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PREPARATION AND EVALUATION OF SUSTAINED RELEASE MICROSPHERES OF CINNARIZINE USING EUDRAGIT RS100

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Keywords:

Cinnarizine, polyvinyl alcohol, microsphere, o/o and o/w solvent evaporation, Eudragit RS100, release kinetics

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ABSTRACT: Cinnarizine was microencapsulated with Eudragit RS100 using an o/o and o/w emulsion solvent evaporation technique. The effects of three formulation variables including the drug: polymer ratio, emulsifier (polyvinyl alcohol) concentration and volume of external medium on the entrapment efficiency and microspheres size distribution were examined. The drug release rate from prepared microspheres and the release kinetics were also studied. The results demonstrated that microspheres with good range of particle size can be prepared, depending on the formulation components. The drug: polymer ratio had a considerable effect on the entrapment efficiency. However, particle size distribution of microspheres was more dependent on the volume polyvinyl alcohol concentration rather than the drug: polymer ratio. The release kinetics was also studied and it was shown that the release profiles of all formulations showed good correlation with the korsmeyer model of release.

INTRODUCTION: The oral route of drug management is the most important method of administering drugs for systemic effects. The parenteral route is not ordinary used or not possible to self- administration of medication. The topical route of administration has not recently been employed for release of the drugs to the body for systemic effects. It is probable that at least 90% of all drugs used to produce systemic effects are administered by the oral route. Oral drug delivery has been known for decades as the most widely used route of administration among all routes. The reasons that oral route achieved such popularity may be in part attributed to its ease of administration as well as traditional belief.

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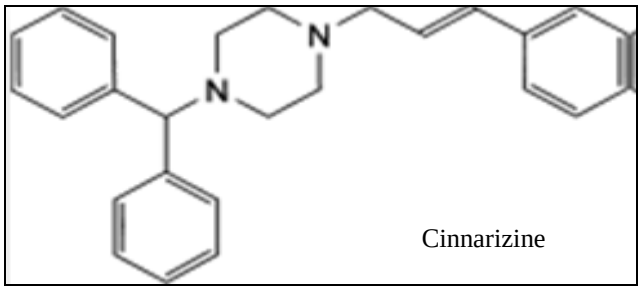
Pharmaceutical products intent for oral; delivery which are currently available in the market mostly are immediate- release or conventional release, which maintains the drug concentration within the therapeutically effective range only even administered several times a day. This results in a significant fluctuation in the drug level [1, 2]. "Microencapsulation is defined as the application of a thin coating to individual core materials that have an arbitrary particle-size range from 5 to 5000 μm" [3, 4].

The microparticulate delivery systems include mainly pellets, microparticles, lipospheres and macroemulsions. The nanoparticulate delivery systems contain mainly lipid or polymeric nanoparticles, microemulsions, liposomes, cochleates, and nonionic surfactant vesicles (niosomes). APIs can be embedded inside a polymeric/proteinic coat or matrix network in either a solid aggregated state or a molecular dispersion, resulting in the formulation of

microcapsules or microspheres, respectively. The term sustained release dosage form was used to identify drug delivery systems that are designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose [5, 6].

Cinnarizine is a (diphenylmethyl)-4-(3-phenylprop-2en-1-yl) piperazine derivative, water insoluble drug It has a short plasma half-life of 1–3 h following oral dosing , which makes it necessary to be administered frequently in order to maintain desired concentration.



Cinnarizine

Therefore, it is an ideal candidate for a sustained release multiple unit preparation, which results in more reproducible drug absorption and reduces the risk of local irritations compared to single unit dosage forms, due to uniform spreading in the gastrointestinal tract. A few studies have been performed on microencapsulation of ibuprofen using different processes. The objective of this study was to prepare and characterize the cinnarizine microspheres obtained by the aqueous emulsion solvent evaporation technique. The effect of different formulation variables on the microspheres properties was also investigated throughout this study [7, 8, 9].

MATERIALS AND METHODS:

Cinnarizine (Wings Pharmaceuticals Pvt Ltd., Baddi), Light liquid paraffin, acetone, methanol, magnesium stearate (Loba Chemie Pvt. Ltd. Mumbai), polyvinyl alcohol (s d Fine- Chem limited), Eudragit RS100 (Evonik Degussa India Pvt. Ltd, Mumbai, India), dichloromethane (Spectrochem Pvt. Ltd, Mumbai) n-hexane, dibasic potassium phosphate (Merck Specialities Pvt. Ltd., Mumbai) Hydrochloric acid (HCl) and sodium (Fisher scientific, Mumbai) were used in this study.

Preparation of microspheres by o/o solvent evaporation method:

Cinnarizine microspheres were prepared by based on an o/o emulsion solvent evaporation technique using Eudragit RS as a polymer. Eudragit RS100 and cinnarizine were co dissolved in a mixture of acetone (2 ml) and methanol (5 ml). Then magnesium stearate was dispersed in polymer drug solution.

The dispersion was then poured drop wise using 10 ml plastic syringe with an 18G × 11/2 needle into light liquid paraffin (50 ml), contained in a beaker (250 ml) at a low stirring speed (500-1000 rpm). After complete addition, the stirring speed was increased and its rate was maintained (1500-1800 rpm) for 3 h till all the acetone and methanol were evaporated.

Then n-hexane (20 ml) was added for hardening of the microspheres and to accelerate settling. Microspheres were separated by filtration and were then washed three times with n-hexane (10 ml) to remove any traces of liquid paraffin adhering to the surface. The washed microspheres were dried in oven maintained at 50°C for 24 h and were stored in desiccators until used. Composition of microspheres prepared by o/o solvent evaporation method as shown in **Table 1**.

Preparation of microspheres by o/w solvent evaporation method:

The microspheres were prepared by o/w solvent evaporation technique. The drug and polymer were dissolved in a mixture of dichloromethane and methanol (3:1) at room temperature. The drug solution was poured into 70 ml of water containing 0.25%, 0.15% and 0.1% w/v polyvinyl alcohol (PVA) for batches. Then the solution was stirred at a speed of 300 - 500 rpm with a propeller agitator and magnetic stirrer for 50 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 h. Composition of microspheres prepared by o/w solvent evaporation method as shown in **Table 2.**

TABLE 1: COMPOSITION OF MICROSPHERES PREPARED BY o/o SOLVENT EVAPORATION METHOD

S.No	Batch	Ratio D/P	CIN (mg)	Eudragit RS100	Magnesium stearate (%)	Stirrer	Result
1	M1	1:1	40	40	10	Propeller/Magnetic stirrer	Clumping
2	M2	1:3	150	450	10	Magnetic stirrer	Failed
3	M2a	1:3	150	450	10	Propeller	Spherical
4	M2b	1:3	200	600	10	Magnetic stirrer	Failed
5	M2c	1:3	200	600	10	Propeller	Spherical
6	M2d	1:3	500	1500	10	Magnetic stirrer	Spherical
7	M3	1:6	100	600	10	Propeller	Spherical
8	M3a	1:6	150	900	2	Propeller	Spherical
9	M4	1:10	100	1000	2	Propeller	Very few formed
10	M4a	1:10	100	1000	10	Propeller	Spherical
11	M4b	1:10	150	1500	10	Magnetic stirrer	Clumping
12	M4c	1:10	150	1500	10	Propeller	Spherical
13	M5	1:12	150	1800	10	Propeller	Spherical

TABLE 2: COMPOSITION OF MICROSPHERES BATCHES PREPARED BY o/w EVAPORATION METHOD.

S.No	Batch	Ratio D/P	CIN (mg)	Eudragit RS100 (mg)	PVA Conc. (w/v)	PVA Volume (ml)	Stirrer used	Result/ Sphericity
1	P1	1:1	200	200	0.25	35	Propeller	Spherical
2	P1a	1:1	200	200	0.30	35	Propeller	Clumping
3	P2	1:2	200	400	0.25	35	Propeller	Spherical
4	P3	1:3	200	600	0.20	70	Propeller	irregular
5	P3a	1:3	200	600	0.25	70	Propeller	Irregular
6	P3b	1:3	200	600	0.25	70	Magnetic stirrer	Failed
7	P3c	1:3	200	600	0.25	70	Propeller	Spherical
8	P4a	1:5	200	1000	0.25	70	Magnetic stirrer	Spherical
9	P4b	1:5	200	1000	0.25	70	Propeller	Spherical
10	P4c	1:5	200	1000	0.25	70	Propeller	Spherical
11	P5	1:10	200	2000	0.25	70	Propeller	Failed
12	P6	1:20	200	4000	0.25	70	Propeller	Failed
13	P7	1:20	200	4000	0.25	80	Propeller	Failed
14	P8	1:40	200	8000	0.25	70	Propeller	Failed

Solid State Studies:

Differential scanning calorimetry(DSC) analysis was performed using METTLER differential scanning calorimeter and PERKIN ELMER. Samples (2-5 mg) were placed in flat bottomed aluminum pan and heated at a constant rate of 10ºC/min. Thermograms were recorded over the temperature range of 25 - 400ºC.

FTIR spectra were recorded using Perkin Elmer 1600 FTIR spectrophotometer using KBr disc technique. The samples were properly diluted with dried KBr and compressed into discs by applying a pressure of 7-10 Newton's. IR spectra were recorded in the scanning range of 4000-400 cm^{-1}.

The X-ray diffraction patterns were recorded using XPERT-PRO diffractometer with Cu Kα filter generated at 45kV voltage and 40mA current over a diffraction angle of 2θ.

Characterization of Microspheres:

Percentage yield:

After the microspheres were completely dried, all the prepared batches of microspheres were weighed over the electronic digital balance and the percentage yield was determined by the formula

$$\% \text{ yield} = \frac{\text{Total weight of dried microspheres}}{\text{Total weight of raw material}} \times 100$$

Drug content analysis:

Microspheres (equivalent to 2 mg of cinnarizine) were dissolved in 10 ml of methanol and volume makes up to 50ml with 0.1 N HCl in a 50 ml volumetric flask by vigorous shaking. Then 1 ml of the above solution was taken and diluted up to 10 ml using 0.1N HCl and absorbance was determined spectrophotometrically at 253.5 nm. Drug content was calculated using calibration curve developed in 0.1N HCl.

Based on the results of drug content, drug loading was determined by the formula.

Percentage drug loading:

$$\text{Drug loading} = \frac{\text{Weight of drug in microspheres}}{\text{Weight of microspheres}} \times 100$$

Percentage encapsulation efficiency

Total drug present in the microspheres was calculated and encapsulation efficiency was determined by the formula

$$\text{Encapsulation efficiency} = \frac{\text{Weight of drug in microspheres}}{\text{Weight of drug added}} \times 100$$

Particle size determination

Particle size of all the prepared batches of microspheres was determined using optical microscopy at 10X. Firstly, the correction factor was calculated using optical and stage micrometer. The microspheres were then placed on glass slide and observed under optical microscope. The size of 100 microspheres was measured using optical micrometer. Then the mean particle size and standard deviation was calculated. Size frequency distribution curves were also plotted.

***In - vitro* dissolution studies:**

USP type II dissolution apparatus was used for studying the drug release properties of microspheres. Microspheres equivalent to 75 mg of cinnarizine were taken in muslin cloth and tied on the paddle which was suspended in the media under test. The test was carried out in 0.1N HCl (900 ml) equilibrated at 37±0.5ºC. The paddles were rotated at 100 rpm. 5 ml of dissolution media was withdrawn at specific time points and replaced with 5 ml of fresh dissolution medium. The collected samples were analyzed spectrophotometrically at 253.5 nm for the absorbance. Using calibration curves developed in respective media concentrations were calculated. Dissolution release profiles were plotted with percentage drug released at different time intervals.

Morphological studies:

Scanning electron microscopy (SEM):

The surface morphology of microspheres was examined using a scanning electron microscope (JEOL JSM-6610 LV scanning electron microscope (SEM), Japan) operating at 15 kV. Dried microspheres were coated with gold for 5–10 min under an argon atmosphere in a gold coating unit prior to observation.

Kinetics Evaluation:

The release kinetics was evaluated considering four different models including zero order, first order and Higuchi equation and korsmeyer and the selection was based on the comparisons of the relevant correlation coefficients. The release rate constants (k), calculated based on the best model [10, 11, 12]. Mathematical representation of models used to describe release profile from microspheres as shown in **Table 3**.

TABLE 3: MATHEMATICAL REPRESENTATION OF MODELS USED TO DESCRIBE RELEASE PROFILE FROM MICROSPHERES

Model	Equation
Zero-order	$Q_t = Q_o + K_o t$
First order	$\log C = \log C_o - Kt/2.303$
Higuichi	$F_t = K_H t^{1/2}$
Korsmeyer-peppas	$M_t / M_\infty = Kt^n$

RESULTS AND DISCUSSION:

Entrapment efficiency (%EE) and mean diameter of microspheres:

The batches containing higher amount of eudragit RS100 produced bigger microspheres and resulted in high encapsulation of CIN [13, 14, 15, 16, 17]. The encapsulation efficiency of microsphere batches ranged from 59.17- 80.44% prepared with o/w solvent evaporation method as shown in table 4. Therefore it can be concluded that eudragit RS100 is potentially useful polymer for the entrapment of lipophillic compound such as cinnarizine. High encapsulation efficiency of microspheres was dependent on the content of quaternary ammonium groups (4.48-6.77 %) present in the chemical structure of the eudragit RS100. It has thick polymeric surfaces due to the presence of lower amount of quaternary ammonium groups that restrict the migration of the surrounding medium, resulting high encapsulation efficiency.

The mean particle size of the microspheres ranged from 46.98 to 314.13 µm. The mean particle size was increased with increasing polymer concentration [18]. By increasing in the D/P ratio caused the mean particle size to shift towards a

higher particle size. It is reported that the amount of PVA as an emulsifying agent did not influence the drug loading and entrapment efficiency in microspheres but increasing the PVA concentration (> 0.75%) led to the decrease in the size of resulted microspheres [15]. So for all the batches lower concentration of PVA i.e. 0.20 to 0.30 % w/v was used.

TABLE 4: **RESULTS OF SELECTED BATCHES OF MICROSPHERES**

Batch	% yield	Drug content (%) ± SD*	Drug loading (%) ± SD*	Theoretical Drug loading (%)	Encapsulation efficiency(%) ± SD*
P1	88.75	73.37 ± 0.87	41.53 ± 0.49	56.33	73.73 ± 0.88
P2	61.0	79.51 ± 0.71	43.43 ± 0.38	54.64	79.49 ± 0.71
P3c	87.25	74.08 ± 0.87	21.21 ± 0.24	28.65	73.48 ± 0.62
P4a	96.5	80.44 ± 0.69	20.83 ± 0.17	25.90	80.44 ± 0.71
P4b	83.16	77.66 ± 0.60	15.56 ± 0.12	20.04	77.75 ± 0.20
P4c	76.75	78.24 ± 0.54	16.88 ± 0.11	21.71	77.78 ± 0.52

Solid State Studies:

DSC thermogram of pure CIN showed a sharp endothermic peak at 123.98ºC corresponding to the sharp melting point and representing the typical crystalline nature of cinnarizine shown in (**Fig. 3a**). DSC thermogram of eudragit RS100 with a broad peak at 60.09ºC, attributed to desolvation of water molecules. Absence of sharp peak indicates the amorphous form of eudragit RS 100 as shown in (**Fig. 3b**). DSC thermogram of physical mixture showed (**Fig. 3c**) no change in the endothermic peak of CIN. This represented that there was very less to no chemical incompatibility between drug and the polymer. The thermal curve of Eudragit RS100 loaded cinnarizine microspheres showed characteristic peak at 115.06°C as shown in (**Fig. 3d**) with decreased intensity showing the presence and stability of cinnarizine during the encapsulation process.

FTIR spectrum of CIN is shown in (**Fig. 4a**) and it revealed various characteristic peaks such as aromatic C-H bands at 3023 cm^{-1}, the 2934 cm^{-1} peak is the sp^3 C-H stretch, , C=C stretching at 1594 cm^{-1} **.**

FTIR spectrum of eudragit RS100 (Fig. 4b) showed various characteristic peaks such as peaks at 2953 cm^{-1} corresponding to C-H aliphatic stretching, at 1732 cm^{-1} corresponding to C=O stretching, at 1454 cm^{-1} corresponding to $–CH_2-$ bending , at 1386 cm^{-1} corresponding to $–CH_3-$ bending, at 1147 cm^{-1} corresponding to C-O ester group stretching, at 1020 cm^{-1} corresponding to C-N stretching and at 848 cm^{-1} corresponding to C=C stretching. Significant peaks of both CIN and eudragit RS100 were present in physical mixture and no significant shift in the peaks was observed which suggested very less to no chemical interaction between drug and polymer as shown in (**Fig.4c**). FTIR spectrum of Eudragit RS100 loaded CIN microspheres showed (Fig. 4d) some of the characteristic peaks of CIN such as at 2954 cm^{-1} corresponding to C-H (alkane stretching), 1597 cm^{-1} corresponding to C=C stretching. Similarly characteristic peaks of eudragit RS100 were also seen in FTIR spectra at 2954 cm^{-1} corresponding to C-H aliphatic stretching, at 1731cm^{-1} corresponding to C=O stretching, at 1450 cm^{-1} corresponding to CH_2 bending, at 1386 cm^{-1} corresponding to CH_3 bending, at 1143 cm^{-1} corresponding to C-O ester group stretching.

From the FTIR study it was found that some of the peaks of the drug were shifted broadened and some vanished. There is no significant shift in the major peaks as shown in (**Fig.4d**). This confirms presence of cinnarizine in microspheres.

X-RD pattern of CIN (Fig.5a) showed several sharp high intensity peaks at diffraction angle 2θ of 10.2731, 13.2753, 18.6133, 18.7573, 20.9253, 21.9808, and 22.8258 which suggested CIN as crystalline material. X-RD pattern of Eudragit RS100 (**Fig.5b**) appeared as halo structure which showed its amorphous nature.

X-RD pattern of physical mixture (**Fig.5c)** showed several characteristic sharp peaks of CIN at diffraction angles of 2θ of 10.3568, 13.3456, 18.2881, 18.7467, 20.9942, 22.0926, and 22.9074. X-RD pattern of Eudragit RS100 loaded CIN microspheres (**Fig.5d**) showed few low intensity peaks at diffraction angles 2θ of 13.28,40.68

indicating that CIN has been molecularly dispersed within the microspheres. The X-RD data of Eudragit RS100 loaded CIN microspheres.

***In Vitro* Release Studies:**

***In vitro* dissolution studies:**

In vitro dissolution study of the microspheres, were conducted in 0.1N HCl and dissolution data is given in **Table 5**. The dissolution profiles for all batches were constructed as shown in **Fig.1**.

Examination of release profile reveals that the drug release was generally faster for cinnarizine microspheres produced with low D/P ratios (batch P1 and P2). The batches prepared with high D/P ratios (batch P4a and P4b) showed slow drug release due to the formation of longer diffusion path. The various release kinetic equations were also applied on the drug release data of the batches (P1 to P4c) i.e. zero order, first order, korsmeyer, higuchi were also applied on the drug release data of batches (P1 to P4c) in which the experimental data can be fitted and drug release rate can be predicted as a function of same variable (e.g. time) are mentioned below in **Table 6** and **Table 7**.

The mechanism responsible for the release of cinnarizine from the polymeric microspheres under consideration may be due to diffusion phenomenon, due to degradation effects, or due to combination of both.

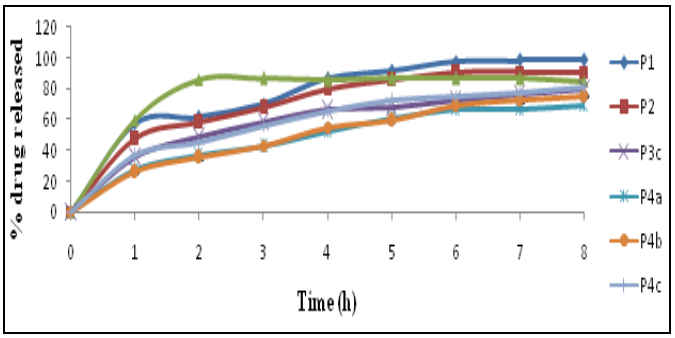


FIG. 1: DISSOLUTION PROFILE OF MICROSPHERES (BATCH P1 TO P4C) PREPARED BY O/W SOLVENT EVAPORATION METHOD IN 0.1N HCL. EACH POINT REPRESENTS THE MEAN ± S.D

SEM:

Scanning electron photomicrographs of CIN at different magnification (100X and 270X) taken and are shown in **Fig 2a** and **Fig 2b**. The SEM picture displays that cinnarizine exist as oblong column shaped crystals and hence confirmed its crystalline nature [4]. Scanning electron photomicrographs of the final batch (P4b) are shown in **Fig 2c**. Microspheres produced were discrete, spherical in shape and appeared to have coarse surfaces. At higher magnification (**Fig. 2d**), drug crystals were not visible on the surface of microspheres which proved that the drug had been completely dispersed in the polymer matrix and had undergone a phase transition from crystalline to amorphous state.

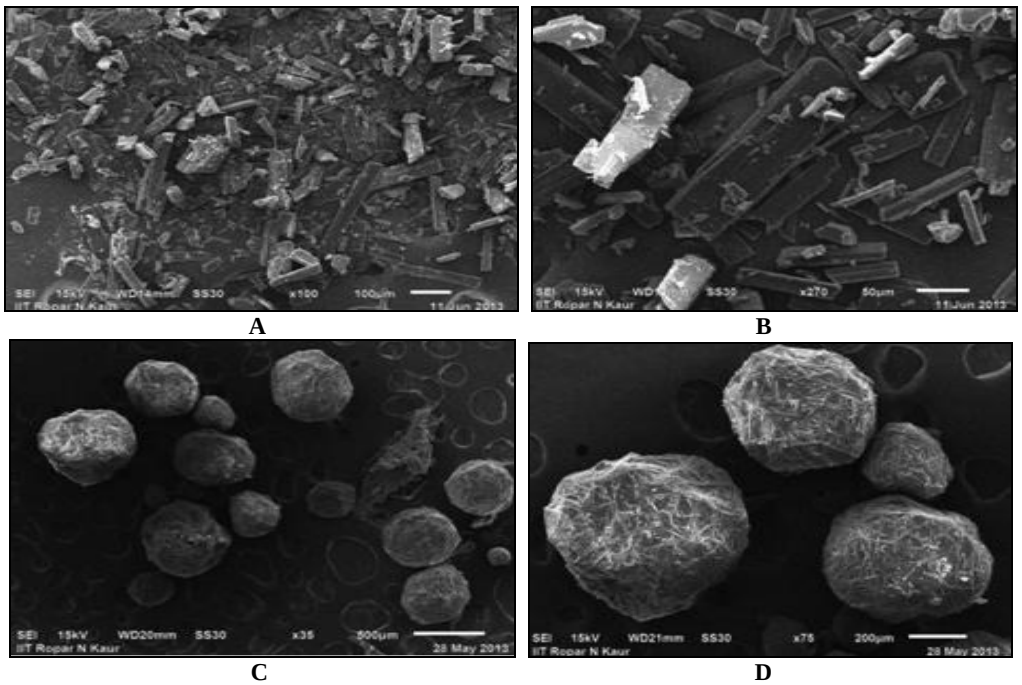
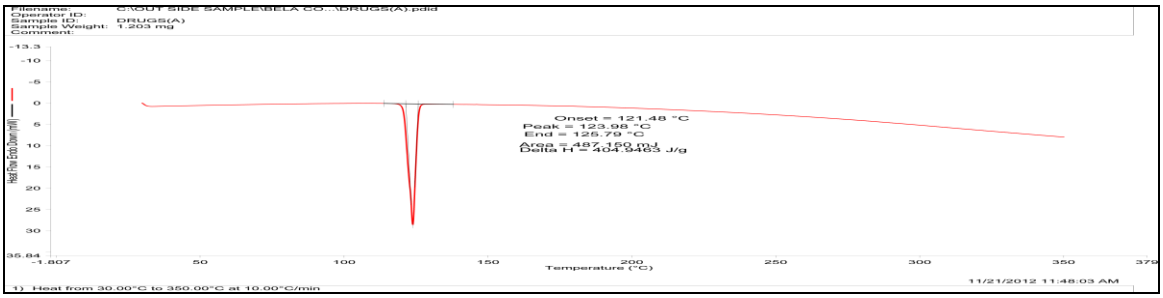


FIG 2: SEM OF PURE DRUG CINNARIZINE AT100X (A) 100X (B) 270X (C) SEM'S OF EUDRAGIT RS100 LOADED MICROSPHERES (BATCH P4B) AT (C) 35X (D) 75X

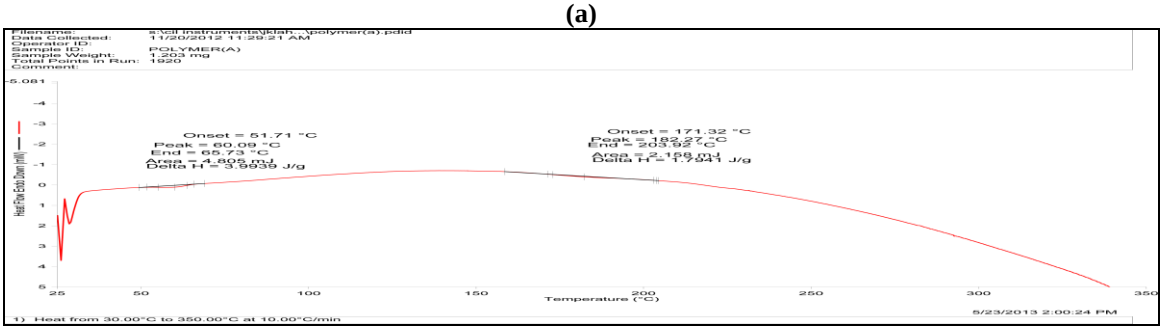
TABLE 5: CINNARIZINE RELEASE DATA OF SIX BATCHES OF MICROSPHERES IN 0.1N HCL

Batch Time (h)	P1	P2	P3c	P4a	P4b	P4c
1	57.25 ± 0.17	47.16 ± 0.964	35.50 ± 0.958	27.18 ± 0.958	26.07 ± 0.965	36.76 ± 1.316
2	61.30 ± 0.092	57.69 ± 0.958	48.81 ± 0.964	36.61 ± 1.66	34.94 ± 1.665	45.48 ± 0.969
3	70.73 ± 0.165	67.68 ± 0.964	58.80 ± 0.961	42.71 ± 0.958	43.27 ± 1.670	56.03 ± 0.964
4	86.71 ± 0.170	79.33 ± 0.964	66.01 ± 0.958	52.14 ± 0.964	54.92 ± 1.665	65.46 ± 0.958
5	91.69 ± 0.132	85.43 ± 0.958	68.24 ± 0.00	60.46 ± 0.964	59.35 ± 0.958	72.67 ± 0.952
6	98.14 ± 0.098	90.42 ± 0.964	72.12 ± 0.958	66.01 ± 0.958	68.79 ± 0.958	75.44 ± 0.964
7	98.30 ± 0.092	90.98 ± 0.964	76.00 ± 0.961	67.12 ± 0.964	72.12 ± 0.958	77.66 ± 0.958
8	98.41± 0.098	90.98 ± 0.964	79.88 ± 1.665	68.79 ± 0.958	74.89 ± 0.00	80.99 ± 0.958

Each value is average of three independent determinations with standard deviation



(a)



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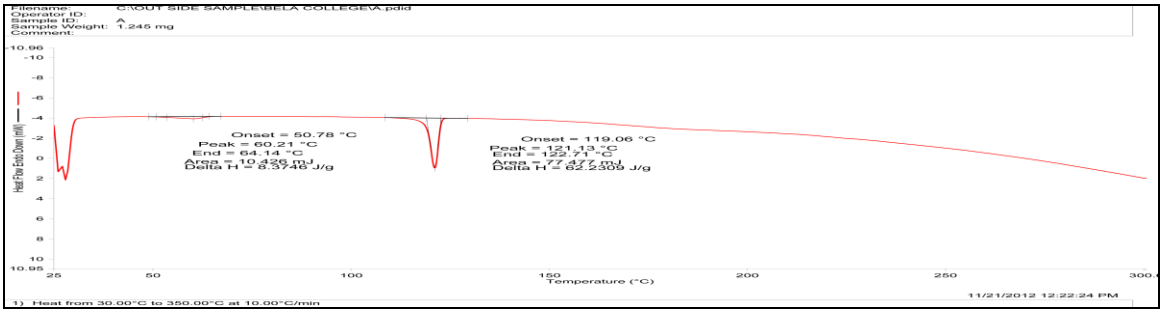
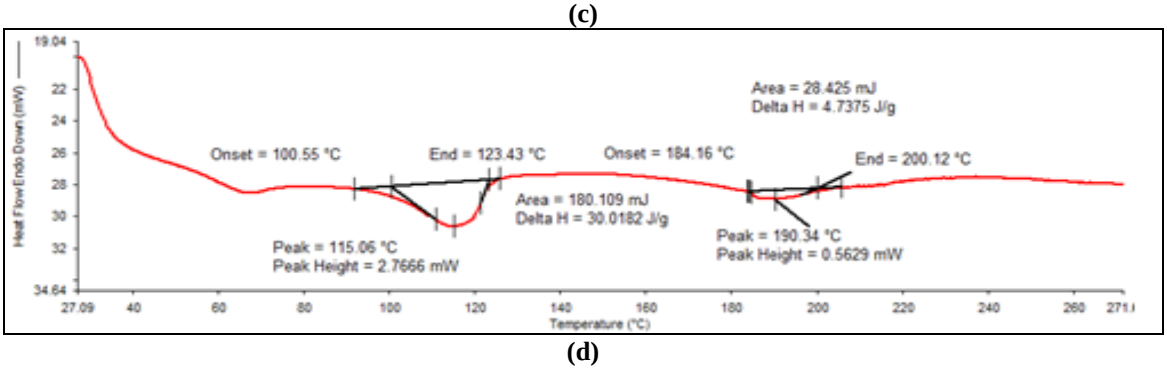
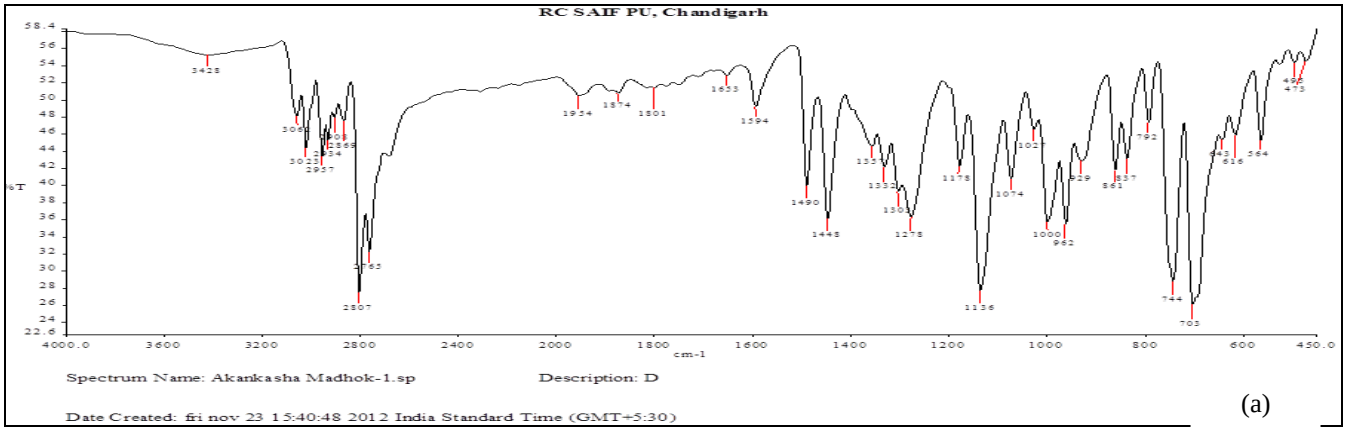


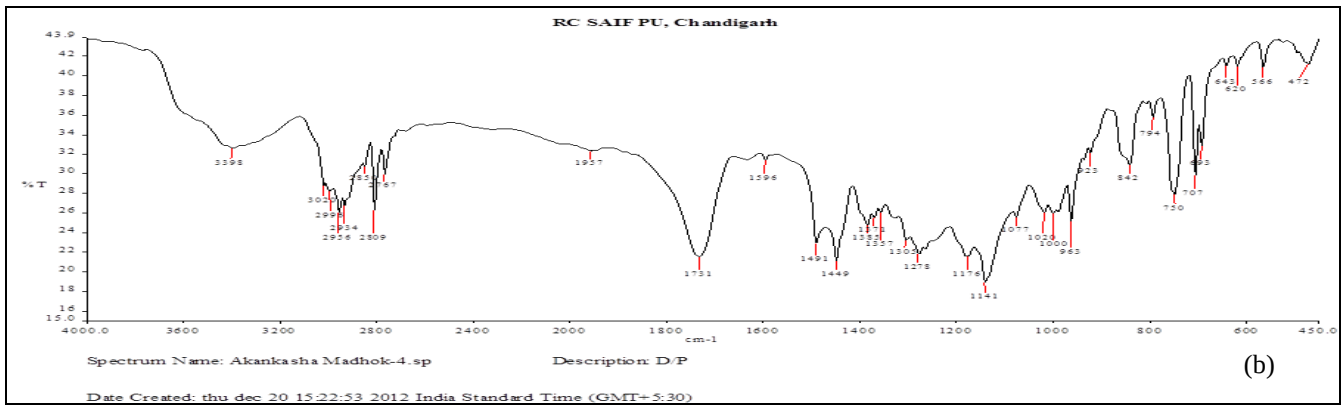
(c)

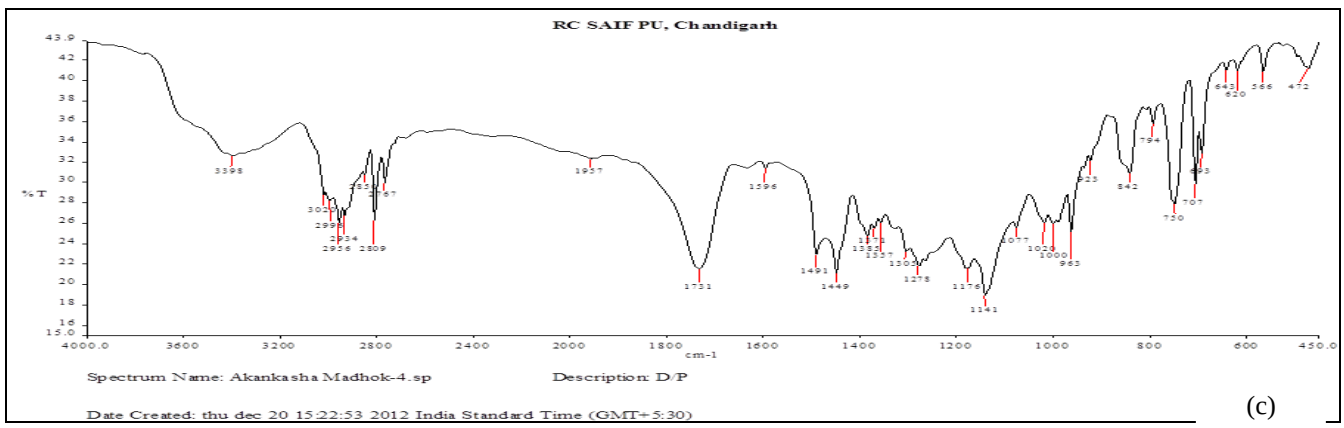


(d)

FIG. 3: DSC CURVES OF (A) PURE CIN (B) EUDRAGIT RS100 (C) PHYSICAL MIXTURE (D) EUDRAGIT RS100 LOADED CIN MICROSPHERES (BATCH P4b)







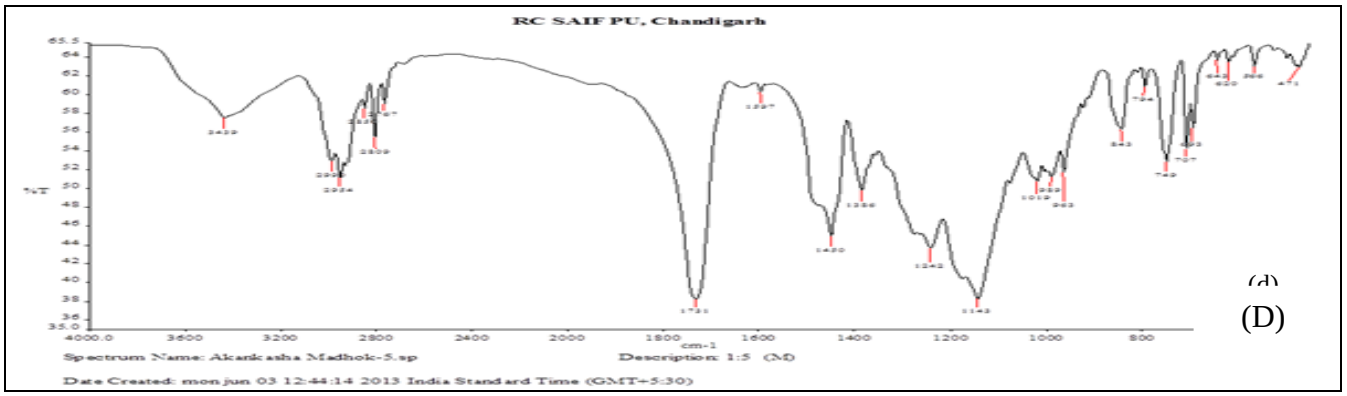


FIG. 4 : FTIR SPECTRA OF (A) PURE CIN (B) EUDRAGIT RS100 (C) PHYSICAL MIXTURE (D) EUDRAGIT RS100 LOADED CIN MICROSPHERES (BATCH P4b).

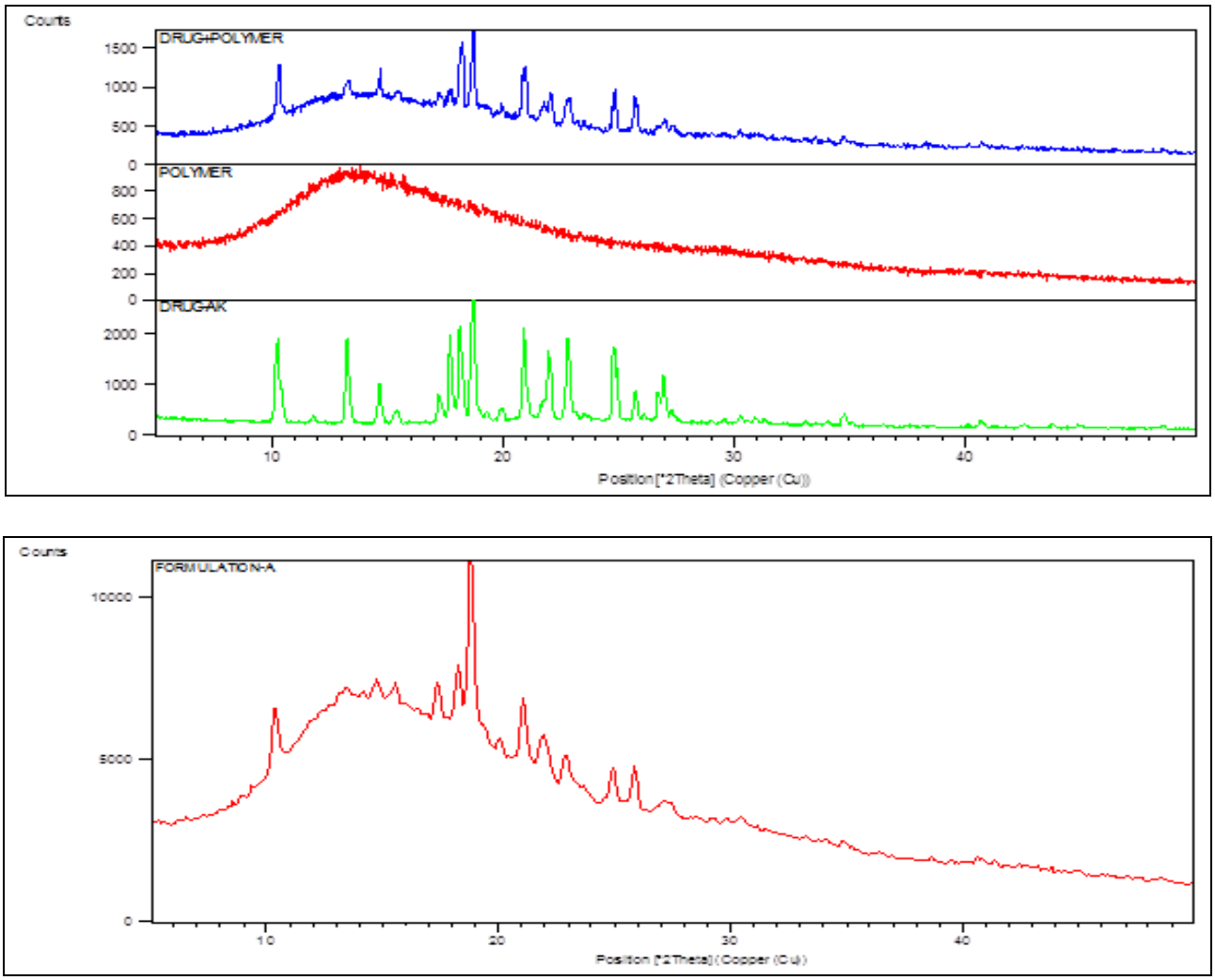


FIG. 5: XRD SPECTRA OF (a) PURE CIN (b) EUDRAGIT RS100 (c) PHYSICAL MIXTURE (d) EUDRAGIT RS100 LOADED CIN MICROSPHERES (BATCH P4b).

Mathematical models:

The various release kinetic equations were also applied on the drug release data of the batches (P1 to P4c) i.e. zero order, first order, korsmeyer, higuchi were also applied on the drug release data of batches (P1 to P4c) in which the experimental data can be fitted as shown in (**Fig.6, Fig.7, Fig.8, Fig.9**) and drug release rate can be predicted as a function of same variable (e.g. time) are mentioned below in **Table 6** and **Table 7**. The mechanism responsible for the release of cinnarizine from the polymeric microspheres under consideration may be due to diffusion phenomenon, due to degradation effects, or due to combination of both.

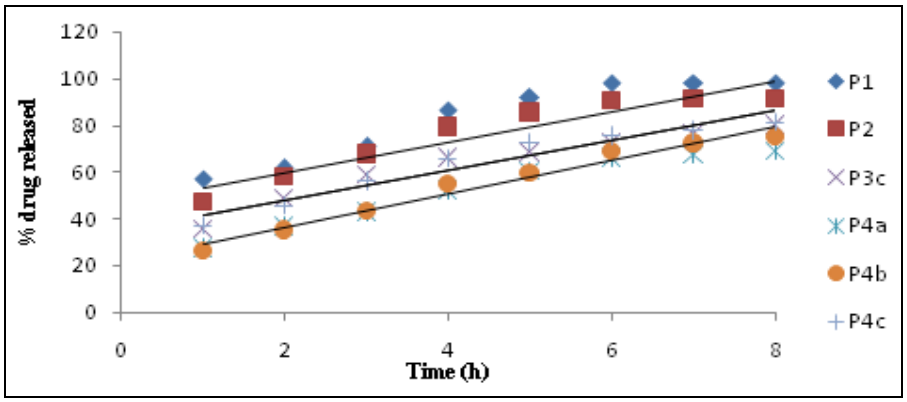


FIG 6: PLOT BETWEEN % DRUG RELEASED AND TIME FORMULATIONS OF P1 TO P4c (ZERO ORDER)

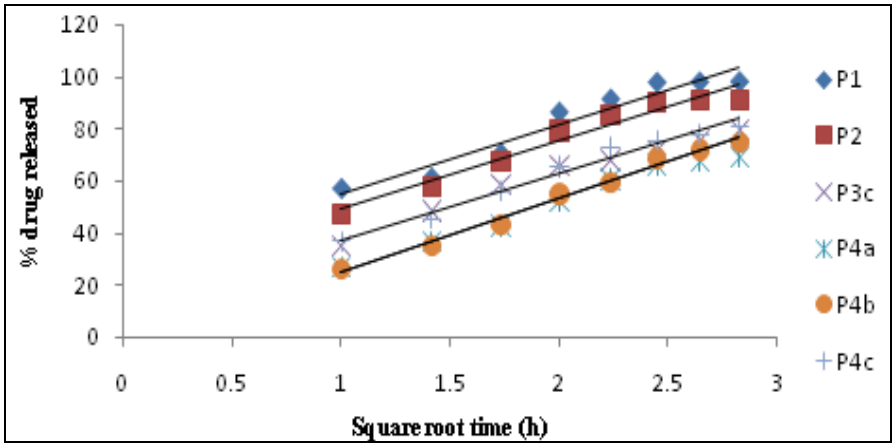


FIG 7: PLOT BETWEEN % DRUG RELEASED AND SQUARE ROOT TIME FORMULATIONS OF P1 TO P4c (HIGUCHI)

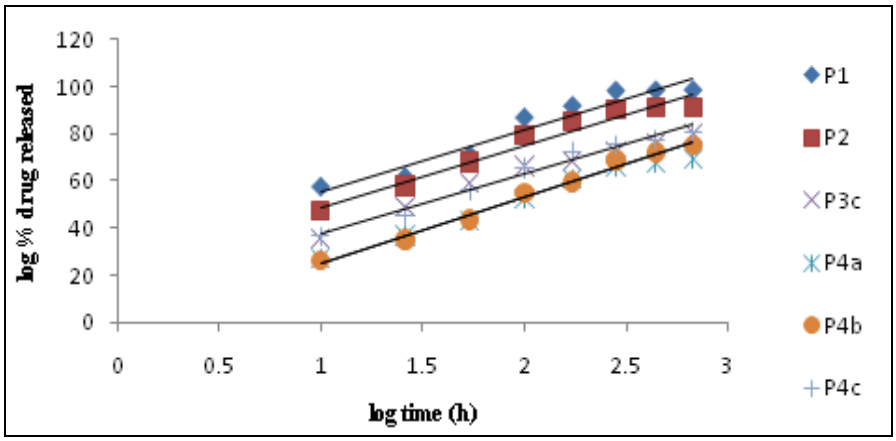


FIG 8: PLOT BETWEEN LOG % DRUG RELEASED AND LOG TIME FORMULATIONS OF P1 TO P4c (KORSMEYER)

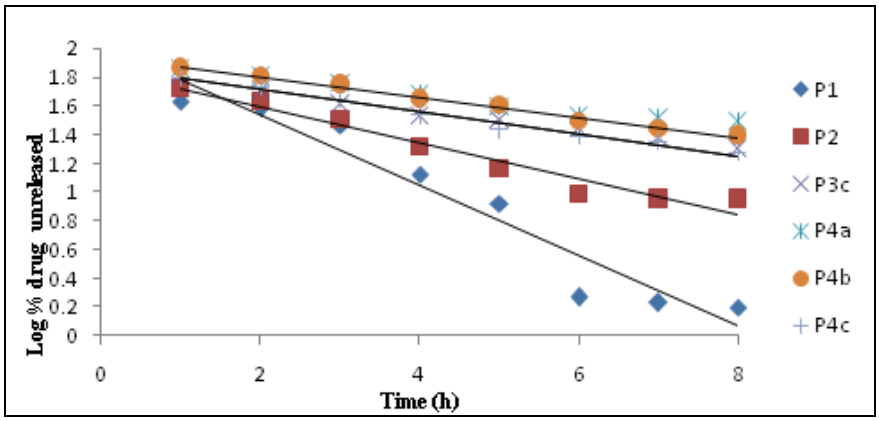


FIG 9: PLOT BETWEEN LOG % DRUG UNRELEASED AND TIME FORMULATIONS OF P1 TO P4c (FIRST ORDER)

The best fit with the highest correlation was shown in (**Table 8**) korsemeyer, than first order and followed by higuichi equations in the formulations (P1, P2, P3c, P4a, P4b, P4c) as given in table 8. According to Korsmeyer and Peppas model, n values of the batches (P1, P2, P3c, P4a, P4b, P4c) were 0.307, 0.344, 0.381, 0.477, 0.536, and 0.402 respectively. The n values of P1, P2, P3c and P4c were less than 0.45 which indicated that the release comply case I or fickian diffusion, which may be due to the leaching of drug by the eluting medium. The batches P4a and P4b contained highest amount of polymer and were having n value >0.45 which is an indicator that the microspheres tends to changing the mechanism of transportation of drug from case I or fickian diffusion to anomalous behavior or non-fickian transport. This suggests that some level of swelling and dissolution of matrix must be operating within the system causing deviation from the fickian release.

TABLE 6: DISSOLUTION PROFILE OF CINNARIZINE FROM THE MICROSPHERE BATCHES P1 TO P4c PREPARED BY O/W SOLVENT EVAPORATION METHOD FOR KINETIC ANALYSIS.

Time (h)	% drug released							Log t	Log % drug unreleased					
	Square root t	P1	P2	P3c	P4a	P4b	P4c		P1	P2	P3c	P4a	P4b	P4c
1	1	57.25	47.16	35.50	27.18	26.07	36.76	0	1.63	1.722	1.809	1.862	1.868	1.800
2	1.414	61.30	57.69	48.81	36.61	34.94	45.48	0.301	1.587	1.626	1.709	1.802	1.813	1.736
3	1.732	70.73	67.68	58.80	42.71	43.27	56.03	0.477	1.466	1.509	1.614	1.758	1.753	1.643
4	2	86.71	79.33	66.01	52.14	54.92	65.46	0.602	1.123	1.315	1.531	1.679	1.653	1.538
5	2.236	91.69	85.43	68.24	60.46	59.35	72.67	0.699	0.919	1.163	1.501	1.597	1.609	1.436
6	2.449	98.14	90.42	72.12	66.01	68.79	75.44	0.778	0.269	0.981	1.44	1.531	1.494	1.39
7	2.645	98.30	90.98	76.00	67.12	72.12	77.66	0.845	0.23	0.955	1.38	1.516	1.444	1.349
8	2.828	98.41	90.98	79.88	68.79	74.89	80.99	0.903	0.201	0.955	1.303	1.494	1.399	1.278

TABLE 7: PERCENT DRUG UNRELEASED DATA OF SELECTED FORMULATIONS (P1 TO P4c)

Time (h)	% drug unreleased					
	P1	P2	P3c	P4a	P4b	P4c
1	1.63	1.722	1.809	1.862	1.868	1.800
2	1.587	1.629	1.709	1.802	1.813	1.736
3	1.466	1.509	1.614	1.758	1.753	1.643
4	1.123	1.315	1.531	1.679	1.653	1.538
5	0.919	1.163	1.501	1.597	1.609	1.436
6	0.269	0.981	1.44	1.531	1.494	1.390
7	0.23	0.955	1.38	1.516	1.444	1.349
8	0.201	0.955	1.303	1.494	1.399	1.278

TABLE 8: STATISTICAL PARAMETER OF VARIOUS FORMULATIONS OBTAINED AFTER FITTING THE DRUG RELEASE DATA TO VARIOUS RELEASE KINETIC MODELS.

Formulations	Zero Order		Higuchi Equation		First order		Korsemeyer- Peppas	
	K_0(mg/h)	R^2	K	R^2	$k_1(h^{-1})$	R^2	n	R^2
P1	6.670	0.901	26.52	0.937	0.243	0.932	0.307	0.935
P2	6.518	0.895	26.24	0.954	0.124	0.953	0.344	0.977
P3c	5.819	0.918	23.37	0.974	0.068	0.982	0.381	0.985
P4a	6.214	0.946	24.64	0.978	0.056	0.969	0.477	0.986
P4b	7.245	0.971	28.51	0.989	0.070	0.990	0.536	0.990
P4c	6.380	0.933	25.46	0.978	0.076	0.981	0.402	0.985

CONCLUSION: The purpose of the present work was to formulate sustained release microspheres of cinnarizine by using o/w emulsion solvent evaporation technique. We have successfully prepared and characterized Eudragit RS100 based cinnarizine loaded microspheres. Based on the *in-vitro* characteristics, formulation P4b was found to be the most promising formulation. Formulations prepared with o/o emulsion solvent evaporation method gave poor results while the batches prepared with the o/w emulsion solvent evaporation method by using non- polar organic solvent i.e. dichloromethane and 0.25% w/v PVA solution as external medium gave better results in terms percentage yield, percentage drug content and encapsulation efficiency.

Formulation studies revealed that drug-to-polymer ratio had a significant influence on the various parameters such as sphericity, drug content, drug loading, drug encapsulation efficiency, mean particle size.

Surface morphology of prepared P4b batch was studied using SEM which proved the formation of spherical, non-aggregated microspheres. DSC studies of the selected batch P4b also showed a similar characteristic peak as that of pure cinnarizine with decreased intensity showing its stability during the encapsulation process. Further XRD analysis showed that there was a considerable decrease in the crystallinity of the drug in the

formulation P4b and no interaction was found between drug and polymer.

The release studies of prepared batch P4b in 0.1N HCl showed slow release of the drug. It was found that the release of drug from selected formulations followed non-fickian or anomalous release, n = 0.536 indicates case II release. Eudragit RS100 was dominated by non-fickian and class II mechanism (n> 0.45). That is why, poor correlation values were obtained for kinetic parameters based on zero order model (r value was 0.971). Correlation coefficients were also poor (r value was 0.989) for the kinetic parameters based on Higuchi's square root equation. However, considering the good fitting of the release data with Korsmeyer model (r value 0.990), it can be concluded that the effect of diffusion on drug release was more than the effect of polymer relaxation. In addition, significant control over the rate of drug released from the system in 8 h could be achieved.

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