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Research Article

FORMULATION & EVALUATION OF GASTRORETENSIVE FLOATING MICROSPHERE OF CINNARIZINE

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ABSTRACT

The aim of the present investigation was to evaluate the potential use of microspheres for gastroretentive delivery of CINNARiZINE. Acrycoat, Eudragit, Ethyl cellulose was used as Gastroretentive microsphere polymers. The polymers and drug were dissolved in a combination of organic solvent (20ml) i.e. ethanol and dichloromethane (1:1) at room temperature. Microspheres were prepared by solvent evaporation technique. Four different ratios (1:1, 1:2, 1:3, and 1:4) from each polymer, i.e., Acrycoat S100 (A1-A4), Eudragit RS 100 (B1-B4) and Ethyl cellulose acetate (C1-C4) were prepared. The release of drug was prolonged to 12 h (98.14±0.78) when incorporated into gastroretentive microspheres. FTIR shows that there is no interaction with pure drug (Cinnarizine), polymer (Acrycoat S 100, Eudragit RS 100, and Ethyl cellulose), and its physical mixture physical mixture while taken by preparing KBr pellets. (Disk method). From the entrapment and dissolution study it was concluded that batch A-2 showed sustained release for 12 hrs. The batch was optimized for the sustained release microspheres of Cinnarizine by using Acrycoat S100 (1:2). Overall, the result indicated prolonged delivery with significant improvement in oral bioavailability of acyclovir from gastroretentive floating microspheres due to enhanced retention in the upper GI tract.

Keywords: Cinnarizine, microspheres, gastroretentive, Acrycoat S100, Eudragit RS 100, Ethyl cellulose acetate, FTIR

INTRODUCTION

Oral delivery of drugs is by far the most preferable route of drug delivery due to the ease of administration, patient compliance and flexibility in formulation etc. From immediate release to site-specific delivery, oral dosage forms have really progressed. However, it is a well-accepted fact that it is difficult to predict the real *in vivo* time of release with solid.

Gastric emptying of dosage form is an extremely variable process and ability to prolong and control the emptying time is a valuable asset for dosage forms, which reside in the stomach for a longer period of time than conventional dosage form.

In such circumstances, prolonged gastric retention is important in achieving control over the gastric retention time (GRT) because this helps to retain the CR system in the stomach for a longer and predicted time. In addition, this improves the bioavailability of the basic drug that has poor solubility in higher pH and drugs having narrow absorption window (Upper part of GIT).

GASTRORETENTIVE DRUG DELIVERY SYSTEM [7-13]

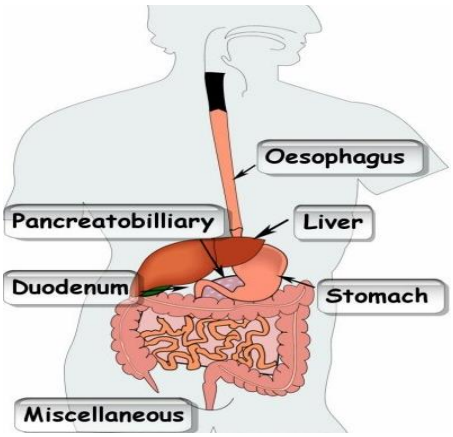

Fig 1: View of Gastrointestinal Tract

DEVELOPMENT OF FLOATING MICROSPHERES: [14]

Conventionally the drug-loaded microspheres have been developed by emulsification and solvent evaporation methods. In these methods the polymer is dissolved in an organic solvent such as

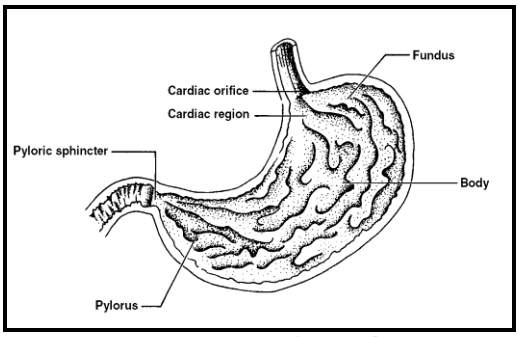

Fig 2 Anatomy of stomach

dichloromethane, chloroform or ethyl acetate, either alone or in combination.

The drug is either dissolved or dispersed into the polymer solution and this solution containing the drug is emulsified in to an aqueous phase to make oil in water emulsion by using a surfactant or an emulsifying agent.

However, the polymer precipitates instantly at the surface of droplets, forming a shell enclosing the dichloromethane (DCM)

The acrylic polymer is dissolved in solvent mixtures such as ethanol (EtOH): dichloromethane (1:1 v/v) along with the drug. The polymer solution is then emulsified in to an aqueous phase containing poly vinyl alcohol (PVA). Then methanol diffuses out of the embryonic micro spheres in to the aqueous phase such that the equilibrium concentration of ethanol or methanol will be retained while hollow to impart the floating properties

Factors considered during formulation are: [15]

a. Method of introducing polymer solution:

This method improved the yield of microspheres and reduced the extent of aggregate formation and made it possible to make microspheres continuously. As the polymer solution is continuously introduced into the main vessel, it will overflow from the top of the vessel together with the prepared microspheres, since most of the formed microspheres will float on the top of the aqueous phase

b. Effect of rotation speed:

As the rotation speed of the propeller increased, the average particle size decreased, while maintaining its morphology. The optimum rotation speed for this experimental system was 250 rpm, the hear force was not sufficient to form stable emulsion droplets, consequently larger droplets, consequently larger droplets were formed and they were aggregated eventually. Above 250 rpm, the emulsion speed was set at 250 rpm.

c. Effect of temperature:

The temperature of the dispersing medium was an important factor in the formation of microspheres, because it controls the evaporation rate of the solvents. At lower temperature (10°C), prepared microsphere had crushed and irregularly shaped morphology. At higher temperatures (40°C), the shell of the microsphere was very thin and some of the microspheres were broken. The optimum temperature to form good microspheres was in the range of 25-28 °C.

Table 1: List of drugs along with floatable drug delivery systems

Drug	Reference	Drug	Reference
Microspheres		Misoprostol	Oth *et al*., 1992; Franz and Oth, 1983
Aspirin, griseofulvin and *p*-nitroaniline	Thanoo *et al*., 1993	Propranolol	Khattar *et al*., 1990
Ibuprofen	Kawashima *et al*., 1992	Ursodeoxycholic acid	Simoni *et al*., 1995
Terfenadine	Jayathi *et al*., 1995	Tablets/Pills	
Tranilast	Kawashima *et al*., 1991 Kawashima *et al*., 1992	Acetylsalicylic acid	Sheth and Tossounian, 1979
Granules	Ikura et al, 1988	Amoxycillin trihydrate	Hilton and Deasy, 1992
Diclofenac sodium	Yuasa *et al*., 1996	Ampicillin	Gupta, 1987
Indomethacin	Miyazaki *et al*., 1988	Chlorpheniramine maleate	Deshpande *et al*., 1997
Prednisolone	Inouye *et al*., 1989	Cinnarizine	Machida *et al*., 1989
Films		Fluorouracil	Watanabe *et al*., 1993
Cinnarizine	Machida *et al*., 1989	Isosorbide mononitrate	Chitnis *et al*., 1991
Powders		Isosorbide dinitrate	Ichikawa *et al*., 1991
Several basic drugs	Dennis *et al*., 1992	*p*-Aminobenzoic acid	Ichikawa *et al*., 1991
Capsules		Piretanide	Rouge *et al*., 1998a
Chlordiazepoxide HCl	Sheth and Tossounian, 1984	Prednisolone	Inouye *et al*., 1988
Diazepam	Sheth and Tossounian, 1984	Quinidine gluconate	Agyilirah *et al*., 1991
Furosemide	Menon *et al*., 1994	Riboflavine-5-phosphate	Deshpande *et al*., 1997; Ingani *et al*., 1987
L-Dopa and benserazide	Erni and Held, 1987	Sotalol	Chueh *et al*., 1995

MATERIALS AND METHODS

Cinnarizine was obtained as a gift sample from FDC Pharma Ltd., Mumbai**, Ethyl cellulose or Surelease** was obtained as a gift sample from Colorcon Pvt. Ltd. Goa.**, Acrycoat S 100** was obtained as a gift sample from Corel Pvt. Ltd., Ahemadabad, **Eudragit RS 100** was obtained as a gift sample from Degussa India Pvt.Ltd. Mumbai, **Dichloromethane, Tween 80** was purchased from Merck Ltd. Mumbai, **Ethanol** was purchased from Changshu Yangyun Chemical**, Polyvinyl alcohol** was purchased from Loba chemie Pvt.Ltd. Mumbai.

PREPARATION OF FLOATING MICROSPHERES [14, 21]

The microspheres were prepared by solvent evaporation technique. The polymers and drug were dissolved in a combination of organic solvent (20ml) i.e. ethanol and dichloromethane (1:1) at room temperature. The drug solution was poured in to 200 ml of water containing 0.25%, 0.15% and 0.05% w/v. polyvinyl alcohol (PVA) for batches using acrycoat, eudragit and ethyl cellulose respectively. Then the solution was stirred at a speed of 300 - 500 rpm with a propeller agitator for 90 minutes at 30 – 40 °C as control temperature. The finely dispersed droplets were solidified in the aqueous phase via diffusion and evaporation of solvent. These solidified microspheres were recovered, washed with water and dried in desiccators for 12 hours. During the drying process, an air cavity was produced inside the sphere giving them a tennis ball like appearance.

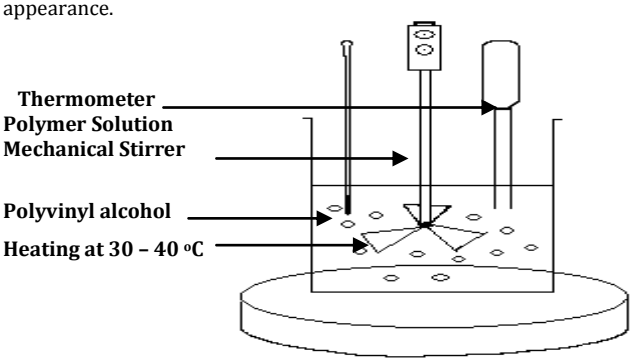

Fig 3: Assembly showing formation of floating microspheres

USING POLYMER: ACRYCOAT\EUDRAGIT\ETHYL CELLULOSE

Table 2: Selection Of Suitable Concentration Of Pva Solution And Temperature For Drug: Polymer (1:1) Using Solvent: Ethanol: Dichloromethane (1:1)

S No	Drug (mg) (Cinnarizine)	Acrycoat\ Eudragit\ Ethyl cellulose (mg)	Solvent (Ethanol: DCM ml)	*PVA* (% w/v)	PVA Temp (°C)	Rejected(R) / Selected(S) for Acrycoat/ Eudragit / Ethyl cellulose
1	50	50	20	0.25	40	R/R/R
2	50	50	20	0.25	30	R/R/R
3	50	50	20	0.15	40	R/R/R
4	50	50	20	0.15	30	R/R/R
5	50	50	20	0.05	40	R/R/R
6	50	50	20	0.05	30	S/S/S

Formulation Table for drug: polymer batch:

Table 3: Drug and Polymer combination in solvent mixture of DCM and EtOH

Batches / ***Ingredients***	**A1**	**A2**	**A3**	**A4**	**B1**	**B2**	**B3**	**B4**	**C1**	**C2**	**C3**	**C4**
Acrycoat S100 (mg)	50	100	150	200	--	--	--	--	--	--	--	--
Eudragit RS 100 (mg)	--	--	--	--	50	100	150	200	--	--	--	--
Ethyl cellulose (mg)	--	--	--	--	--	--	--	--	50	100	150	200
DRUG (mg)	50	50	50	50	50	50	50	50	50	50	50	50

RESULT AND DISCUSSION

PRE-FORMULATION STUDY

a) **Purity of cinnarizine:**[16,17,18]

Cinnarizine is a white or almost white powder of (E)-1-

(Diphenylmethyl)-4-(3-phenylprop-2-enyl) piperazine derivatives with other suitable inert excipient which permits safe handling. So its purity was estimated as per B.P.

b) **Determination of λmax**: [19]

Cinnarizine solution 20 µg/ml in 1.2 pH buffer was scanned between the ranges of 200 290 nm.

c) Physical Characteristics of Drug: [61]

1. Nature : Amorphous powder
2. Color : White
3. Odour : Odourless
4. Taste : Bitter taste
5. Melting point : 121° C
6. Solubility

a. In distilled water : < 0.07mg/ml
b. In ethanol : 90.10 mg/ml
c. In Dichloromethane : 1100 mg/ml
d. In acetone : 35 mg/ml
e. In chloroform : 965 mg/ml

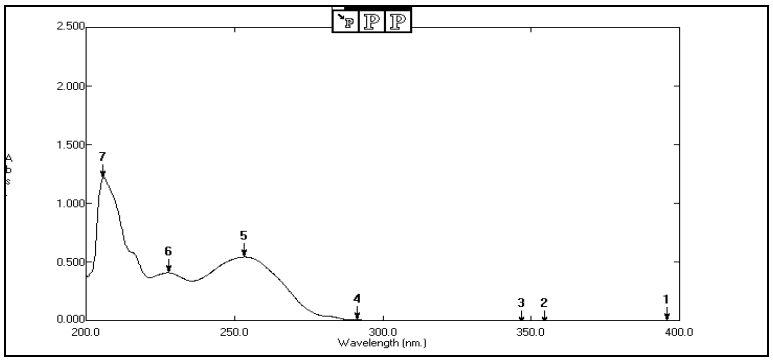

Fig 4 : Observation: The λmax was found to be at 253.4 nm as shown in Fig. No. 7.

IR INTERPRETATION FOR DRUG AND POLYMER:

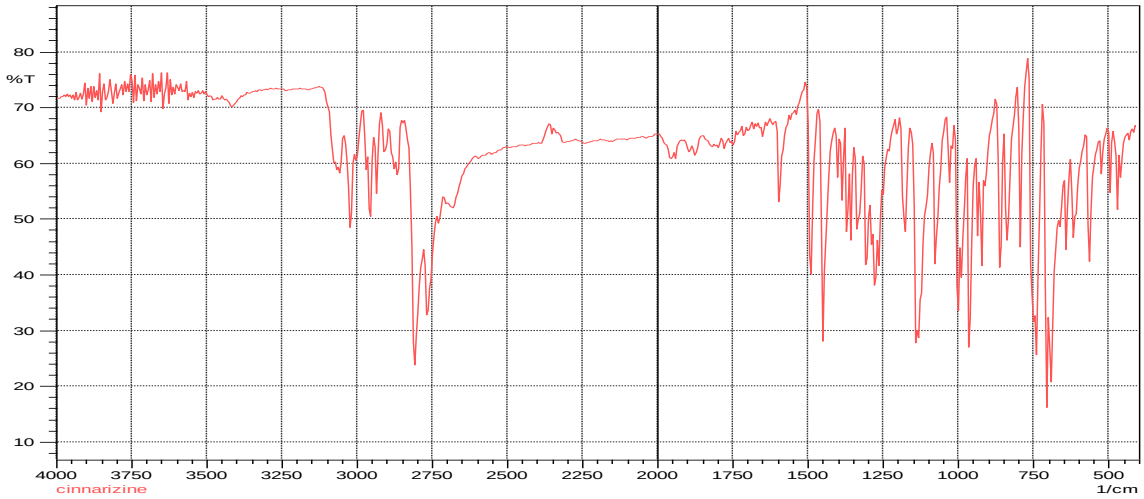

Fig 5: I.R. spectra of Cinnarizine

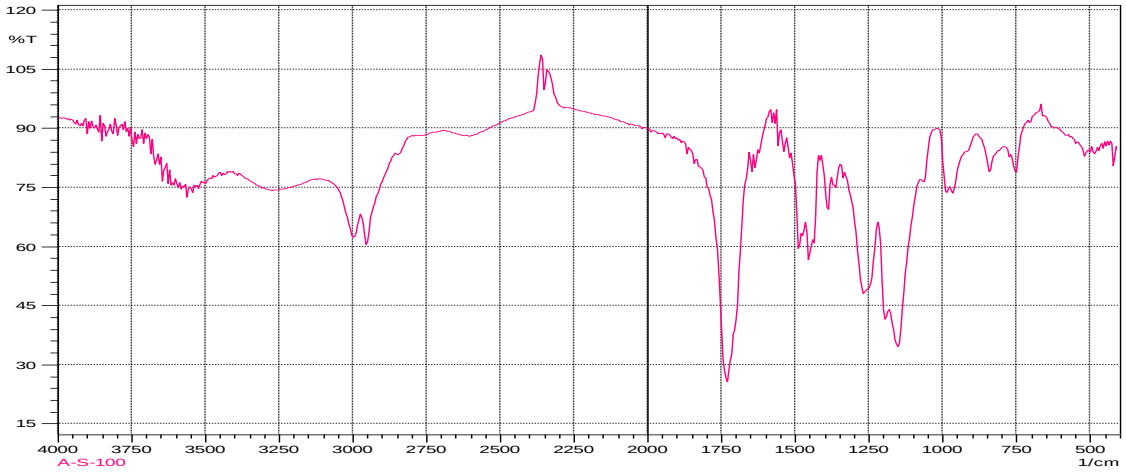

Fig 6: IR spectra of Acrycoat S 100 polymer

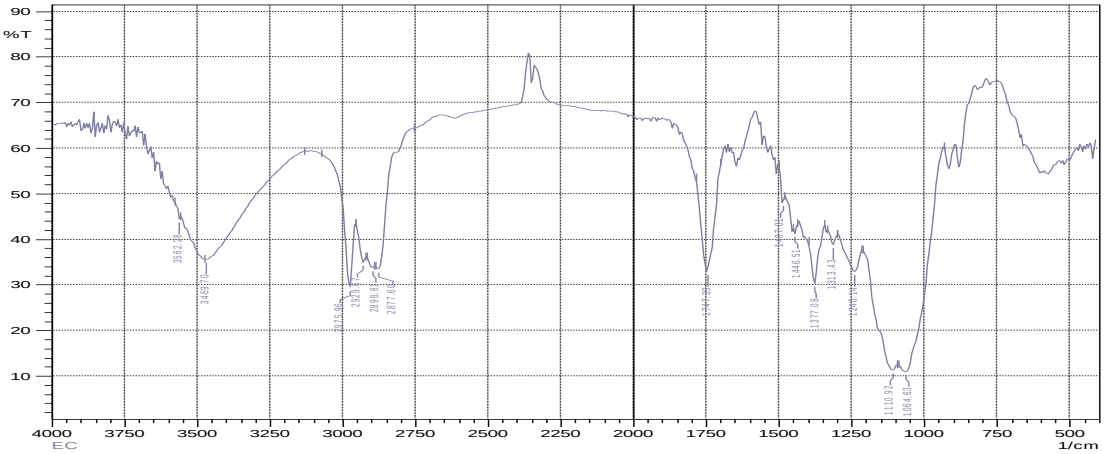

Fig 7: I.R. spectra of Ethyl cellulose

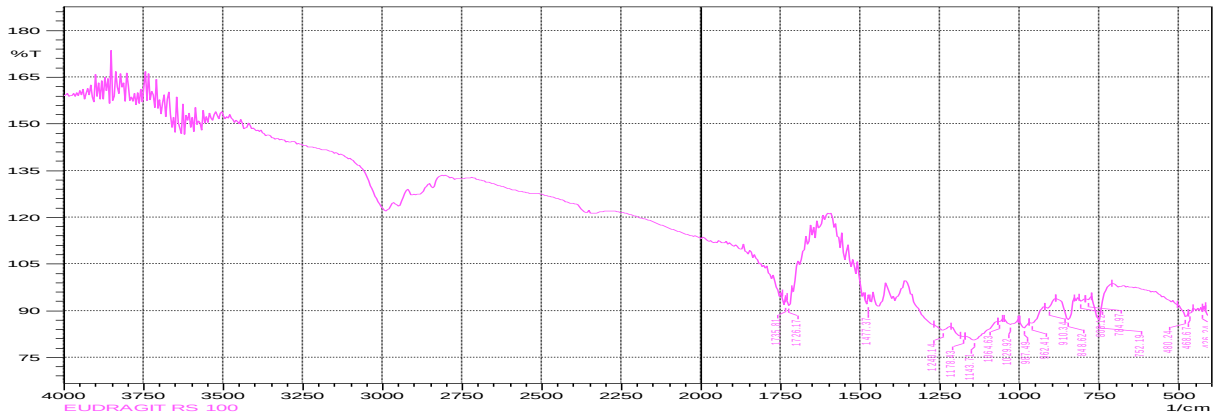

Fig 8: I.R. spectra of Eudragit RS 100

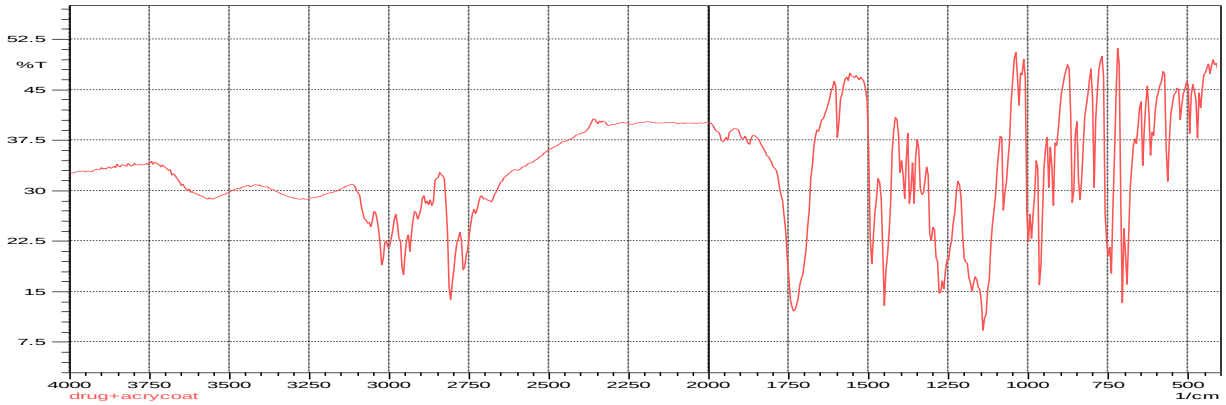

Fig 9: IR spectra of physical mixture of Cinnarizine and Acrycoat S 100

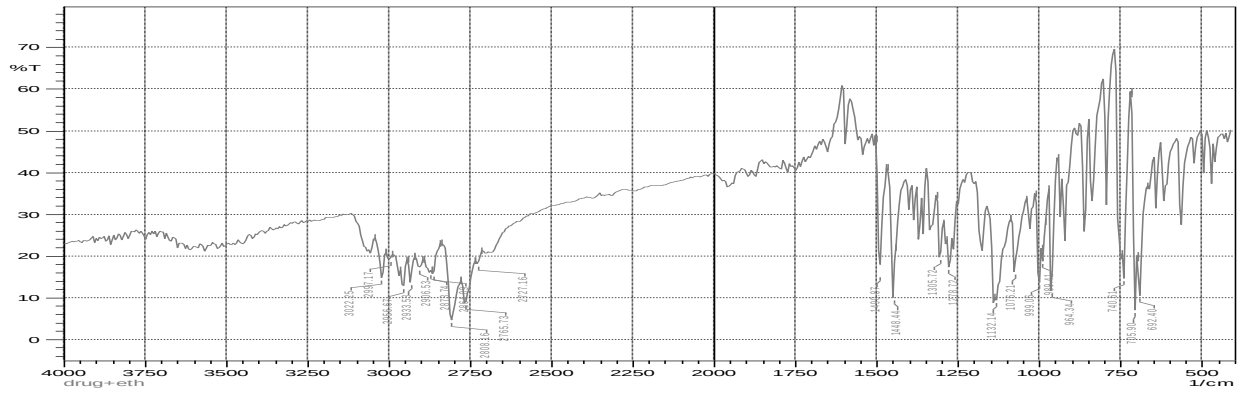

Fig 10: IR spectra of physical mixture of Cinnarizine and Ethyl cellulose

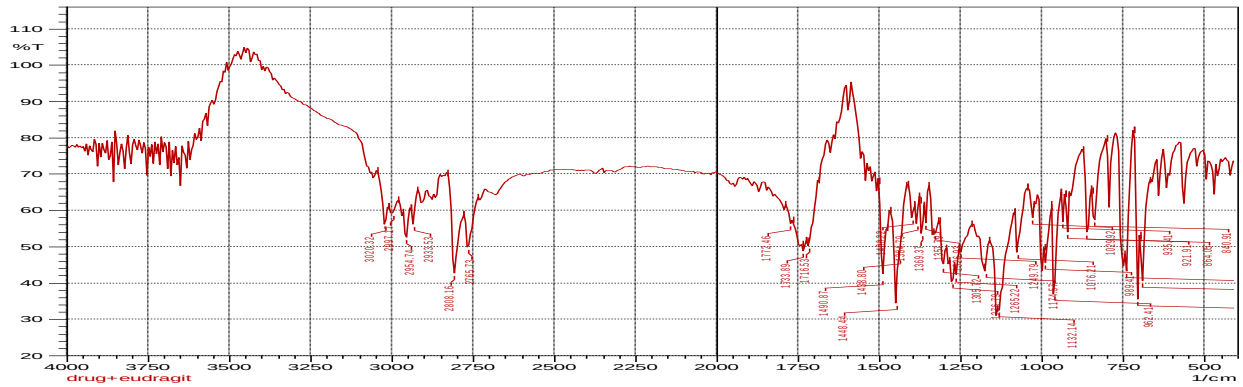

Fig 11: IR spectra of physical mixture of Cinnarizine and Eudragit RS 100

d) IR Spectral analysis: [20]

FTIR spectrum of pure drug (Cinnarizine), polymer (Acrycoat S 100, Eudragit RS 100, and Ethyl cellulose), and its physical mixture was carried with FTIR (Shimadzu 8400S Japan) in the range of from 400cm^{-1} to 4000cm^{-1} by using KBr disc method. The IR spectral data was obtained for pure drug and the physical mixture of the drug and polymer using FT-IR. Fig 5-11

Table 4: Micromeritic studies

Parameters / Batches	Average particle size(μm)	Tapped density (g/cm³)	Bulk density (g/cm³)	% Compress-ibility index	Hausner ratio	Angle of repose (θ)
A1	140.0 ± 8.3	0.416	0.357	14.28	1.16	40 °60’
A2	175.0 ± 13.7	0.454	0.384	15.37	1.18	37 ° 40’
A3	223.8 ± 19.3	0.454	0.384	15.37	1.18	33 ° 69’
A4	233.3 ± 23.3	0.416	0.357	14.28	1.16	34 ° 43’
B1	305.1 ± 8.1	0.333	0.294	11.7	1.13	26 ° 56’
B2	313.6 ± 9.2	0.384	0.312	18.7	1.2	31 ° 32’
B3	334.0 ±18.8	0.357	0.277	22.4	1.28	30 ° 41’
B4	339.7 ±19.9	0.357	0.312	12.60	1.14	30 ° 96’
C1	325.7 ± 15.8	0.416	0.333	19.9	1.124	37 ° 40’
C2	337.0 ± 19.6	0.333	0.294	11.7	1.13	32° 15’
C3	348.0 ± 23.7	0.357	0.312	12.60	1.14	27 ° 55’
C4	352.0 ±33.6	0.357	0.294	17.64	1.21	31° 89’

Table 5: Percentage recovery (i.e. Yield) of microsphere formed:

Batch no.	Percentage yield
A1	84.5%
A2	85.2%
A3	73.25%
A4	72%
B1	71%
B2	70.3%
B3	65.5%
B4	66.8%
C1	70%
C2	69.6%
C3	66.25%
C4	67.4%

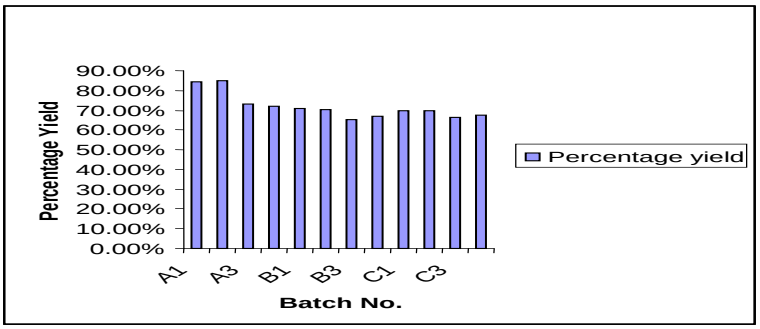

Fig 12: Percentage yield of different batches

Table 6: Percentage buoyancy

Batch. No	Percentage Buoyancy
A1	68.5
A2	72
A3	69
A4	70
B1	69
B2	66
B3	65.5
B4	64.5
C1	68.8
C2	69.1
C3	70
C4	68

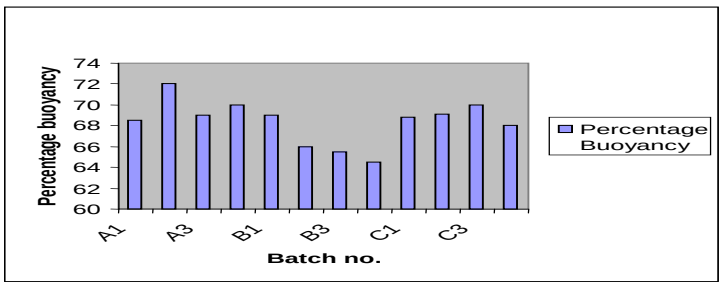

Fig 13: Percentage buoyancy of different batches

Table 7: Standard calibration curve of Cinnarizine in 1.2 pH buffer with ethanol.

Sr. no	Concentration (µg/ml)	absorbance
1	0	0.000
2	2	0.101
3	4	0.219
4	6	0.298
5	8	0.423
6	10	0.606
7	12	0.692
8	14	0.800
9	16	0.919
10	18	1.041
11	20	1.096

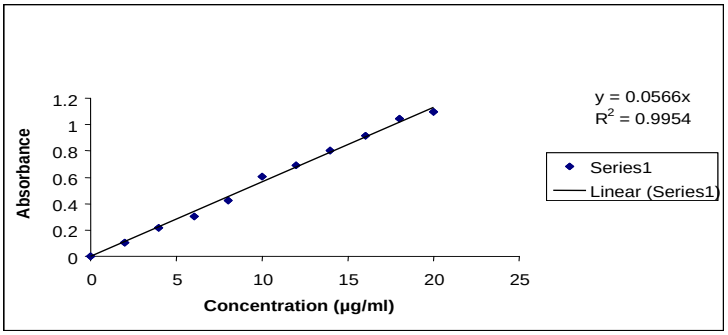

Fig 14: Standard calibration curve of Cinnarizine in Ethanol.

PERCENT DRUG ENTRAPMENT:

Table 8: % Drug entrapped

Batch no.	Drug incorporation efficiency	
	Drug Concentration (mg)	% Drug entrapment
A1	38	76±0.31
A2	45.5	91±0.25
A3	42.5	85±0.53
A4	41.25	82.5±0.69
B1	29.75	59.5±0.56
B2	32.5	65±0.63
B3	35.75	71.5±0.73
B4	28.25	56.5±0.48
C1	35.25	70.5±0.69
C2	34.75	69.5±0.89
C3	35.75	71.5±0.73
C4	32.75	65.5±0.74

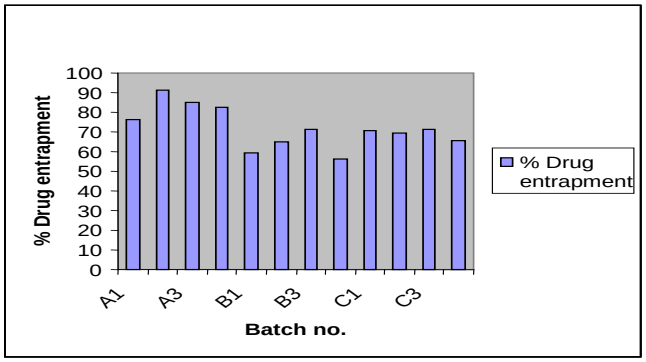

Fig 15: Percentage Drug entrapment

Table No. 9: Cummulative drug release of all batches of Floating microspheres

Time (hrs)	PERCENTAGE CUMULATIVE RELEASE			
	A1	A2	A3	A4
0	0	0	0	0
1	44.03±0.61	22.06±0.98	18.96±0.67	9.99±0.76
2	63.77±0.67	29.61±0.89	20.30±1.43	14.07±0.43
3	78.05±0.71	35.96±1.23	22.30±1.52	16.00±0.87
4	86.21±0.56	43.89±1.12	26.73±0.45	20.42±0.98
5	93.50±0.78	52.80±1.21	31.83±0.13	24.25±0.76
6	100.20±0.56	63.61±1.02	36.33±0.87	29.95±0.78
7	100.02±0.67	74.17±0.98	41.17±0.67	36.30±0.67
8	100.22±0.45	82.62±0.45	48.21±0.57	40.21±0.98
9	100.00±0.65	88.02±0.34	54.04±0.76	46.00±0.48
10	99.34±0.29	91.90±0.56	60.83±0.67	51.21±0.56
11	99.89±0.87	95.18±0.68	68.59±0.34	58.91±0.34
12	100.69±0.78	98.14±0.78	75.76±0.34	64.18±0.34

***Represents mean ± S.D. (n = 3)**

Table No. 10: Cummulative drug release of all batches of Floating microspheres

Time (hrs)	PERCENTAGE CUMULATIVE RELEASE			
	B1	*B2*	*B3*	*B4*
0	0	0	0	0
1	41.93±0.78	41.20±0.78	41.07±0.98	35.78±0.56
2	65.09±0.23	47.65±0.34	42.96±0.78	42.41±0.55
3	83.73±0.56	51.21±0.67	45.71±0.45	46.64±0.54
4	90.0±0.90	58.84±0.45	51.38±0.67	51.52±0.23
5	97.04±1.45	62.41±0.89	57.64±0.45	52.08±0.89
6	97.12±1.34	78.94±0.23	57.77±0.67	56.07±0.68
7	97.17±1.23	84.97±0.89	57.80±0.76	57.41±0.55
8	97.08±0.56	88.18±0.45	57.82±0.66	60.51±0.76
9	97.30±0.23	90.41±0.23	57.86±0.53	62.59±0.45
10	97.21±0.56	94.30±0.47	57.86±0.43	63.14±0.34
11	97.56±0.34	94.31±0.89	58.92±0.57	64.28±0.45
12	97.85±0.78	94.34±0.83	58.94±0.34	66.05±0.90

***Represents mean ± S.D. (n = 3)**

Table No. 11: Cummulative drug release of all batches of Floating microspheres

Time (hrs)	PERCENTAGE CUMULATIVE RELEASE			
	C1	C2	C3	C4
0	0	0	0	0
1	56.35±0.37	45.93±0.89	58.01±0.93	32.81±0.53
2	63.56±0.45	57.49±1.34	61.65±0.67	45.62±0.49
3	89.87±0.38	57.97±1.05	52.34±0.47	48.58±1.21
4	98.36±0.33	61.71±0.98	63.57±1.89	54.38±1.09
5	98.32±0.57	64.01±0.87	60.78±1.24	55.89±0.45
6	98.32±0.45	83.40±0.63	70.78±0.64	59.72±1.19
7	98.67±0.44	96.53±0.41	89.13±0.92	63.98±0.63
8	98.54±0.34	96.53±0.78	96.14±1.02	65.07±0.29
9	98.86±0.43	98.54±1.34	97.33±1.43	67.09±1.64
10	98.89±0.78	99.00±1.87	97.98±0.82	68.46±0.89
11	98.91±0.67	98.87±1.23	97.89±0.89	70.03±0.58
12	98.93±0.23	99.06±0.37	97.92±0.48	70.00±0.25

***Represents mean ± S.D. (n = 3)**

Fig No. 16-18: Cummulative drug release of all batches of Floating microspheres:

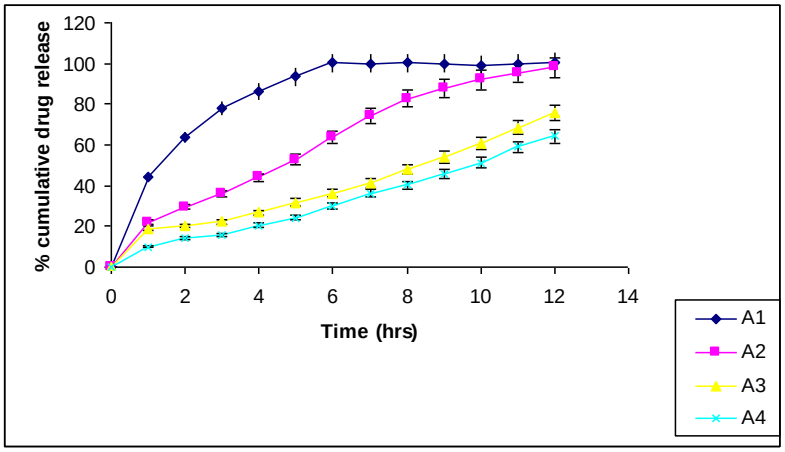

Fig 16: % cumulative drug release of batch A1 to A4

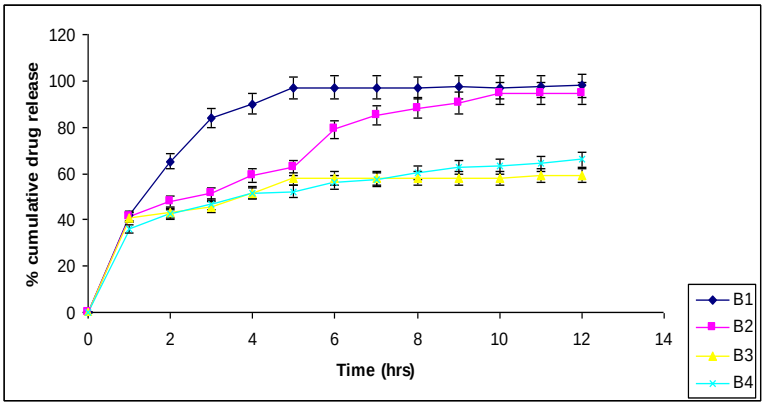

Fig 17: % cumulative drug release of batch B1 to B4

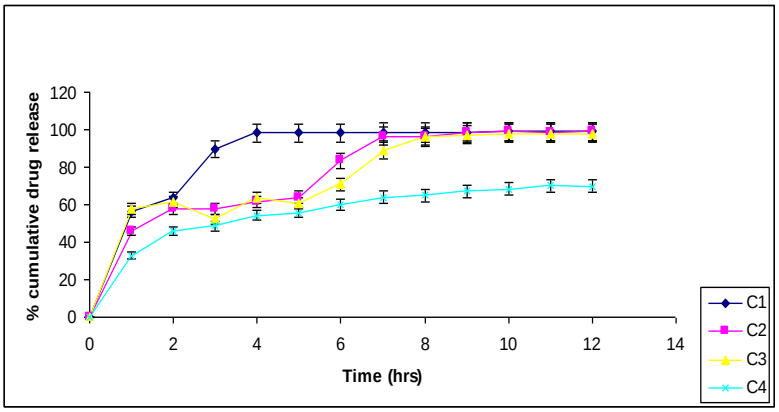

Fig 18: % cumulative drug release of batch C1 to C4

STUDY OF FLOATATION BEHAVIOR (OR BUOYANCY) OF MICROSPHERES: **Accurately weighed, 50 mg of floating microparticles were placed in each of four 50 ml beakers containing 20 ml of 0.1N HCl containing 0.02% tween 80. The beakers were shaken in a biological shaker at 37°C ± 0.5°C at 40 r.p.m. Floating microspheres were collected at 4,8 and 12 hrs and dried till constant weight was obtained. The percentage of floating microspheres was calculated by the following equation:** (Fig 13 and Table 9, 10).

% Floating microsphere (B %) = Weight of floating microspheres after time t

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Initial weight of floating microspheres

x 100

Buoyancy or Floating test:

IN VITRO RELEASE STUDY OF MICROSPHERE: [21]

The dissolution test was performed using dissolution apparatus USP Π (Rotating paddle method). The dissolution studies on microspheres containing cinnarizine was put in to dissolution medium 900 ml of 0.1 N HCL (pH 1.2) at 37ºC ±0.5ºC and paddle

was rotated at 100 rpm. Then 5 ml of samples were withdrawn at an interval of 1 hr upto 12 hr appropriate time interval upto 12 hr. and analysed spectrophotometrically at 253.4 nm. **(Fig: 16-118 and C4**

DISCUSSION

The procured sample of Cinnarizine was tested for its purity. The drug sample showed Compliance with the data given in British pharmacopoeia which reflected its quality and purity. The polymer Acrycoat. Eudragit, ethyl cellulose, and all excipients provided by the supplier confirmed by their identification test official in BP and EP. All the excipients showed results in compliance with standard specifications. From the scanning of drug in simulated gastric fluid, it was concluded that the drug had λmax of 253.4 nm. From the standard calibration curve of drug, it was concluded that drug obeys Beer-Lamberts law in concentration range of 0-20 mcg/mL. The linear equation were obtained as Simulated gastric fluid $Y = 0.0685x$ $R^2 = 0.9952$. The various batches has the average particle size in the range of 75μm to 600μm. where as Carr's index in between 11-23% and Hausner ratio with in 1.28 and angle of repose was found with in the range of 26^0 to 41^0, which is a appreciable limit for microspheres to show flow property while formulating in the dosage form. And concluded that particle size of the microspheres using different polymer are in following order: AcrycoatS 100<Eudragit RS 100<Ethyl cellulose. The maximum percentage yield (85.2%) of A2 batch was found while percentage yield of batches A1,A3 and C1 were found to be 84.5%, 73.25%, 70% respectively. It was found that average percentage yield was greater than 60 % for all. The microspheres of batch A2 formulation showed an entrapment of 91%. While formulation A3 (85%), A4 (82.5), and C1 (70.5%) showed lesser entrapment. Some drug was lost to the external phase during preparation and recovery. Various Polymers (Acrycoat S100, Eudragit RS100 and Ethyl cellulose) were taken in different ratio with drug to formulate batches from A1-A4, B1-B4 and C1-C4 and were subjected to the *in vitro* dissolution studies. However, based on the release rate studies of our formulations, we could conclude that the formulations containing 50mg of Cinnarizine, 100mg of Acrycoat S100 released approximately 98.14% drug over a period of 12 hours, % drug entrapment of this batch is 91% ,Percentage Buoyancy is 72% after 12 hrs., . Since it met our requirement, it was chosen as the optimized formulation.

CONCLUSION

We have used various polymers (Acrycoat S100, Eudragit RS100, EC) with drug (Cinnarizine) to formulate batches from A1-A4, B1-B4, and C1-C4. We could conclude that the floating microsphere of A2 batch contains Acrycoat S-100 as a polymer was found to be satisfactory result in terms of drug release, floatability and drug entrapment than the others. The batch was stable for three months under accelerated stability conditions.

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