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Original Article

Development and evaluation of sustained release microparticles of Ketorolac Tromethamine

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ABSTRACT

The aim of the present study was to prepare and characterize microparticles for delivery of Ketorolac Tromethamine using EudragitRS100, ethyl cellulose, hydroxy propyl methyl cellulose E5 as polymeric retardant material. Microparticles were prepared by oil-in-oil emulsification method. The effect of process variables on microparticle size, percentage yield, percentage entrapment efficiency and in-vitro release characteristics of microparticles were studied. FT-IR and thin layer chromatography were performed to evaluate interaction between drug and polymer. Morphology of microparticles were characterized by scanning electron microscopy and found that the microparticles were spherical with rough surface. Mechanism of release was found Higuchi and Korsmeyer-Peppas type. This study indicated that the sustained release microparticles of Ketorolac Tromethamine could be prepared successfully by using emulsion solvent evaporation technique.

1. INTRODUCTION

Oral drug administration still remains the route of choice for the majority of clinical application. The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper sight in the body to achieve promptly and then maintain the desired drug concentration. The drug delivery system should deliver drug at a rate detected by the needs of the body over entire period of treatment, controlled or sustained release technology as rapidly emerged over the past three decades, as a new inter disciplinary science that offers novel approaches to the bioactive agents. Controlled drug delivery design involves the application of physical and polymer chemistry to dosage form design, to produces a well characterized and reproducible drug delivery profile. Environmental bioactive active agents to the target environment for an extended period of time controlled release delivery systems can achieve optimum therapeutic response, prolong efficacy and decreased toxicity [1].

Ketorolac Tromethamine is non-steroidal anti-inflammatory drug which has potent analgesic and anti-inflammatory activity due to prostaglandin related effect of drug. This drug, like other NSAID(S) may produce gastrointestinal side effects. After oral administration, it is rapidly eliminated from blood exhibiting a short biological half life of 2.5-5 hrs. NSAID(S) are widely used therapeutic agents that have anti-inflammatory, analgesic and antipyretic activities. NSAID (S) are involved in the suppression of prostaglandin synthesis by inhibiting cyclooxygenase enzymes that catalyze the formation of prostaglandin precursor from arachidonic acid. In unit dosage form gastrointestinal irritation may occur on sudden increase in drug concentration in the GIT [2]. Microparticulate system is the best alternative to overcome this problem. Microparticulate drug delivery has more advantages in comparison to single unit dosage form as they are uniformly distributed through the GIT thereby reducing local concentration of drug. Microparticles are one of the microparticulate delivery system and are prepared to obtain prolonged or controlled drug delivery to improve bioavailability or stability and to target drug to specific sites. Microparticles can also offer advantages like limiting fluctuation within therapeutic range, reducing side effects, decreasing dosing frequency and improving patient compliance [3]. Eudagit polymers are series of acrylate and methacrylate polymers available in different ionic forms. Eudragit Rs100 is referred to as aminomethacrylate copolymer having 5% functional quaternary ammonium groups. Ethyl cellulose, a biocompatible polymer, is extensively studied in encapsulation of material for controlled release of pharmaceuticals. Several

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researchers have investigated the utilization of ethyl cellulose as a polymer to prepare microparticulate delivery systems by solvent evaporation technique. Hydroxy propyl methyl cellulose (HPMC) is one of the cellulose ether commonly used in the formulation of controlled release dosage forms. HPMC offers the advantage of being non-toxic and relatively inexpensive [4].

2. EXPERIMENTAL

Materials

The active ingredient Ketorolac Tromethamine, Eudragit RS100, ethyl cellulose, hydroxy propyl methyl cellulose E5, ethanol, dichloromethane, acetone, light liquid paraffin, Tween-80, n-hexane, petroleum ether, hydrochloric acid (HCl), monobasic potassium phosphate, sodium hydroxide (NaOH), sodium chloride (NaCl) were procured from Rankem India. Pepsin and pancreatin were procured from CDH Pvt. Ltd. Mumbai and all materials used were of analytical grade. Distilled water was used throughout the study.

Table 1. Formulation chart of microparticles of Ketorolac Tromethamine

S. No.	Formulation Code	DRUG (gm)	Eudragit RS100 (gm)	Ethyl Cellulose (gm)	HPMC E5 (gm)
1.	F_1	0.5	0.5	------	------
2.	F_2	0.5	1.0	------	------
3.	F_3	0.5	1.5	------	------
4.	F_4	0.5	2.0	------	------
5.	F_5	0.5	------	0.5	------
6.	F_6	0.5	------	1.0	------
7.	F_7	0.5	------	1.5	------
8.	F_8	0.5	------	2.0	------
9.	F_9	0.5	------	------	0.5
10.	F_{10}	0.5	------	------	1.0
11.	F_{11}	0.5	------	------	1.5
12.	F_{12}	0.5	------	------	2.0

Preparation of Microparticles

Microparticles containing Ketorolac Tromethamine as a core material were prepared by a non-aqueous solvent evaporation method. Drug and polymer were dissolved or dispersed in the organic solvents (dichloromethane and ethanol in 1:1 ratio for EC and HPMC E5, acetone and ethanol in 6:4 ratio for Eudragit RS100). The slurry was poured drop-wise into 60 ml of light liquid paraffin (used as a base material) containing tween-80 (0.02% w/v) as an emulsifying agent [also contained magnesium stearate (0.2%w/v) for Eudragit RS100] with continuous stirring at 1000 rpm using a propeller type mechanical stirrer at room temperature. The solution was stirred for 2 hrs. To this mixture, n-hexane (10 ml) was added for hardening of microparticles, stirred further for 30 minutes to bring about complete evaporation of solvent and filtered. The microparticles thus obtained were washed 3-4 times with slightly hot petroleum ether for complete removal of liquid paraffin. These were then dried at room temperature for 1-2 hours until free flowing microparticles were obtained [5].

Drug-polymer Interaction Study

The compatibility of drug and polymers (Eudragit RS100, EC and HPMC E5) were studied by using FTIR spectra and thin layer chromatography. It was found that all the additives used were compatible with the drug [6].

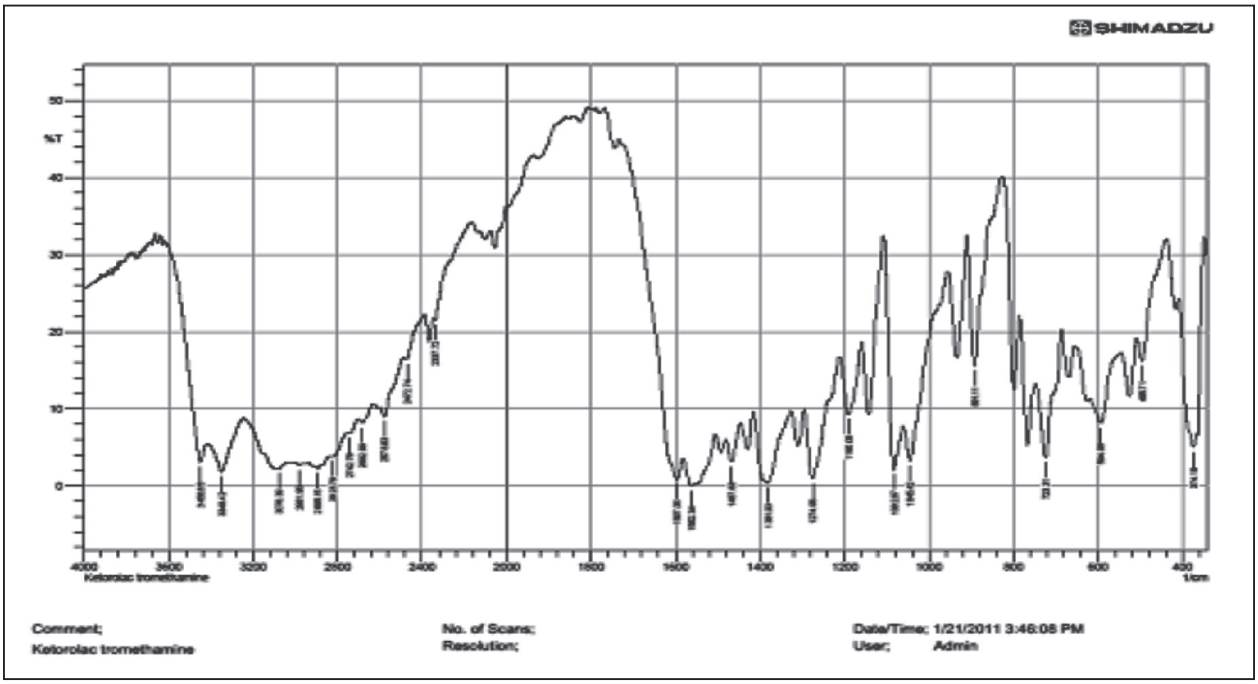

Fig. 1. FT-IR Spectra of Ketorolac Tromethamine Pure Drug

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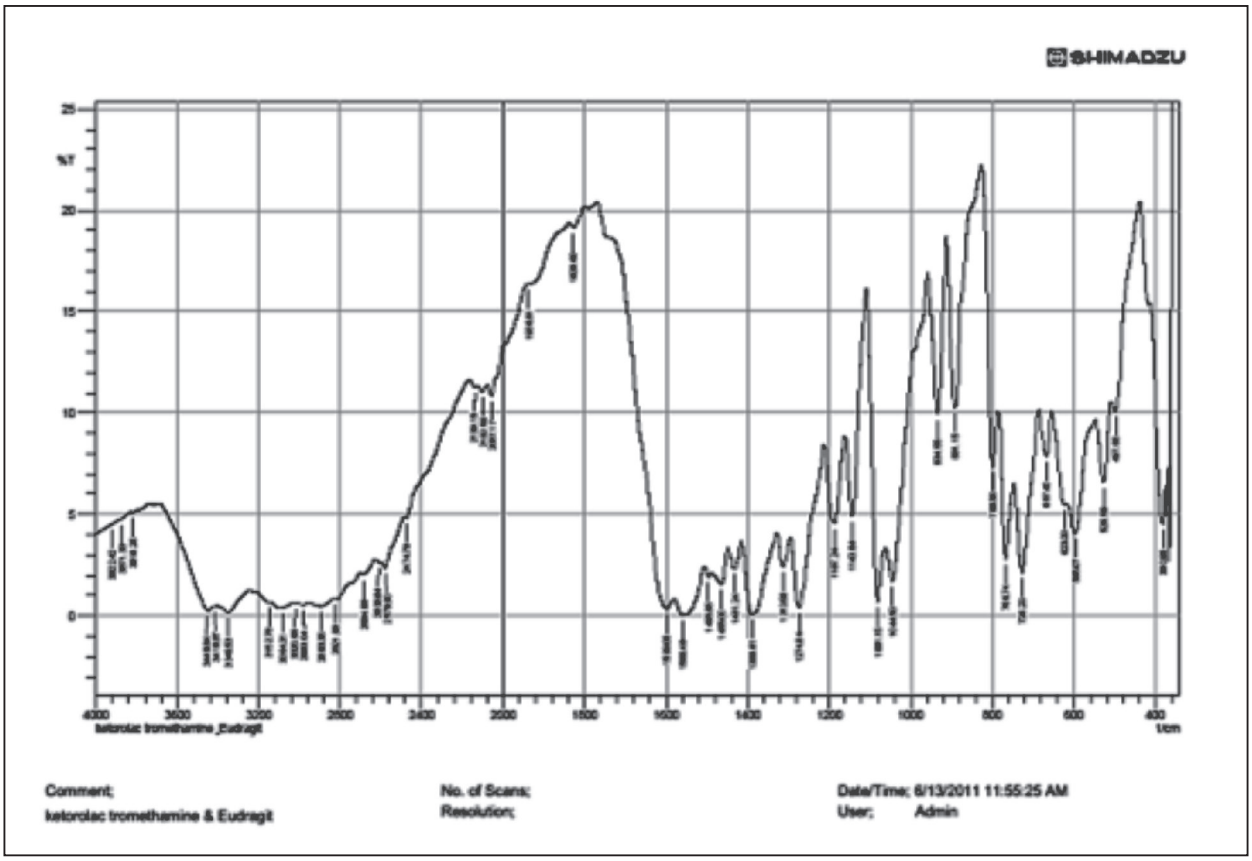

Fig. 2. FT-IR Spectra of Ketorolac tromethamine + Eudragit RS100

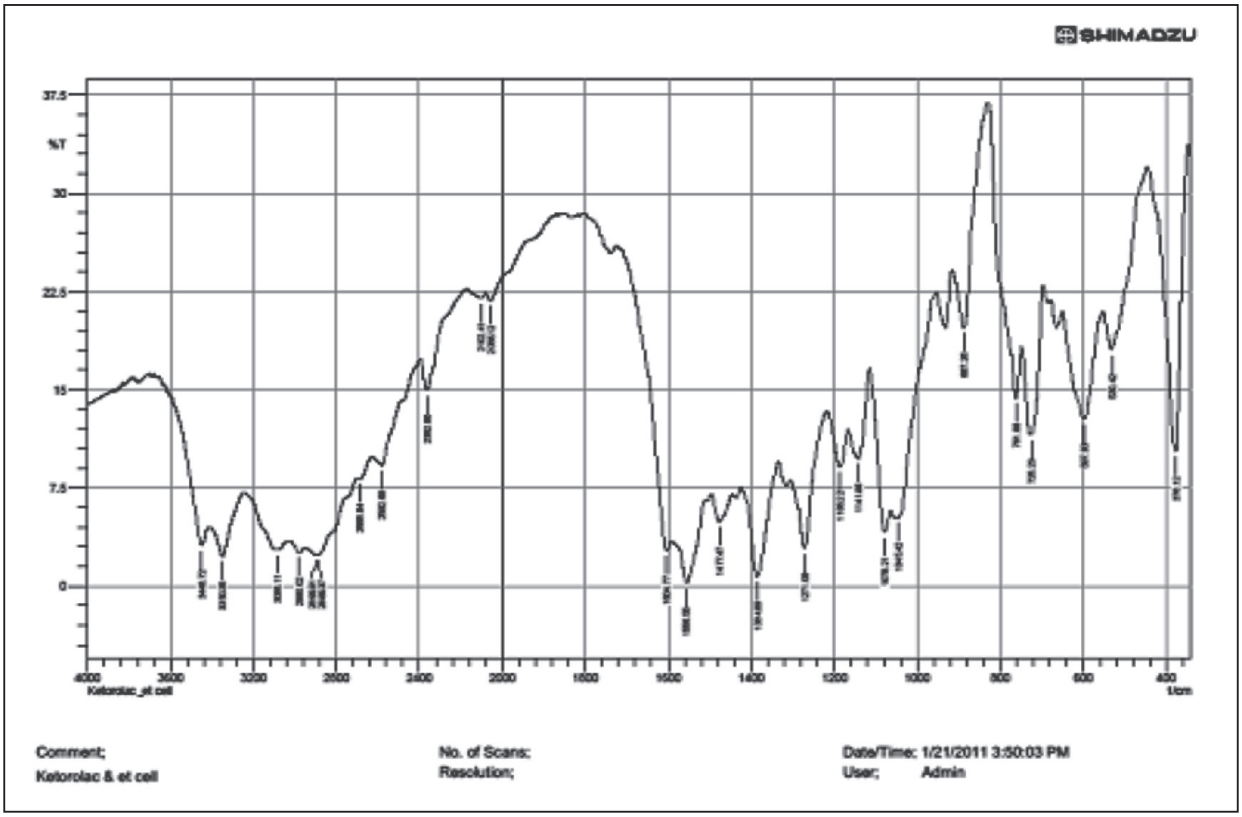

Fig. 3. FT-IR spectra of ketorolac tromethamine + Ethyl cellulose

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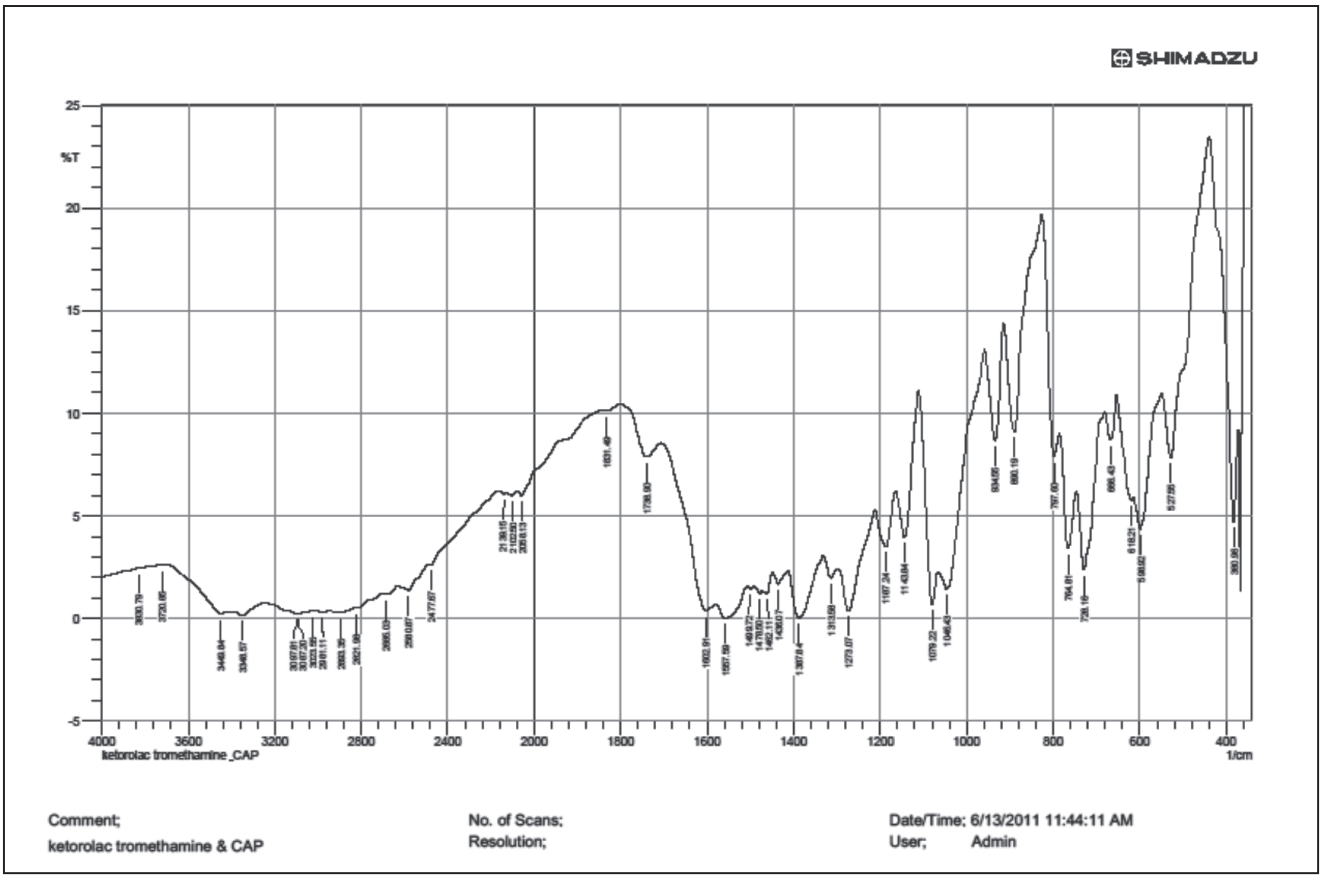

Fig. 4. FT-IR spectra of Ketorolac Tromethamine + HPMC E5

3. RESULTS AND DISCUSSION

Evaluation of Microparticles

Morphology: Surface morphology of microparticle formulation was carried out by Scanning Electron Microscopy (SEM). It revealed rough texture of microparticles with minute dense on the surface [7].

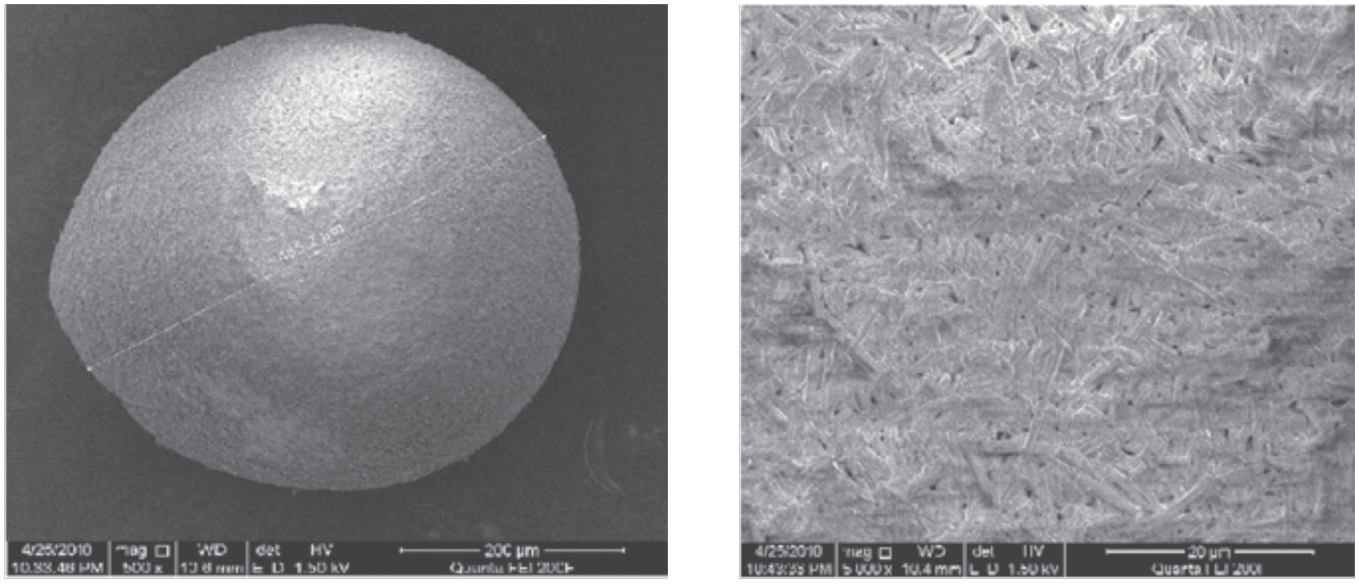

Fig. 5. SEM of F_4 formulation

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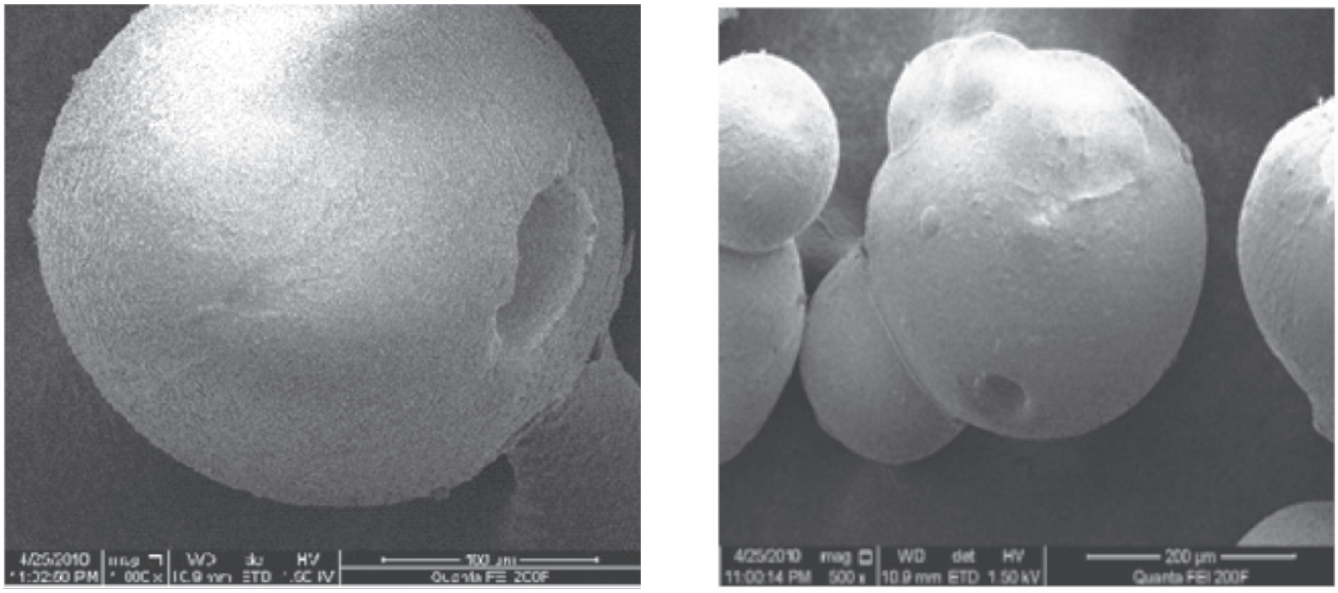

Fig. 6. SEM of F_8 formulation

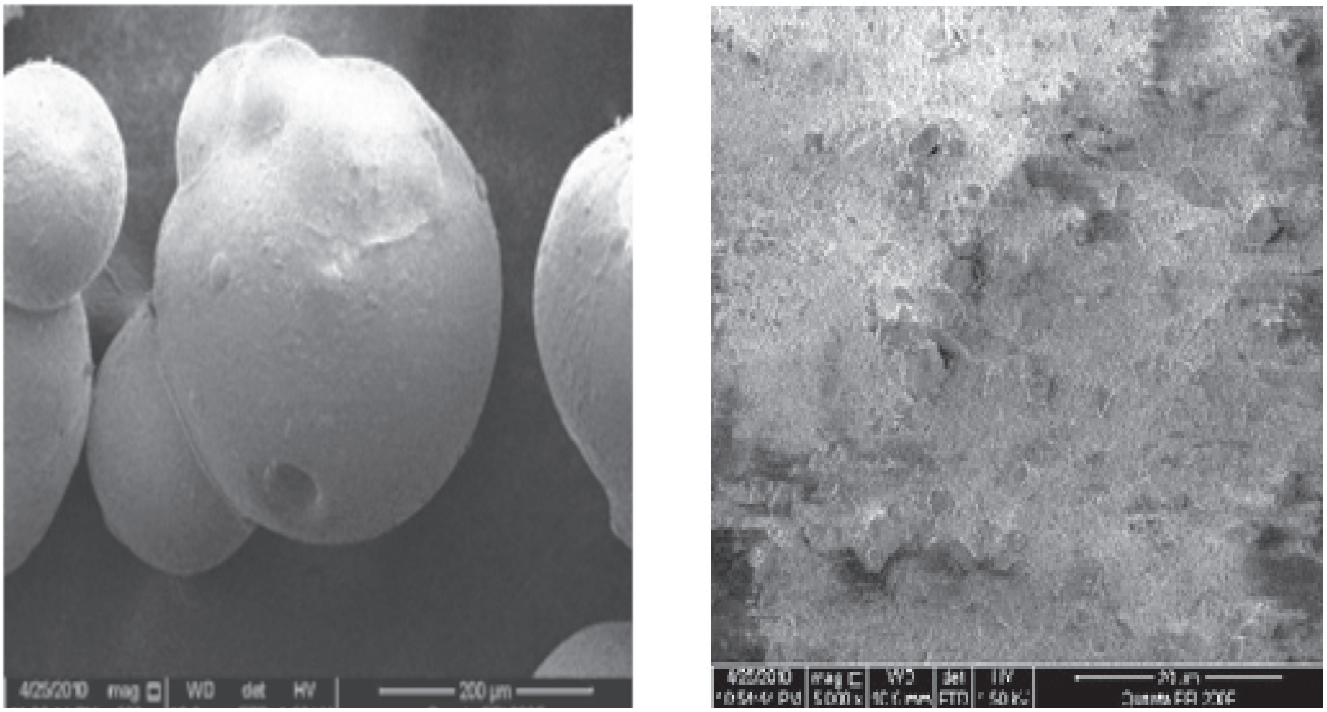

Fig. 7. SEM of F_{12} formulation

Particle Size Determination

Particle size was determined by using a photomicroscope fitted with micrometric tools. The mean particle size ranged from 235.24-463.39μm [8].

Percentage Yield

The percentage yield of all the formulations ranged between 71.00-82.40% [9].

Percent Drug Entrapment

The drug entrapment efficiency of all the formulations was in the range of 55.73 %- 73.50 % [10].

Determination of Flow Properties

The bulk density, tapped density, angle of repose and carr's index for all samples were found to be in the range of 0.37-0.79, 0.39-0.74, 7.18-24.37 and 3.13-23.53 respectively [11].

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Release Kinetics

In-vitro comparative study of finalized formulations F4, F8 & F12 in pH1.2 acidic and pH7.2 phosphate buffer were found [12].

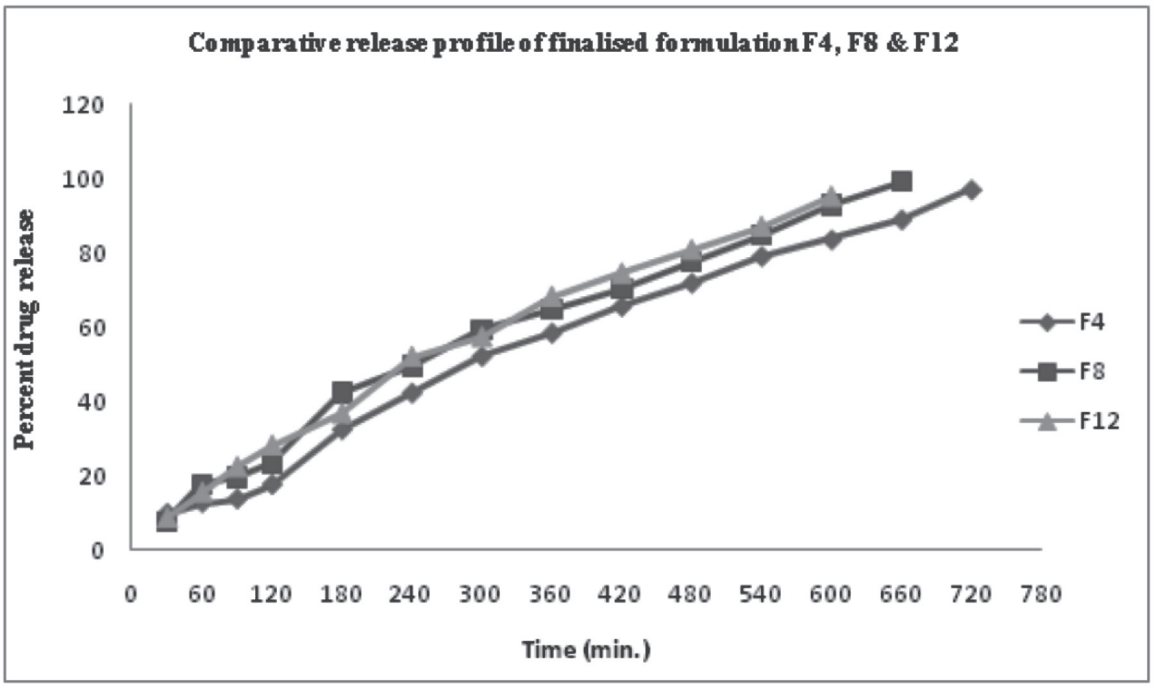

Fig. 8. Comparative release profile

Table 2. Estimation value of r^2 and n after fitting of dissolution data into various releases kinetic models in pH 1.2 SGF and pH 7.2 SIF respectively.

Formulation	Zero order		First Order		Higuchi		Korsmeyer-Peppas	
	Slope	r^2	slope	r^2	Slope	r^2	slope	r^2
F_1	0.155	0.978	-0.002	0.694	4.804	0.980	0.817	0.973
F_2	0.160	0.984	-0.002	0.860	4.952	0.986	0.863	0.982
F_3	0.147	0.985	-0.002	0.728	4.732	0.989	0.870	0.984
F_4	0.132	0.980	-0.001	0.811	4.426	0.984	0.810	0.964
F_5	0.166	0.979	-0.002	0.814	4.943	0.997	0.774	0.989
F_6	0.157	0.976	-0.002	0.824	4.873	0.991	0.824	0.989
F_7	0.147	0.977	-0.002	0.877	4.572	0.995	0.773	0.987
F_8	0.140	0.968	-0.002	0.720	4.546	0.990	0.799	0.983
F_9	0.170	0.99	-0.003	0.736	4.035	0.994	0.759	0.999
F_{10}	0.166	0.989	-0.002	0.856	4.898	0.991	0.721	0.993
F_{11}	0.154	0.981	-0.002	0.717	4.782	0.993	0.779	0.995
F_{12}	0.154	0.982	-0.002	0.810	4.789	0.994	0.798	0.996

All the release data were fitted into various kinetic models like, zero order, first order, Higuchi, and Korsmeyer-Peppas in order to find out the mechanism of drug release from polymeric microparticles. The correlation coefficient, rate constant and diffusion coefficient were calculated as given in the table.

When the release data was analyzed as per Peppas equation, the release exponent 'n' was in the range of 0.721-0.870 with all the microparticles indicating non-fickian diffusion as the release mechanism. Plots of percent cumulative release Vs square root of time (Higuchi's plots) were found to be linear ($R^2 > 0.927$) indicating that the dug release from the microparticles followed non-fickian diffusion mechanism.

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Stability Data of Ketorolac Tromethamine Microparticles

The stability study was performed on the best formulation (F_4) as per ICH guidelines at accelerated conditions ($40^o \pm 2^oC$, 75% ± 5% RH) which showed that the formulation (F_4) underwent no physical changes and there was no significant reduction in drug contents.

4. CONCLUSION

Ketorolac Tromethamine microparticles were prepared by oil-in-oil emulsification method using EudragitRS100, Ethyl Cellulose, Hydroxy Propyl Methyl Cellulose E5. Morphology of microparticles were characterized by Scanning Electron Microscopy and found that the microparticles were spherical with rough surface. Other physiological parameters determined with the microparticles were Particle size determination (235.24-463.39μm.), Percentage Yield (71.00-82.40 %), Percent Drug Entrapment (55.73 %- 73.50 %), and flow properties which includes bulk density, tapped density, angle of repose and carr's index for all samples were found to be in the range of 0.37-0.79, 0.39-0.74, 7.18-24.37 and 3.13-23.53 respectively.

Conclusively microparticulate system has more advantages in comparison to single unit dosage form as they are uniformly distributed through the GIT thereby reducing local concentration of drug. Microparticles are one of the microparticulate delivery system and are prepared to obtain prolonged or controlled drug delivery to improve bioavailability or stability and to target drug to specific sites. It also offers advantages like limiting fluctuation within therapeutic range, reducing side effects, decreasing dosing frequency and improving patient compliance. On the basis of this study, we can try to prepare this formulation on pilot scale for sustained release dosage form.

REFERENCES

[1] Lippincott Williams Wilkins. Reminton, The science and practice of pharmacy. 2006; 21st edition, volume 1, pp. 939-953.

[2] Tripathi, K.D. Essential Medical Pharmacology, Jaypee Publications (P) Ltd. New Delhi, 2003, 5th edition, pp.167-184.

[3] Nicoleta, B.; Olivier, J.; Pierre, B.; Pierre, S.; Alkepetri, F.; Heinrich, H.; Eric, D. Dexamethasone-containing biodegradable supermagnetic microparticles for intra-articular administration. Physiochemical and magnetic properties, in-vitro and in-vivo drug release. *European Journal of Pharmaceutics and Biopharmaceutics* 2009, 72(3), pp 529-538.

[4] Rowe, C. R.; Paul, S. J.; Quinn, E. M. Hand Book of Pharmaceutical Excipients. Pharmaceutical Press and the American Pharmaceutical Association USA 2009, 6th edition, pp. 262-266.

[5] Vyas, S.P.; Khar, R.K. Controlled Drug Delivery; Concepts and Advances. 1st Edition, C B S Publishers and Distributers, New Delhi, 2002, pp.419-424.

[6] Gowda, D.V.; Shivakumar, H.G. Preparation and evaluation of waxes/fat microspheres loaded with lithium carbonate for controlled release:. Scientific Publication of the Indian Pharmaceutical Association, 2007, 69, 251-256.

[7] Ghosh, A.; Nayak, U.K.; Rout, P.; Nag T.; Roy, P. Preparation, evaluation and in-vitro in-vivo correlation (IVIVC) study of Lamivudine loaded Microspheres. *Research Journal Pharm. and Tech.* 2008, 353-356.

[8] Patil, H.S.; Patil, M.P.; Tekade, B.W.; Thakare, V.M.; Patil, V.R. Formulation and in-vitro Evaluation of floating Microspheres of Acyclovir. *Arch Pharm. Sci. & Res.* 2009, 1, 194-198.

[9] Gllhotra, R.M.; Bharadwaj, V.P.; Mishra, D.N. A comparative review of recently developed particulate drug carrier systems. *Pharmainfo.net* 2009, 7(3), 55-59.

[10] Lamprecht, A.; Schafer, U.; Claus-Michael, L. Structural Analysis of Microparticles by confocal Laser Scanning Microscopy. *AAPS Pharm. Sci. Tech.* 2001, 1(3), 87-91.

[11] Subrahmanyam, C.V.S. Text Book of Physical Pharmaceutics, Delhi, Vallabh Prakashan, 2000, 2nd Edition, 85, 215-227.

[12] The United States Pharmacopoeia NF, The official compendia of standards, USP Convention Inc, 2009, Vol. 1; pp. 865-866., Vol. 2; pp. 2740.