Innovat International Journal Of Medical & Pharmaceutical Sciences, 2018; 3(1)

www.innovatpublisher.com

ISSN No. 2456-8694

Research Article

FORMULATION DEVLOPMENT AND CHARACTERIZATION OF FLOATING MICROSPHERES CONTAINING CINNARIZINE

T ACHUTH KUMAR, N.M.VAGEESH, H.M.SOWJANYA*, SURENDRA NAIK
St.Johns College of pharmaceutical sciences, Yerrakota, Yemmiganur Kurnool (dist) A.P. *Email: vageesh.swamy@gmail.com*

Received 2017.12.25-Accepted 2017.12.18

ABSTRACT

Gastroretentive dosage forms have potential for use as controlled- release drug delivery systems. The present Research work is formulation development and characterization of floating microspheres using Cinnarizine as a model drug for the management of Emesis. Floating microspheres were prepared by solvent evaporation technique using Sodium Alginate, Guar gum and Eudragit S100 as release retarding polymers. The floating microspheres were evaluated for percentage yield (%), Mean particle size, drug content, drug entrapment efficiency, *In vitro* Buoyancy and *in vitro* drug release studies. Compatibility studies were performed by fourier transform infrared (FTIR) technique. The prepared microspheres showed prolonged drug release of 12 h. The optimized formulation (F11) showed better drug release 99.61% for 12 hours. It was concluded that developed floating microspheres of Cinnarizine offers a suitable and practical approach for prolonged release of drug over an extended period of time and thus oral bioavailability, efficacy and patient compliance is improved.

Key word: Cinnarizine, Floating Microspheres, Eudragit

INTRODUCTION

To obtain maximum therapeutic efficacy, it becomes necessary to deliver the agent to the target tissue in the optimal amount in the right period of time there by causing little toxicity and minimal side effects[1]. There are various approaches in delivering a therapeutic substance to the target site in a sustained controlled release fashion. One such approach is using microspheres as carriers for drugs. The development of new delivery systems for the controlled release of drugs is one of the most interesting fields of research in pharmaceutical sciences.[1] A well designed controlled drug delivery system can overcome some of the problems of conventional therapy and enhance the therapeutic efficacy of a given drug. To obtain maximum therapeutic efficacy, it becomes necessary to deliver the agent to the target tissue in the optimal amount in the right period of time there by causing little toxicity and minimal side effects. There are various approaches in delivering a therapeutic substance to the target site in a sustained controlled release fashion. The process of targeting and site specific delivery with absolute accuracy can be achieved by attaching bioactive molecule to liposome, bio erodible polymer, implants, monoclonal antibodies and various particulate. One such approach is using microspheres as carriers for drugs. Microsphere can be used for the controlled release of drugs, vaccines, antibiotics, and hormones[2].

Materials Used[5]

Microspheres used usually are polymers. They are classified into two types.

Synthetic Polymers
Natural polymers

Bioadhesive Microspheres

Adhesion can be defined as sticking of drug to the membrane by using the sticking property of the water soluble polymers. Adhesion of drug delivery device to the mucosal membrane such as buccal, ocular, rectal, nasal etc can be termed as bio adhesion. These kinds of microspheres exhibit a prolonged residence time at the site of application and causes intimate contact with the absorption site and produces better therapeutic action.

Magnetic Microspheres

This kind of delivery system is very much important which localizes the drug to the disease site. In this larger amount of freely circulating drug can be replaced by smaller amount of magnetically targeted drug. Magnetic carriers receive magnetic responses to a magnetic field from incorporated materials that are used for magnetic microspheres are chitosan, dextran etc. The different types are therapeutic magnetic microspheres and diagnostic microspheres.

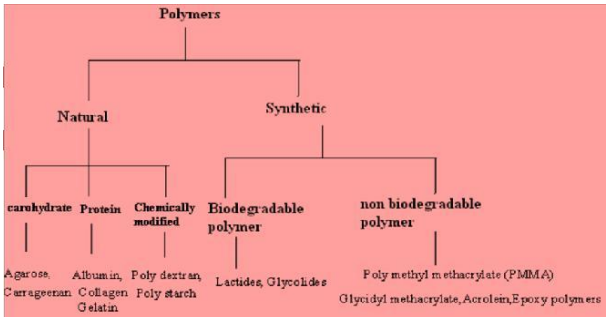

Fig.1: Polymers used in Microspheres Development

Therapeutic Magnetic Microspheres: It is used to deliver chemotherapeutic agent to liver tumor. Drugs like proteins and peptides can also be targeted through this system.

Diagnostic Microspheres: It can be used for imaging liver metastases and also can be used to distinguish bowel loops from other abdominal structures by forming nano size particles supramagnetic iron oxides.

Floating microspheres

In floating types the bulk density is less than the gastric fluid and so remains buoyant in stomach without affecting gastric emptying rate. The drug is released slowly at the desired rate, if the system is floating on gastric content and increases gastric residence and increases fluctuation in plasma concentration. Moreover it also reduces chances of striking and dose dumping. One another way it produces prolonged therapeutic effect and therefore reduces dosing frequencies.

Polymeric Microspheres

The different types of polymeric microspheres can be classified as follows and they are biodegradable polymeric microspheres and synthetic polymeric microspheres.

Biodegradable Polymeric Microspheres

Natural polymers such as starch are used with the concept that they are biodegradable, biocompatible, and also bioadhesive in nature. Biodegradable polymers prolongs the residence time when contact with mucous membrane due to its high degree of swelling property with aqueous medium, results gel formation. The rate and extent of drug release is controlled by concentration of polymer and the release pattern in a sustained manner. The main drawback is in clinical use drug loading efficiency of biodegradable microspheres is complex and is difficult to control the drug release.

Synthetic Polymeric Microspheres

The interest of synthetic polymeric microspheres are widely used in clinical application, moreover that also used as bulking agent, fillers, embolic particles drug delivery vehicles etc and proved to be safe and biocompatible. But the main disadvantage of these kinds of microspheres, are tend to migrate away from injection site and lead to potential risk, embolism and further organ damage.

Emulsion Solvent Evaporation Technique

In this technique the drug is dissolved in polymer which was previously dissolved in chloroform and the resulting solution is added to aqueous phase containing 0 .2 % sodium of PVP as emulsifying agent. The above mixture was agitated at 500 rpm then the drug and polymer (eudragit) was transformed into fine droplet which solidified into rigid microspheres by solvent evaporation and then collected by filtration and washed with demineralised water and desiccated at room temperature for 24 hrs[28].

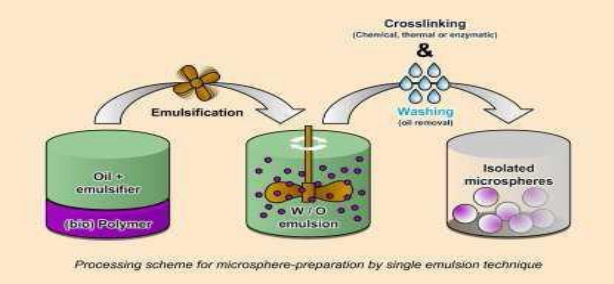

Fig. 2: Microspheres by Double Emulsion Technique

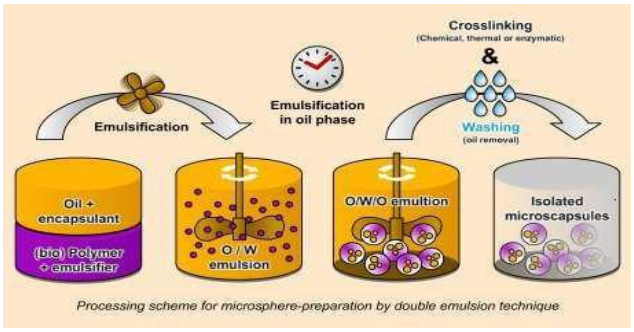

Fig. 3: Microspheres by Single Emulsion Technique

Microspheres in Vaccine Delivery

The prerequisite of a vaccine is protection against the micro organism or its toxic product. An ideal vaccine must fulfill the requirement of efficacy, safety, convenience in application and cost. Biodegradable delivery systems for vaccines that are given by parenteral route may overcome the shortcoming of the conventional vaccines[31]. The interest in parenteral (subcutaneous, intramuscular, intradermal) carrier lies since they offer specific advantages including:

Targeting using Microparticulate Carriers

The concept of targeting, i.e. site specific drug delivery is a well established dogma, which is gaining full attention. The therapeutic efficacy of the drug relies on its access and specific interaction with its candidate receptors.

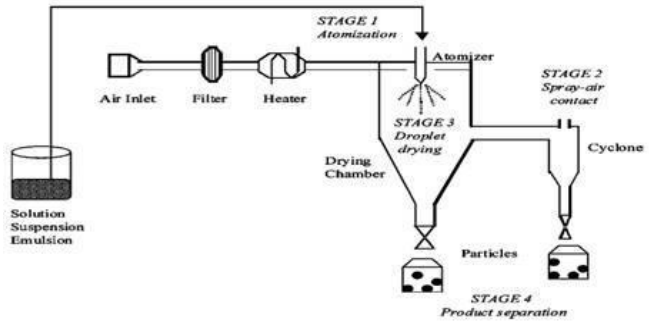

Fig. 4: Microspheres by Spraying Drying Technique

Monoclonal Antibodies Mediated Microspheres Targeting

Monoclonal antibodies targeting microspheres are immune microspheres. This targeting is a method used to achieve selective targeting to the specific sites. Monoclonal antibodies are extremely specific molecules. The free aldehyde groups, amino groups or hydroxyl groups on the surface of the microspheres can be linked to the antibodies. The Mabs can be attached to microspheres by any of the following methods

Chemoembolisation

Chemoembolisation is an endovascular therapy, which involves the selective arterial embolisation of a tumour together with simultaneous or subsequent local delivery the chemotherapeutic agent. The theoretical advantage is that such embolisations will not only provide vascular occlusion but will bring about sustained therapeutic levels of chemotherapeutics in the areas of the tumour. Chemoembolisation is an extension of traditional percutaneous embolisation techniques.

MATERIALS AND METHODS

Table 1: List of Materials Used

Name of the material	Source
Cinnarizine	SURA LABS, Dilsukhnagar, Hyderabad
Sodium Alginate	Merck Specialities Pvt Ltd, Mumbai, India
Calcium carbonate	Merck Specialities Pvt Ltd, Mumbai, India
Sodium bicarbonate	Merck Specialities Pvt Ltd, Mumbai, India
Citric Acid	Merck Specialities Pvt Ltd, Mumbai, India
HPMC K100M	Merck Specialities Pvt Ltd, Mumbai, India
Glutaraldehyde	Merck Specialities Pvt Ltd, Mumbai, India

Table 2: List of Equipments used

Name of the Equipment	Manufacturer
Weighing Balance	Sartourius
Automatic dissolution test apparatus	Electrolab TDT-60
pH meter	Systronic, 361-micro pH meter
Brookfield digital viscometer	Model No: LV II +Pro
Sartorious digital IR balance	Model MA-45
Fluorescence microscope	Leica DMIL
Scanning electron microscope	Jeol JSM-6380LV, Japan
Magnetic stirrer	Electroquip, DSK instrument
Peristaltic pump	Electrolab, Mumbai
DissolutionApparatus	Labindia, Mumbai, India
UV-Visible Spectrophotometer	Labindia, Mumbai, India
pH meter	Labindia, Mumbai, India
FT-IR Spectrophotometer	Bruker, Alpha

METHODOLOGY

Analytical method development

Determination of absorption maxima

100mg of Cinnarizine pure drug was dissolved in 15ml of Methanol and make up to 100ml with 0.1N HCL (stock solution-1). 10ml of above solution was taken and make up with100ml by using 0.1 N HCL (stock solution-2 i.e 100µg/ml). From this 10ml was taken and make up with 100 ml of 0.1 N HCl (10µg/ml). Scan the 10µg/ml using Double beam UV/VIS spectrophotometer in the range of 200 – 400 nm.

Preparation calibration curve

100mg of Cinnarizine pure drug was dissolved in 15ml of Methanol and volume make up to 100ml with 0.1N HCL (stock solution-1). 10ml of above solution was taken and make up with100ml by using 0.1 N HCl (stock solution-2 i.e 100µg/ml). From this take 0.1, 0.2, 0.3, 0.4 and 0.5ml of solution and make up to 10ml with 0.1N HCl to obtain 2, 4, 6 ,8, and 10 µg/ml of Cinnarizine solution. The absorbance of the above dilutions was measured at 254nm by using UV-Spectrophotometer taking 0.1N HCl as blank. Then a graph was plotted by taking Concentration on X-Axis and Absorbance on Y-Axis which gives a straight line Linearity of standard curve was assessed from the square of correlation coefficient (R^2) which determined by least-square linear regression analysis. The experiment was preformed in triplicate and based on average absorbance; the equation for the best line was generated. The results of standard curve preparation are shown in table-5.1 & figure-6.3

Drug – Excipient compatibility studies

Fourier Transform Infrared (FTIR) spectroscopy

Drug excipient interaction studies are significant for the successful formulation of every dosage form. Fourier Transform Infrared (FTIR) Spectroscopy studies were used for the assessment of physicochemical compatibility and interactions, which helps in the prediction of interaction between drug and other excipients. In the current study 1:1 ratio was used for preparation of physical mixtures used for analyzing of compatibility studies. FT-IR studies were carried out with a Bruker, ATR FTIR facility using direct sample technique

Standard graph of Cinnarizine in 0.1N HCL

The scanning of the 10µg/ml solution of Cinnarizine in the ultraviolet range (200-400 nm) against 0.1 N HCL the maximum peak observed at λ_{max} as 254 nm. The standard concentrations of Cinnarizine (2-10 µg/ml) was prepared in 0.1N HCL showed good linearity with R^2 value of 0.999, which suggests that it obeys the Beer-Lamberts law.

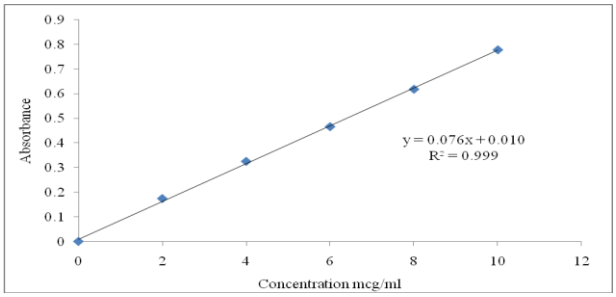

Fig. 5: Calibration curve of Cinnarizine in 0.1 N HCL at 254nm

Table 3.Composition of floating microsphere

Formulation code	Drug(mg)	Dispersing agent	Polymers			Floating agents		Floating agents	Cross linking agent	
	Cinnarizine	Aluminium Tristearate (w/v)	Sodium Alginate	Guar gum	Eudragit S100	$NaHCO_3$ (mg)	Tartaric acid			Glutaraldehyde (%)
F1	25	5	12.5	--	-	10	5			5
F2	25	5	25	--	-	20	10			5
F3	25	5	31.25	--	-	30	15			5
F4	25	5	50	--	-	40	20			5
F5	25	5	--	12.5	-	10	5			5
F6	25	5	--	25	-	20	10			5
F7	25	5	--	31.25	-	30	15			5
F8	25	5	--	50	-	40	20			5
F9	25	5	-	-	12.5	10	5			5
F10	25	5	-	-	25	20	10			5
F11	25	5	-	-	31.25	30	15			5
F12	25	5	-	-	50	40	20			5

Table 4: Standard curve of Cinnarizine in 0.1N HCL

S.No	Concentration mcg/ml	Absorbance
1.	0	0
2.	2	0.174
3.	4	0.325
4.	6	0.466
5.	8	0.618
6.	10	0.778

Drug and Excipient Compatibility Studies

FTIR study

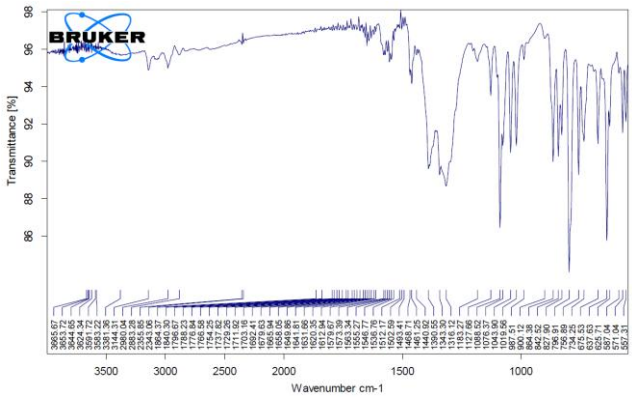

Fig. 6: FTIR GRAPH OF PURE DRUG

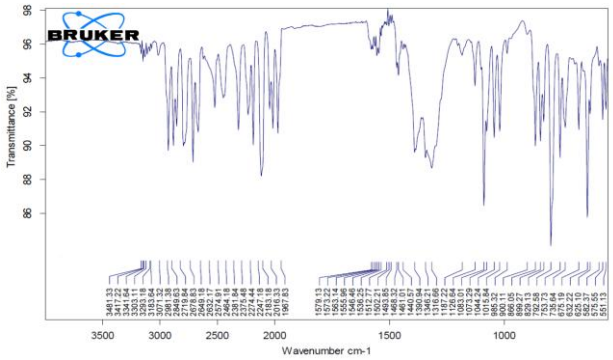

Fig.7: FTIR GRAPH OF OPTIMISED FORMULATION

From the FTIR data it was evident that the drug and excipients doses not have any interactions. Hence they were compatible

EVALUATION PARAMETERS

Table 5: Evaluation of Floating Microspheres

Batch No	Mean Particle size(µm)	Bulk Density (gm/ml)	Tapped density (gm/ml)	Carr's Index	Hausner's ratio	Angle of repose (θ)
F1	322.49	0.52	0.62	13.88	1.16	29.14º
F2	441.94	0.53	0.68	13.91	1.16	27.14º
F3	561.66	0.57	0.66	12.7	1.14	25.14º
F4	340.48	0.53	0.63	15.07	1.17	29.26º
F5	463.99	0.54	0.62	12.82	1.14	26.23º
F6	584.64	0.51	0.61	15.08	1.17	29.37º
F7	350.75	0.44	0.52	15.48	1.18	28.52
F8	307.85	0.53	0.68	13.91	1.16	27.14º
F9	251.8	0.53	0.63	15.07	1.17	29.26º
F10	340.47	0.57	0.66	12.7	1.14	25.14º
F11	350.75	0.44	0.52	15.48	1.18	24.42º
F12	307.85	0.45	0.525	14.5	1.2	28.60 º

Table 6: *In vitro* drug release of containing Cinnarizine F1 to F4 formulations

TIME	CUMULATIVE PERCENT DRUG RELEASED			
(HR)	**F1**	**F2**	**F3**	**F4**
0	32.94	28.47	21.68	19.83
0.5	38.04	34.49	29.39	26.62
1	45.13	41.74	36.65	34.95
2	57.63	48.84	45.29	44.67
3	65.5	56.09	53	47.29
4	71.83	64.58	63.5	52.23
5	76.46	72.65	65.81	57.63
6	81.55	77.39	69.21	62.57
7	87.11	82.48	71.52	67.07
8	94.21	88.19	76.62	72.29
9	99.76	92.36	81.71	79.7
10		95.83	87.42	83.87
11		98.68	91.12	87.11
12			96.33	91.23

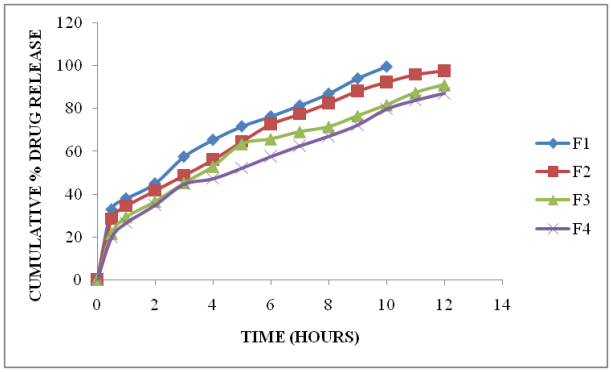

Fig. 8: Dissolution study of Cinnarizine Floating Microspheres (F1 to F4)

Table 7: *In vitro* drug release of Cinnarizine F5 to F8 formulations

TIME	CUMULATIVE percent drug released			
(hr)	**f5**	**f6**	**f7**	**f8**
0	0	0	0	0
0.5	14.96	13.97	10.95	8.34

1	23.2	22.28	15.72	11.13
2	34.81	36.51	21.01	15.06
3	46.85	43.79	28.76	18.04
4	57.48	48.14	35.02	21.78
5	67.31	52.43	41.65	23.89
6	73.43	57.69	48.36	25.33
7	76.17	62.5	55.06	27.25
8	78.47	71.21	61.62	29.46
9	80.87	75.17	68.25	31.67
10	84.36	79.98	73.98	49.37
11	91.36	87.66	79.58	56.13
12	96.52	92.33	84.67	72.23

Table 8: *In vitro* drug release of sodium Alginate containing Cinnarizine F9 to F12 formulations

TIME	CUMULATIVE PERCENT DRUG RELEASED			
(HR)	**F9**	**F10**	**F11**	**F12**
0	0	0	0	0
0.5	36.31	21.07	19.83	19.52
1	42.05	26.46	23.22	23.07
2	53.46	32.94	31.17	29.99
3	66.89	39.56	37.73	36.8
4	72.29	45.29	44.36	43.44
5	79.79	53.63	52.7	49.92
6	86.95	62.42	59.96	57.63
7	93.44	68.72	65.97	63.31
8	96.68	78.93	74.76	69.52
9	99.3	85.57	83.56	76.15
10		91.28	89.58	86.34
11		99.15	95.44	89.27
12			99.61	96.45

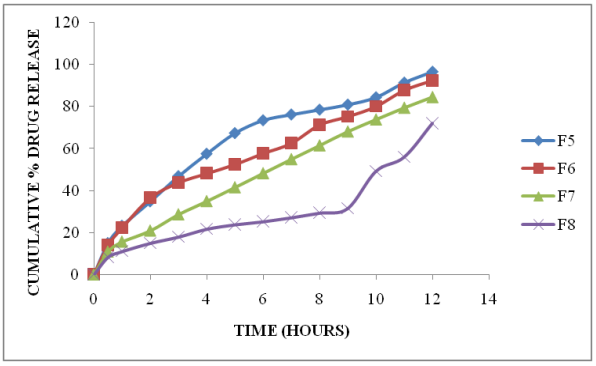

Fig.9: Dissolution study of Cinnarizine Floating Microspheres (F5 to F8)

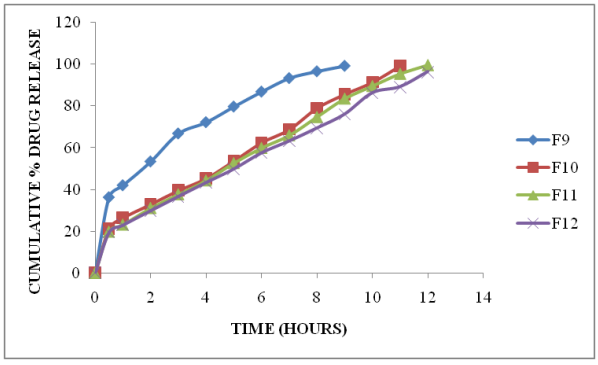

Fig. 10: Dissolution study of Cinnarizine Floating Microspheres (F9 to F12)

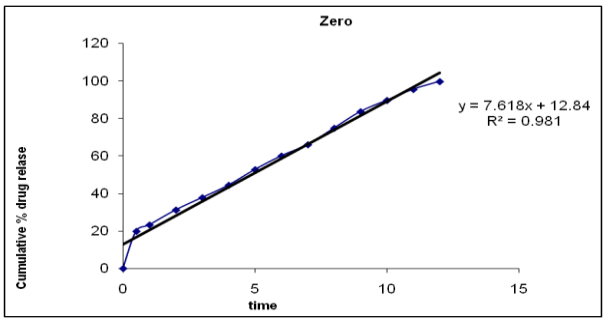

Fig.11: Graph of Zero Order kinetics

The % drug release of F9 to F12 formulations depends on polymer ratio Eudragit S100. The concentration of Eudragit S100, 1:0.5 to 1:1 ratios was Unable To retard the drug release up to desired time. In F11 formulations, Eudragit S100 **contain 1:1.5 ratio** showed maximum % drug release i.e 99.61% at 12 hours.

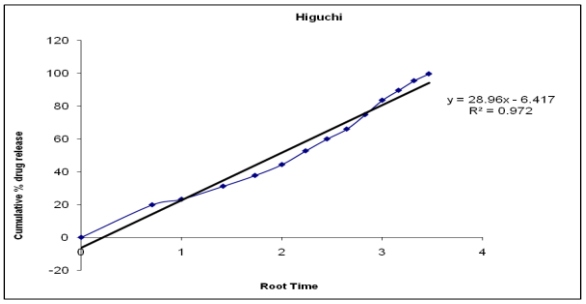

Fig. 12: Graph of Higuchi Release kinetics

Table 9: Release kinetics data for optimized formulation

CUMULATIVE (%) RELEASE Q	TIME (T)	ROOT (T)	LOG(%) RELEASE	LOG (T)	LOG (%) REMAIN	RELEASE RATE (CUMULATIVE % RELEASE / t)	1/CUM% RELEASE	PEPPAS log Q/100	% Drug Remaining	Q01/3	Qt1/3	Q01/3-Qt1/3
0	0	0			2				100	4.642	4.642	0
19.83	**0.5**	0.707	1.297	-0.301	1.904	39.66	0.0504	-0.703	80.17	4.642	4.312	0.33
23.22	**1**	1	1.366	0	1.885	23.22	0.0431	-0.634	76.78	4.642	4.25	0.391
31.17	**2**	1.414	1.494	0.301	1.838	15.585	0.0321	-0.506	68.83	4.642	4.098	0.543
37.73	**3**	1.732	1.577	0.477	1.794	12.577	0.0265	-0.423	62.27	4.642	3.964	0.678
44.36	**4**	2	1.647	0.602	1.745	11.09	0.0225	-0.353	55.64	4.642	3.818	0.824
52.7	**5**	2.236	1.722	0.699	1.675	10.54	0.019	-0.278	47.3	4.642	3.616	1.025
59.96	**6**	2.449	1.778	0.778	1.602	9.993	0.0167	-0.222	40.04	4.642	3.421	1.22
65.97	**7**	2.646	1.819	0.845	1.532	9.424	0.0152	-0.181	34.03	4.642	3.241	1.401
74.76	**8**	2.828	1.874	0.903	1.402	9.345	0.0134	-0.126	25.24	4.642	2.933	1.708
83.56	**9**	3	1.922	0.954	1.216	9.284	0.012	-0.078	16.44	4.642	2.543	2.099
89.58	**10**	3.162	1.952	1	1.018	8.958	0.0112	-0.048	10.42	4.642	2.184	2.457
95.44	**11**	3.317	1.98	1.041	0.659	8.676	0.0105	-0.02	4.56	4.642	1.658	2.983
99.61	**12**	3.464	1.998	1		8.301	0.01	-0.002	0.39	4.642	0.731	3.911

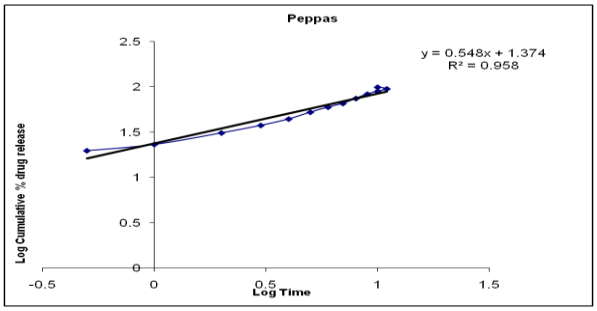

Fig.13: Graph of Peppas Release kinetics

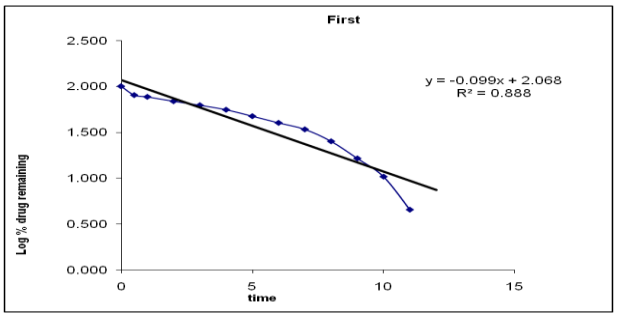

Fig. 14: graph of First Order release kinetics

Based on the data above results the optimized formulation followed Zero order release kinetics.

CONCLUSION

The purpose of present work was to develop floating microspheres of Cinnarizine for sustained drug delivery. From the results it seem that formulation F11 was found to be satisfactory in terms of excellent micromeritic properties, yield of microsphere **Encapsulation efficiency** 99.58**%** and highest in vitro drug release of 99.61% in a sustained manner with constant fashion over extended period of time for 12 hrs. It was observed that concentration drug and polymer (Eudragit S100) 31.25 mg and 30 mg of $NaHCO_3$ and 15 mg Tartaricacid affected all the evaluation parameter significantly. Hence the prepared floating microspheres of Cinnarizine may prove to be potential candidate for safe and effective sustained drug delivery.

REFERENCES

1. N. K. Jain, Controlled and Novel drug delivery, 04 Edition, CBS Publishers New Delhi, India; 21, 236-237.
2. Chein YW. Oral Drug Delivery Systems: In Novel drug delivery systems. Vol.50, Marcel Dekker, Inc., New York. 1992, 139- 177.
3. Mathew Sam T., Devi Gayathri S., PrasanthV.V., Vinod B; NSAIDs as microspheres, The Internet Journal of Pharmacology.6(1), 2008, 67-73.
4. Li, S.P., Kowalski C.R., Feld K.M., Grim W.M. Recent Advances in Microencapsulation Technology and Equipment, Drug Dev Ind. Pharm. 14, 1988, 353-376.
5. P.M. Dandagi, VS. Mastiholimath, M.B. Patil, M.K. Gupta, Biodegradable microparticulate system of captopril. International Journal of Pharmaceutics. 307, 2006, 83-88.
6. Chinna Gangadhar B, Shyam Sunder R., Vimal Kumar Varma. M., Sleeva Raju M., Sai Kiran M, Formulation and Evaluation of Indomethacin Microspheres using natural and synthetic polymers as Controlled Release Dosage Forms. International Journal of Drug Discovery, 2(1), 2010,8-16.
7. Rana mazumder, lila K. Nath, Anwarul, Haque, Tarasankar Maity, Prasant K. Choudhary, Bhupendra Shreshta, Formulation and in vitro evaluation of natural polymers based microsphere for colonic drug delivery, International journal of pharmacy and pharmaceutical sciences, 2(1), 2010, 211-219.
8. Kavitha K, Chintagunta Pavanveena, Anil Kumar S. N., Tamizh Mani T, Formulation and evaluation of trimetazine hydrochloride loaded gelatin microsphere. International Journal of Pharmacy and Pharmaceutical Sciences, 2(3), 2010, 67-70.
9. Lorenzo-Lamosa ML. Design of microencapsulated chitosan microspheres for colon drug delivery. J. Control. Release, 52(1-2), 1998, 109-118.
10. Sudha Mani T and Naveen Kumar K, At preparation and evaluation of ethyl cellulose microspheres of ibuprofen for sustained drug delivery. International Journal of Pharma Research and Development. 2(8), 2010, 120-121.
11. Bunty Chanu Irom, K. Kavitha, M. Rupeshkumar1, SD. Jagadeesh Singh, Natural Polymeric Microsphere for Drug Delivery: A Review. International Journal of Pharmaceutical Research And Development. 4(07), 2012, 31-37.
12. Imran Abdul Kayyum Tadwee, Sadhana Shahi, M. Thube, Ankit S. Review on Microspheres. International Journal of Pharmaceutical ResearchAllied Sciences, 1(1), 2012, 24-33.
13. Saravana Kumar K., Jayachandra Reddy P., Chandra Sekhar K.B., A Review on Microsphere for Novel drug delivery System. Journal of Pharmacy Research, 5(1), 2012, 420-424.
14. Kataria Sahil, Middha Akanksha, Sandhu Premjeet, Ajay Bilandi and Bhawana Kapoor, Microsphere: A Review, International Journal of Research In Pharmacy and Chemistry, 1(4), 2011, 1184-1198.
15. Sipai Altaf Bhai. M. Vandana yadav, Mamatha. Y, Prasanth V. V., Mucoadhesive Microsphere An overview. American journal of Pharmtech Research, 2(1), 2012,237-258.