food, pH of gastro intestinal tract, gastro intestinal motility and so on. Uncontrolled rapid release of drug may cause local gastro intestinal or systemic toxicity. Hence, various approaches are made in designing the formulations, which will overcome the disadvantages of

conventional dosage forms, which include sustained/controlled drug delivery system. There are three main classes of controlled-release drug delivery system; transdermal, intravenous, and oral systems.^[2] Oral osmotically controlled release (CR) delivery systems exploit osmotic pressure for controlled delivery of active agents.^[3] Drug release from these systems is independent of pH and other physiological parameters to a large extent and it is possible to modulate the release characteristics by optimizing the properties of drug and system.^[2] Alza Corporation R of USA was the first to develop an oral osmotic pump.

Principle and basic concept of osmotic drug delivery system

It is based on the principle of osmotic pressure. Osmotic pressure is a colligative property, which is dependent on concentration of solute that contributes to osmotic pressure. Solutions of different concentrations having the same solvent and solute system show an osmotic pressure proportionate to their concentrations. Thus a constant osmotic pressure, and thereby a constant influx

of water can be achieved by an osmotic drug delivery system. This results a constant zero order release rate of drug. The rate of drug release from osmotic pump depends on the osmotic pressure of the core and the drug solubility; hence, these systems are suitable for delivery of drugs with moderate water solubility.

Osmotic pressure is proportionate to temperature and concentration and the relationship can be described by following equation.

$$\pi = n_2 RT$$

Where, π = osmotic coefficient

n_2 = molar concentration of solute in the solution

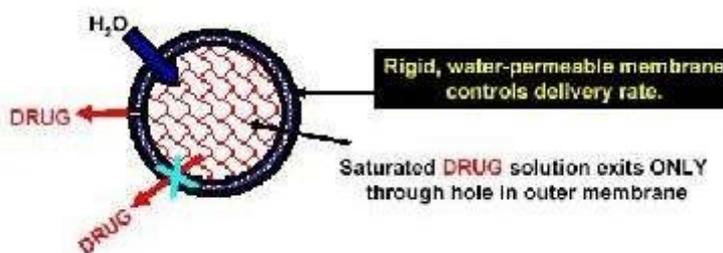
R = gas constant

T = Absolute temperature.^[3]

Basic formulation concept

Osmotic drug delivery devices are composed of an osmotically active drug core, which is surrounded by a rate controlling semipermeable membrane. Osmotic drug delivery system differ from diffusion based systems in that the way of delivery of the active agents is driven by an osmotic gradient somewhat than the concentration of drug in the device. In the most simple type of osmosis-controlled drug release the following sequence of steps is involved in the release process:

1. Osmotic transport of liquid in to release unit.
2. Dissolution of drug within the release unit.
3. Convecting transport of a saturated drug solution by pumping of the solution through a single orifice through pores in the semi permeable membrane.^[4]



Limitations

- ❖ Mfg. feasibility e.g. orifice
- ❖ Toxicity due to dose dumping

Controlled Porosity Osmotic Pump: Delivery orifice



Coating containing pore forming agent

Aqueous Environment
→



Pore formation and subsequent drug release

The delivery of active agent from oral osmotic systems is controlled by the influx of solvent through the semi-permeable membrane, which in turn transfers the active agent to the outside environment. Considering the relationship between osmotic pressure and chemical potential, the rate of water transport through the membrane can be

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.

Osmotic Pump

Osmosis Spontaneous movement of a solvent from a solution of **lower** solute concentration to a solution of **higher** solute concentration across a semipermeable membrane.

is formed by the incorporation of a leachable component in the coating, Cellulose acetate as semi permeable membrane.

Eudragit L 100-55 as a pore forming agent, which has pH dependent solubility.

Multi unit system

Multiplicity of small discrete units, each exhibiting desired Characteristics.

Advantages

- Low risk of dose dumping.
- Distribution throughout GIT
- Short gastric residence time
- Less dependent on gastric emptying - less inter and intra-subject variability

Aim & Objective

Aim

Development of MR formulations based on principles of controlled porosity osmotic pumps & multi-unit systems.

Objectives

Multiunit MR osmotic tablets formulation.

Investigate the effect of formulation variables- solubilizer, pore former, coating thickness and simulating dissolution condition-hydrodynamic conditions & pH. Drug release mechanism evaluation. Drug release kinetics evaluation

RESULTS AND DISCUSSION

The various physical parameters evaluated for all fabricated formulations were found within official 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.

Pre formulation studies

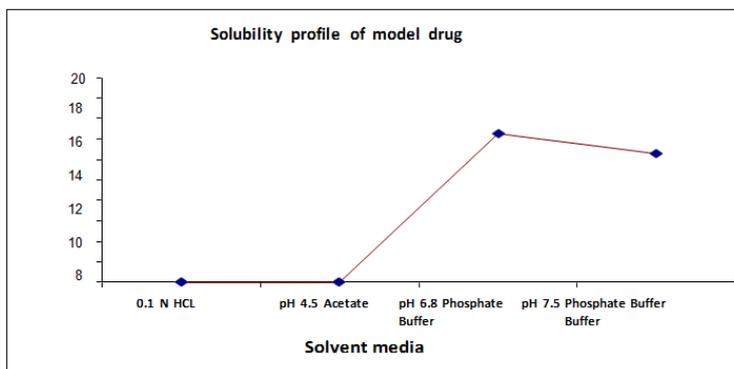


Fig. 01: Solubility studies.

Table 1: solubility studies.

Medium	Solubility (mg/ml)
0.1 N HCL	0.0016
pH 4.5 Acetate Buffer	0.0074
pH 6.8 Phosphate Buffer	14.50
pH 7.5 Phosphate Buffer	12.60

Analytical Method Development

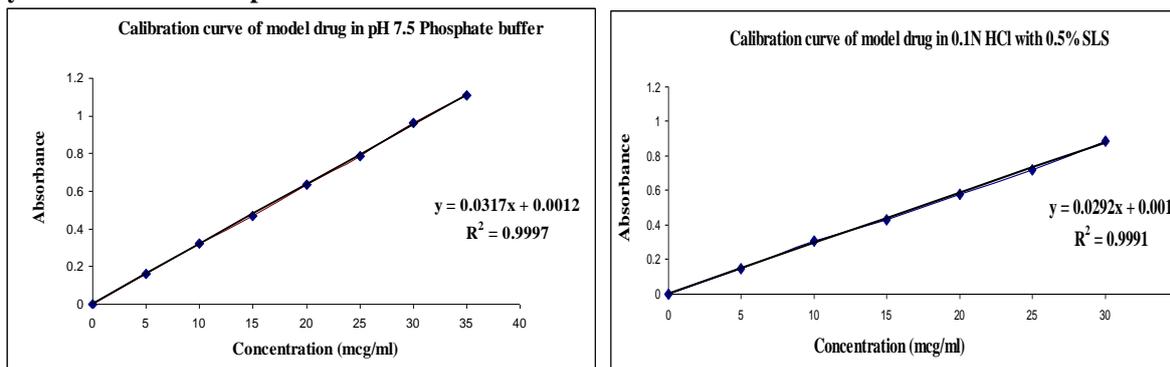


Fig.02: Calibration curves.

Table 2: Process parameters for coating.

Parameter	Set value
Inlet temperature (°C)	40-45
Outlet temperature (°C)	30-35
Atomization Pressure (MPa)	0.1
Spray rate (ml/min)	5-6
Speed of the pan (rpm)	10-12

Table 3: Effect of solubility modifier on drug release.

S. No	Ingredient	Function	Formulation (mg/unit)	
			Without TMT (F1)	With TMT (F2)
1	Model drug	API	75	75
2	Tromethamine	Solubility modifier	0	260 (65%)
3	Sodium chloride	Osmogen	28	28
4	Mannitol	Filler	285	25
5	PVP K-30	Binder	5	5
6	Aerosil 200	Glidant	1	1
7	Talc	Anti-adherent	2	2
8	Magnesium stearate	Lubricant	4	4
	Core tablet weight		400 mg	400 mg
	SPM COATING			
9	Cellulose acetate	Semipermeable membrane	43.1	43.1
10	Eudragit L 100-55	Pore former	8.6 (20% of CA)	8.6
11	Triethyl citrate	Plasticizer	4.3 (10% of CA)	4.3
12	Acetone	Solvent	q.s	q.s
13	Isopropyl alcohol	Solvent	q.s	q.s
	Weight build up (%)		14	14
	Coated tablet weight		456 mg	456 mg

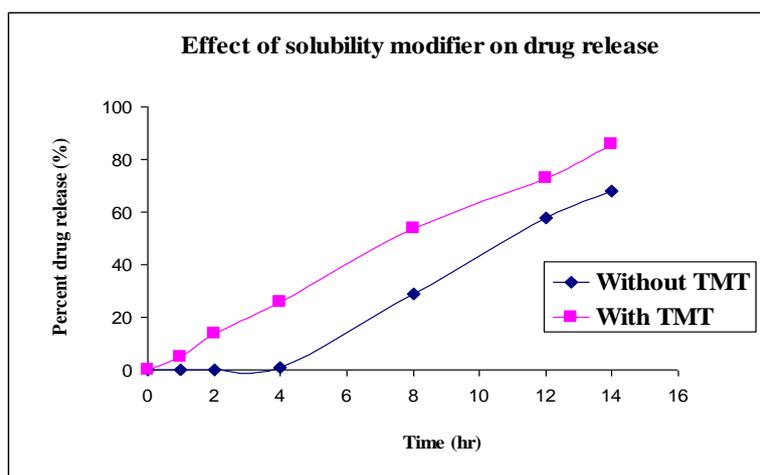


Fig.03: Effect of solubility modified on drug release.

Table 4: Effect of functional coat weight build up on drug release.

S.No	Ingredient	Function	F3	F4	F5
1	Model drug	API	75	75	75
2	Tromethamine	Solubility modifier	260	260	260
3	Sodium chloride	Osmogen	28	28	28
4	Mannitol	Filler	25	25	25
5	PVP K-30	Binder	5	5	5
6	Aerosil 200	Glidant	1	1	1
7	Talc	Anti-adherent	2	2	2
8	Magnesium stearate	Lubricant	4	4	4
	Core tablet weight		400 mg	400 mg	400 mg
	SPM COATING				

9	Cellulose acetate	Semipermeable membrane	21.5	43.1	61.4
10	Eudragit L 100-55	Pore former	4.3 (20% of CA)	8.6	12.4
11	Triethyl citrate	Plasticizer	2.1 (10% of CA)	4.3	6.2
12	Acetone	Solvent	q.s	q.s	q.s
13	Isopropyl alcohol	Solvent	q.s	q.s	q.s
	Weight build up (%)		7	14	20
	Coated tablet weight		428 mg	456 mg	480 mg

Each capsule contains eight mini tablets each of 50 mg eight.

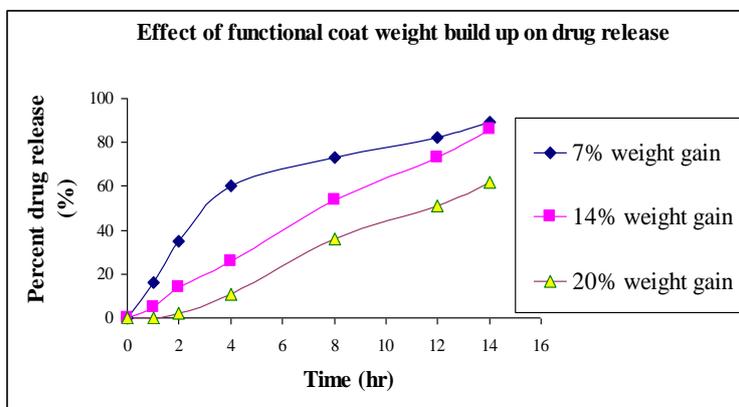


Fig. 4: Effect of functional coat weight build up on drug release.

Time (hr)	Percent drug release		
	7%	14%	20%
1	16	5	0
2	35	14	2
4	60	26	11
8	73	54	36
12	82	73	51
14	89	86	62

Coating thickness increases the time for release media penetration through semipermeable membrane which might increase the lag time.

Table 5: Effect of level of pore former on drug release.

S.No	Ingredient	Function	Formulation		
			F6	F7	F8
1	Model drug	API	75	75	75
2	Tromethamine	Solubility modifier	260	260	260
3	Sodium chloride	Osmogen	28	28	28
4	Mannitol	Filler	25	25	25
5	PVP K-30	Binder	5	5	5
6	Aerosil 200	Glidant	1	1	1
7	Talc	Anti-adherent	2	2	2
8	Magnesium stearate	Lubricant	4	4	4
	Core tablet weight		400 mg	400 mg	400 mg
	SPM COATING				
9	Cellulose acetate	Semipermeable membrane	46.8	43.1	37.4
10	Eudragit L 100-55	Pore former	4.6 (10% of CA)	8.6 (20% of CA)	14.9 (40% of CA)
11	Triethyl citrate	Plasticizer	4.6 (10% of CA)	4.3 (10% of CA)	3.7 (10% of CA)
12	Acetone	Solvent	q.s	q.s	q.s
13	Isopropyl alcohol	Solvent	q.s	q.s	q.s
	Weight build up (%)		14	14	14
	Coated tablet weight		456 mg	456 mg	456 mg

Each capsule contains eight mini tablets each of 50 mg weight.

Effect of level of pore former on drug release

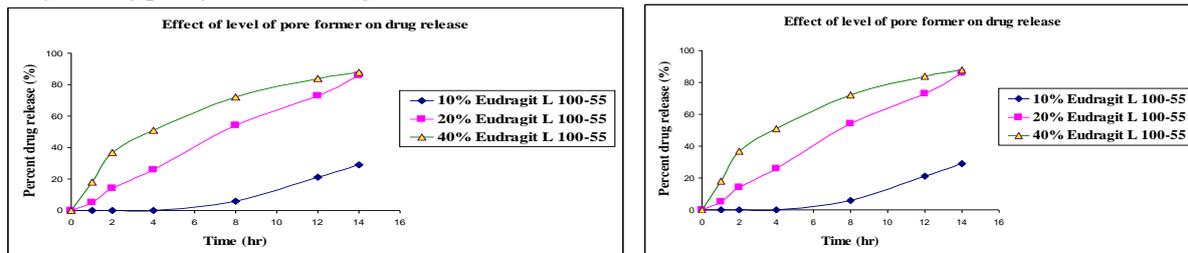


Fig.06: Effect of level of pore former on drug release.

Time (hr)	Percent drug release		
	10%	20%	40%
1	0	5	18
2	0	14	37
4	0	26	51
8	6	54	72
12	21	73	84
14	29	86	88

As the level of pore former increases, the membrane becomes more porous after coming into contact with the aqueous environment, resulting in faster drug release.

Performance of the formulation in simulated dissolution conditions

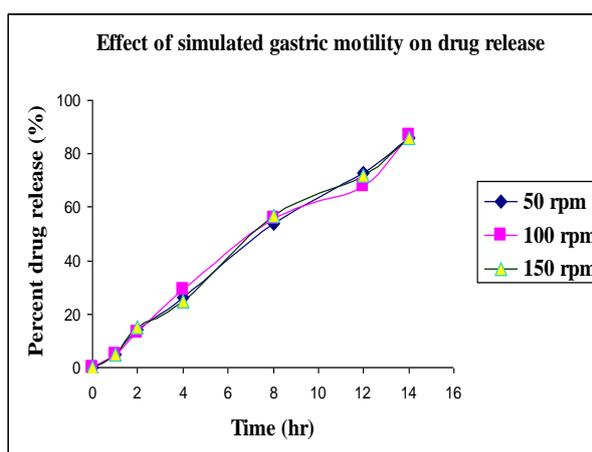
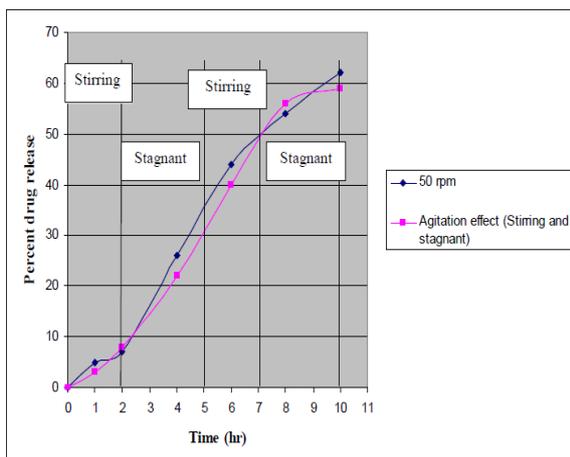
1. Effect of agitational intensity
2. Effect of gastrointestinal pH

Effect of agitational intensity on drug release

- Rotational speeds - 50, 100, and 150 rpm

- In another experiment, stirred and stagnant conditions were induced in a single run. The rotational speed was kept at 50 rpm (stirred conditions), which, however, was stopped intermittently to induce the stagnant conditions. The protocol used was:

- Stirred conditions for first 3 h (0–3 h)
- Stagnant conditions for next 2 h (3–5 h),
- Stirred condition for next 3 h (5–8 h), and
- Stagnant condition for next 2 h (8–10 h).



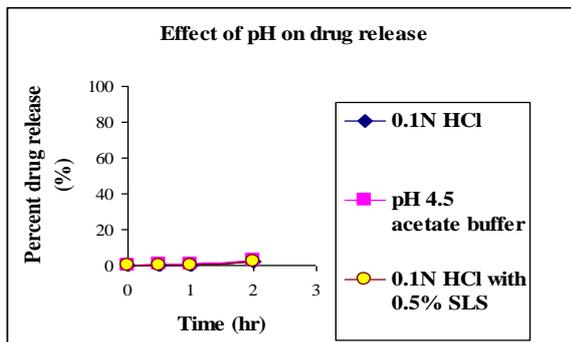
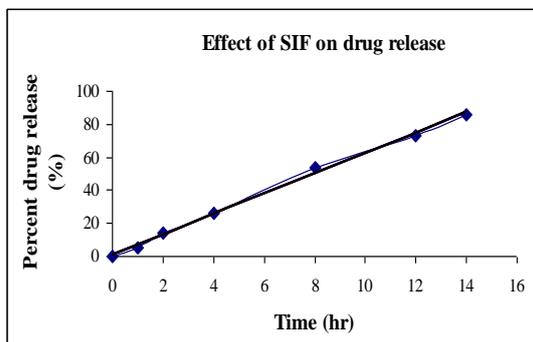
Time (hr)	Percent drug release		
	50 rpm	100 rpm	150 rpm
1	5	5	5
2	14	13	15
4	26	29	25
8	54	56	57
12	73	68	72
14	86	87	86

Release was fairly independent of the agitational intensity of the release media.

Effect of pH on drug release

Release studies were performed in three dissolution media as follows:

- Simulated gastric media (pH 1.2 buffer)
- pH 4.5 acetate buffer
- Simulated intestinal fluid (pH 7.5 phosphate buffer)

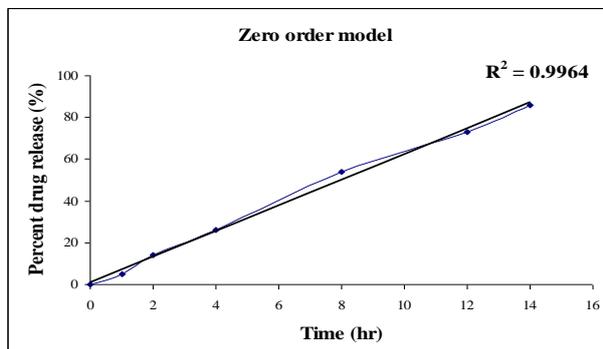
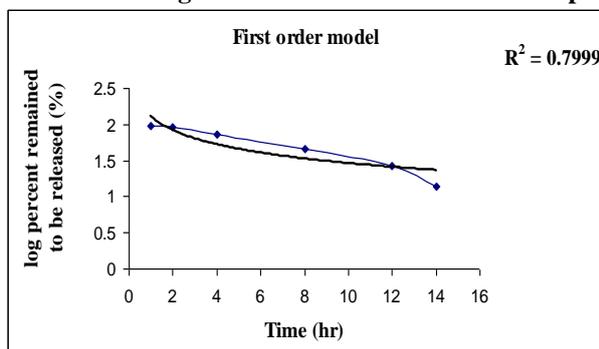


Time (hr)	Percent drug release in pH 7.5 phosphate buffer
1	5
2	14
4	26
8	54
12	73
14	86

Time (hr)	Percent drug release		
	0.1 N HCl	pH 4.5 acetate buffer	0.1 N HCl with 0.5% SLS
0.5	0	1	0
1	0	1	0
2	2	3	2

An insignificant release of drug (less than 5% in 2hrs) in 0.1N HCl with and without SLS, and pH 4.5 acetate buffer. 86% release in 14 hr in pH 7.5 phosphate buffer

Evaluation of Drug Release Kinetics For The Developed Formulations



Formulation	Correlation coefficient (R ²)	
	Zero order	First order
F1	0.9351	0.6444
F2	0.9931	0.7999
F3	0.8451	0.5721
F4	0.8945	0.9072
F5	0.8423	0.9256
F6	0.9612	0.8014
F7	0.9125	0.8548
F8	0.9063	0.8863

CONCLUSION

MR Multiunit osmotic system were prepared from which the release was found to be directly proportional to the level of eudragit L 100-55 as a pore former and inversely related to the membrane weight gain. Lag time in drug release was found to be affected by the TMT in the core formulation and eudragit L 100-55 in the membrane. Zero-order drug release was achieved for 14 hr in SIF with an insignificant release in SGF, independent of agitational intensity, and inversely proportional to the osmotic pressure of the release media, assuring osmotic pumping to be the major mechanism of drug release fairly independent of hydrodynamic conditions of the body. In view of overall results reported in the present study, it may be proposed that MR multiunit osmotic system can be a better drug delivery platform for controlled delivery of candidate drugs.

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