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Research Article

COMPARATIVE BIOEQUIVALENCE STUDIES OF CINNARIZINE AND ITS DIFFERENT AVAILABLE MARKETED FORMULATION DRUGS

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ABSTRACT

Objective: The main focus of the study was to investigate the marketed formulations of cinnarizine and it is marketed analogous.

Methods: The study involved the analysis of basic pre-formulation studies, namely, physical properties, melting point, Fourier-transform infrared, loss on drying, assay of cinnarizine, standard curve, and partition co-efficient of various marketed tablets of cinnarizine.

Results: Cinnarizine is an H1-receptor antagonist drug which is widely used for the treatment of dynamical sickness, vomiting, and vertigo. In this study, five known marketed formulations of cinnarizine were evaluated for weight variation, hardness, drug content, friability, disintegration time, and *in vitro* dissolution as well as the drug release kinetics of the tablets. As per the study, the drugs show low disintegration time and good hardness, also *in vitro* dissolution studies have shown near about 90% drug release at the end of the first 10 min and then cumulative drug release of not less than 92% in the nearby 10 min. Hence, these formulations show lower friability, acceptable taste, and shorter disintegration time which make them suitable to be accepted. Thus, the tablets are good for the use, so allow them to be marketed for the wellbeing of humans.

Conclusion: It had been found that all the tablets show acceptable limits for various parameters of analysis, in a sustained manner. Thus, all the tablets are effective for usage under standard conditions.

Keywords: Antihistamine, Cinnarizine, Bioequivalence, Vertigo, Vomiting.

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INTRODUCTION

The delivery of drugs to the human body can be carried out through several routes such as oral topical, transdermal, and parenteral administration [1]. Among these, the oral ingestion is the predominant and most preferable route for drug delivery, as the oral system has the obvious advantage of the ease of administration and patient acceptance [2]. There are also many obvious reasons but also due to the fact that there is more flexibility in dosage design since constraints such as sterility and potential damage at the site of administration are minimized.

If a new product is intended to be as a substitute for an approved medicinal product as a pharmaceutical equivalent, the equivalence with this product should be justified like bioequivalent [3]. To ensure the clinical performance of such drug products, bioequivalence studies are conducted. Bioequivalence studies are conducted if there, whether there is a risk of bioequivalence or risk of pharmacotherapeutic failure clinical safety [4,5]. Furthermore, bioequivalence study can be demonstrated either *in vivo* or *in vitro*.

METHODS

The following mentioned marketed drugs have been used for analysis. All the chemicals and the equipment were of analytical grade and sterilized before the experimentation. The following studies have been conducted as basic pre-formulation studies, namely, physical properties, melting point, Fourier-transform infrared (FTIR), loss on drying, assay of cinnarizine, standard curve, and partition coefficient.

FTIR spectral studies of cinnarizine

FTIR spectrum of cinnarizine was obtained by means of an FTIR spectrophotometer. The given sample of cinnarizine was prepared and scanning was done by Cary 360 FTIR Agilent Technologies (measurements were attempted with the accumulation of 8 scans and a resolution of 4 cm^{-1} over the range of 400–4000 cm^{-1}).

Loss on drying

The loss on drying test is designed to measure the amount of water and volatile matters in a sample when the sample is dried under specified conditions. It should be NMT 0.5%.

Assay of cinnarizine

The UV spectrophotometry has been used for structural validation of drug in the identification studies. The drug was dissolved in pH 5.8 to produce 10 µg/ml solutions. This 10 µg/ml drug solution was scanned between 200 and 400 nm using the UV spectrophotometer (Cary 60 UV visible Agilent Technologies).

Solubility studies of drug

The solubility of was determined in different solvents (e.g., distilled water, ethanol, and di-ethyl ether). A known amount of drug (100 mg) was suspended in 10 ml of different solvents in tightly closed test tubes. Excess amount of drug was added to different solvents until the solution became saturated and these tubes were shaken for 1 h. The supernatant was then analyzed by UV spectrophotometer (Cary 60 UV-visible Spectrophotometer, Agilent Technologies) at 205.0 nm with appropriate dilutions. Three determinations were carried out for each sample to calculate the solubility of cinnarizine.

Determination of partition coefficient

Partition coefficient of a drug is a measure of its hydrophilicity. It can be defined as the ratio of unionized drug distributed between the organic and aqueous phase at equilibrium. For a drug delivery system, hydrophilicity/hydrophilic balance has shown to be a contributing

factor for the rate and extent of drug absorption. The partition coefficient provides a means of characterizing lyophilic/hydrophilic nature of a drug. It is the measurement of drug hydrophilicity and its ability to cross the lipid bilayer cell membrane.

Drug content uniformity [7]

Twenty tablets from each batch were weighed accurately and powdered powder equivalent to 100 mg cinnarizine was shaken with 100 ml of (0.1 N) HCl in 100 ml volumetric-flask and from this 1 ml was pipette out and then dilute up to 100 ml. The resulting solution was filtered and assayed at 205 nm using UV/visible spectrometer and the content of different formulation of cinnarizine was calculated and the results are as.

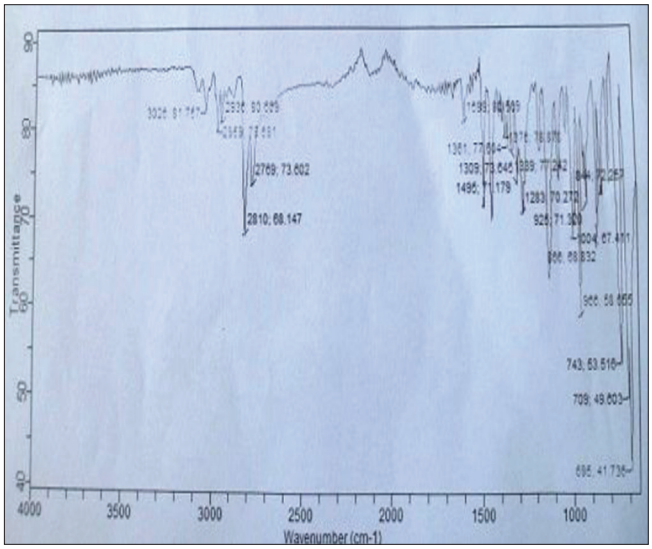

Fig. 1: Fourier-transform infrared spectral studies of cinnarizine

Table 1: Marketed formulation of cinnarizine [6]

S. No.	Brand name	Dosage form	Manufacturer
1.	Stugeron	Tablet (25 mg)	Johnson and Johnson Ltd.
2.	Vertigon	Tablet (25 mg)	Geno Pharmaceuticals Ltd.
3.	Cinzan	Tablet (25 mg)	FDC Ltd.
4.	Sinarzine	Tablet (25 mg)	Leeford Healthcare Ltd.
5.	Cinnifit	Tablet (25 mg)	Galpha Laboratories Ltd.

Table 2: Melting point of cinnarizine

Melting point	
Reported value	**Observed value**
117–120°C	117°C

Table 3: Characteristic peaks of cinnarizine

Functional group	Range cm^{-1}	Drug cm^{-1}
C-H	3000–2700	2810
C=C	1670–1580	1599
C-N	1700–1600	1699
N-H	3000–3700	3028

Table 4: Absorbance of cinnarizine at 205 nm

S. No.	Concentration (µg/ml)	Absorbance (mg/ml) (205.0 nm)
1.	0.2	0.0173
2.	0.4	0.0325
3.	0.6	0.0479
4.	0.8	0.0652
5.	1.0	0.0821

Determination of tablet hardness [7]

Five tablets were sampled randomly selected from each batch and the hardness of the tablets was determined by the help of the Pfizer Hardness Tester (kg/cm^2).

Determination of friability of the tablet [7]

This experiment is applicable to compressed tablets and is intended to determine the physical strength of tablets.

A maximum loss of weight (from a single test or from the mean of the three tests) not superior to 1.0% is acceptable for most tablets. If observably cracked, chipped, or broken tablets are present in the sample later than tumbling, the sample fails the test.

***In vitro* dissolution study [7]**

The dissolution study was carried out in USP – II type dissolution apparatus (paddle type) in (Dissolution Test Apparatus [DS8000] LABINDIA). The dissolution study was performed at 50 rpm in 900 ml of simulated gastric fluid of pH 1.2. For tablets of cinnarizine, the dissolution media was 0.1 N HCl which was prepared using 8.8 ml of 35% HCl. The above-mentioned amount of acid is measured by measuring cylinder and then transfer it to 1000 ml of volumetric flask and volume was made up to the mark with distilled water.

OBSERVATIONS AND RESULTS

Physical properties

- Color – crystalline white
- Odor – suspicious.

Table 5: Results are interpreted as

Solvents	Solubility
Distilled water	Practically insoluble
Ethanol	Slightly soluble
Di-ethyl ether	Soluble

Table 6: Weight variation of the tablets

S. No.	Formulation	Weight variation (g)
1.	Stugeron	0.2455±0.02455
2.	Vertigon	0.121±0.0121
3.	Cinzan	0.176±0.0176
4.	Sinarzine	0.187±0.0187
5.	Cinnifit	0.205±0.0205

Table 7: Hardness of the tablets

S. No.	Formulation name	Hardness (kg/cm^2)
1.	Stugeron	2.0
2.	Vertigon	0.0
3.	Cinzan	4.0
4.	Sinarzine	0.8
5.	Cinnifit	0.2

Table 8: Drug content of cinnarizine formulations

S. No.	Formulation name	Drug content (%)
1.	Stugeron	96.23
2.	Vertigon	99.54
3.	Cinzan	98.57
4.	Sinarzine	97.01
5.	Cinnifit	99.80

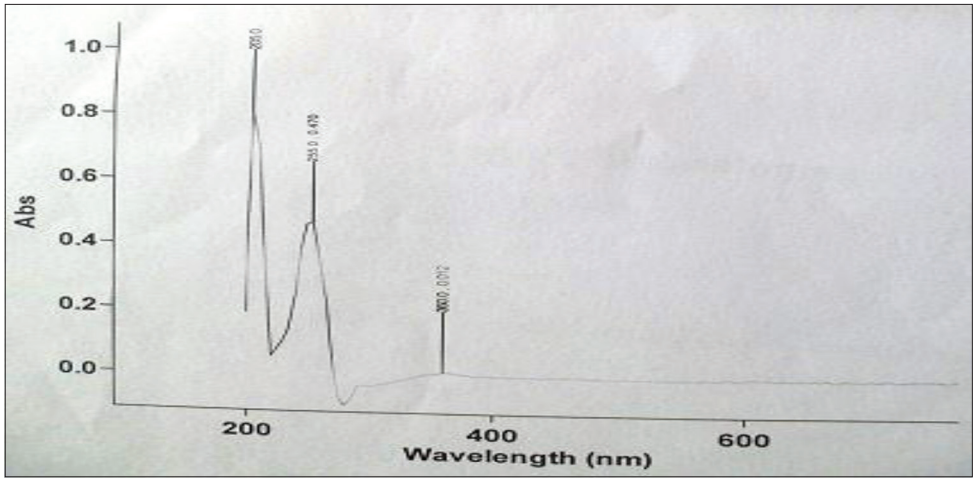

Fig. 2: UV-spectrophotometric curve (λ_{max}) of cinnarizine at 205 nm

Table 9: *In vitro* dissolution study data for stugeron

Time (min)	Absorbance (205 nm)	Conc. (µg/ml)	Amt. in 1 ml	Amt. in 900 ml	Cumulative release	% Cumulative drug release
0	0	0	0	0	0	0
5	0.0224	2.7654	0.0027	2.4888	2.4888	9.9555
10	0.0418	5.1604	0.0051	4.6444	4.6472	18.5888
15	0.0614	7.5802	0.0075	6.8222	6.8273	27.3095
20	0.0877	10.827	0.0108	9.7444	9.7520	39.0080
25	0.1102	13.604	0.0136	12.2444	12.2552	49.0210
30	0.127	15.679	0.0156	14.1111	14.1247	56.4988
35	0.151	18.641	0.0186	16.7777	16.7934	67.1738
40	0.174	21.481	0.0214	19.3333	19.3519	77.4079
45	0.196	24.197	0.0241	21.7777	21.7992	87.1970
50	0.2187	27.111	0.027	24.3211	24.3241	97.2967

Table 10: *In vitro* dissolution study data for vertigon

Time (min)	Absorb (205 nm)	Conc. (µg/ml)	Amt. in 1 ml	Amt. in 900 ml	Cumulative release	% Cumulative drug release
0	0	0	0	0	0	0
5	0.0298	3.6790	0.0036	3.3111	3.311	13.2444
10	0.0486	6.0000	0.006	5.4221	5.403	21.6147
15	0.0672	8.2962	0.0082	7.4666	7.472	29.8906
20	0.0865	10.679	0.0106	9.6111	9.619	38.4776
25	0.1106	13.654	0.0136	12.288	12.29	49.1982
30	0.1369	16.901	0.0169	15.211	15.22	60.8990
35	0.1617	19.962	0.0199	17.966	17.98	71.9342
40	0.1813	22.382	0.0223	20.144	20.164	80.6576
45	0.2064	25.481	0.0254	22.933	22.955	91.8228
50	0.2194	27.086	0.0270	24.377	24.403	97.6130

Table 11: *In vitro* dissolution study data for cinnarizine

Time (min)	Absorb (205 nm)	Conc. (µg/ml)	Amt. in 1 ml	Amt. in 900 ml	Cumulative release	% Cumulative drug release
0	0	0	0	0	0	0
5	0.0212	2.6172	0.002	2.355	2.355	9.422
10	0.0419	5.1728	0.005	4.655	4.658	18.632
15	0.0572	7.0617	0.007	6.355	6.360	25.442
20	0.0805	9.9382	0.009	8.944	8.951	35.806
25	0.1003	12.382	0.012	11.14	11.15	44.617
30	0.1223	15.098	0.015	13.58	13.60	54.405
35	0.1403	17.320	0.017	15.588	15.603	62.415
40	0.1623	20.037	0.020	18.033	18.050	72.202
45	0.1824	22.518	0.022	20.266	20.286	81.146
50	0.2071	25.567	0.025	23.011	23.033	92.13

Melting point

The melting point of cinnarizine was determined by the capillary method using the melting point apparatus (MEPA, LABINDIA).

FTIR results: The spectra are shown in Fig. 1 and characteristic peaks are given in Table 3.

Loss on drying

Loss on drying of cinnarizine was found 0.0198%.

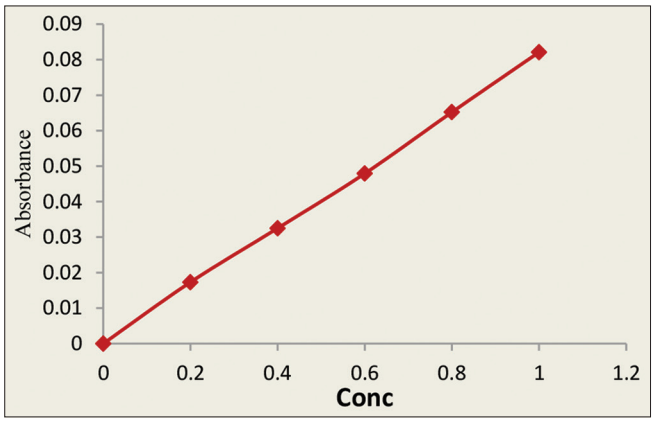

Fig. 3: Calibration curve for cinnarizine

Assay of cinnarizine

The spectrum of the drug is shown in Fig. 2 and the value of λ_{max} was found to be 205.0 nm.

Calibration curve of cinnarizine

Nearly 10 mg of cinnarizine was dissolved in 100 ml ethanol in a volumetric flask (stock solution I). From stock solution I, 10 ml solution was taken and the volume was made (l00 ml) with ethanol (stock solution II). From stock solution II, aliquots of 0.2, 0.4, 0.6, 0.8, and 1.0 ml solution were drawn and transferred to 50 ml volumetric flasks and finally, the volume was made up to the mark. UV absorbance was noted at 205 nm using ethanol as blank.

Solubility studies of drug

The results were interpreted as practically insoluble, freely soluble, or soluble and shown in Table 5.

The partition coefficient as per the calculations was found to be 2.139.

Comparative study and evaluation of the concerned drugs and the brand nature of drug and amount are given as under.

Tab	Tab	Tab	Tab	Tab
Stugeron (25 mg)	Vertigon (25 mg)	Cinzan (25 mg)	Sinarzine (25 mg)	Cinnifit (25 mg)

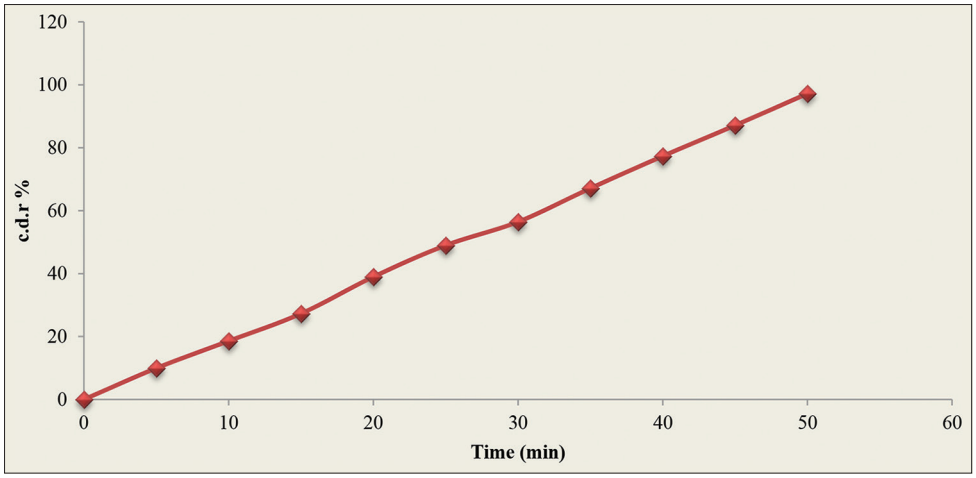

Fig. 4: *In vitro* dissolution study curve for stugeron at 205 nm

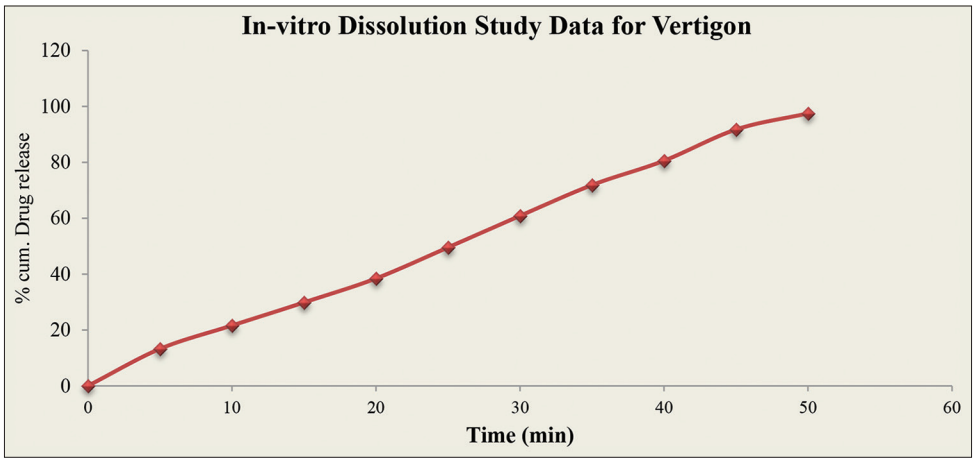

Fig. 5: *In vitro* dissolution curve for vertigon tablet at 205 nm

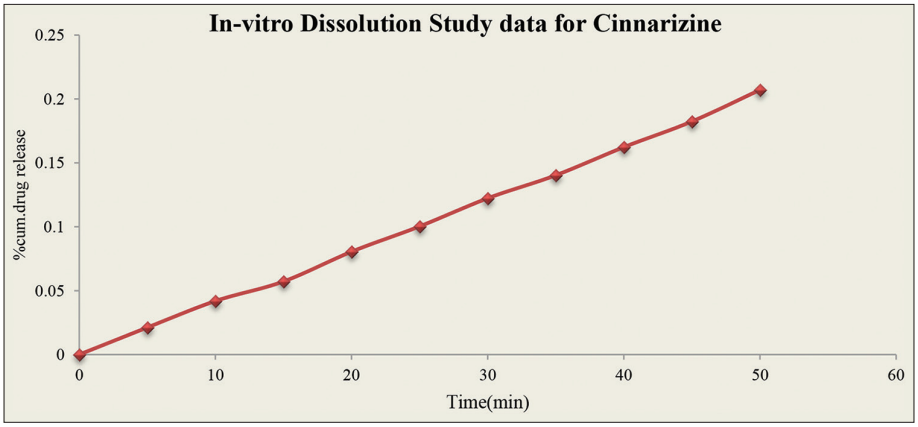

Fig. 6: *In vitro* dissolution curve of cinzan tablet at 205 nm

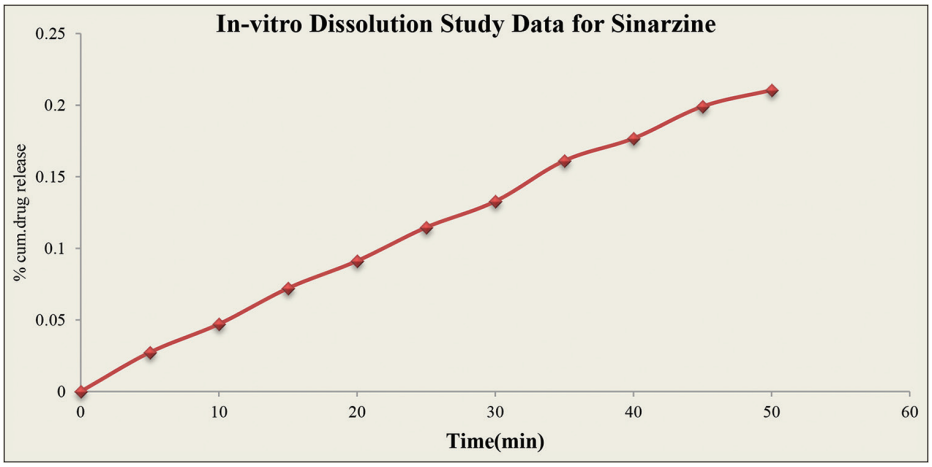

Fig. 7: *In vitro* dissolution curve of sinarzine tablet at 205 nm

Table 12: *In vitro* dissolution study data for sinarzine

Time (min)	Absorb (205 nm)	Conc. (µg/ml)	Amt. in 1 ml	Amt. in 900 ml	Cumulative release	% Cumulative drug release
0	0	0	0	0	0	0
5	0.0273	3.370	0.003	3.033	3.033	12.133
10	0.0471	5.814	0.005	5.233	5.236	20.946
15	0.0721	8.901	0.008	8.011	8.016	32.067
20	0.0912	11.259	0.011	10.133	10.14	40.568
25	0.1146	14.148	0.014	12.733	12.744	50.978
30	0.1328	16.395	0.016	14.755	14.76	59.078
35	0.1612	19.901	0.019	17.911	17.927	71.710
40	0.1768	21.827	0.021	19.644	19.664	78.657
45	0.1991	24.580	0.024	22.122	22.144	88.576
50	0.2105	25.987	0.025	23.388	23.413	93.650

Table 13: *In vitro* dissolution study data for cinnifit

Time (min)	Absorb (205 nm)	Conc. (µg/ml)	Amt. in 1 ml	Amt. in 900 ml	Cumulative release	Cumulative drug release %
0	0	0	0	0	0	0
5	0.0229	2.8271	0.002	2.544	2.544	10.177
10	0.0462	5.7037	0.005	5.133	5.136	20.533
15	0.0632	7.8024	0.007	7.022	7.027	28.088
20	0.0868	10.7160	0.010	9.644	9.652	38.577
25	0.1058	13.0617	0.013	11.75	11.76	47.022
30	0.1242	15.3333	0.015	13.8	13.81	55.210
35	0.1428	17.6296	0.017	15.86	15.88	63.466
40	0.1658	20.4691	0.020	18.422	18.43	73.688
45	0.1951	24.0864	0.024	21.677	21.698	86.711
50	0.2202	27.1851	0.027	24.466	24.490	97.866

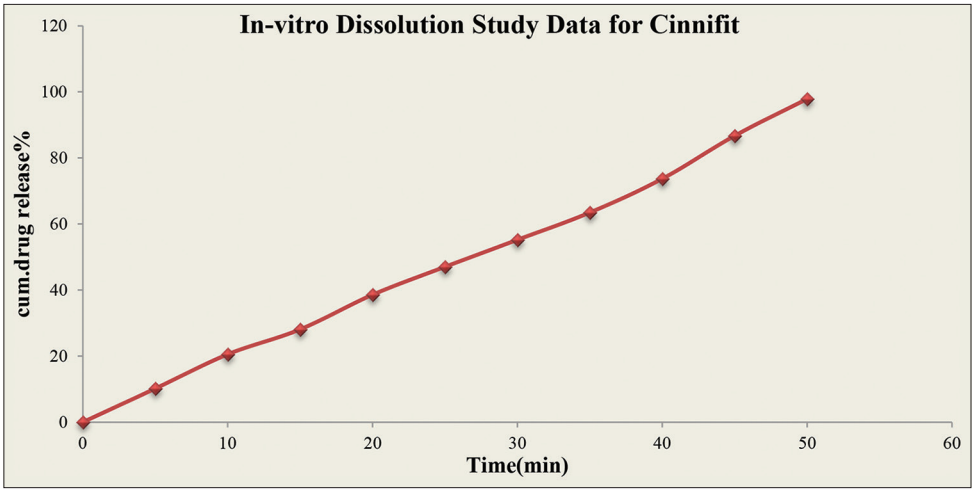

Fig. 8: *In vitro* dissolution curve of cinnifit tablet at 205 nm

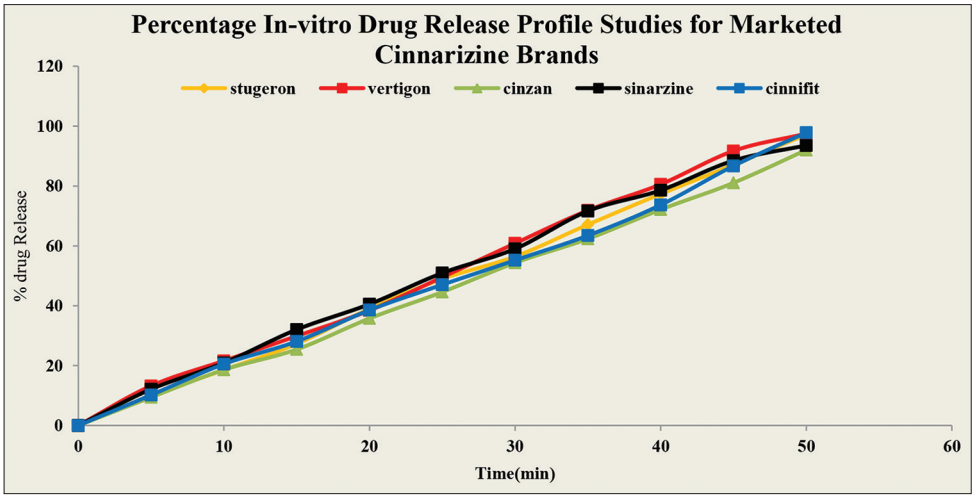

Fig. 9: *In vitro* release profile of all marketed formulations

Table 14: Pre-formulation studies

S. No.	Parameters	Observation	Inference
1.	Color	Crystalline white	Confirms to reference standards
2.	Melting point	117°C	
3.	FTIR	C-H, C=C, C-N, N-H	
4.	Loss on drying	0.0198%	
5.	Assay	205.0 nm, slope 0.081	
6.	Solubility	Di-ethyl ether	
7.	Partition coefficient	2.139	

The evaluation parameters which have been carried out include uniformity of weight, determination of tablet hardness, drug content uniformity, friability of tablet, determination of disintegration time, and *in vitro* dissolution study.

Uniformity of weight [7]

Twenty tablets were selected randomly from each batch and were weighed accurately, and the average weight was calculated, and the deviation of individual weights from the average weight and the standard deviation was calculated.

The weight variation limits are within the range of acceptability as the deviation percentage is 10 for 80 mg tablet, 7.5 for 80 mg to 250 mg, and 5 for 250 mg tablets.

Determination of tablet hardness

The average hardness and standard deviation were calculated and the results are as.

Determination of friability of the tablet

The friability value of the uncoated tablets was found to be as stugeron – 0.4%, vertigon – 0.0% cinzan – 0.5%, sinarzine – 0.0%, and cinnifit – 0.0%.

Determination of disintegration time [7]

In vitro disintegration time of six tablets from each of the formulation was determined using a digital tablet disintegration apparatus. *In vitro* disintegration was carried out (at 37±2°C) in 900 ml (0.1 N) hydrochloric acid buffer and the observed results are as.

Drug	Stugeron	Vertigon	Cinzan	Sinarzine	Cinnifit
Time	90 s	15 s	29 s	17 s	5 s

DISCUSSION

The result of pre-formulation study is shown in the above table [8], which are very closely to the actual and standard values of different pre-formulation studies of the pure cinnarizine API. The pre-formulation study of any drug is a very important tool for further investigation of the sample. The pre-formulation study of cinnarizine API is very useful for the further evaluation parameters of the tablets.

Table 15: Pre-formulation studies of cinnarizine tablet

Formulation (25 mg)	Weight variation (mg)	Hardness (kg)	Drug content (%)	Friability (%)	Disintegration time (s)
Stugeron	0.245±0.0245	2.0	96.23	0.4	90
Vertigon	0.121±0.0121	0.0	99.54	0.0	15
Cinzan	0.176±0.0176	4.0	98.57	0.5	29
Sinarzine	0.187±0.0187	0.8	97.01	0.0	17
Cinnifit	0.205±0.0205	0.2	99.80	0.0	5

Table 16: Percentage drugs release profile studies for cinnarizine brands

S. No.	Time (min)	Cumulative drug release %				
		Stugeron (25 mg)	Vertigon (25 mg)	Cinzan (25 mg)	Sinarzine (25mg)	Cinnifit (25 mg)
1.	5	9.955	13.24	9.422	12.133	10.17
2.	10	18.577	21.6	18.622	20.933	20.53
3.	15	27.288	29.86	25.422	32.044	28.08
4.	20	38.977	38.44	35.777	40.533	38.57
5.	25	48.977	49.54	44.577	50.933	47.02
6.	30	56.444	60.84	54.355	59.022	55.2
7.	35	67.111	71.86	62.355	71.644	63.46
8.	40	77.333	80.57	72.133	78.577	73.68
9.	45	87.111	91.73	81.066	88.488	86.71
10.	50	97.20	97.51	92.044	93.555	97.86

All brand's tablets were evaluated for the determination of weight variation; hardness; drug content; friability; disintegration; and dissolution. After evaluation, the different parameters were determined successfully and the resulted value of different parameters is shown in the given table [9], respectively.

The comparative dissolution study of the various marketed formulation was carried out. The release profile of all brand's tablets is shown in the given Table 4.3. The release of drug was shown as % cumulative drug release (%CDR) with respect to a time interval (minutes). The resulted graph was shown below to describe the *in vitro* drug release of all brand's tablets.

The *in vitro* drug release kinetics of all marketed tablets were shown in Figure 9. All marketed tablets release the drug in a good manner. The %CDR was found as 97.20, 97.51, 92.04, 93.55, and 97.86 for the stugeron, vertigon, cinzan, sinarzine, and cinnifit, respectively. The maximum drug release was found for cinnifit marketed formulation.

CONCLUSION

The study was conducted to determine different evaluation parameters as well as the drug release kinetics of the tablets in relation to consider the five concerned tablets as bioequivalent. In the study, it had been concluded that all brand tablets are of good quality. The tablets after evaluation for different parameters meet the standard acceptance criteria. All the tablets show acceptable limits for weight variation and hardness, and all tablets show efficient drug release in a sustained release manner. Thus, it can be concluded that all the tablets are effective for usage under standard conditions.

REFERENCES

1. Li S. Biodegradable polymers: Polyesters. In: Mathiowitz E, editor. Encyclopedia of Controlled Drug Delivery. New York: John Willey and Sons Inc.; 1999. p. 71-3.
2. Streubel A. Drug Delivery to the upper small intestine window using gastroretentive technologies. Curr Opin Pharmacol 2006;6:501-8.
3. Lachman L, Lieberman HA, Kanig JL. The Theory and Practice of Industrial Pharmacy. 3rd ed. Dadar, Bombay: Varghese Publishing House Hind Rajasthan Building; 1987. p. 400014.
4. Kesharvani S, Jaiswal PK, Mukerjee A, Singh AK. Formulation and evaluation of metformin hydrochloride loaded floating microspheres. Int J Pharm Pharm Sci 2019;12:74-82.
5. Patel M, Patel NV, Patel TB. Design and development of rilpivirine nanoparticle containg chitosan using ionic gelation method for HIV infections. Int J Pharm Pharm Sci 2020;12:113-8.
6. Ministry of Health and Family Welfare. Indian Pharmacopoeia. Vol. 2. India: Government of India, Ministry of Health and Family Welfare; 2010. p. 187-95.
7. Lieberman L, Herbert A, Lachmann L, Schwartz J. Pharmaceutical Dosage Forms: Tablets. Vol. 1. New York: Marcel Dekker; 2005. p. 1-69.
8. Halakatti P. Development of mouth dissolving tablets of cinnarizine. Int J Pharm Sci 2010;2:631-40.
9. Ringard J, Hermann AM. Calculation of disintegrant critical conc. In order to optimize tablet disintegration. Drug Dev Ind Pharm 1997;14:2321-39.