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FORMULATION AND EVALUATION OF MUCOADHESIVE MICROSPHERES OF LORATADINE FOR NASAL DRUG DELIVERY

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ABSTRACT

Intranasal administrative is an ideal alternative to the parenteral route for systemic drug delivery. Nasal mucosa consists of a rich vasculature and a highly permeable structure for systemic absorption. Drug administration through the nasal cavity is easy and convenient. Avoidance of first pass metabolism is the main advantage of nasal route drug delivery. Bioadhesive polymers are used as drug carriers for the nasal drug delivery. The advantage of using Bioadhesive polymer is increase in residence time of the formulation in the nasal cavity and thereby minimizing rapid mucociliary clearance of the therapeutic agent from the site of deposition.

KEYWORDS:- Loratadine, Mucoadhesive, Transdermal, Bioadhesive, Polymers, Nasal Delivery, Microspheres.

INTRODUCTION

Mucoadhesive microspheres include microparticels and microcapsules (having a core of the drug) of 1-1000um in diameter and consisting either entirely of a mucoadhesive polymer or having an outer coating of it, respectively. Microspheres, in general, have the potential to be used for targeted and controlled release drug delivery; but coupling of mucoadhesive properties to microspheres has additional advantages, e.g. efficient absorption and enhanced bioavability of the drug due a high surface to volume ratio, a much more intimate contact with the mucus layer, specific targeting of drug to the absorption site achieved by anchoring plant lectins bacterial adhesion and antibodies *etc*. on the surface of the microspheres. Mucoadhesive microsphere can be tailored to adhere to any mucosal tissue including those found in eye, nasal cavity, urinary and gastrointestinal tract, thus offering the possibilities of

localized as well as systemic controlled release of drugs. Application of mucoadhesive microspheres to the mucosal tissues of ocular cavity, gastric and colonic epithelium is used for administration of drugs for localized action. Prolonged release of drug and reduction in frequency of drug administration to the ocular cavity can highly improve the patient compliance. The latter advantage can also be obtained for drug administered intra-nasal due to reduction in mucociliary clearance of drug adhering to nasal mucosa.

MATERIAL AND METHOD

Table no. 1: List of material used.

S. No.	Chemicals/ Materials	Manufactures/Suppliers
1.	Loratadine	Microlab PVT.LTD. Baddhi, Himachal Pradesh
2.	Chitosan	Thermo Fischer Scientific India PVT.LTD.,B-Wing, Delphi, Mumbai-400076
3.	Methanol	Jiangsu Huaxi International Trade Co. LTD., Made in China.
4.	Acetic acid	Qualinges Fine Chemicals
5.	Glutaraldehyde	Qualinges Fine Chemicals
6.	Light liquid paraffin	Thermo Fischer Scientific India,PVT.LTD.,B-Wing, Delphi, Mumbai-400076
7.	Heavy liquid paraffin	Qualinges Fine Chemicals
8.	Acetone	Sd Fine CHEM LIMITED, Mumbai
9.	Hexane	Sd Fine CHEM LIMITED, Mumbai
10.	DOSS	Thermo Fischer Scientific India PVT.LTD.,B-Wing, Delphi, Mumbai-400076
11.	Sodium hydroxide	Qualinges Fine Chemicals, Thermo Electro, India PVT.LTD.,Navi Mumbai

Table no. 2: List of equipments used.

S. No.	Equipments	Manufacturers/Suppliers
1.	Digital balance	VibraEssae
2.	Melting point apparatus	Scientex
3.	UV-1700 Spectrophotometer	Shimadzu Corporation, Japan
4.	Magnetic stirrer	IKA®RW 20 digital, Remi Lab Stirrer
5.	Scanning electron microscopy	Shimadzu Corporation, Japan
6.	Dissolution apparatus USPXXII	Electrolab Dissolution tester(USP)-TDT-06L
7.	Digital oven	Alkolite industries Ltd.
8.	Refrigerator	LG Refrigerator
9.	pHep® pocket sized pH meter	Hanna Instruments
10.	FTIR Spectrophotometer	Shimadzu corporation, Japan

Formulation development

Spectrophotometric methods for estimation of Loratadine-Spectrophotometric methods or estimation of Loratadine[16,42]

3.1.2.1. UV Spectrophotometric studies

Caliberation curve of Loratadine

A standard curve from the stock solution was obtained in the range of 10-50µg/ml concentration using methanol, distilled water and pH 6.8 phosphate buffer by measuring absorbance at specific range (nm).

a) Caliberation curve of Loratadine in Distilled water

Date	20.08.2013
Caliberation curve for	Loratadine
Solvent	Distilled water
λ_{max}	246
Unit of concentration	mcg/ml
Slope of Caliberation curve	0.022
Constant of Caliberation curve	0.009
Coefficient correlation of Caliberation curve	0.999

Table 3: Standard caliberation table for loratadine in distilled water.

S. NO.	Concentration	Absorbance
1.	0.0	0.00
2.	10.0	0.245
3.	20.0	0484
4.	30.0	0.680
5.	40.0	0.888
6.	50.0	1.142

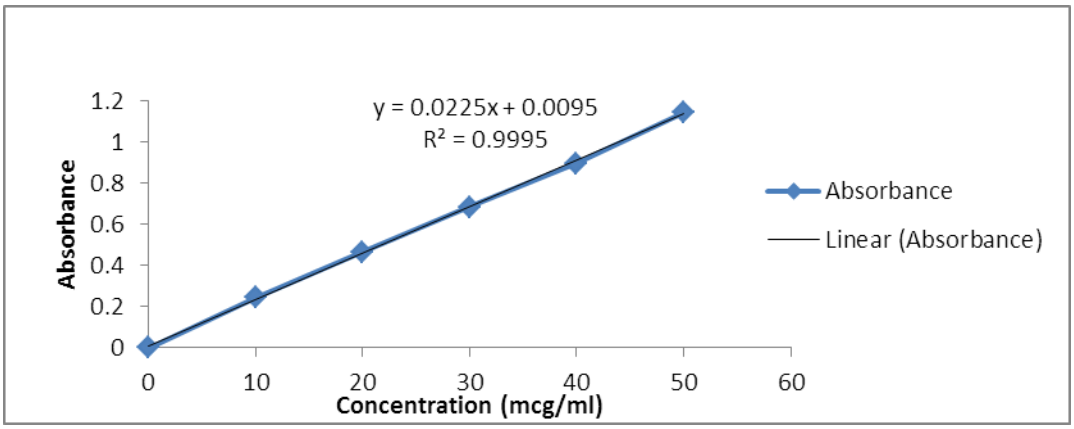

Fig. no. 1 Caliberation curve of loratadine in distilled water.

b) Caliberation curve of Loratadine in methanol

Date	19.08.2013
Caliberation curve for	Loratadine
Solvent	Methanol
λ_{max}	247
Unit of concentration	mcg/ml
Slope of Caliberation curve	0.0035
Constant of Caliberation curve	0.008
Coefficient correlation of Caliberation curve	0.998

Table 4: Standard caliberation table for loratadine in methanol.

S. NO.	Concentration	Absorbance
1.	0.0	0.0
2.	10.0	0.356
3.	20.0	0.709
4.	30.0	1.026
5.	40.0	1.399
6.	50.0	1.806

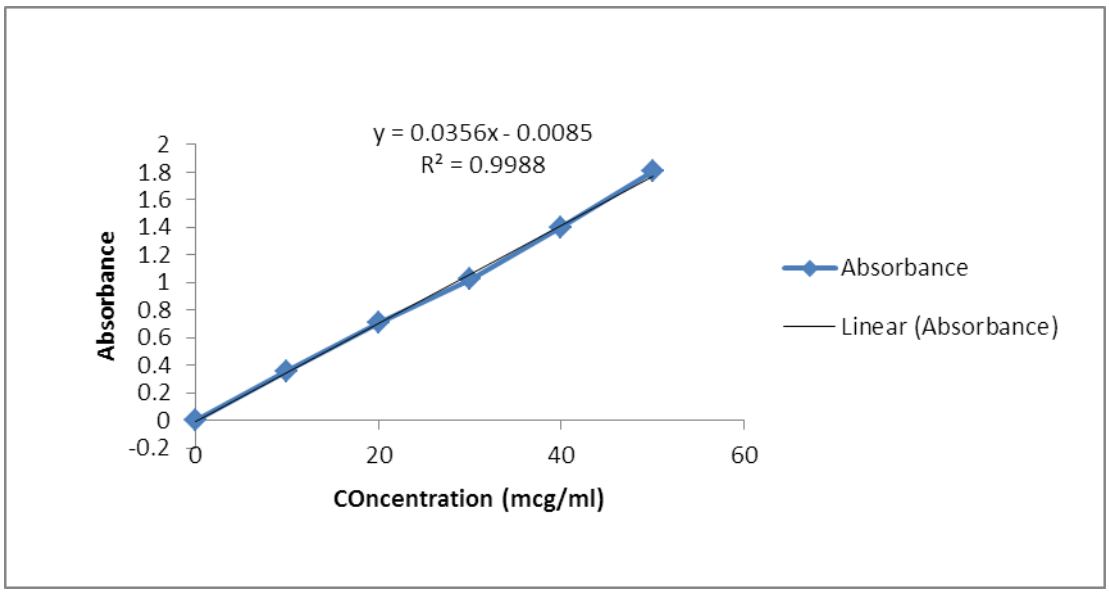

Fig. no. 2: Caliberation curve of loratadine in methanol.

c) Caliberation curve of Loratadine in Phosphate buffer pH 6.8

Date	14.08.2013
Caliberation curve for	Loratadine
Solvent	phosphate buffer 6.8
λ_{max}	247

Unit of concentration	mcg/ml
Slope of Caliberation curve	0.016
Constant of Caliberation curve	0.022
Coefficient correlation of Caliberation curve	0.997

Table 5: Standard caliberation table for loratadine in phosphate buffer 6.8.

S. NO.	Concentration	Absorbance
1.	0.0	0.0
2.	10.0	0.198
3.	20.0	0.356
4.	30.0	0.520
5.	40.0	0.685
6.	50.0	0.852

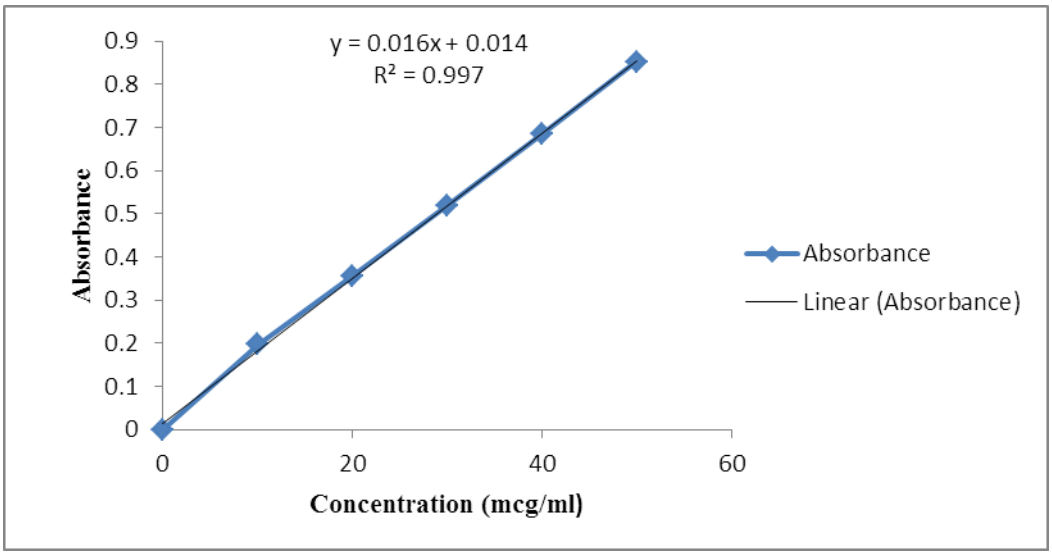

Fig. no. 3: Caliberation curve of loratadine in phosphate buffer 6.8.

RESULTS AND DISCUSSION

Characterisation of mucoadhesive microspheres[52,53,54]

a) Determination of particle size

The mean particle sizes of the formulations is shown in the table 3.8 and mean particle size is depicted in fig No.3.8. The particle size mainly depends on the stirring rate and slow effect of concentration of mucoadhesive polymers, it is clear that stirring rate increases particle size decreases both at higher and lower concentration of polymers while concentration of mucoadhesive polymer had opposite effect on particle size.

Micromeasurement test report	
Name : Shilpi sonkar	Application:
	Operator:
Sample info id :	Microscope obj: Formulation of loratadine and chitosan

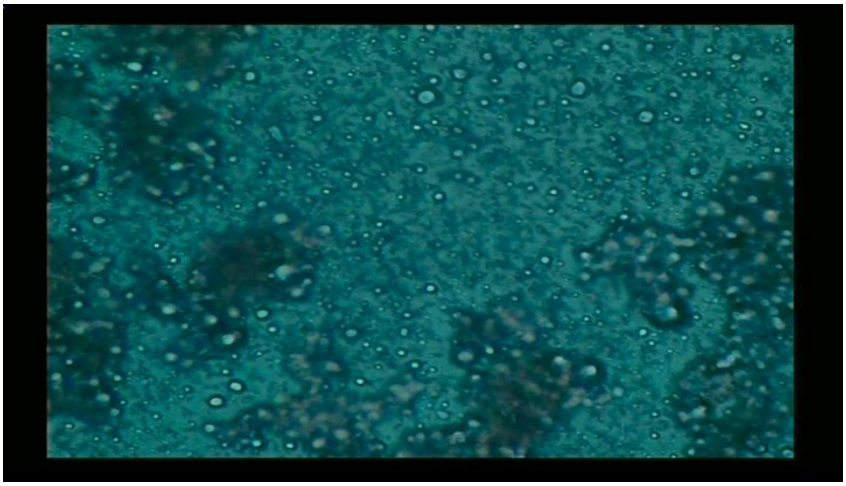

Fig. no. 4: Optical microscopy of formulation (F3).

Table No. 3.8: Optical microscopy of formulation (F6).

S. NO.	**1**	**2**	**3**	**4**
Length (Micron)	58.79	11.448	11.448	11.448
Length (Micron)	47.352	8.119	8.119	8.119
Area (Micron Sqr.)	100.00	73.046	73.046	73.046
Asp. Ratio	1.242	1.41	1.41	1.41
Roundness	100	100	100	100
Shape	0.01	0.01	0.01	0.01

b) Determination of particle size distribution by scanning electron microscopy.

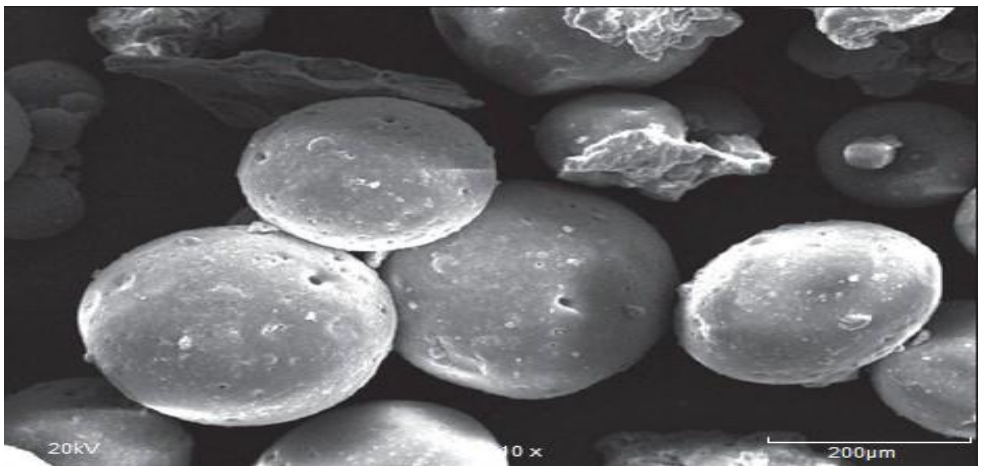

Fig. no. 5: S. E. M. of Formulation (F3).

c) Production yield and Encapsulation efficiency.

The production yields of microspheres prepared by emulsion cross-linking method were found to be between 80-85 as shown in table No.3.9.

Table 7: Production yield and Encapsulation Efficiency of formulations.

Formulation code	Production yield (%)	Encapsulation Efficiency (%)
F1	83.5	39.5
F2	84.5	62.157
F3	85.0	66.921
F4	83.0	45.036
F5	86.0	63.101
F6	87.25	75.298

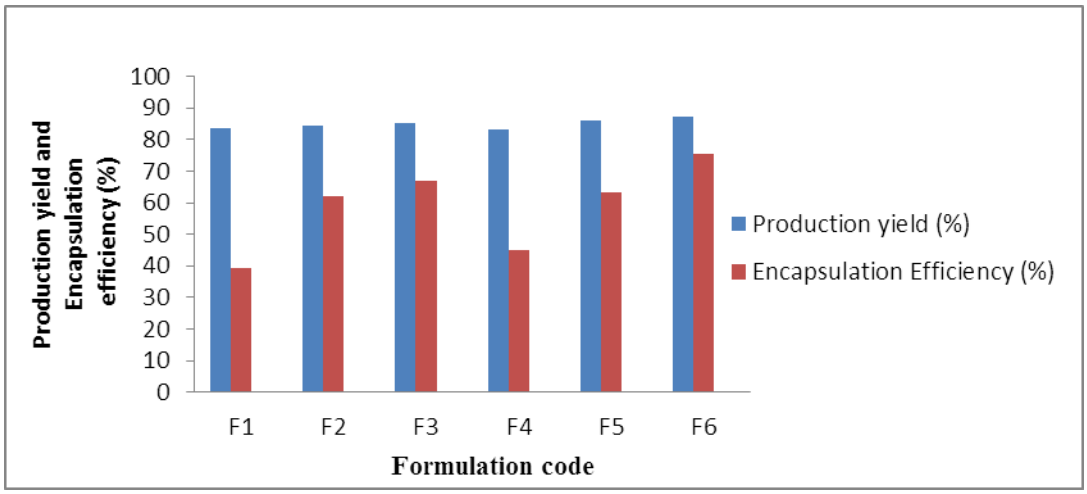

Fig. no. 6: Bar Diagram to show production yield and encapsulation efficiency of formulations.

Swelling index

The swelling index of all formulation is shown in Table 3.

Table 8: Swelling index of formulations.

Formulation	Swelling index (%)
F1	0.615
F2	0.945
F3	1.115
F4	0.675
F5	0.955
F6	1.215

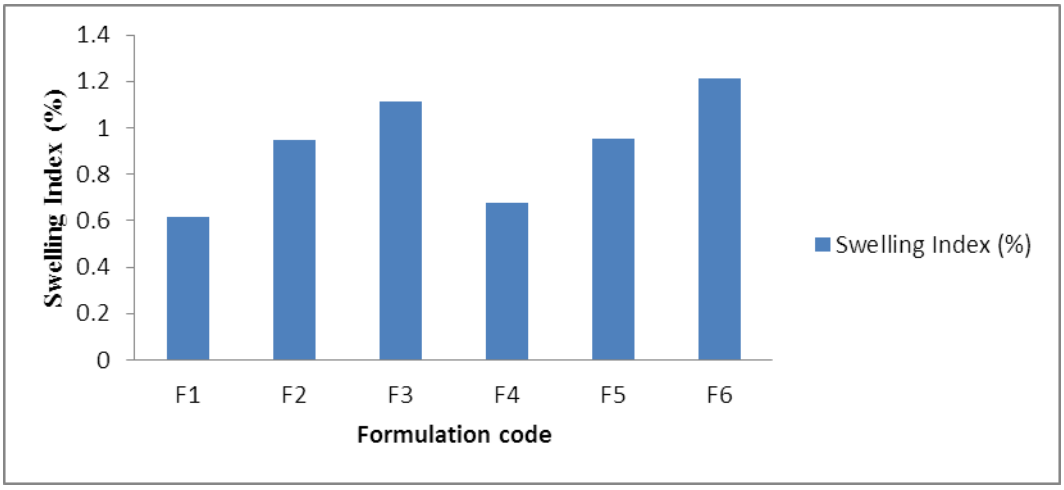

Fig. no. 7: Bar diagram to show swelling index of formulations.

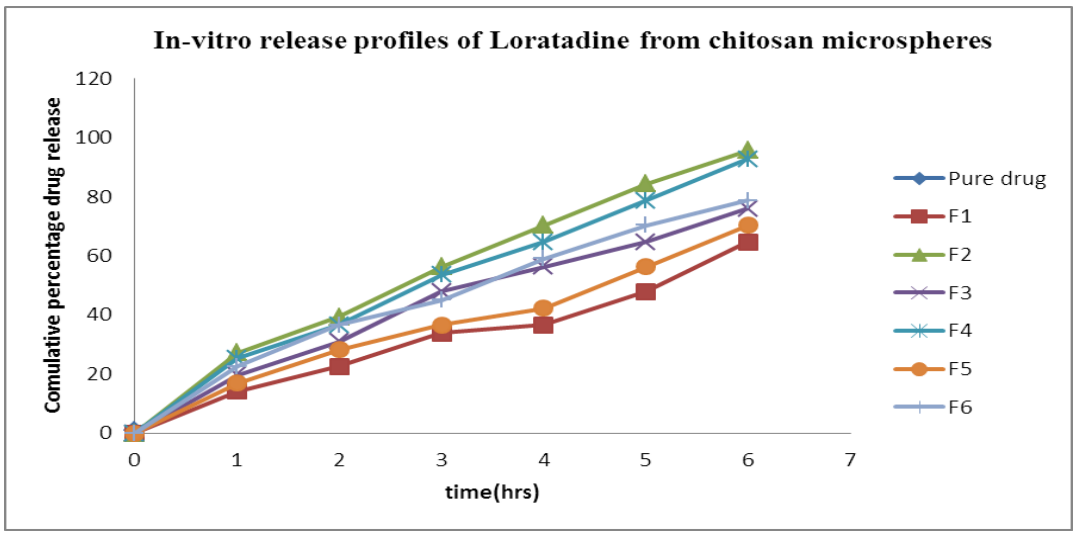

Fig. no. 8 In vitro drug release of all formulations.

d) In vitro drug release kinetics studies

The in-vitrodrug release data of all the formulations were fit into Zero order, First order, Higuchi Equation and Korsemeyer-Peppas model. The results are shown in table

Table no. 10: Correlation coefficient 'R' values in the analysis of release data of microspheres as per various kinetics model and 'n' value of Peppas equation.

Formulations	Zero order	First order	Higuchi matrix	Peppas plot	
	R^2 value	R^2 value	R^2 value	R^2 value	'n' value
F1	0.977	0.931	0.908	0.976	0.811
F2	0.980	0.976	0.963	0.933	0.762
F3	0.988	0.947	0.958	0.989	0.733
F4	0.983	0.982	0.931	0.982	0.761
F5	0.984	0.896	0.965	0.995	0.701
F6	0.992	0.889	0.960	0.987	0.704

Table no. 11: Zero order release kinetics of all formulations.

Time (hrs)	Cumulative percentage drug release					
	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
1	14.06	19.687	25.312	16.875	22.50	27.125
2	22.50	30.937	36.56	28.125	36.562	39.37
3	33.75	47.81	53.437	36.56	45.00	56.25
4	36.56	56.25	64.687	42.187	59.062	70.31
5	47.81	64.687	78.75	56.25	70.312	84.375
6	64.687	75.93	92.812	70.31	78.75	95.625

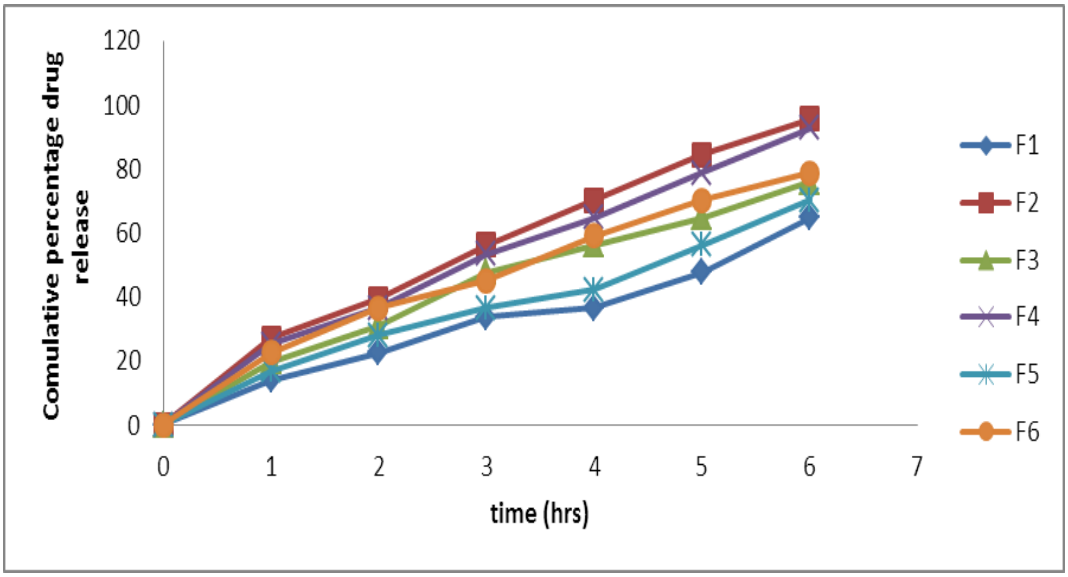

Fig. no. 9: Zero order release kinetics of all formulations.

Table no. 12: First order release kinetics of all formulations.

Time (hrs)	log Cumulative percentage drug remaining					
	F1	F2	F3	F4	F5	F6
0	2	2	2	2	2	2
1	1.934	1.904	1.873	1.919	1.889	1.856
2	1.889	1.839	1.821	1.856	1.802	1.782
3	1.821	1.717	1.668	1.802	1.74	1.6409
4	1.802	1.6409	1.547	1.762	1.612	1.4752
5	1.717	1.547	1.327	1.6409	1.4752	1.1938
6	1.547	1.3814	0.856	1.4752	1.327	0.64

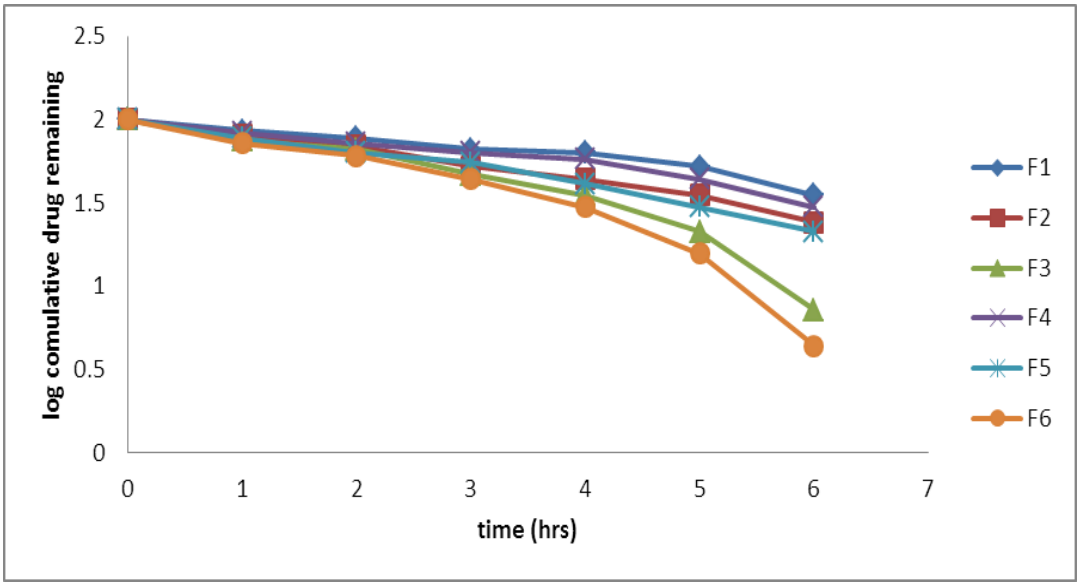

Fig. no. 10: First order release kinetics of all formulation.

Table no. 13: Higuchi matrix release kinetics of all formulations.

Square root of time	Cumulative percentage drug release					
	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
1	14.06	19.687	25.31	16.875	22.5	27.125
1.414	22.5	30.937	36.56	28.125	33.75	39.37
1.732	33.75	47.81	53.437	36.56	45	56.25
2	36.56	56.25	64.687	42.187	59.062	70.31
2.236	47.81	64.687	78.75	56.25	70.312	84.375
2.449	64.687	75.93	92.812	70.31	78.75	95.625

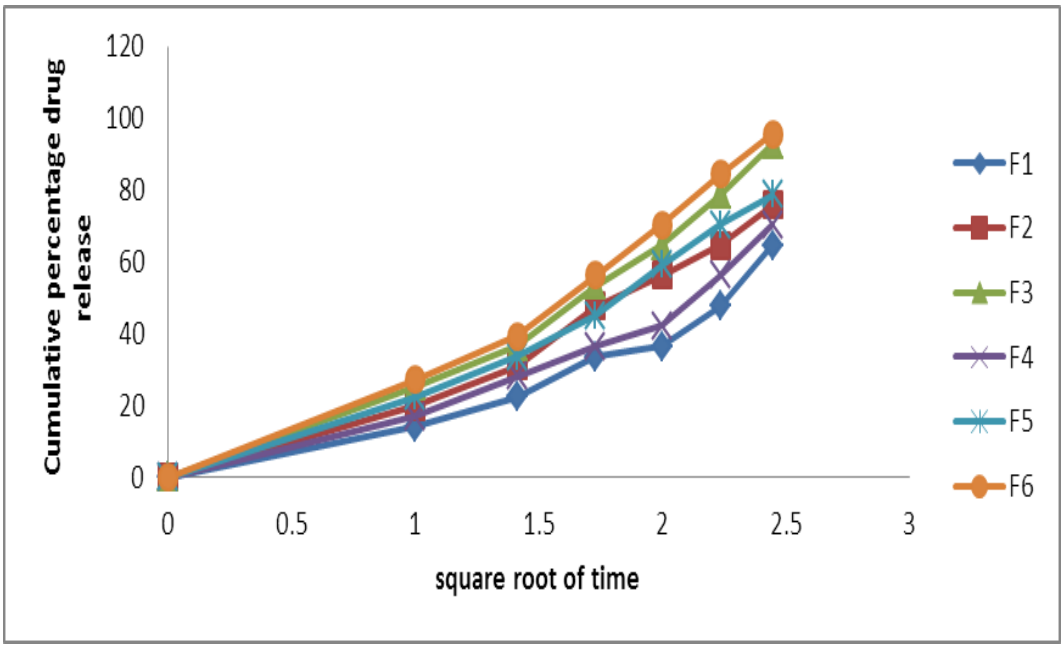

Fig. no. 11: Higuchi matrix release kinetics of all formulations.

Table no. 14: Korsmeyer peppas release kinetics of all formulations.

Log time	log Cumulative percentage drug release					
	F1	F2	F3	F4	F5	F6
0	1.147	1.294	1.4032	1.227	1.3521	1.449
0.301	1.352	1.4904	1.563	1.449	1.563	1.5951
0.4771	1.5282	1.6795	1.727	1.563	1.6532	1.751
0.602	1.563	1.751	1.8108	1.625	1.771	1.847
0.6989	1.6795	1.8108	1.896	1.751	1.847	1.926
0.7781	1.8108	1.88	1.9676	1.847	1.896	1.9805

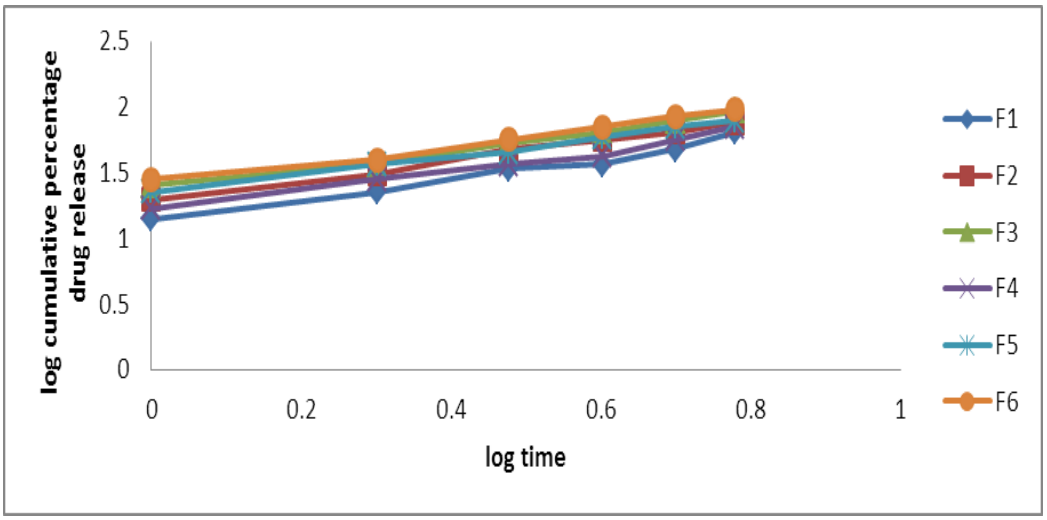

Fig. no. 12: Korsmeyerpeppas release kinetics of all formulations.

g) In-Vitro Mucoadhesion test for microspheres

The result of in-vitro mucoadhesion is shown in Table No.3.23. The percent mucoadhesion increased with increase in the concentration of mucoadhesive polymer. Such excellent mucoadhesion of chitosan microspheres was from the electrostatic attraction between chitosan and mucin. Moreover, the linear molecules of chitosan expressed sufficient chain flexibility for interpenetration and entanglement.

Table no. 15: Percentage mucoadhesion of formulations.

Formulation code	Ratio (Drug : polymer)	Mucoadhesion (%)
F1	1:1	56
F2	1:2	68
F3	1:3	72
F4	1:1	64
F5	1:2	68
F6	1:3	76

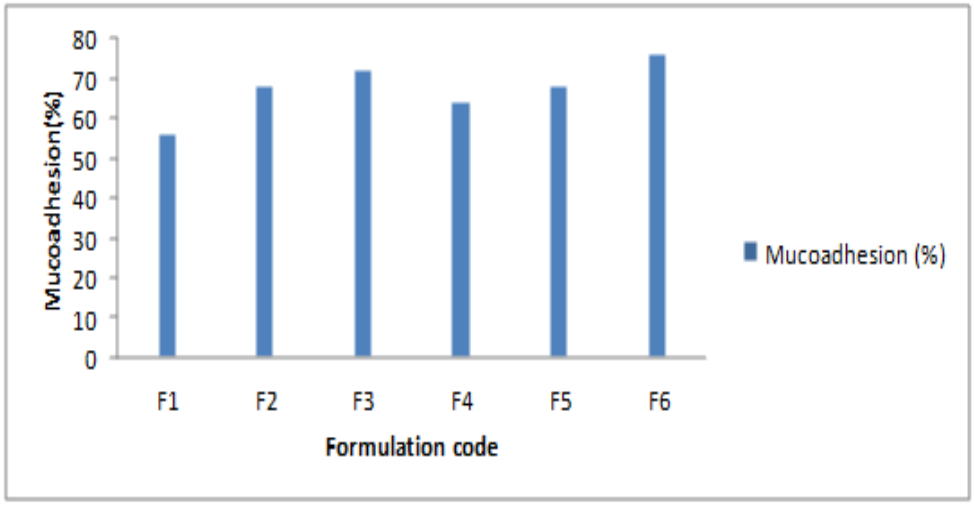

Fig. no. 13: Bar diagram to show percentage mucoadhesion of all formulations.

h) Stability studies

Stability studies of the prepared Loratadine microspheres were carried out by storing the best formulation F3 & F6 at 4±1˚C, 25±2˚C & 60±5˚C RH and 37 ± 2˚C & 65 ± 5% RH for one month.

Table no. 16: Stability studies of formulation (F3 & F6).

Formulation code	4± 1˚C	25±2˚C& 60±5% RH	37±2˚C& 65±5% RH
	Entrapment Efficiency (%)		
F3	65.038	66.758	60.123
F6	74.345	75.192	71.678

SUMMARY AND CONCLUSION

Toachieveclinicalefficacyisthemostimportantcriteriaforanynoveldrugdeliverysystem.Anovelbiodegradableandbioadhesivemicrospheressystemshasbeendevelopedfortheintranasaldelivery.Loratadineisaperipheralhistamine H1eceptorsantagonist,whichisusedinthetreatmentofallergy&rhinitis.Itisgenerallygivenbyoral&parenteralroute.However,ithaspoorbioavailability(%)byoralroutewhichmakesoraltreatmentunsatisfactory. Intranasalroutemaybeviablealternativeforself-administrationwherethelimitationsoforalandparenteralroutecouldbeovercome.Conventionaldosageformsmaybeunsatisfactoryduetotheirpoorresidencetimeinnasalcavity.Mucoadhesivepolymerlikechitosancanbeemployedtoincreasetheresidencetimeoftheformulationtoenhancethebioavailability.

Hence,inthepresentwork,anattemptwasmadetoformulateandevaluateMucoadhesivemicrospheresofLoratadinethatwillincreaseresidencetimeinthenasalcavityandatthesametimeincreasetheabs

orptionofdruganditsbioavailability.Themicrospheresweerepreparedbyemulsioncrosslinkingmethodindifferentratiobyusingmucoadhesivepolymer,chitosan.Thepreparedmicrospheresweremcharacterizedfortheirdrugentrapmentefficiency&drugloading,particlesizeanalysis,surfacemorphology,degreeofswelling, in-vitromucoadhesion, invitrodrugreleasebehavior. Almostalltheformulationsshowedfairlyacceptablevaluesforallthevalueforalltheparameterevaluated.Theresultsofallparametersaretabulatedanddepictedgraphicallyintheresultsanddiscussion section.Stabilitystudiesrevealedthatthemicrosphereskeptat25˚Cshowedthemaximumstability.Thus,thepreparedmicrospheresprovedtobepotentialcandidateasamicroparticulateintranasalcontrolleddrugdeliverysystem.

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