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Formulation and Evaluation of Cinnarizine Extended Release Tablets

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A B S T R A C T

Cinnarizine is an anti histaminic, derivative of piperazine and has high affinity to H1 receptors, extensively used for the treatment of motion sickness, vertigo / menieres disease, nausea and vomiting. Cinnarazine as an immediate release dosage form causes GI irritation and has less halflife (2- 4 hrs). So the present study was to formulate an extended drug delivery system of cinnarizine. The tablets were prepared by direct compression technique using different hydrophobic and hydrophilic polymers like ethyl cellulose (EC), hydroxy propyl methyl cellulose (HPMC) in different ratios. The formulated tablets were evaluated for hardness, thickness, weight variation, content uniformity, in-vitro drug release and stability. Seven formulations with different proportion of aforementioned polymers were prepared to access their efficacy. The formulation containing 20% ethyl cellulose (CNZ-1) of cinnarizine has achieved 98% drug release for 12 Hrs. The drug release has been retarded with increase in the concentrations of hydrophobic polymer (Ethyl cellulose), and with increase in concentration of hydrophilic polymer (HPMC) the drug released within 7 hrs (CNZ-7). CNZ-1 shows more retarding effect and thus found that T_{50} % value increases as concentration of EC increases. Korsemeyer-Peppas release exponent (n) values of all cinnarizine extended release tablets are greater than 1 indicating drug diffusion is rapid due to swelling in the polymer (case 2 transport).

Keywords: Cinnarizine, HPMC, Drug release kinetics, Ethyl cellulose, Diffusion exponent (n)

A R T I C L E I N F O

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1. Introduction

Cinnarizine is an antihistamine drug derivative of piperazine, having additional anticholinergic activity, anti-5HT, sedative and vasodilator properties used to treat the motion sickness, vertigo/menieres disease, nausea, vomiting and also used to the vestibular organs of other origins [1, 2]. It is a calcium channel blocker, inhibits the influx of calcium intracellularly, inhibits vestibular sensory nuclei in the inner ear, suppresses postrotatory labyrinthine reflexes and also inhibits the contraction of smooth muscle cells [3].

It is a H1 receptor antagonist, poorly water soluble class II drug [4]. Motion sickness is an uncomfortable dizziness, nausea, and vomiting. Sense of balance and equilibrium is disturbed by constant motion. Riding in a car, on board a ship or boat, or riding on a swing all cause stimulation of the vestibular system, visual stimulation that often leads to discomfort [5].

Oral route is the most oldest and convenient route for the administration of therapeutic agents because of low cost of therapy and ease of administration leads to higher level of patient compliance. Approximately 50% of the drug delivery systems available in the market are oral drug delivery systems and oral drug administration has been the predominant route for drug delivery. It does not pose the sterility problem and minimal risk of damage at the site of administration. During the past three decades, numerous oral delivery systems have been developed to act as drug reservoirs from which the active substance can be released over a defined period of time at a predetermined and controlled rate. The oral controlled release formulation have been developed for those drug that are easily absorbed from the gastrointestinal tract (GIT) and have a short half-life are eliminated quickly from the blood circulation. As these will release the drug slowly into the GIT and maintain a constant drug concentration in the plasma for a longer period of time [6].

The active ingredients are administered in a regular medication usually released within 15 to 30 minutes. So they are prescribed to be taken three or four times a day. The active ingredients in extended-release medications are released over a much longer period of time and are usually taken only once or twice a day [7].

The mechanisms by which extended-release medications are released into the body vary according to the medication. The important thing to know is that the medication is gradually released into your body so that it remains at a more constant level throughout the day. Extended release formulations allow greater reduction in frequency of administration of a drug in comparison with the frequency administration of drug in conventional dosage form. Characteristically ER tablets release the drug with time periods of 8hrs, 12hr, 16hrs, and 24hrs [8].

2. Materials and Methods

Cinnarizine (API), polymers like HPMC K15 and EC were purchased from Drugs India Hyderabad and all the other chemicals and reagents used were obtained from commercial sources and were of analytical grade.

Formultion of Cinnarizine Extended Release Tablets:

Cinnarizine extended release tablets (CNZ-1 to CNZ-7) were prepared by developing the formulae using variable concentrations of different polymers like HPMC K15 and EC as shown in table 1. The dose of cinnarizine is kept constant for all batches of formulations. The materials were weighed, mixed and passed through a sieve #40 to ensure complete mixing. The tablets were prepared by compressing the mixed materials using 13mm round, flat punches on 16 station tablet punching machine (cadmach).

Table 1: Formulation Table for Cinnarizine Extended Release Tablets

S.No	Formulation ratios in (mg)	CNZ-1	CNZ-2	CNZ-3	CNZ-4	CNZ-5	CNZ-6	CNZ-7
1.	Drug	75	75	75	75	75	75	75
2.	Lactose	305	305	305	305	305	305	305
3.	Starch	50	50	50	50	50	50	50
3.	EC	120	115	110	105	100	95	90
4.	HPMC	0	5	10	15	20	25	30
5.	Magnesium Stearate	20	20	20	20	20	20	20
6.	Talc	30	30	30	30	30	30	30
7.	Total	600	600	600	600	600	600	600

DRUG-Cinnarizine (CNZ), HPMC- Hydroxy propyl methyl cellulose, ERT- Extended Release Tablets, EC- Ethyl Cellulose

Evaluation:

Pre Compression Parameters:

Drug and Excipients Compatibility Study:

FT-IR Spectroscopy

FT-IR patterns were studied by Shimadzu 8400S, Japan FT-IR spectrometer. The samples (cinnarizine and Excipients) were previously ground and mixed thoroughly with potassium bromide, an infrared transparent matrix, at 1:5 (Sample: KBr) ratio, respectively. The KBr discs were prepared by compressing the powders at a pressure of 5 tons for 5 min in a hydraulic press. The scans were obtained at a resolution of 4 cm-1, from 4000 to 400 cm-1. The formulations were evaluated for various physicochemical parameters including angle of repose, bulk density, tapped density, compressibility index and Hausner's ratio.

Bulk density:

A 15 g quantity of the powder samples was placed in a 100 ml dry measuring cylinder and volume VO, occupied by it,

without tapping, was determined. The bulk density were calculated by following formula

Bulk density = W/Vo

Tapped density:

The cylinder was then given 100 taps using tap density apparatus and the resulting volume, V100, was noted determined. The tap density was calculated by using following formula [9].

Tapped density = W/VX100

Angle of repose:

The fixed-funnel method was used to determine angle of repose. The granule formulation was carefully poured through a funnel until the apex of the conical pile just touched the tip of funnel. The height (h) of the pile of the powder and the radius (r) of its conical base were measured and applied to compute the angle of repose10.

ɵ= tan-1 h/r

Carr's index (compressibility index)

Compressibility index is based on poured density and tapped density, carr's index was calculated by using this formula11. Carr's index (%) = poured density-tapped density/poured densityX100

Hausner's ratio:

This parameter was calculated as the ratio of tap density to bulk density of the granules.

Hausner's ratio = TD/BD

Post Compression Evaluation Parameters: The tablets were evaluated for hardness, thickness, friability, weight variation, drug content, in -vitro dissolution and stability.

Determination of drug content:

Two tablets from each formulation were crushed to powder. Crushed powder were transferred into 100 ml flask and diluted to 100 ml with 0.1N HCL solution and stirred magnetically for 1 hr, centrifuged and filtered. 1 ml of this solution was taken and it was diluted to 100 ml with 0.1N HCL and then absorbance was noted at 253.5 nm using UV-visible spectrophotometer. Using calibration curve the drug content was determined from absorbance of tablets12.

Hardness: The hardness of each of 10 tablets randomly selected from each batch was measured with a tablet hardness tester [13.

Thickness:

From each formulation ten tablets were selected randomly and thickness of tablets was calculated by using vernier callipers. The average thickness was calculated7. Weight variation: For uniformity of weight, ten tablets from each batch of formulation were selected at random and determined their individual weights by using electronic balance. Then, average weight and standard deviation of the tablets was calculated.

Friability: The friability of tablets using 10 tablets as a sample was measured using a Roche Friabilator. Tablets were rotated at 25 rpm for 4 minutes or up to 100 revolutions. The tablets were taken out, dedusted and reweighted. The percentage friability was calculated from the loss in weight as given in equation below. The weight loss should not more than 1%.

%friability = W0-W /W0 X100

Friability test was performed to evaluate ability of tablet to withstand wear and tear in packing, handling and transporting [14].

In vitro study:

The release of cinnarizine extended release tablets was determined by using dissolution apparatus LAB India DS 8000. This test was performed by using 900ml phosphate buffer 6.8 at 37°c ± 2oc temperature with 50 rpm. Sample intervals are taken for every hour and the absorbance of the solution is measured at 253.5nm using UV visible spectrophotometer. The cumulative percentage was calculated.

Stability study:

Overall observations from different evaluation studies such as drug-polymer interactions, evaluation of prepared formulations and drug release studies were carried out. Based on the obtained results best formulation was subjected for further stability study. The stability study was conducted as per ICH guidelines for the period of three months at various accelerated temperature and humidity conditions of 25°C/60% RH, 40°C/70 % RH, 60°C/80% RH.

Mathematical Modelling for Drug Release Profile:

The cumulative amount of cinnarizine released from the formulated tablets at different time intervals were fitted in to several kinetic models such as Zero order kinetics, first order kinetics, Higuchi model and Korsmeyer-peppas model to characterize mechanism of drug release.

3. Results and Discussion

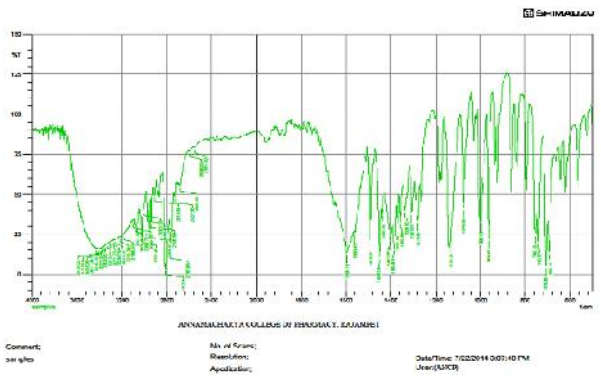

Figure 1: FTIR Spectra of cinnarizine (pure drug)

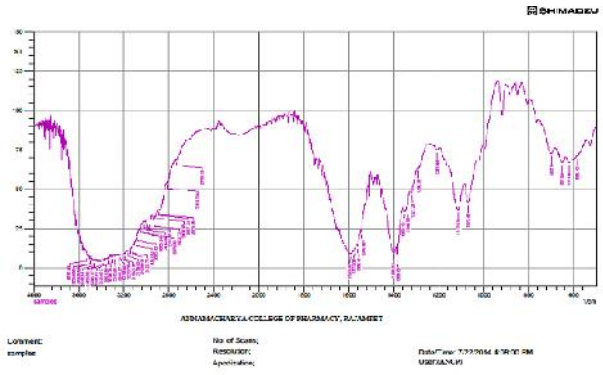

Figure 2: FTIR spectra of EC

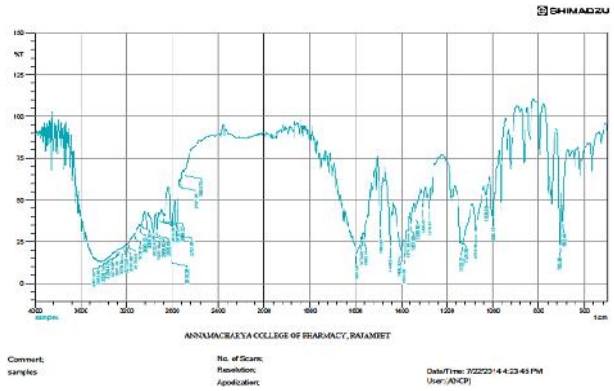

Figure 3: FTIR spectra of Cinnarizine + EC

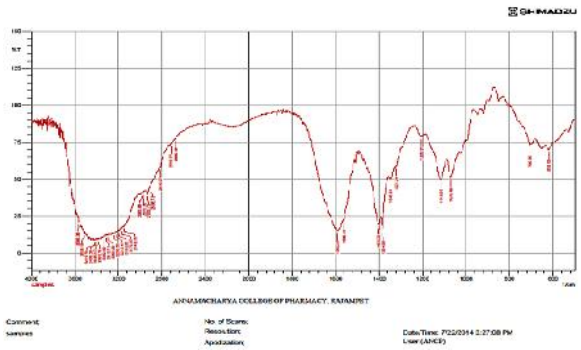

Figure4: FTIR spectra of HPMC

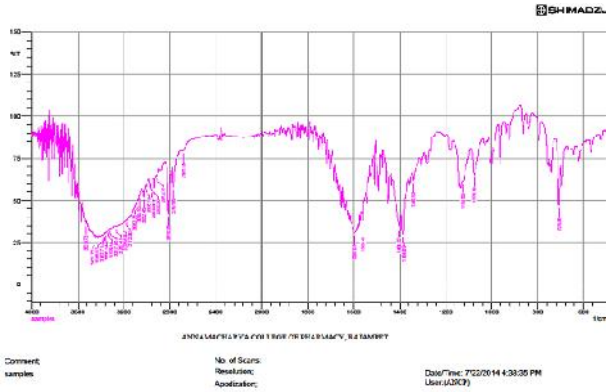

Figure.5: FTIR Spectra of Cinnarizine+EC +HPMC

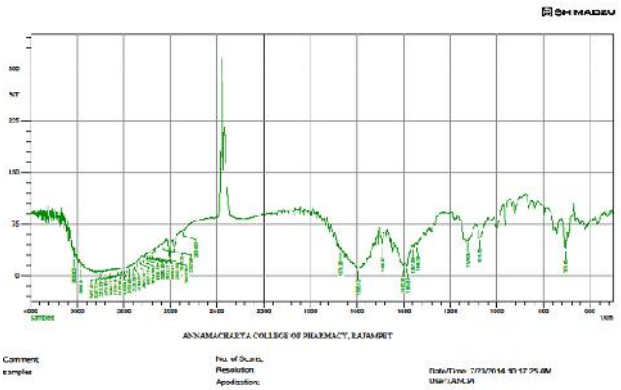

Figure 6: FTIR Spectra of Cinnarizine + EC + polymer mixture

Pre compression (micromeritic) parameters for Cinnarazine extended release tablets

Table 2: Micromeritic parameters

F. Code	Derived Properties		Flow Properties		
	Bulk density (mean ± SD) (g/cm^3)	Tapped density (mean ± SD) (g/cm^3)	Angle of repose (mean ± SD) (Degree)	Carr's index (mean ± SD) (%)	Hausner's ratio (mean ± SD) (%)
CNZ-1	0.370	0.495	0.564	25.1	1.33
CNZ-2	0.359	0.515	0.543	30.2	1.43
CNZ-3	0.348	0.535	0.522	35.1	1.53
CNZ-4	0.359	0.515	0.543	30.2	1.43
CNZ-5	0.370	0.495	0.564	25.1	1.33
CNZ-6	0.348	0.535	0.522	35.1	1.53
CNZ-7	0.359	0.520	0.552	32.1	1.50

Table 3: Results of physicochemical parameters of all formulations

F.Code	Thickness (mean±SD) (mm)	Hardness (mean±SD) (kg/cm^2)	Friability (mean±SD) (%)	Weight variation (mean±SD) (mg)	Drug content (mean±SD)
CNZ-1	3.21	6.4	0.158	597±0.5	98.2±0.5
CNZ-2	3.34	6.8	0.168	598±0.6	98.4±0.1
CNZ-3	3.49	6.4	0.215	599±0.3	99.1±0.6
CNZ-4	3.51	6.5	0.156	596±0.8	96.3±0.7
CNZ-5	3.54	6.7	0.115	597±0.7	97.1±0.1
CNZ-6	3.49	6.4	0.155	596±0.4	99.1±0.6
CNZ-7	3.39	6.5	0.179	599±0.3	98.2±10

Table 4: zero order kinetics of CNZ1-CNZ7

Time (hrs)	Cumulative % drug release						
	CNZ-1	**CNZ-2**	**CNZ-3**	**CNZ-4**	**CNZ-5**	**CNZ-6**	**CNZ-7**
1	10.4	10.9	11.05	11.30	11.89	12.6	13.0
2	16.3	17.8	22.4	25.9	29.9	31.9	35.1
3	28.9	30.9	32.9	35.9	38.2	45.2	49.1
4	37.2	39.1	43.2	49.1	50.1	55.2	56.9
5	49.5	50.1	54.14	59.3	65.4	66.1	69.2
6	58.1	59.6	60.3	62.1	70.9	71.0	88.7
7	60.2	69.2	65.6	70.1	80.1	86.9	98.6
8	69.1	75.3	77.56	79.9	86.7	97.1	.....
9	78.4	80.1	81.24	82.5	98.1	.....	.....
10	82.6	85.7	89.1	98	.....	.....	.....
11	89.3	90	97.4	.....	.....	.....	.....
12	98.4	97.4	.....	.....	.....	.....	.....

Table 5: First order Kinetics CNZ1-CNZ7

Time in (hrs)	Log cumulative % drug release						
	CNZ-1	**CNZ-2**	**CNZ-3**	**CNZ-4**	**CNZ-5**	**CNZ-6**	**CNZ-7**
1	1.01	1.03	1.04	1.05	1.07	1.10	1.11
2	1.21	1.25	1.35	1.41	1.47	1.50	1.54
3	1.46	1.48	1.51	1.55	1.58	1.65	1.69
4	1.57	1.59	1.63	1.69	1.69	1.74	1.75
5	1.69	1.69	1.73	1.77	1.81	1.82	1.84
6	1.76	1.77	1.78	1.79	1.85	1.85	1.94
7	1.77	1.84	1.81	1.84	1.90	1.93	1.99
8	1.83	1.87	1.88	1.90	1.93	1.98	....
9	1.89	1.90	1.90	1.91	1.99	....	....
10	1.91	1.93	1.94	1.99	....	.....	....
11	1.95	1.95	1.98	....	....	.....	....
12	1.99	1.98	....	....	....	....	....

Table 6: Higuchi Kinetics CNZ1-CNZ7

SQRT of Time	Cumulative % drug release						
	CNZ-1	**CNZ-2**	**CNZ-3**	**CNZ-4**	**CNZ-5**	**CNZ-6**	**CNZ-7**
1.00	10.40	10.90	11.05	11.30	11.89	12.60	13.00
1.41	16.30	17.80	22.40	25.90	29.90	31.90	35.10
1.73	28.90	30.90	32.90	35.90	38.20	45.20	49.10
2.00	37.20	39.10	43.20	49.10	50.10	55.20	56.90
2.23	49.50	50.10	54.14	59.30	65.40	66.10	69.20
2.44	58.10	59.60	60.30	62.10	70.90	71.00	88.70
2.64	60.20	69.20	65.60	70.10	80.10	86.90	98.60
2.82	69.10	75.30	77.56	79.90	86.70	97.10	....
3.00	78.40	80.10	81.24	82.50	98.10	....	....
3.16	82.60	85.70	89.10	98.00	....	....	....
3.31	89.30	90.00	97.4	....	....	....	....
3.46	98.40	97.4	....	....	....	....	....

Table 7: Korsmeyer peppas kinetics CNZ1-CNZ7

Log Time	Log Cumulative % drug release						
	CNZ-1	CNZ-2	CNZ-3	CNZ-4	CNZ-5	CNZ-6	CNZ-7
0.00	1.017	1.03	1.04	1.05	1.07	1.10	1.11
0.30	1.21	1.25	1.35	1.41	1.47	1.50	1.54
0.47	1.46	1.48	1.51	1.55	1.58	1.65	1.69
0.60	1.57	1.59	1.63	1.69	1.69	1.74	1.75
0.69	1.69	1.69	1.73	1.77	1.81	1.82	1.84
0.77	1.76	1.77	1.78	1.79	1.85	1.85	1.94
0.84	1.77	1.84	1.81	1.84	1.90	1.93	1.99
0.90	1.83	1.87	1.88	1.90	1.93	1.98	....
0.95	1.89	1.90	1.90	1.91	1.99	....	....
1.00	1.91	1.93	1.94	1.99	....	....	....
1.04	1.95	1.95	1.988	....	....	....	....
1.07	1.99	1.98	....	....	....	....	....

Table8: Parameters and determination coefficients of release profile from Cinnarizine extended release tablets

Formulation code	Correlation Coefficient values (R^2)				Diffusion Exponent value (n)
	Zero order	First order	Higuchi	Korsemayer-peppas	
F1	0.99	0.86	0.94	0.99	1.00
F2	0.98	0.85	0.95	0.99	1.03
F3	0.98	0.85	0.95	0.99	1.07
F4	0.98	0.83	0.95	0.98	1.11
F5	0.98	0.84	0.95	0.98	1.13
F6	0.98	0.84	0.94	0.97	1.16
F7	0.99	0.85	0.92	0.97	1.17

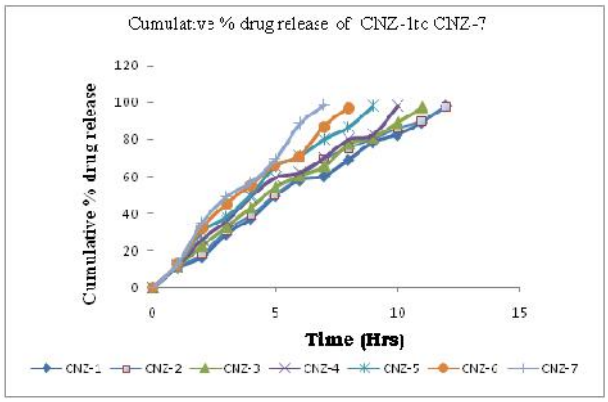

Figure 7: Cumulative % drug release plots of CNZ-1 to CNZ-7 (ZERO ORDER)

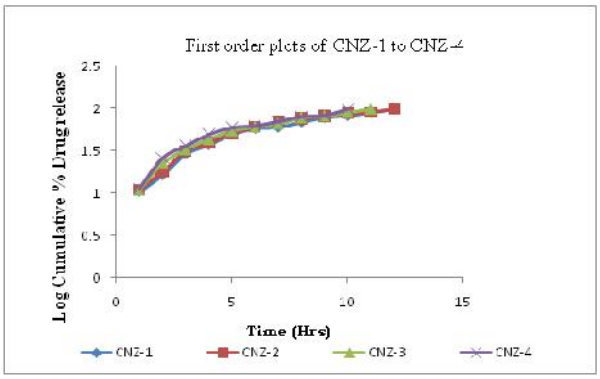

Figure 8: First order plots of CNZ-1 to CNZ-4

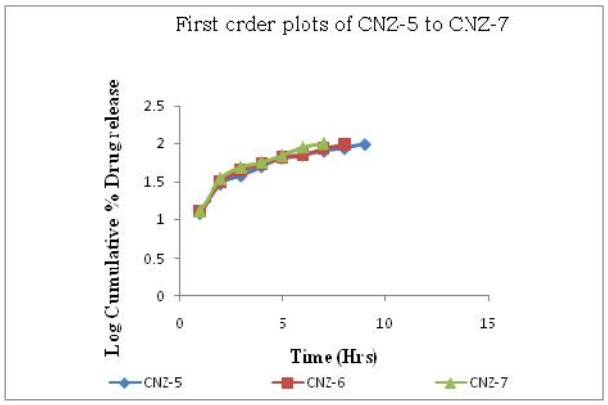

Figure 9: First order plots for CNZ-5 to CNZ-7

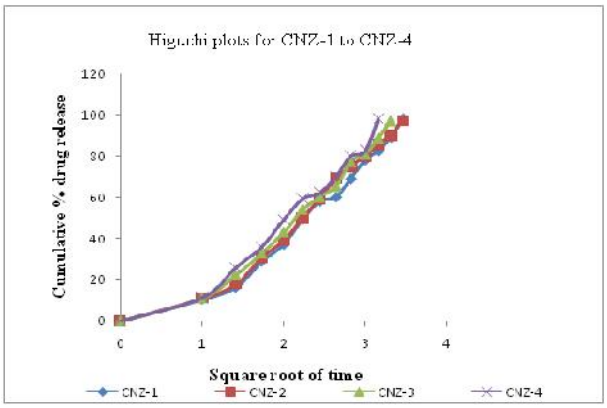

Figure 10: Higuchi plots for CNZ-1 to CNZ-4

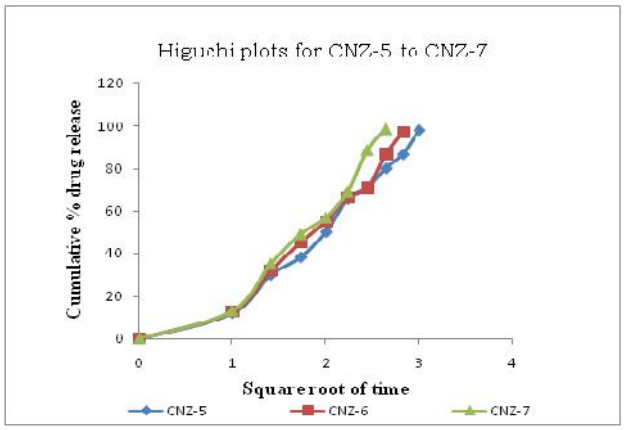

Figure 11: Higuchi plots for CNZ-5 to CNZ-7

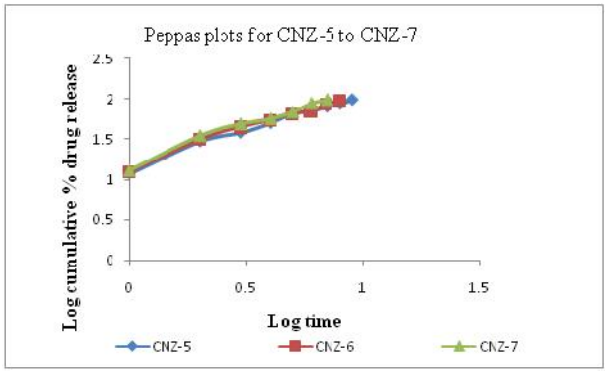

Figure 13: Peppas plots for CNZ-5 to CNZ-7

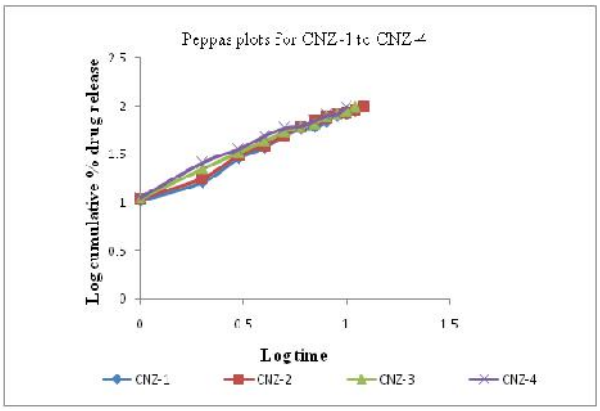

Figure 12: Peppas plots for CNZ-1 to CNZ-4

Discussion

Cinnarizine is an anti histaminic, derivative of piperazine and has high affinity to H1 receptors, extensively used for the treatment of motionsickness, vertigo, nausea and vomiting. From the FT-IR results it is evident that when cinnarazine fig 1 - was compared with ethyl cellulose, HPMC and mixture fig- 2, 3, 4, .5 and 6 there is no characteristic change in the peaks. These results confirm that there is no any chemical interaction between cinnarazine and excipients. Micromeritic properties showed poor flow properties for cinnarazine API due to its amorphous nature when compared with the formulations CNZ-1 to CNZ-7 and the results are tabulated in table no-4. Post-formulation parameters concluded that there should be certain amount of strength and resistance to friability for the tablet, so that tablet should not break during handling which also shows affect on dissolution. The hardness of cinnarazine extended release tablet ranges from 6.4 to 6.8 kg/cm^2. Friability ranges from 0.115 % to 0.215%. This indicates that acceptable resistance is shown by cinnarizine ER tablets to withstand handling and the results are given in table no – 3

In-vitro dissolution studies showed that, with increase in the hydrophobic polymer (ethyl cellulose), the percent drug release has been retarded, shown in table-4 and fig no -7. For all the formulations the dissolution was conducted for twelve hours and among all the formulations, CNZ-1 showed optimum release profile indicating it to be the best formulation in present research. Different model dependent approaches (Zero order, First order, Higuchi, Korsemayer-Peppas plots) were performed for all extended release tablets.

The results of these models follow Korsemayer-Peppas model as “best fit model” follows diffusion mechanism. This is due to previously proved fact depending on R^2 value obtained from model fitting. From the results, CNZ-1 shows more retarding effect and thus found that T_{50} % value increases as concentration of EC increases. Korsemayer-Peppas release exponent (n) values of all cinnarazine extended release tablets are greater than 1 indicating drug diffusion is rapid due to swelling in the polymer (case 2 transport). The results are tabulated in table no-8.

4. Conclusion

From the present research it was concluded that the formulation CNZ-1 (Drug with 20% ethyl cellulose and 0 % HPMC) of cinnarazine has achieved 98% drug release for 12 Hrs. Results indicated that, drug release has been retarded with increase in the concentrations of hydrophobic polymer (Ethyl cellulose), and with increase in concentration of hydrophilic polymer (HPMC) the drug release has been completed within 7 hrs (CNZ-7). The above formulation may also decrease the gastric irritation and may improve patient compliance with reduction in dosage frequency.

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