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Research

Formulation Development And In-Vitro Evaluation Of Lornoxicam Mucoadhesive Microspheres

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Abstract

Inthepresent work, bioadhesive microspheres of Lornoxicam using Sodium alginate along with Carbopo l934 and Span 80 asco polymers were formulated to deliver Lornoxicam via oral route.The results of this investigation indicate thatIonotropic gelationmethod can be successfully employed to fabricate Lornoxicam microspheres than emulsion cross linking method. FT-IR spectraof the physical mixture revealed that the drug is compatible with the polymers and copolymer used. Micromeritic studies revealed that the mean particle size of the prepared microspheres was in the size range 548-612µm for ionotropic gelation method and 625-648 µm for emulsion cross linking method,size of ionotropic gelation have high mean partice size than emulsion cross link method andaresuitablefor bioadhesive microspheres for oral administration.Increase in thepolymerconcentrationledto increase in% Yield,%Drugentrapment efficiency, Particle size, % swelling and % Mucoadhesion.The*in-vitro* mucoadhesive study demonstrated that microspheres of Lornoxicam using Span80 as polymer and glutaraldehyde as cross linking agent adhered tothe mucusto a greater extent than sodiumalginate along with Carbopol934. The *invitro* drug releasedecreased with increase in thepolymer and copolymerconcentration.T3 of Ionotropic gelationmethod was optimized based on optimum swelling index, percentage mucoadhesion , drug entrapment and drug relaese.The kinetic data analysis ofdrug release mechanism showedthatthedrug release fromthe formulations followed non-Fickian diffusion and the best fit model was found tobe Krosmeyer-Peppas.Based on the results of evaluation tests formulation codedT_3 was concluded as best formulation.

Keywords: Microspheres, Mucoadhesive

INTRODUCTION

Controlled drug delivery system

For many decades, medication of an acute disease or a chronic illness has been accomplished by delivering drugs to the patients via various pharmaceutical dosage forms like tablets, capsules, pills, creams, ointments, liquids, aerosols, injectables and suppositories as carriers. This results in a fluctuated drug level and consequently undesirable toxicity and poor efficiency. This factor as well as other factors such as repetitive dosing and unpredictable absorption lead to the concept of controlled drug delivery systems.[1,2,3]

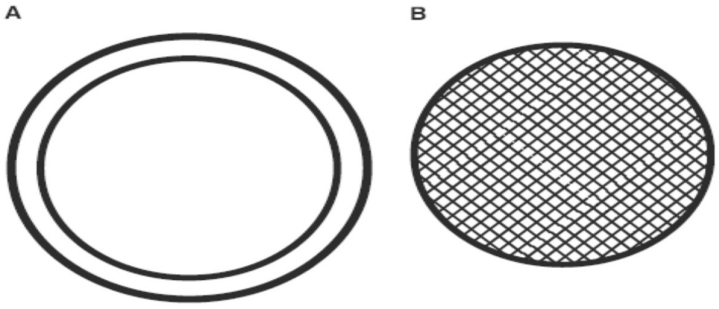
Spatial placement relates to targeting a drug to a specific organ or tissue, while temporal delivery refers to controlling the rate of drug delivery to the target tissue.
Controlled release systems includes any drug delivery system that "achieves slow release of the drug over an extended period of time." If the system can provide some control weather this is of a temporal or spatial nature, in other words, if the system is successful in maintaining predictable and reproducible kinetics in the target tissue or cell, it is considered as a controlled release system[4].

Microencapsulation

Microencapsulation is a rapidly expanding technology. As a process, it is a means of applying relatively thin coatings to small particles of solids or droplets of liquids and dispersions. Microencapsulation is arbitrarily differentiated from macrocoating techniques in that the former involves the coating of particles ranging dimensionally from several tenths of a micron to 5000 microns in size.[6] Microencapsulation provides the means of converting liquids to solids, of altering colloidal and surface properties, of providing environmental protection, and of controlling the release characteristics or availability of coated materials[5,6].

Microspheres can be defined as solid, approximately spherical particles ranging in size from 1 to 1000 µm. They are made of polymeric, waxy, or other protective materials, that is, biodegradable synthetic polymers and modified natural products such as starches, gums, proteins, fats, and waxes. The natural polymers include albumin and gelatin[9-10] the synthetic polymers include polylactic acid and polyglycolic acid[11-12] Microcapsules, where the entrapped substance is completely surrounded by a distinct capsule wall, and micromatrices, where the entrapped substance is dispersed throughout the microsphere matrix[7,8].

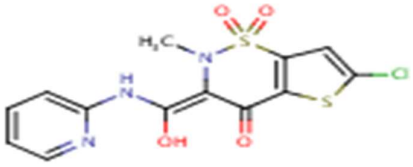
Microspheres are small and have large surface to volume ratios. At the lower end of their size range they have colloidal properties. The interfacial properties of microspheres are extremely important, often dictating their activity[9,10].



(A) Microcapsule consisting of an encapsulated core particle
(B) micromatrix consisting of homogeneous dispersion of active ingredient in particle.

Fig 1: Schematic diagram illustrating microspheres.

Drug profile
Name: Lornoxicam
Structure: Lornoxicam



Chemical Formula: $C_{13}H_{10}ClN_3O_4S_2$
Weight: Average:371.819
Monoisotopic: 370.98012491
IUPAC Name:(3E)-6-chloro-3-{hydroxy[(pyridin-2-yl)amino]methylidene}-2-methyl-2H,3H,4H-1$l^{6},5,2-thieno[2,3-e][2]thiazine-1,1,4-trione

MATERIALS

Table 1: List of materials used in the formulation

S.No.	List of Chemicals	Manufacturing Company
1	Lornoxicam	Chandra labs, hyderabad.
2	Sodium alginate	STANDARD reagents Hyderabad.
3	Carbopol-934	STANDARD reagents Hyderabad.
4	Chitosan	STANDARD reagents Hyderabad.
5	Glutaraldehyde	STANDARD reagents Hyderabad.
6	Calcium chloride dihydrate	Thermo Fisher Scientific India Pvt. Ltd.
7	Span -80	Sisco research laboratories Pvt.Ltd Mumbai
8	Liquid paraffin	Sisco research laboratories Pvt.Ltd Mumbai
9	n-hexane	Sisco research laboratories Pvt.Ltd Mumbai

Instrumentation

Table 2: List of instruments used

S.No.	Instruments/Equipments	Model and Manufacturer/Supplier
1	UV-Visible spectrophotometer	Elico
2	Electronic weighing balance	Electrolab
3	Magnetic stirrer	Remi motor
4	Dissolution Apparatus	LAB INDIA Instruments Pvt. Ltd.
5	Disintegration Apparatus	THERMO LAB.
6	Ultrasonic cleaner	Spectra lab model UCB 3
8	FT – IR Spectrometer	SHIMADZU FT-IR 8400

Methodology
Preformulation studies
PREPARATION OF 0.1N 0.1N naoh
Dissolve 40 g NaOH in 1L water(1000ml) to give 0.1N NaOH solution.

Preparation 0.2M naoh
Dissolve 8.0g of sodium hydroxide in 1000ml of water to 0.2M NaOH solution.

Preparation 0.2mpotassium dihydrogen phosphate
Dissolve 27.218g of potassium dihydrogen phosphate in water and dilute with water to produce 1000ml.

Preparation of 7.4ph phosphate buffer
Place 50.0ml of 0.2M potassium dihydrogen phosphate in a 200ml volumetric flask and add 39.1ml 0f 0.2M NaOH solution in 1000ml volumetric flask and made up to with distiiled water.

Determination of λmax
Stock solution (1000µg/ml)of Lornoxicam was prepared in 0.1N NaOH solution. This solution was appropriately diluted with 7.4pH Phosphate buffer to obtain a concentration of 10µg/ ml. There sultant solution was scanned in the range of 200nm to 400nm on UV-Visible spectrophotometer. The drug exhibited a λmax at 378nm.

The Linear Regression Analysis
The linear regression analysis was done on Absorance points. The standardcalibrationcurveobtained had a Correlation Coefficient of 0.999 with of slopeof0.047andinterceptof 0.003.

Compatibility studies
A proper design and formulation of a dosage form requires considerations ofthephysical, chemical and biological characteristics of both drug and excipients used in fabrication of the product. Compatibility must be established between the active ingredient and other excipients to produce a stable,efficacious, attractive and safe product.Hence,before producing the actual formulation,compa tibility of Lornoxicam with different polymers and other excipients was tested using the Fourier Transform Infrared Spectroscopy (FT-IR) technique.

RESULTS AND DISCUSSION

Spectroscopic studies

The calibration curve data of Lornaxicamin 7.4pH Phosphate buffer at 378nm.The standard calibration curve with a regression value of 0.999, with a slope of 0.047 and intercept of 0.003 in 7.4pH Phosphate buffer. The curve was found to be linear in the concentration range of 2-10µg/ml.

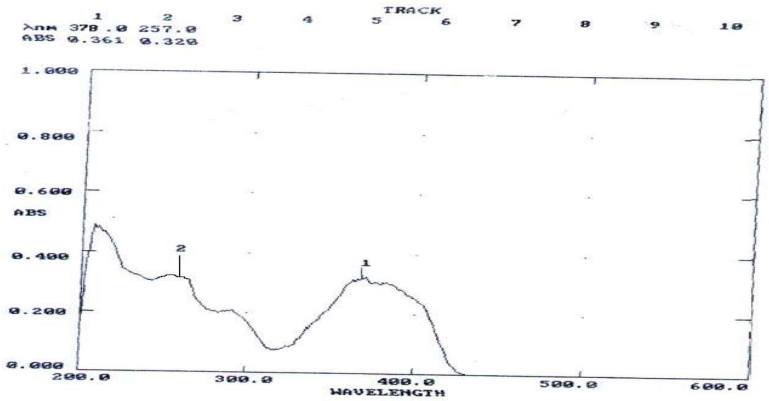


Fig 1: Calibration curve of Lornaxicam in simulated gastric fluidpH 1.2

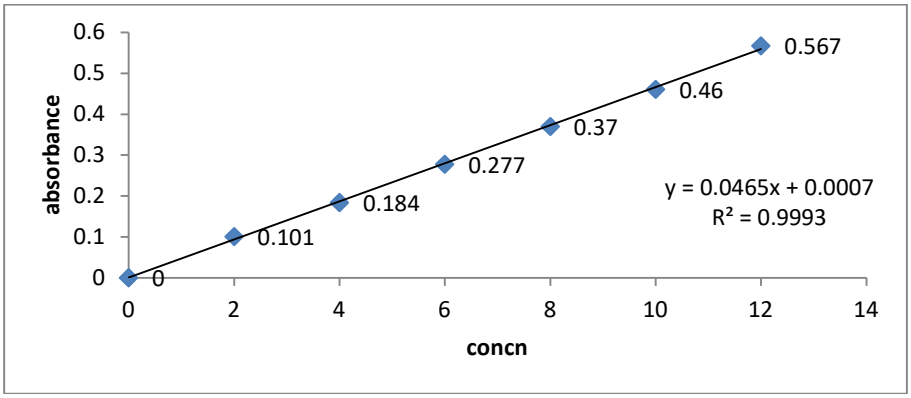


Fig 2: Standard graph Of Lornaxicam in 7.4pH Phosphate buffer

Compatibility studies

Drug excipient compatibility studies

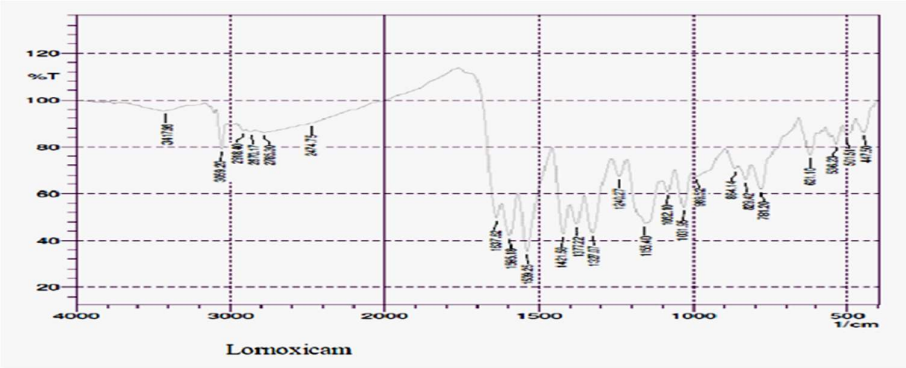


Fig 3: FTIR Spectra of Lornoxicam

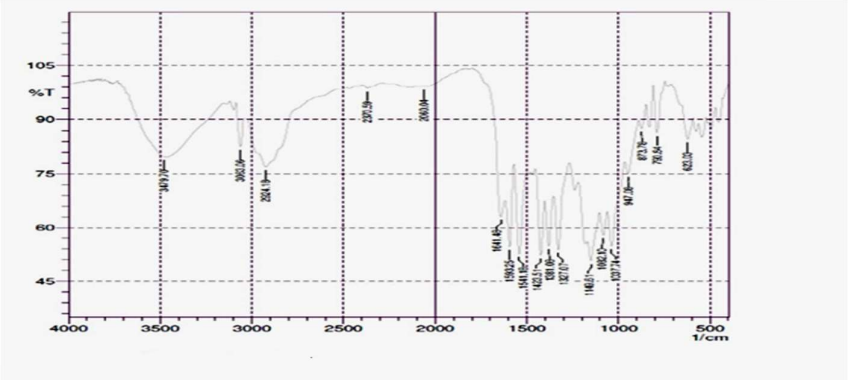


Fig 4: FTIR Spectra of Lornoxicam optimized formulation

Micromeritics

Table 3: Pre-formulation parameters

Formulations	Angle of Repose (θ)	Loose Bulk Density (g/ml)	Tapped Bulk Density (g/ml)	% Compressibility	Hausner's ratio
F1	26.39	0.37	0.42	11.90	1.14
F2	28.10	0.35	0.41	14.63	1.17
F3	27.12	0.34	0.39	12.82	1.15
F4	26.14	0.36	0.42	14.29	1.17
F5	27.37	0.30	0.35	14.29	1.17
F6	26.35	0.33	0.38	13.16	1.15
F7	25.38	0.38	0.44	13.64	1.16
F8	26.25	0.31	0.36	13.89	1.16

Evaluationandcharacterisation of microspheres

Table 4: % yield and % drug entrapment efficiency of the prepared microspheres

S.No.	Formulation code	% yield	%Drug entrapment efficiency
1	**T1**	82.1	77.9
2	**T2**	85.4	79.3
3	**T3**	86	85.2
4	**T4**	88.8	85.6
5	**T5**	79.9	72.1

6	**T6**	81.2	78.7
7	**T7**	84.6	82.3
8	**T8**	84.9	84.6

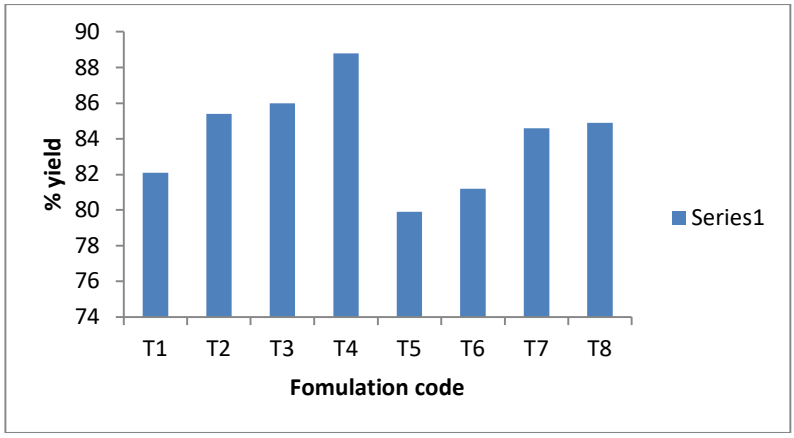


Fig 5: Graphical representation of % yield of formulations T1 - T8

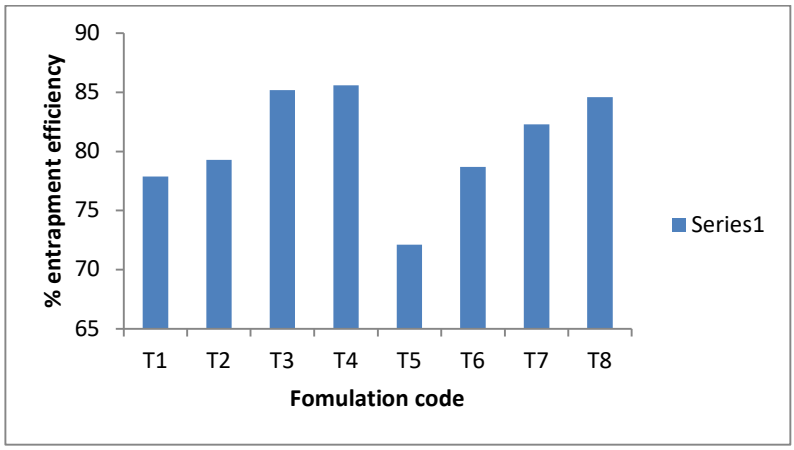


Fig 6: Graphical representation of % drug entrapment efficiency of formulationsT1 - T8

Particle size analysis

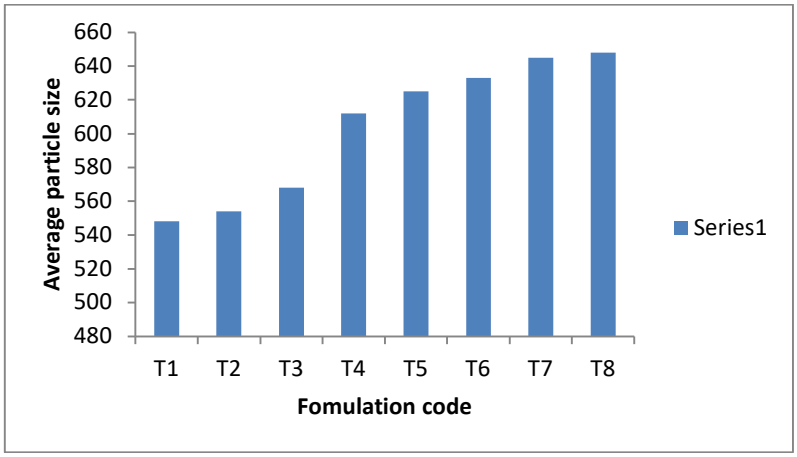


Fig 7: Graphical representation of average particle size for formulations T1-T8.

In-vitro drug release studies

Table 5: In-Vitro drug release data of Lornoxicam microspheres containing sodium alginate along with carbopol 934 as copolymer

TIME (hrs)	Cumulative Percent Of Drug Released			
	T1	T2	T3	T4
0	0	0	0	0
1	15.08	12.60	27.96	28.86
2	29.70	28.01	38.84	34.10
3	32.68	34.80	43.17	45.42
4	39.54	40.68	50.8	56.62
5	44.25	47.13	62.26	67.71
6	51.36	53.69	72.18	70.92
7	72.74	76.82	81.11	79.21
8	80.74	82.31	88.62	83.40

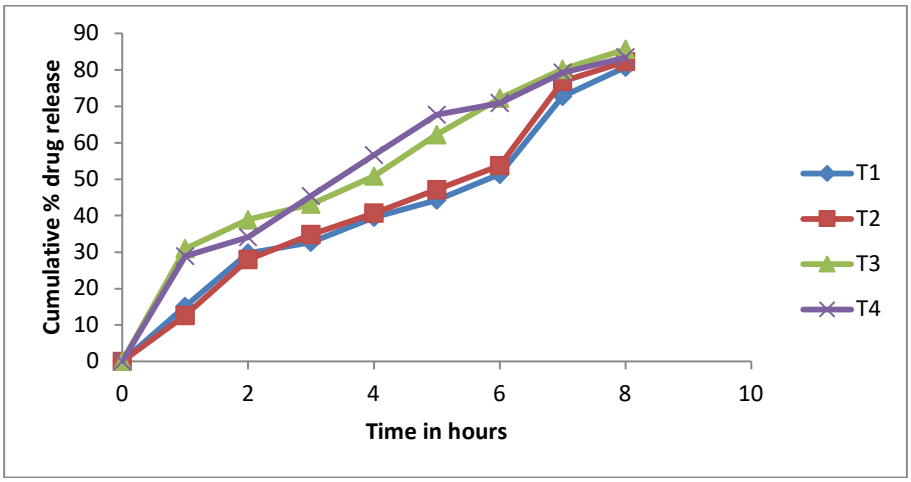


Fig 8: Comparison of In-Vitro drug release profile of Lornoxicam microspherescontaining sodium alginate along with carbopol 934 as copolymer

Table 6: In-Vitro drug release data of Lornoxicam microspheres containing Chitosan solution in 2% aqueous acetic acid as copolymer

TIME (hrs)	Cumulative Percent Of Drug Released			
	T5	T6	T7	T8
0	0	0	0	0
1	22.40	22.46	20.34	18.79
2	36.16	28.60	28.00	26.55
3	43.80	36.90	34.31	36.50
4	50.91	47.22	45.52	43.64
5	55.40	55.07	55.61	54.52
6	61.82	58.09	57.70	58.30
7	68.70	66.58	65.98	62.66
8	75.51	72.80	70.11	64.48

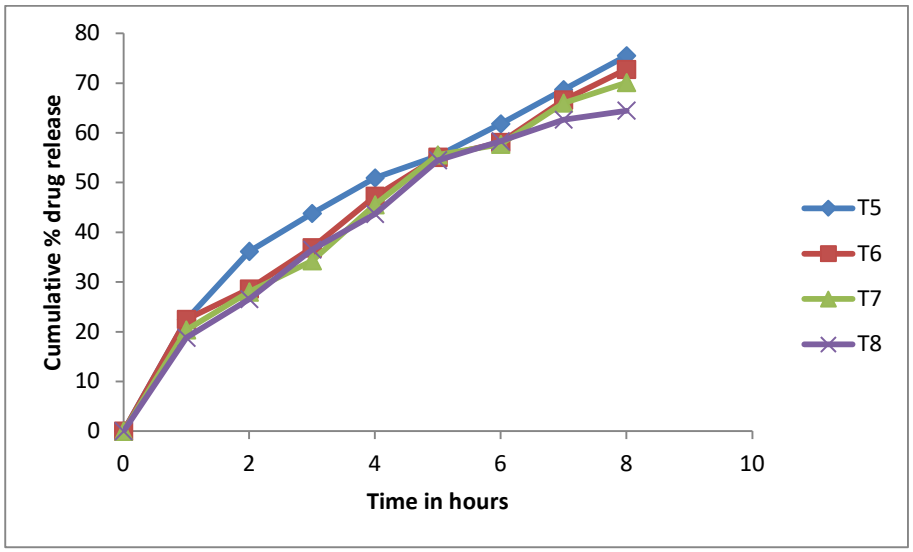


Fig 9: Comparison of In-Vitro drug release profile of Lornoxicam microspherescontaining Chitosan solution in 2% aqueous acetic acid as copolymer

Morphological study of Microspheres

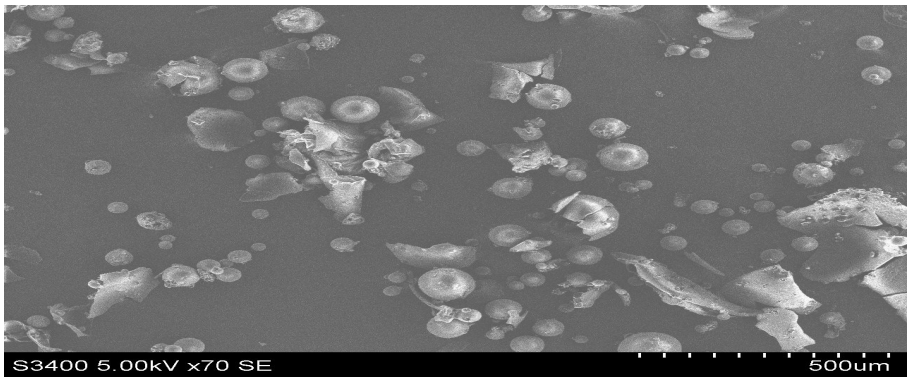


Fig 10:Scanning Electron Photomicrograph of Microspheres

SUMMARY AND CONCLUSION

Inthepresent work, bioadhesive microspheres of Lornoxicam using Sodium alginate along with Carbopo l934 and Span 80 ascopolymerswereformulated to deliver Lornoxicam via oral route.

Details regarding thepreparation and evaluation ofthe formulations have been discussed inthe previous chapter. From the study following conclusions couldbedrawn:-

- The results of this investigation indicate thatIonotropic gelationmethod can be successfully employed to fabricate Lornoxicam microspheres than emulsion cross linking method.
- FT-IR spectra of the physical mixture revealed that the drug is compatible with the polymers and copolymer used.
- Micromeriticstudies revealedthatthe meanparticlesizeofthepreparedmicrospheres was in the size range 548-612µm for ionotropic gelation method and 625-648 µm for emulsion cross linking method,size of ionotropic gelation have high mean partice size than emulsion cross link method andaresuitablefor bioadhesive microspheres for oral administration.
- Increase in thepolymerconcentrationledto increase in% Yield,%Drugentrapment efficiency, Particle size, % swelling and % Mucoadhesion.
- The *in-vitro* mucoadhesive study demonstrated that microspheres of Lornoxicam using Span 80 as polymer and glutaraldehyde as cross linking agent adhered to the mucusto a greater extent than sodium alginate along with Carbopol934.

- The *invitro* drug release decreased with increase in the polymer and copolymer concentration.
- T3 of Ionotropic gelationmethod was optimized based on optimum swelling index, percentage mucoadhesion , drug entrapment and drug relaese.
- The kinetic data analysis ofdrug release mechanism showedthatthedrug release fromthe formulations followed non-Fickian diffusion and the best fit model was found tobe Krosmeyer-Peppas.
- Based on the results of evaluation tests formulation codedT_3 was concluded as best formulation.

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