DESIGN AND EVALUATION OF EXTENDED RELEASE TABLETS OF KETOROLAC

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ABSTRACT:

The basic goal of therapy is to achieve a steady state blood or tissue level that is therapeutically effective and non-toxic for an extended period. Sustained release drug delivery systems, with an aim of improved patient compliance, better therapeutic efficacy, less side effects and reduced dosage regimen with less toxicity for treatment for many acute and chronic diseases. Antihypertensive drugs are used for the treatment of hypertension. Losartan has been demonstrated to be superior to previous peptide receptor antagonists and angiotensin converting enzyme (ACE) inhibitors because of its enhanced specificity, selectivity and tolerability. Matrix tablets are very useful in the field of healthcare for sustained release dosage regimen. Ketorolac is a water-soluble drug its release from the matrix is largely dependent on the polymer swelling, drug diffusion and matrix erosion. The concentration of polymer in the sustained release tablet was a key factor in controlling the drug release. Various Extended release formulations were formulated with HPMC K100M, Eudragit (rspo, L100, S100) polymer alone; polyvinyl pyrrolidone as binder and microcrystalline cellulose was used as diluents. When cumulative percentage drug release plotted versus time, it was observed that, for three of the polymers used, an increase in polymer concentration induce a decrease in the release rate.

Key words: Ketorolac, angiotensin converting enzyme (ACE) inhibitors, HPMC K100M, polyvinyl pyrrolidone and microcrystalline cellulose.

INTRODUCTION

Ketorolac is a nonsteroidal anti-inflammatory drug [a pyrrolo-pyrrolo derivative]. It acts by the inhibition of cyclo-oxygenase enzyme that metabolizes arachidonic acid to endoperoxide intermediates & prostaglandins that promote pain[1]. It particularly inhibits PGE_2/PGE_2 alpha. Administration of the trimethamine salt enhances its solubility & facilitates better bioavailability. Intramuscular Ketorolac 30 mg is known to have an analgesic efficacy equivalent to pethidine 100 mg & at least as efficacious as morphine[2]. Over the past 30 years as the expense and complications involved in marketing new drug entities have increased, with concomitant recognition of the therapeutic advantages of extended drug delivery, greater attention has been focused on development of extended or controlled release drug delivery systems. The attractiveness of these dosage forms is due to awareness to toxicity and other properties of drugs when administered or applied by conventional method in the form of tablets, capsules, injectables, ointments, etc. Usually conventional dosage forms produce wide range fluctuation in drug concentration in the blood stream and tissues with consequent undesirable toxicity and poor efficiency. The factors such as repetitive dosing and unpredictable absorption led to the concept of extended drug delivery systems[3]. The design of extended-release delivery system is subjected to several variables of considerable importance. Among these, the properties of the drug, the route of drug delivery, and the disease being treated and length of the therapy have major importance[4]. All extended release products share the common goal of improving drug therapy over that achieved with their non-controlled counter parts. This improvement in drug therapy is represented by several potential advantages of the use of extended release systems are to avoid patient compliance problems, employ less total drug, minimize or eliminate local side effects, minimize drug accumulation with chronic dosing and improve efficiency in treatment[5].

MATERIALS AND METHODS

Table 1. List of excipients used

S. No.	Name of ingredients	Name of the supplier
1	Ketorolac	Sd fine chem. Ltd., Mumbai, India.
2	HPMC K100M	Leo chem. Bangalore, India.
3	Eudragit	Yarrow Chem. PVT, Ltd. Mumbai
4	MCC	Spectrochem Pvt. Ltd. Mumbai.
5	Polyvinylpyrolidone	Alembic Pharma, Baroda, India.
6	Magnesium stearate	RoehmPharma, Germany.
7	Aerosil	MSN Laboretories. Pvt.ltd

8	Isopropyl alcohol	Baris Pharma. Pvt.ltd

Table 2. List of equipments used

S. No.	Equipment	Model/ Make
1	Electronic balance	EasseTeraoka Solutions
2	Bulk density apparatus	Indolabs
3	Standard sieve (20 and 40#)	Labindia, IND.
4	Hot air oven	Labindia, IND.
5	Sixteen punch tablet compression machine	Remek Mini PressII
6	Friability apparatus	Labindia, IND.
7	Hardness tester	Monsanto
8	Varnier caliper	MITUTOYO, Indolabs.
9	USP dissolution test apparatus Type II	Labindia, IND..
10	UV spectrophotometer	Labindia, IND.

Preparation of standard graph of Ketorolac:

Preparation of solutions:

Preparation of 0.1N Hydrochloric acid:
0.1N HCl was prepared according to I.P. A quantity of 8.5 ml of HCl was diluted with fresh distilled water to produce 1000 ml.

Preparation of stock solution of Ketorolac:
Accurately weighed 50 mg of Ketorolac was dissolved in little quantity of distilled water and volume was adjusted to 100 ml with the same to prepare standard solution.

Procedure:
From the stock solution, aliquots of 1, 2, 3, 4, 5, 6, 7, 8 ml were transferred to 100 ml volumetric flasks and final volume was made to 100 ml with 0.01N HCl. Absorbance values of these solutions
were measured against blank (0.01N HCl) at 205.5nm using Shimadzu-1700 UV spectrophotometer.

RESULTS:

Table 3. Flow properties of powder

Formulation No.	Angle of repose (Ɵ)	Bulk density (gm/c)m3)	Tapped density (gm/cm3)	Carr's index (%)
F1	19	0.5144	0.5896	14.61
F2	18	0.5102	0.5952	16.66
F3	16	0.5122	0.5814	14.03
F4	14	0.5208	0.5966	14.60
F5	34	0.5081	0.6053	19.13
F6	17	0.5091	0.5924	16.36
F7	28	0.5197	0.5966	14.79
F8	19	0.5144	0.5980	16.26
F9	18	0.5319	0.6024	13.25

Table 4. Dissolution data of formulations

Time (hours)	Dissolution medium	% Drug release of F1	% Drug release of F2	% Drug release of F3	% Drug release of F4	% Drug release of F5	% Drug release of F6	% Drug release of F7	% Drug release of F8	% Drug release of F9
0	0.1 N HCl	0	0	0	0	0	0	0	0	0
0.5		0.45	0.16	0.69	1.56	1.44	3.59	4.00	0.45	0.05
1		1.38	1.27	1.85	3.47	2.31	7.88	5.21	1.84	1.21
2		2.06	2.66	4.40	7.07	2.83	14.79	6.71	3.41	2.89
3	pH 6.8 Phosphate Buffer	11.06	9.43	17.17	31.10	11.56	40.03	26.19	25.98	22.96
4		20.82	16.32	31.66	48.53	20.88	55.42	44.07	42.79	38.09
5		30.05	23.15	42.41	59.28	30.39	67.35	53.46	57.82	47.38
6		43.39	30.17	53.76	67.66	43.22	75.85	62.78	71.72	71.80

7		47.64	36.74	59.12	69.47	50.77	83.01	66.41	74.69	75.66
8		57.24	43.20	64.40	76.13	59.17	86.79	89.87	91.03	86.94
9		63.72	49.76	70.40	79.07	67.87	93.27	97.30	104.57	95.99
10		75.60	54.20	76.54	85.07	80.83	98.31			

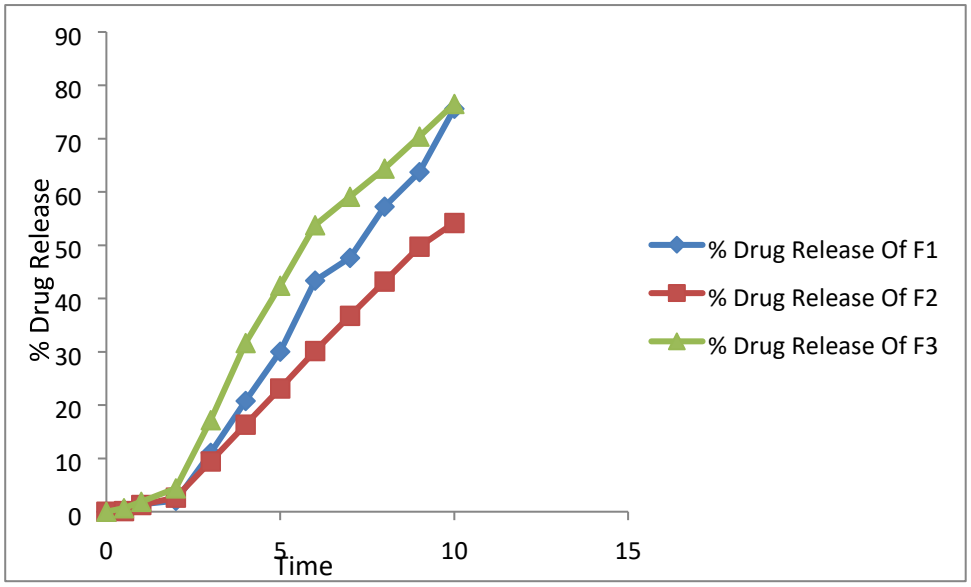

Figure 1. % Drug Release of Formulations (F1, F2, F3)

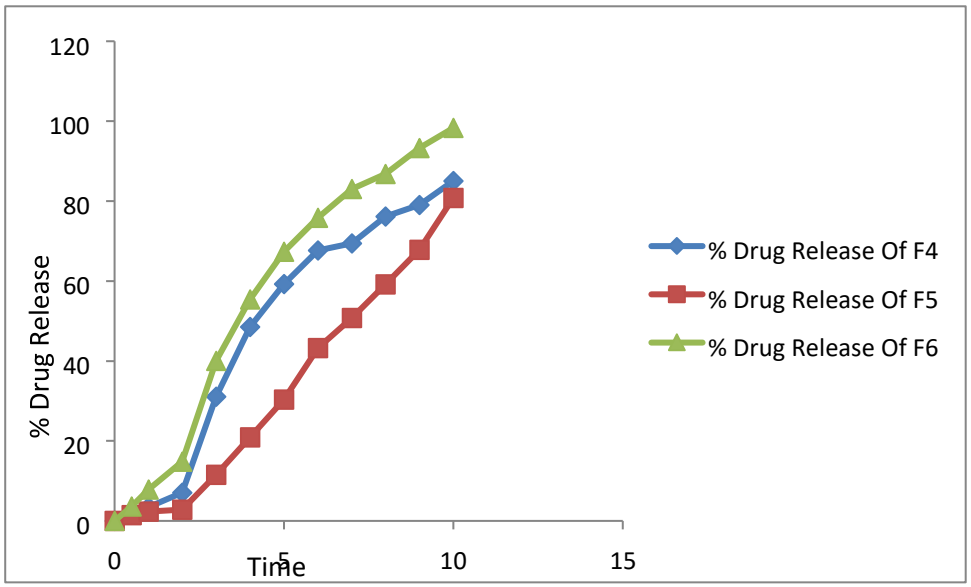

Figure 2. % Drug Release of Formulations (F4, F5, F6)

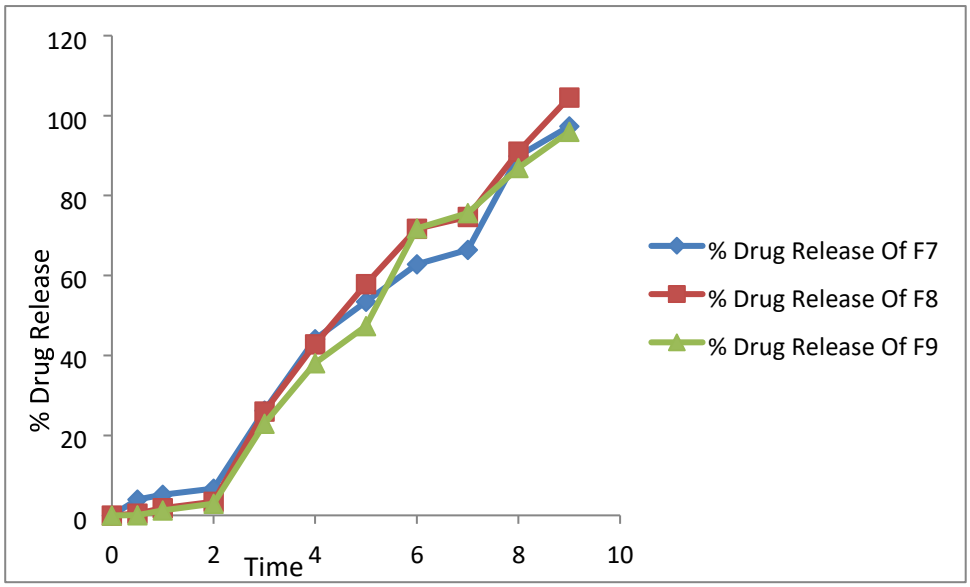

Figure 3. % Drug Release of Formulations (F7, F8, F9)

Kinetics of *In-vitro* Drug Release:

The drug diffusion through most type of polymeric system is often best described by Fickian diffusion (diffusion exponent, n=0.5), but other process in addition to diffusion are important. There is also a relaxation of the polymer chain, which influences the drug release mechanism. This process is described as non- fickian or anomalous diffusion (n=0.5-1.0). Release from initially dry, hydrophilic glassy polymer that swell when added to water and become rubbery, show anomalous diffusion as a result of the rearrangement of macromolecular chain. The thermodynamics state of the polymer and penetrant concentration are responsible for the different type of the diffusion. A third class of diffusion is case-II diffusion (n=1), which is a special case of non- Fickian diffusion. To obtain kinetic parameter of dissolution profile, data were fitted to different kinetic models.

CONCLUSION

The basic goal of therapy is to achieve a steady state blood or tissue level that is therapeutically effective and non-toxic for an extended period. Sustained release drug delivery systems, with an aim of improved patient compliance, better therapeutic efficacy, less side effects and reduced dosage regimen with less toxicity for treatment for many acute and chronic diseases. Antihypertensive drugs are used for the treatment of hypertension. Losartan has been demonstrated to be superior to previous peptide receptor antagonists and angiotensin converting enzyme (ACE) inhibitors because of its enhanced specificity, selectivity and tolerability. Matrix tablets are very useful in the field of healthcare for sustained release dosage regimen. Ketorolac is a water-soluble drug its release from the matrix is largely dependent on the polymer swelling, drug diffusion and matrix erosion. The concentration of polymer in the sustained release tablet was a key factor in controlling the drug release. Various Extended release formulations were formulated with HPMC K100M, Eudragit (rspo, L100, S100) polymer alone; polyvinyl pyrrolidone as binder and microcrystalline cellulose was used as

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