Original Research Article

Formulation and evaluation of sustained release floating microspheres of ketorolac using chitosan as a natural polymer

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Abstract

Sustained release medication conveyance Systems is a way to deal with broaden the gastric duration of medication in stomach. This technique is intended for site-explicit oral medications with low mass thickness than gastric liquid so on light the measurement structures in stomach to expand the span of the medication and consequently improve the bioavailability of medication. As a response to the issue, gastroretentive medication conveyance frameworks (SRDDS), which highlight an improved gastric length (GRT), were created.

The in vitro data indicated that pure drug showed 100% release within 2 hr. The drug release from the microspheres prepared in formulation F6 achieved 92.40±0.2% in 24 hr. per model fitting methods the very best parametric statistic (R2) value was 0.978 through Higuchi order model. Hence from all aspects; we concluded that the discharge of drug Ketorolac will be controlled by proper designing of the formulation and selection of an acceptable method of preparation.

Introduction

Sustained release Drug Delivery System

Gastroretentive medication conveyance framework (GRDDS) is most encouraging framework concocted for accomplishing an extended medication conveyance profile inside the GIT. These framework stays inside the gastric locale for stretched out length prompting improved bioavailability, remedial productivity and diminished portion. Numerous pharmacokinetic favorable circumstances could even be seen like, upkeep of restorative levels, improvement of the medication dissolvability that is less solvent in high pH climate[1].

Factors that affect SRDDS

1. Density impact: A thickness of under 1.0 g/ml has been recorded, for example not as much as that of the gastric content[2].
2. Impact of size:The maintenance in the stomach of gliding measurement types relies upon the size of the tablets[3].
3. Shape impact: Compared to different shapes, tetrahedron and ring-formed gadgets have better GRT[4].
4. Consequence of supper nature: Later than the other, sleek layers framed by fats are discharged on gastric substance[5].
5. Gender impact: Typically, females have a more slow pace of gastric exhausting than guys.
6. Effect of devoured volume: The more prominent the volume, the exhausting is faster. Liquids taken at internal heat level are speedier to leave the stomach than cooler or hotter liquids.
7. Effect of stance: GRT will contrast between the patient's recumbent and upstanding mobile states.
8. Effect old enough: Relative to older subjects, youngsters have higher gastric exhausting paces[6].

Limitations of sustained release drug delivery system[7-9]

- Not ideal in acidic conditions for medications that are not stable.
- Not appropriate for the drugs in the lower part of GIT that are best absorbed.
- Difficulty in accomplishing the ideal result and the portion unloading issue.
- Gastric maintenance is influenced by numerous factors, for example, gastric motility, pH and food presence. Hence the measurement type should have the option to withstand the peristaltic stomach wave's crushing and agitating energy.
- Poor in vitro and in vivo connection.
- Higher cost of detailing.

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Material and methodology

Materials

Table 1: List of Instruments

S. No.	Instruments	Manufacturer
1	UV/VIS Spectrophotometer,	Shimadzu, Japan
2	Weighing balance, (CY220)	Grey Scientific, Ambala
3	Mechanical stirrer	Remi Equipments, Mumbai
4	Magnetic stirrer	Remi Equipments, Mumbai
5	Dissolution apparatus	Gery Scientific Ambala, India
6	Vortex mixer	Remi (SLM-VM-3000), Bangalore
7	Hot air oven	Vortex India, Delhi
8	Microscope	Biolux-CTX(2), Kyowa
9	pH Meter	Ohaus, USA
10	Melting Point Apparatus	Remi Equipment, Mumbai
11	Infrared spectrophotometer (FTIR)	Perkin Elmer, Germany

Pre-formulation studies

Organoleptic Characteristics

For the physical characterization of shape, colour and odour, the drug sample was characterized[10].

Melting point

The melting point of the solid is defined as the temperature at which, at complete pressure, the solid and liquid are in equilibrium. The melting point apparatus is used to calculate the melting point of the medication.

Formulation and evaluation Standard Curve of Ketorolac

Standard Curve of Ketorolac by UV-visible spectrophotometer

Methanol was used to prepare a regular stock solution of Ketorolac (1mg/ml). To obtain different dilutions of 5-40 µg/ml, this solution was diluted with methanol.

Evaluation of Chitosan floating microspheres of ketorolac

Production yield

The prepared Microspheres were collected and weighed. The measured weight was divided by the total weight of all the excipients and drug. The % yield was calculated[11].

Percentage Drug Entrapment

The unmistakable supernatant arrangement was measured spectrophotometrically (UV-1800 spectrophotometer, Shimadzu, Japan) for drug content at 270 nm after reasonable weakening.[12]

Results and discussion

Studies for Preformulation

The goal of preformulation studies is to examine a drug substance's physical and chemical properties. ketorolac, the selected compound, was subjected to physical characterization parameters.

Melting Point: The melting point of a material is the temperature at which the solid layer is converted under one atmosphere of pressure into a liquid phase. The determination of the melting point means drug purity. The melting point of ketorolac was measured by the capillary tube process.

UV Spectroscopy

Determination of absorption maxima in methanol

For quantitative examination of the compound, a double beam UV-visible spectrophotometer was used. In the 200- 400 nm region, a 40 µg/ml solution of ketorolac in methanol was scanned.

Solubility Studies

The solubility of the substance in different solvents was completed all together to test for the components to be used in the production of the formulation. The compound was tested using a UV spectrophotometer at 272 nm.

Evaluating partition coefficient

The ketorolac partition coefficient was calculated using n-octanol and water. Log P greater than one suggests that the drug is lipophilic in nature, while the hydrophilic drug is representative of those with partition coefficients smaller than one.

Results and discussion

Formulation development

Procedure

Floating microsphere of ketorolac is prepared by emulsion solvent evaporation method.

Formulation code	Amt of Drug(in mg)	Chitosan(in gm)	HPMC:Carbopol in mg
F1	500	1	25:150
F2	500	2	50:125
F3	500	3	75:100
F4	500	4	100:75
F5	500	5	125:50
F6	500	6	150:25

Preformulation studies

Solubility study -Preformulation solubility analysis was done to select a suitable solvent system to dissolvethe drug and to rest its solubility in the dissolution medium which was to be used.

Table 2- Solubility studies in different solvents

S.no.	Solvents	Solubility
1.	Water	Insoluble
2.	Ethanol	Freely soluble
3.	Methanol	Freely soluble
4.	Acetone	Insoluble

Melting point determination-The melting rate of microspheres of Ketorolac has been observed by utilizing capillary tube melting points. Ketorolac microspheres were defined as a melting point at 224 ° C.

Identification of Ketorolac-The IR Spectrum of ketorolac was found to be similar to the standard spectrum of ketorolac. The spectrum of ketorolac shows the following functional groups at their frequencies shown in Fig 1

Drug polymer interaction (FTIR) study-Ketorolac, a physical blend of ketorolac and polymer, has identified the stability of the ketorolac and the polymer in all standard Metformin HCl peaks in the mixture range.IR spectra are shown in Figures

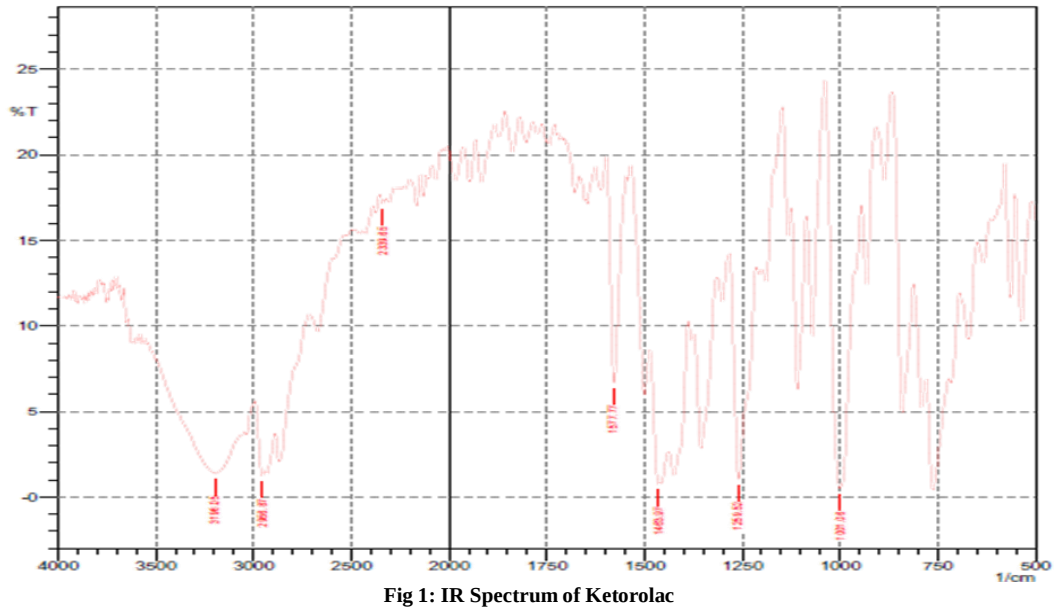

Fig 1: IR Spectrum of Ketorolac

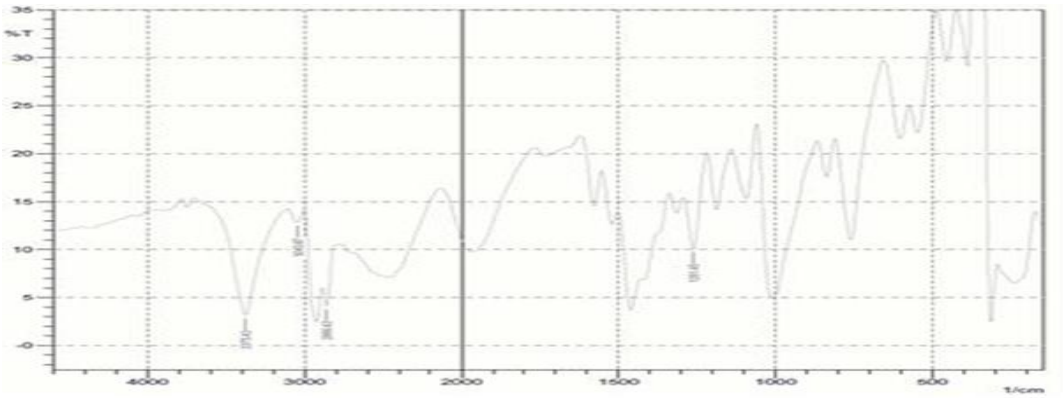

Fig 2 IR Spectrum of Chitosan

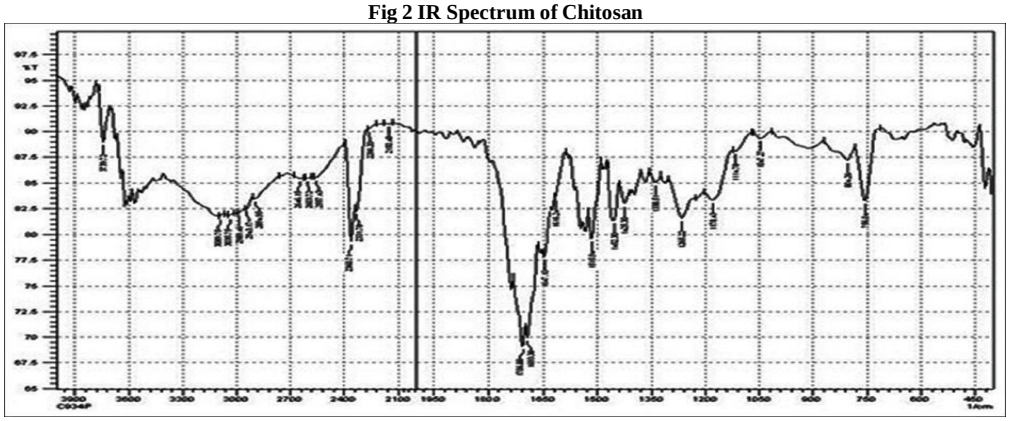

Fig 3: IR Spectrum of HPMC

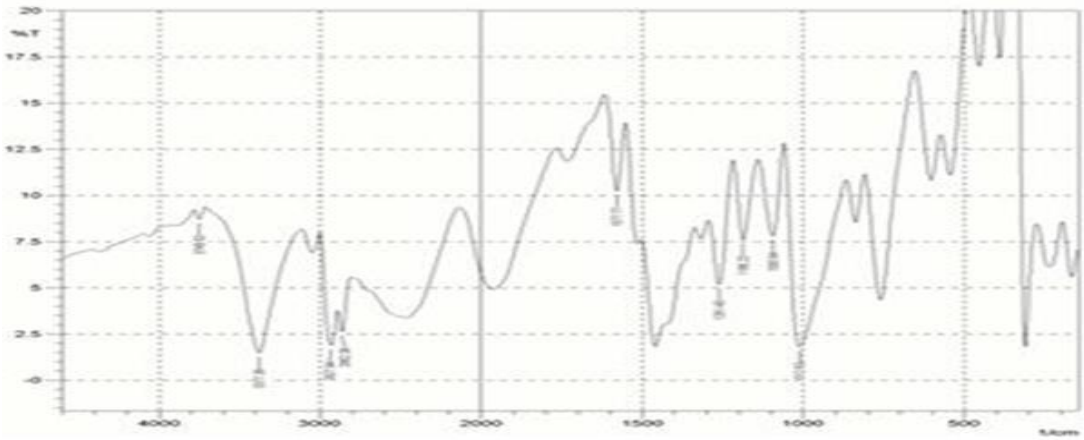

Fig 4: IR Spectrum of formulation of ketorolac microspheres

Surface morphology of ketorolac microspheres (SEM)

Surface morphology of prepared ketorolac microspheres was performed by SEM (Scanning electron microscopy) techniques. Filgen's Vacuum Electron Staining apparatus enables highly efficient, reproducible, and safe electron staining for various electron microscopy(TEM/SEM) specimens.

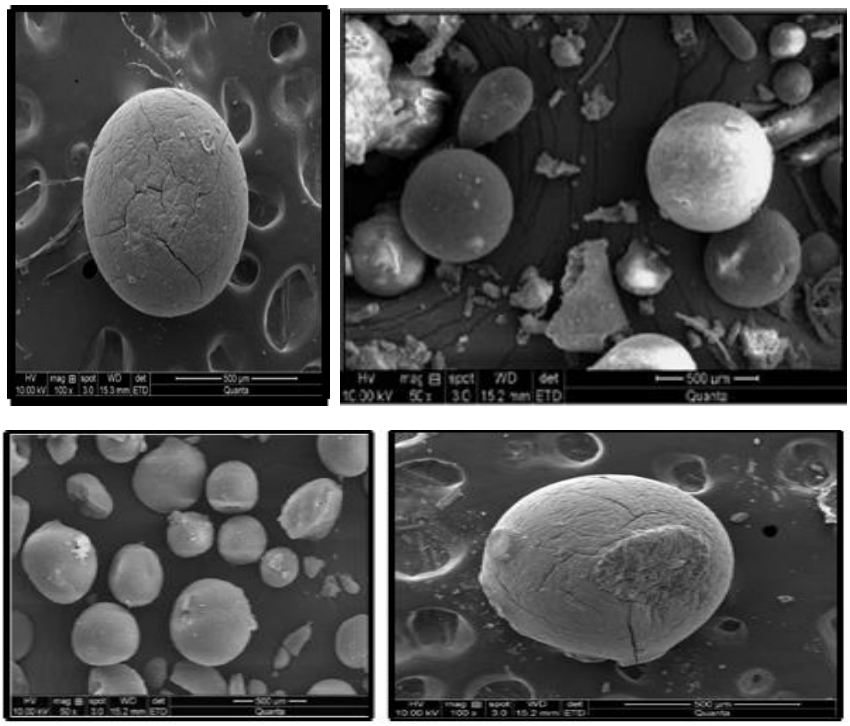

Fig 4:SEM photographs of ketorolac microspheres

Frequency distribution analysis

Determination of Average particle size

Table .3 Average diameter of ketorolac microspheres

Sl no.	Formulation code	Average size (µm)±SEM
1	F1	47.6±2.73
2	F2	76±6.53
3	F3	99.8±8.62
4	F4	107.2±9.97
5	F5	113.1±7.17
6	F6	150.3±5.32

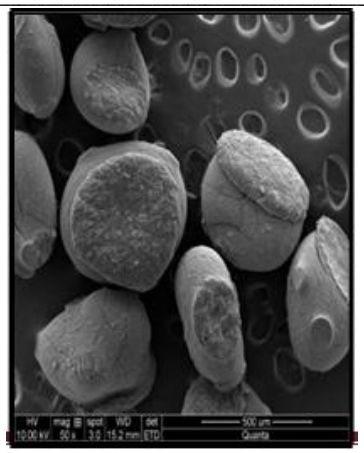

Fig 5: Average diameter of ketorolac microspheres

Frequency distribution analysis

Table 4: Frequency distribution data of ketorolac microspheres

Size in µm	F1	F2	F3	F4	F5	F6
0-50	184	83	30	-	-	-
50-100	113	136	112	161	-	54
100-150	-	60	101	66	84	102
150-200	-	25	36	72	82	72
200-300	-	-	-	-	40	46
300-400	-	-	-	-	-	-

Frequency distribution of ketorolac microspheres

Percentage drug entrapment efficiency

Table 5:Data for the standard calibration curve of ketorolac at 272 nm

Sl.no.	Conc (µg/ml)	Absorbance (272nm)
1.	0	0
2.	2	0.226
3.	4	0.424
4.	6	0.636
5.	8	0.832
6.	10	1.125

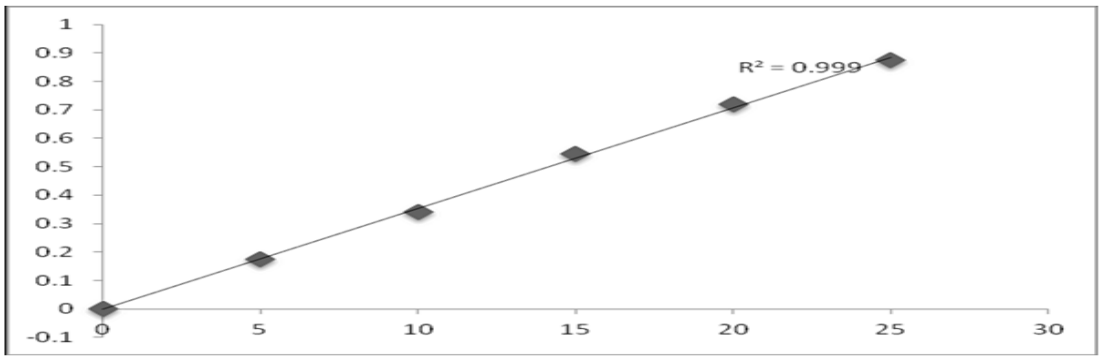

Fig6: Standard calibration curve for ketorolac 272 nm

Table 6:Drug entrapment efficiency of ketorolac microspheres

Sl.no	Formulation code	Percentage yield	Drug content(%)	Entrapment efficiency(%)
1.	F1	60.21	25.45	53.78 ± 1.02
2.	F2	64.41	24.56	58.71 ± 1.11
3.	F3	77.35	23.67	61.35 ± 2.25
4.	F4	84.02	19.65	70.80 ± 1.10
5.	F5	89.67	15.95	77.88 ± 0.98
6.	F6	92.88	14.57	88.60 ± 1.12

SD=Standard deviation (n=3).

In vitro dissolution studies

Table 7:The standard calibration of ketorolac was 272nm shown in Table 5 and Fig1.8

Sl no.	Time(hr)	F1±SD	F2±SD	F3±SD	F4±SD	F5±SD	F6±SD
1.	0	0	0	0	0	0	0
2.	1	23.815 ±0.62	20.97 ±0.10	13.23 ±0.60	17.47 ±0.09	8.68 ± 0.50	7.33 ± 0.59
3.	2	30.64 ±0.49	28.44 ±0.20	17.35 ±0.62	21.52 ±0.14	13.98 ±0.54	7.86 ± 0.55
4.	3	37.65 ±0.69	33.53 ±0.10	24.30 ±0.60	26.45 ±0.06	16.48 ±0.60	10.66 ±0.66
5.	4	44.44 ±0.68	38.49 ±0.04	31.48 ±0.61	33.24 ±0.12	23.61 ±0.68	15.39 ±0.57
6.	5	56.17 ±0.67	44.62 ±0.26	36.74 ±0.56	36.75 ±0.10	28.34 ±0.60	17.49 ±0.66
7.	6	63.59 ±0.60	51.51 ±0.41	43.01 ±0.59	42.01 ±0.24	34.30 ±0.58	21.00 ±0.58
8.	7	71.96 ±0.67	59.18 ±0.16	49.02 ±0.57	47.28 ±0.09	38.16 ±0.60	26.25 ±0.57
9.	8	77.65 ±0.52	66.38 ±0.07	53.29 ±0.61	52.55 ±0.27	44.11 ±0.69	28.02 ±0.66
10.	9	82.76 ±0.68	73.63 ±0.16	61.31 ±0.63	56.82 ±0.14	48.04 ±0.73	31.53 ±0.58
11.	10	86.42 ±0.56	79.39 ±0.16	66.41 ±0.61	63.09 ±0.14	54.84 ±0.66	45.52 ±0.66
12.	11	91.08 ±0.59	82.41 ±0.36	71.35 ±0.62	66.45 ±0.06	58.56 ±0.56	51.51 ±0.69
13.	12	94.64 ±0.53	87.43 ±0.15	78.47 ±0.59	72.53 ±0.09	64.35 ±0.66	59.50 ±0.63

SD=Standard deviation (n=3).

The differences in mean of % cumulative drug release between batch series 'F1-F6'were significant ($p < 0.0001$).

Release kinetics of ketorolac microspheres

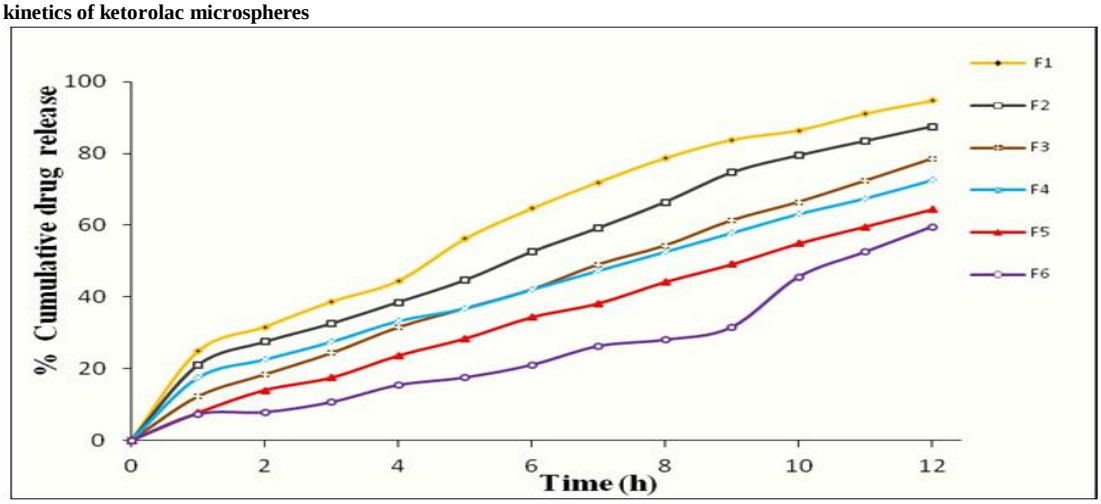

Fig 7: Release kinetics of ketorolac microspheres

Table 8: Zero order release kinetics data of ketorolac microspheres

Sl.no.	Time(h)	% cum. Drug release LP1±SD	LP2±SD	LP3±SD	LP4±SD	LP5±SD	LP6±SD
1.	0	0	0	0	0	0	0
2.	1	23.815 ±0.62	20.97 ±0.10	11.23 ±0.60	16.47 ±0.09	7.68 ± 0.50	7.13 ± 0.59
3.	2	30.64 ±0.49	26.44 ±0.20	18.35 ±0.62	23.52 ±0.14	12.98 ±0.54	7.86 ± 0.55
4.	3	37.55 ±0.69	32.53 ±0.10	24.30 ±0.60	27.25 ±0.06	16.38 ±0.60	10.66 ±0.66
5.	4	43.44 ±0.68	37.39 ±0.04	32.47 ±0.61	33.24 ±0.12	23.61 ±0.68	14.39 ±0.57
6.	5	56.17 ±0.67	44.62 ±0.26	36.74 ±0.56	36.75 ±0.10	28.34 ±0.60	17.49 ±0.66
7.	6	64.59 ±0.60	52.51 ±0.41	42.01 ±0.59	42.01 ±0.24	34.30 ±0.58	21.00 ±0.58
8.	7	71.96 ±0.67	59.18 ±0.16	49.02 ±0.57	47.28 ±0.09	38.16 ±0.60	26.25 ±0.57
9.	8	78.65 ±0.52	66.38 ±0.07	54.29 ±0.61	52.55 ±0.27	44.12 ±0.69	28.02 ±0.66
10.	9	83.76 ±0.68	74.63 ±0.16	61.31 ±0.63	57.82 ±0.14	49.04 ±0.73	31.53 ±0.58
11.	10	86.42 ±0.56	79.39 ±0.16	66.41 ±0.61	63.09 ±0.14	54.84 ±0.66	45.52 ±0.66
12.	11	91.08 ±0.59	83.41 ±0.36	72.35 ±0.62	67.46 ±0.06	59.56 ±0.56	52.51 ±0.69
13.	12	94.64 ±0.53	87.43 ±0.15	78.47 ±0.59	72.53 ±0.09	64.35 ±0.66	59.50 ±0.63

SD=Standard deviation (n=3). The differences in mean of % cumulative drug release between batch series F1-F6' were significant ($p < 0.0001$).

Summary and conclusion

An attempt is made to prepare microspheres of ketorolac using chitosan. It was observed that the preparation process for microspheres was simple and reproducible. The percentage yield was between 71.2±1.52 and 91.62±1.5. Percentage drug entrapment of drug was obtained in all formulations with successful microspheres formation in a range of 81.09±0.043 to 93.07±0.045. Due to higher drug-lipid ratio microspheres the size of bead slightly increased produce. The average size of microspheres range was between 3.67±0.45 to 3.91±0.74 µm. The in vitro data indicated that pure drug showed 100% release within 2 hr. The drug release from the microspheres prepared in formulation F6 achieved 92.40±0.271% in 24 hr.

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