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Journal of Chemical and Pharmaceutical Research, 2015, 7(12):378-388

Research Article

ISSN : 0975-7384
CODEN(USA) : JCPRC5

Novacap technique for pulsatile drug delivery of ketorolac tromethamine microspheres

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ABSTRACT:

The multi-phase multi-compartment capsule based combination pulsatile delivery system was developed which consist of four parts i.e. fast dissolving tablet of Ketorolac Tromethamine, Microspheres of Ketorolac Tromethamine, Floating tablet of Omeprazole and Plug. Fast dissolving tablets were prepared by varying proportion of disintegrant such as Sodium starch glycollate, Croscarmelose sodium, Crospovidone by Direct Compression Method. Microspheres are prepared by Solvent Diffusion Method. Floating tablet of Omeprazole was prepared by varying proportion of HPMC K4M, HPMC K15M, HPMC K 100M and Plug was prepared by using HPMC E5. The prepared formulations were evaluated for different physicochemical parameters and in vitro studies. Promising results indicated the usefulness of the Innercap technique for pulsatiledrug delivery of Ketorolac Tromethamine.

Key words: Pulsatile, Innercap technique, HPMC, Disintegrant, Microspheres, Direct Compression.

INTRODUCTION

Innercap technique is one of the multiphase, multi-compartment capsule based delivery system. The system can be used to enhance the value and benefits of pharmaceutical, biopharmaceutical, nutraceutical and dietary supplement and herbal products. Inner cap is used for combination product therapies.[2 5] The multi-phase multi-compartment capsule based combination product delivery system is a very effective way to deliver multiple active chemical compound in different physical phases with controlled release profiles. The delivery system is an exciting solution that will be used to overcome issue such as life cycle management, bioavailability, stability, difficult combination drug therapies and other combination products. [1, 2]

The emphasis of pharmaceutical galenic research is turned towards the development of more efficacious drug delivery systems with already existing molecule rather going for new drug discovery because of the inherent hurdles posed not only in drug discovery but also in development process.[3]However, in the field of modern drug therapy, growing attention has lately been focused on pulsatile delivery of drugs. In a present work combination of release profiles can be incorporated in the system. The combination dosage form consists of a primary HPMC capsule containing a fast dissolving tablet, floating tablet, plug and microspheres. [4, 19-24]

Ketorolac is a nonsteroidal anti-inflammatory drug (NSAID). Its anti-inflammatory effects are believed to be due to inhibition of both cylooxygenase-1 (COX-1) and cylooxygenase-2 (COX-2) which leads to the inhibition of prostaglandin synthesis leading to decreased formation of precursors of prostaglandins and thromboxanes from

arachidonic acid. Analgesia is probably produced via a peripheral action in which blockade of pain impulse generation results from decreased prostaglandin activity. However, inhibition of the synthesis or actions of other substances that sensitize pain receptors to mechanical or chemical stimulation may also contribute to the analgesic effect. [1, 8, 20-24]

Omeprazole is a highly effective inhibitor of gastric acid secretion used in the therapy of stomach ulcers. Omeprazole belongs to a class of antisecretory compounds, the substituted benzimidazoles that suppress gastric acid secretion by specific inhibition of the H+ /K+ ATPase enzyme system at the secretory surface of the gastric parietal cell.

The goal of present study was to prepare formulation of Ketorolac Tromethamine which inhibit prostaglandin synthesis. Simultaneously the side effect of chronic use of NSAID was treated by giving combination therapy with Omeprazole. From a Capsule initially Sustained release tablet was released then plug followed by Fast dissolving tablet of Ketorolac Tromethamine further the release pattern was extended by preparing sustained release microspheres of Ketorolac Tromethamine. Due to suchcombination therapy frequency of drug administration is reduced, patient compliance can be improved and drug administration can be made more convenient.

EXPERIMENTAL SECTION

Formulation table:-

1. Preparation of Ketorolac Tromethamine Fast Dissolving Tablet

Table No.1

Ingredients	A_1	A_2	A_3	A_4	A_5	A_6	A_7	A_8	A_9
Drug	20	20	20	20	20	20	20	20	20
Sodium Starch Glycollate	3	3.5	4	-	-	-	-	-	-
Crosspovidone	-	-	-	1.5	2	2.5	-	-	-
Croscarmelose Sodium	-	-	-	-	-	-	2	3	4
Directly Compressible Lactose	53.8	53.3	52.8	55.3	54.8	54.3	54.8	53.8	52.8
Talc	1.6	1.6	1.6	1.6	1.6	1.6	1.6	1.6	1.6
Magnesium stearate	1.6	1.6	1.6	1.6	1.6	1.6	1.6	1.6	1.6

2. Preparation of Omeprazole Floating Tablet

Table No. 2

Ingredients	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
Drug	20	20	20	20	20	20	20	20	20
HPMC K4M	20	40	60	-	-	-	-	-	-
HPMC K15M	-	-	-	20	40	60	-	-	-
HPMC K100M	-	-	-	-	-	-	20	40	60
Sodium bicarbonate	20	20	20	20	20	20	20	20	20
Talc	51	31	11	51	31	11	51	31	11
Lactose	35	35	35	35	35	35	35	35	35
Magnesium Stearate	4	4	4	4	4	4	4	4	4

3. Preparation of Microspheres by solvent evaporation method.

Table No.3

Batch No.	Drug: Polymer Ratio
M1	1:1
M2	1:2
M3	1:3
M4	1:4

Required amount of Ethyl cellulose was dissolved into a 7 ml mixture of dichloromethane (DCM): acetonitrile (ACN) in a ratio of 1:1. Then, required amount of Ketorolac tromethamine was added to the (EC) solution by stirring with a magnetic stirrer at 500 rpm. The resultant solution was poured into 100 ml 2% PVA solution, in a 250

ml beaker. The resulting microspheres were filtered through a Whatman no. 1 filter paper. The residue was washed 4 to 5 times in distilled water each. Microspheres were dried at room temperature for 24 hrs. The various batches of formulations were prepared by varying drug polymer ratio.[11]

4. Formulation of plug (lag time 6Hrs)

Table No.4

Ingredients	P1	P2	P3	P4
HPMC E5	85	85	85	85
Spray Dried Lactose	15	15	15	15
Pressure Applied	1	2	3	4

III. EVALUATION AND CHARACTERIZATION

1. Evaluation of FDT of Ketorolac Tromethamine [1-6]:-

Evaluation of Pre-compression Parameters:

Determination of bulk density, tapped density, Hausner's ratio, Carr's index and angle of repose is important before formulation because it may influence compressibility, tablet porosity and dissolution. Determination of Hausner's ratio is simple method to evaluate stability of powder column and estimate flow properties. From the evaluation results of powder it can be attributed that prepared powder were within the limit of all specified values and properties and showed good powder characteristics.[12,13]

Evaluation of Post compression Parameters: The formulated tablets were evaluated for the following parameters such as weight variation, hardness, friability, thickness, disintegration, wetting time, water absorption ratio, drug content and In-vitro dissolution studies are carried out.[14]

2. Evaluation of Floating tablet of Omeprazole [7-11]:-

Evaluation of Pre-compression Parameters:

It is predicted in terms of bulk density, tapped density, Hausner's ratio, Carr's index and angle of repose. From the evaluation results of powder it can be attributed that prepared powder were within the limit of all specified values and properties and showed good powder characteristics.[16]

Evaluation of Post compression Parameters: [12-18]

The formulated tablets were evaluated for the following parameters such as weight variation, hardness, friability, thickness, disintegration, In vitro buoyancy, drug content and In-vitro dissolution study.

3. Evaluation of plug: Prepared plug is evaluated for hardness, thickness and dissolution time.[17]

4. Evaluation of Microspheres: Formulated microspheres are evaluated for its Entrapment efficiency, % yield, Drug content, Drug Loading and In vitro release.

RESULTS AND DISCUSSION

1. FAST DISSOLVING TABLET OF KETOROLAC TROMETHAMINE [1-6]

1.1 Preformulation Study- Pre compression Parameter

Table No.5

Sr. no.	Batch No.	Angle of repose	Bulk density	Tapped density	Compressibility Index	Hausner's ratio
1.	**A1**	22.13	0.4	0.47	15	1.176
2.	**A2**	23.57	0.39	0.43	10	1.11
3.	**A3**	22.90	0.40	0.43	7.5	1.08
4.	**A4**	22.61	0.39	0.43	10	1.11
5.	**A5**	22.13	0.39	0.45	12.5	1.14
6.	**A6**	22.13	0.39	0.45	12.5	1.14
7.	**A7**	22.13	0.39	0.45	12.5	1.14
8.	**A8**	22.13	0.4	0.45	12.5	1.14
9.	**A9**	22.13	0.39	0.45	12.5	1.14

1.2 Calibration curve of Ketorolac Tromethamine in distilled water

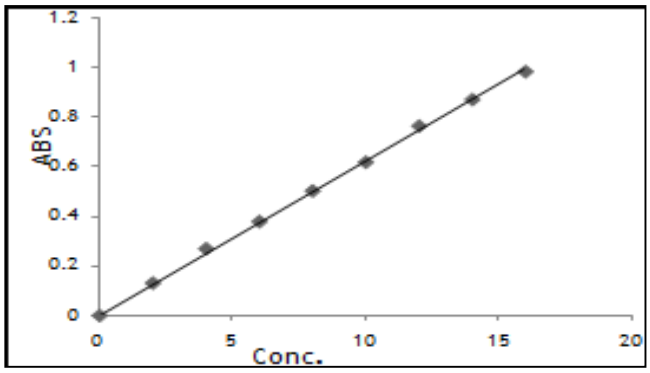

Fig. No.1 Calibration curve of KT

From the calibration curve equation is given as,

Y = 0.0613X+ 0.01, The value of R^2 = 0.998.

1.3 Melting point: - Melting point of KT was observed at 164-166^0 C.

1.4 Infrared spectrum analysis

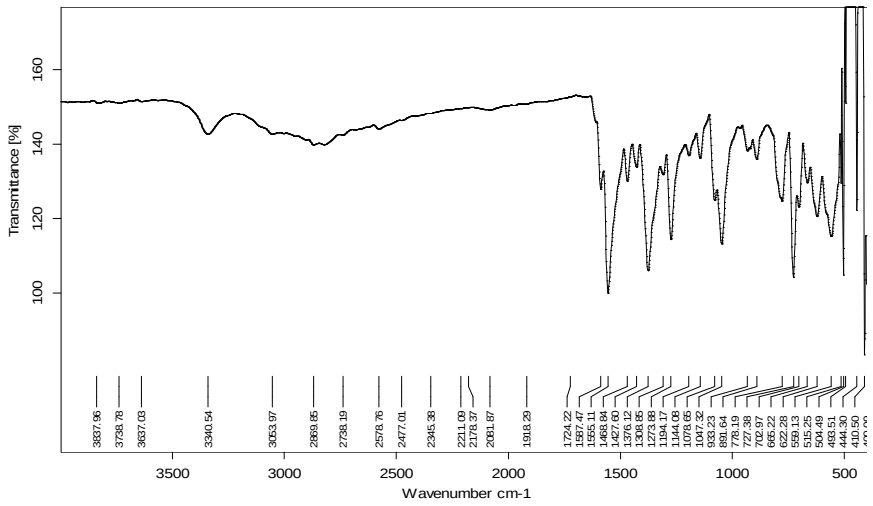

Fig. No 2. IR of Ketorolac Tromethamine

1.5Post Compression Parameter

Table No.6

Batch No.	Thickness n= 10 (mm)	Diameter n= 10 (mm)	Hardness n= 5 (kg/cm^3)	In vitro disintegration time n= 5 (Sec.)
A1	3.01±0	7.01±0	3±0	31.6±0.54
A2	3.01±0	7.01±0	3±0	30.6±0.54
A3	3.01±0	7.01±0	3±0	29.4±0.54
A4	3.01±0	7.01±0	3±0	36.4±0.54
A5	3.01±0	7.01±0	3±0	34.6±0.54
A6	3.01±0	7.01±0	2.5±0	34.4±0.54
A7	3.01±0	7.01±0	3±0	40.4±0.54
A8	3.01±0	7.01±0	3±0	38.8±0.44
A9	3.01±0	7.01±0	3±0	38.6±0.54

1.6 In vitro dissolution test

Table No.7

Batch No.	Friability(%)	Wetting time (Sec.)	Water absorption ratio	Drug content (mg)
A1	0.012	74±7.07	2.66±1.006	17.36
A2	0.012	79±6.7	3.486±0.438	18.4
A3	0.037	71±6.7	4.25±1.0009	18.61
A4	0.05	58±8.36	3.498±0.55	17.95
A5	0.025	55±5	3.44±0.27	16.49
A6	0.073	57.2±1.92	5.002±0.92	17.64
A7	0.039	57±4.69	4.56±0.98	18.33
A8	0.065	59±4.18	6.098±0.25	16.28
A9	0.076	64±4.18	7.55±0.39	17.21

In vitro drug release profiles of KT from tablet are given in table. Formulations containing sodium starch glycollate showed fast dissolution than the formulation containing crosspovidone and croscarmelose sodium. The rapid increase in dissolution of KT with increase in concentration of sodium starch glycollate was observed. Tablets prepared with sodium starch glycollate have maximum drug release with minimum disintegration time because higher concentration of SSG probably made large pores with continuous network or skeleton providing enough pressure for faster disintegration. Among nine formulations of KT, it was observed that when SSG used in concentration of 3-4%, it act as a potential disintegrant.

Table No.8

Batch No. Time	A1	A2	A3	A4
0	0	0	0	0
5	67.50±0.476	84.54±0.2	77.28±0.15	67.65±0.2
10	94.93±0.47	90.70±0.4	89.69±0.3	86.13±0.1
15	97.02±0.2	90.90±0.37	95.29±0.6	88.87±0.4
20	97.66±0.23	92.54±0.15	97.12±0.5	90.86±0.2
25	98.79±0.2	94.02±0.15	99.85±0.47	91.07±0.15
30	99.97±0.1	96.04±0.2	100.12±0.15	91.28±0.15
35	100.13±0.2	98.07±0.15	100.90±0.015	91.54±0.15
40	100.44±0.1	99.54±0.15	101.05±0.2	91.67±0.15
45	100.63±0.1	99.93±0.2	101.33±0.15	91.88±0.15
50	100.82±0.2	101.17±0.2	101.52±0.2	94.14±0.15
55	100.91±0.2	102.56±0.2	101.65±0.15	95.34±0.15
60	100.94±0.1	101.18±0.32	101.80±0.4	95.91±0.2

Table No.9

Batch No. Time	A5	A6	A7	A8	A9
0	0	0	0	0	0
5	80.51±0.2	66.66±0.15	81.05±0.25	80.61±0.15	80.51±0.25
10	89.99±0.3	94.39±0.2	90.61±0.26	89.71±0.2	84.62±0.20
15	89.80±0.1	95.55±0.32	91.21±0.39	90.35±0.15	85.39±0.43
20	89.99±0.2	95.71±0.15	90.98±0.2	91.27±0.2	85.62±0.15
25	90.90±0.1	96.36±0.15	91.34±0.1	91.99±0.25	86.46±0.015
30	91.27±0.1	96.41±0.2	91.63±0.15	92.92±0.015	87.57±0.25
35	92.01±0.1	96.58±0.15	91.74±0.26	92.98±0.20	88.87±0.35
40	92.31±0.2	97.18±0.15	91.89±0.25	93.00±0.32	91.08±0.30
45	93.17±0.02	97.24±0.2	92.08±0.15	93.07±0.20	93.98±0.20
50	95.04±0.2	97.58±0.25	92.18±0.27	93.20±0.15	95.86±0.15
55	97.14±0.2	99.98±0.32	92.55±0.15	94.90±0.20	96.46±0.20
60	97.68±0.4	98.97±0.2	92.71±0.20	93.89±0.015	96.39±0.4

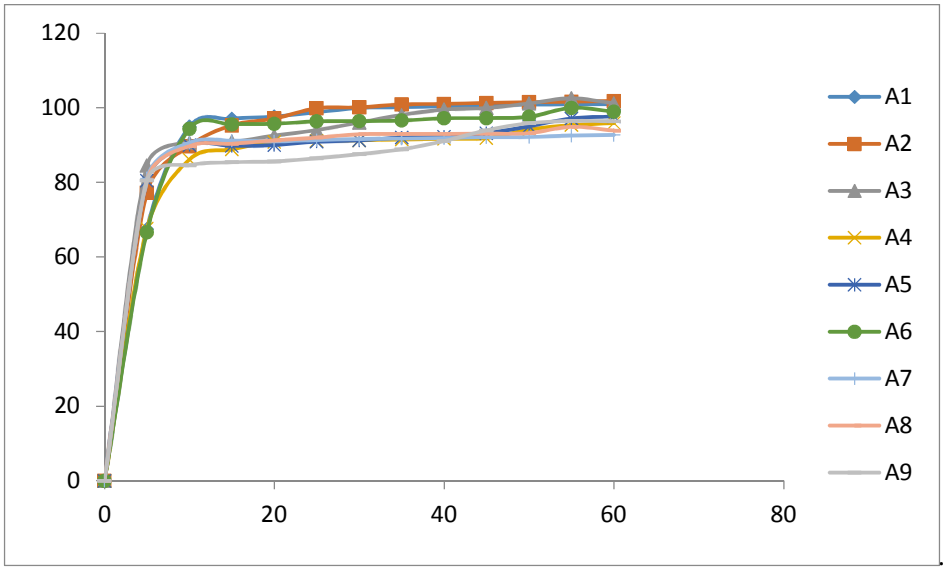

Fig. No. 3 *Invitro* Dissolution study

2. Floating tablet of Omeprazole [7-11]

2.1 Preformulation Study- Pre compression Parameter

Table No.10

Sr. no.	Batch No.	Angle of repose	Bulk density	Tapped density	Compressibility Index	Hausner's ratio
1.	F1	19.70	0.42	0.46	8.57	1.09
2.	F2	20.91	0.45	0.47	4.41	1.04
3.	F3	20.55	0.42	0.45	7.14	1.07
4.	F4	21.28	0.37	0.42	10.29	1.11
5.	F5	18.67	0.42	0.44	2.85	1.02
6.	F6	19.54	0.37	0.39	5.71	1.06
7.	F7	19.76	0.42	0.44	4.28	1.04
8.	F8	20.20	0.37	0.40	8.57	1.09
9.	F9	19.81	0.42	0.46	8.57	1.09

2.2 Calibration curve of Omeprazole

From the calibration curve equation is given as,

Y = 0.0628 X+ (-0.00075), The value of R^2 = 0.999.

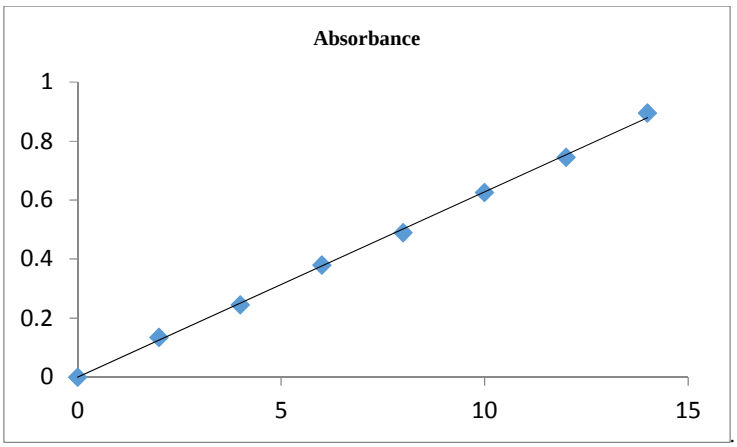

Fig. No. 4

2.3 Melting point: -Melting point of Omeprazole was observed at 153-155 ^{0} C.

2.4 Infrared Spectrum Analysis

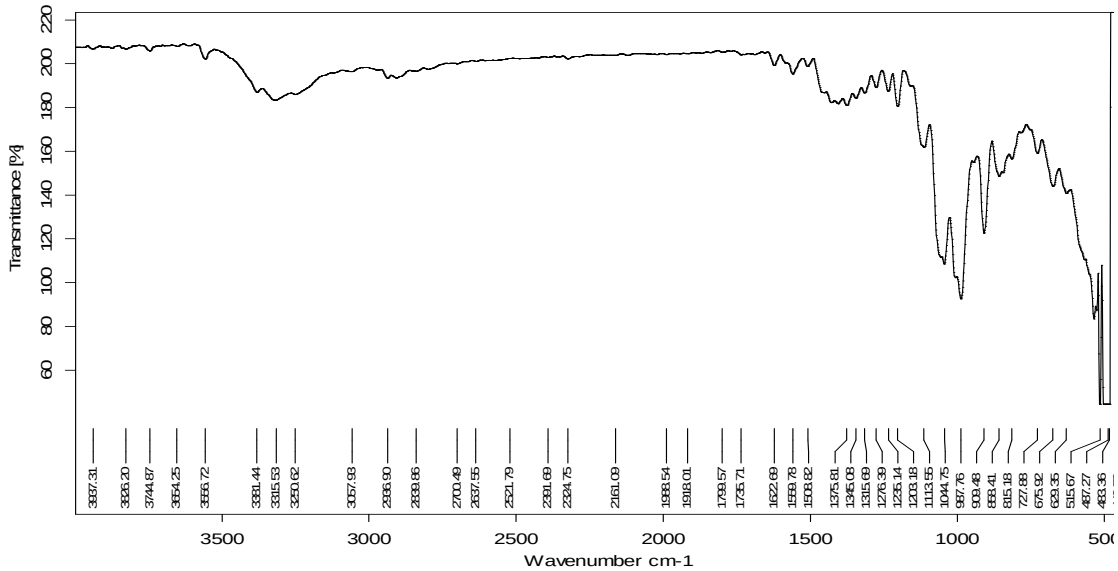

Fig. No.5 IR Spectra of Omeprazole

2.5 Post Compression Parameter

Table No.11

Batch No.	Thickness n= 10 (mm)	Diameter n= 10 (mm)	Hardness n= 5 (kg/cm^3)
F1	4.01±0	7.02±0	5.38±0.044
F2	4.01±0	7.02±0	5.5±0.122
F3	4.01±0	7.02±0	5.54±0.167
F4	4.01±0	7.02±0	5.44±0.054
F5	4.02±0	7.02±0	5.68±0.083
F6	4.01±0	7.02±0	5.4±0
F7	4.01±0	7.01±0	5.36±0.089
F8	4.01±0	7.02±0	5.66±0.089
F9	4.01±0	7.02±0	5.66±0.089

Table No.12

Batch No.	Friability (%)	In-vitro buoyancy		Drug content
		Floating lag time	Total floating time	
F1	0.02	71.8±2.04	>8	15.62
F2	0.08	62±2.12	>8	14.88
F3	0.07	63±1.87	>8	16.45
F4	0.02	64±1	>8	16.61
F5	0.06	63±2.12	>8	17.72
F6	0.08	65.6±0.54	>8	16.25
F7	0.068	70.6±0.54	>8	15.43
F8	0.046	72±2.73	>8	14.97
F9	0.11	73±2.73	>8	15.80

2.6 In-Vitro Dissolution Studies

In-vitro dissolution studies of all the formulations of floating tablets of Omeprazole were carried out in 0.1 N HCl. The study was performed for 8 hours, and percentage drug release was calculated at 1 hours' time intervals. The results of in vitro dissolution studies of all formulations were shown in table. The variation in drug release was due to different types of polymers and different concentrations of polymer in all the nine formulations. Formulation F2

shows about 79.46 % of cumulative drug release up to 8 hrs. This formulation shows good drug release profile than all other formulations.

In-Vitro Dissolution of Omeprazole

Table No.13

Batch No. Time	F1	F2	F3	F4
0	0	0	0	0
1	9.39±0.02	8.82±0.02	13.67±0.05	14.44±0.01
2	13.75±0.03	21.19±0.07	21.1±0.04	20.9±0.01
3	20.42±0.01	28.7±0.03	34.93±0.37	26.36±0.01
4	28.69±0.02	37.67±0.02	45.72±0.22	34.77±0.02
5	42.61±0.01	50.46±0.04	51.16±0.04	42±0.03
6	53.24±0.03	60.7±0.02	60.75±0.35	48.99±0.02
7	61.96±0.18	70.33±0.49	70.77±0.47	56.66±0.04
8	71.02±0.14	72.55±0.11	79.46±0.03	61.7±0.01

Table No.14

Batch No. Time	F5	F6	F7	F8	F9
0	0	0	0	0	0
1	14.09±0.03	14.54±0.03	13.77±0.02	7.49±0.05	13.53±0.02
2	28.42±0.02	25.81±0.07	17.78±0.02	17.65±0.03	19.7±0.02
3	34.9±0.02	33.91±0.02	28.39±0.04	26.3±0.01	26.35±0.02
4	39.02±0.03	42.59±0.01	34.16±0.03	34.92±0.03	34.91±0.03
5	49.69±0.01	47.13±0.02	41.35±0.03	41.36±0.03	42.81±0.01
6	53.03±0.04	56.54±0.03	49.07±0.02	46.16±0.02	50.58±0.01
7	56.78±0.03	60.75±0.03	56.78±0.02	56.95±0.01	62.84±0.01
8	61.08±0.03	64.05±0.01	63.56±0.02	66.92±0.03	68.1±0.03

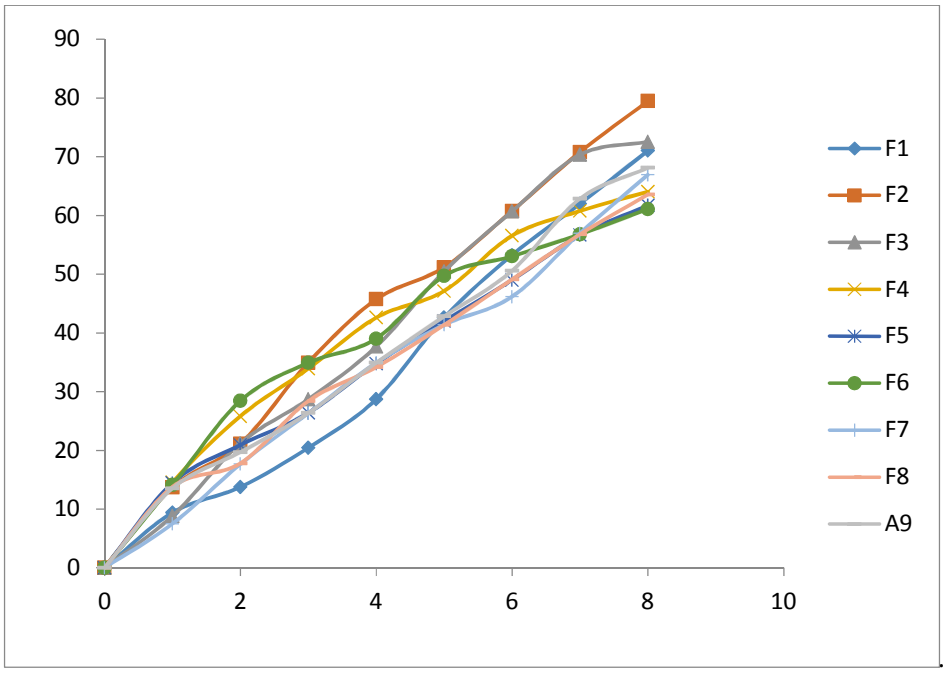

Fig. No. 6 In vitro Drug Release Profile of Omeprazole Tablet

3. MICROSPHERES OF KETOROLAC TROMETHAMINE [12-18]

3.1 Preformulation Study

Table No.15

Sr. no.	Batch No.	Angle of repose (θ)	Bulk density	Tapped density	Compressibility	Hausner's ratio
1.	**M1**	15.66	0.26	0.31	15	1.17
2.	**M2**	16.09	0.33	0.37	10	1.11
3.	**M3**	15.38	0.47	0.51	7.5	1.08
4.	**M4**	15.45	0.57	0.63	10	1.11

3.2 Evaluation of Ketorolac Tromethamine Microspheres

Table No.16

Batch No.	Entrapment efficiency	% yield	Drug content	Drug Loading	*InVitro* Release
M1	73.7 %	106.3%	17.77 mg	47.03 %	76.25 %
M2	80.24 %	88.86%	18.25 mg	37.50 %	69.93 %
M3	81.2 %	90.7%	16.66 mg	27.56 %	64.12 %
M4	81.5 %	88.08%	18.57 mg	22.70 %	62.31 %

3.3 *In vitro* drug release of Ketorolac Tromethamine from microspheres

Table No.17

Batch No. Time	M1	M2	M3	M4
1 hr	9.82±0.07	8.65±0.02	8.45±0.11	8.05±0.1
2 hr	25.93±0.24	26.42±0.11	17.7±0.05	14.9±0.15
3 hr	47.43±0.05	34.36±0.28	32.01±0.13	28.14±0.16
4 hr	54.46±0.05	46.17±0.09	38.17±0.07	35.75±0.12
5 hr	62.07±0.07	51.94±0.014	49.38±0.13	40.34±0.16
6 hr	65.95±0.22	58.74±0.13	52.57±0.07	47.94±0.09
7 hr	69.49±0.07	65.62±0.13	58.71±0.08	52.52±0.12
8 hr	76.25±0.22	69.93±0.16	64.12±0.16	62.31±0.15

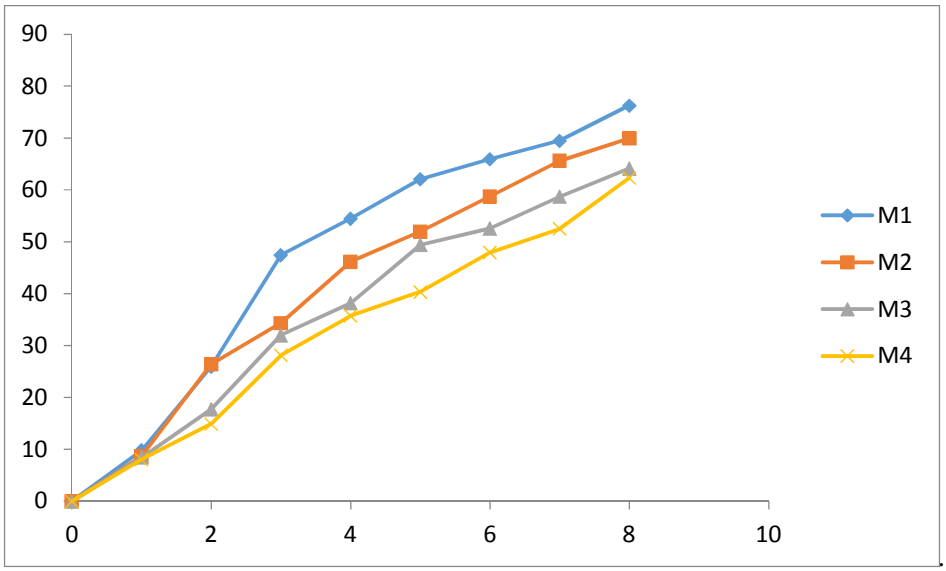

Fig. No.7 In vitro Drug Release Profile of Microspheres of KT

4. EVALUATION OF PLUG

Table No.18

Batch no.	Thickness (mm)	Hardness (Kg/cm3)	Diameter (mm)	Lag time (hr)
P1	3.02	5.4	6.01	4
P2	3.05	5.5	6.05	4.30
P3	3.02	5.2	6.02	5
P4	3.05	5.5	6.01	6

5. IN VITRO RELEASE PROFILE OF FINAL CAPSULE

Table No.19

Time	% C.D.R
Floating tablet of Omeprazole	
1 Hr	19.38±0.02
2 Hr	37.31±0.03
3 Hr	52.05±0.02
4 Hr	58.14±0.01
5 Hr	67.33±0.02
6 Hr	80.6±0.04
Lag time of Plug 6 Hrs	
Fast dissolving tablet of Ketorolac Tromethamine	
5 min	61.33±0.04
10 min	66±0.04
15min	71.32±0.02
20 min	74.46±0.02
25 min	75.87±0.04
30 min	77.58±0.02
35 min	80.08±0.02
40 min	80.45±0.02
45 min	81.92±0.02
50 min	85.21±0.01
55 min	86.39±0.03
60 min	88.27±0.05
Ketorolac Tromethamine microspheres	
1 Hr	14.13±0.16
2 Hr	32.55±0.2
3 Hr	51.95±0.13
4 Hr	59.08±0.14
5 Hr	65.99±0.1
6 Hr	70.42±0.14

CONCLUSION

A novel pulsatile drug delivery system for oral use was developed and evaluated. Prepared system mainly consist of 4 parts: A floating tablet of Omeprazole, Plug, A fast dissolving tablet of Ketorolac tromehamine, Microspheres of Ketorolac tromehamine. A FDT of Ketorolac tromethamine were prepared by direct compression by using Sodium Starch Glycollate, Crosspovidone, and Croscarmelose sodium as a superdisintegrants. Floating tablet of Omeprazole were prepared by using HPMC K4M, HPMC K100M, HPMC K15M along with sodium bicarbonate. Microspheres were prepared by Solvent Diffusion Method.

Among the fast dissolving tablet of Ketorolac tromehamine, the formulation prepared by using sodium starch glycollate emerged as an overall best formulation based on disintegration time characteristics. Among the floating tablet of Omeprazole, the formulation prepared by using HPMC K4M were selected as a best formulation. The floating lag time of all formulation was found to be less than 100 second and floating time was more than 8Hr. The lag time of plug was found to be 6hr. At last this novel release control technology using superdisintegrants, various

grades of HPMC and sodium bicarbonate was appropriate to obtain a pulsatile release that has regulated lag time with prolonged residence in stomach.

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