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FORMULATION DEVELOPMENT AND EVALUATION OF ORODISPERSIBLE TABLET OF CINNARIZINE SOLID DISPERSION

Dhananjay M. Patil*, Kaveri R. Wagh, Sapna S. Chaudhari, Vinod A. Bairagi, Valmik R Patil

Department of Pharmaceutics-K.B.H.S.S Institute of Pharmacy, Malegaon, Nasik-423203.

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Abstract:

The objective of present study was to formulate directly compressible orodispersible tablets of Cinnarizine with improved solubility and bioavailability by using solid dispersion technique. Cinnarizine is a H1 receptor antagonist and widely used in the treatment of motion sickness, vomiting and vertigo disorder. Solid dispersion of Cinnarizine was prepared by Solvent evaporation method and physical mixture using novel polymer soluplus as carrier. 1:1, 1:2 and 1:3 these three different weight ratios of drug and carrier respectively were taken. Saturation solubility of drug was determined in physical mixture and solid dispersion formulation. The prepared solid dispersion formulations were further characterized by drug contents, FTIR spectroscopy, DSC and in-vitro drug release. From that crystalline form of Cinnarizine is converted into amorphous state during formulation of solid dispersion. Solid dispersion by solvent evaporation method in 1:3 ratios showed better results than other formulations. Orodispersible tablets of Cinnarizine were compressed using selected solid dispersion 1:3 formulation and excipients with kyron T 314 as a superdisintegrant. Orodispersible tablet shows disintegration time 13 seconds and in-vitro drug release 99.75 %, which is better as compare to marketed conventional tablet 66.92 % within 15 minutes. Thus formulation of orodispersible tablet of Cinnarizine solid dispersion showed increased solubility and bioavailability with patient complies and convenience.

Keywords: *Cinnarizine, Soluplus, Kyron T-314, Solid dispersion, Orodispersible tablet, Solubility.*

Corresponding author:

Dhananjay M. patil,
Department Of Pharmaceutics,
K.B.H.S.S Trust Institute of Pharmacy
Bhaygoan Road Opp, Jajuwadi Malegoan Camp,
Nasik-423203,
Email-drdhananjaypatil@hotmail.com
Mob No-09823385304

QR code

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INTRODUCTION:

Limited and variable drug absorption resulting in poor bioavailability is the major problem that can be encountered when delivering an active agent via oral route. Bioavailability of the drug is one critical parameter for determining the efficacy of pharmaceutical formulations[1-2]. Drug absorption from GIT can be limited and varied by a variety of factors with most significant contributors being poor aqueous solubility and/or membrane permeability of the drug molecule. The therapeutically effective amount of a medicine in a composition should be made available to the organism, with optimum blood concentrations of the active ingredients reached within the shortest possible time. Since the development cost of a new chemical entity is very high, the pharmaceutical companies are focusing on the development of new drug delivery systems for existing drug with an improved efficacy and bioavailability together with reduced dosing frequency to minimize side effects[3-5]. Solubility enhancement of poorly water soluble drugs are needed. Solid dispersion technique is extensively used to increase the solubility of poorly soluble drug [6].

For the past two decades, there has been enhanced demand for more patient compliance dosage forms. As a result, the demand for their technologies has been increasing three-fold annually. Solid dosage forms like tablets and capsules are more popular and preferred drug delivery system because they have, accurate dosing, good physical and chemical stability. But the most evident drawback of the commonly used oral dosage forms like tablets and capsules is difficulty in swallowing, leading to patients incompliance particularly in case of pediatric and geriatric patients, but it also applies to people who are ill in bed and to those active working patients who are busy or traveling, especially those who have no access to water[7].

Difficulty in swallowing (dysphasia) is a common problem of all age groups, especially the elderly and pediatrics, because of physiological changes associated with these groups[8,9]. Other categories that experience problems in using conventional oral dosage forms include the mentally ill, uncooperative and patients suffering from nausea, motion sickness, sudden episodes of allergic attack or coughing. It is estimated that 35-50% of the population is affected by this problems. Recent advances in Novel Drug Delivery Systems aim to enhance safety and efficacy of drug molecule by formulating a convenient dosage form for administration and to achieve better patient compliance. One such approach is to enhance the solubility of drug by solid dispersion technique and further to formulate orodispersible tablet[9].

Cinnarizine is a piperazine derivative, H1 receptor antagonist. Cinnarizine is classified as a selective antagonist of T-type voltage-operated calcium ion channels, because it's binding blocks the channels and keeps them inert. In treatment of nausea motion sickness and vertigo Cinnarizine exerts its effects by inhibiting the calcium currents in voltage gated channels in type II vestibular hair cells within the inner ear. Cinnarizine is BCS class II drug (Low solubility and high permeability). Cinnarizine is practically insoluble in water, low and invariably bioavailability and thus delays onset of action. It is well established fact that, dissolution is the rate limiting step in the absorption process. Consequently, numerous attempts have been made to modify the dissolution characteristics of insoluble drugs in an attempt to attain fast and more complete dissolution[10,11]. In an attempt to enhance the solubility, dissolution rate and bioavailability of slightly soluble drugs, solid dispersion by using novel polymer soluplus has been extensively applicable.

Many patients find it difficult to swallow tablets and hard gelatin capsules and thus not comply with prescription that results in high incidence of non-compliance and ineffective therapy. Orodispersible tablets are gaining prominence as new drug delivery systems. These dosage forms dissolves or disintegrate in oral cavity within a minute without the need of water or chewing before swallowing[12]. Kyron T-314 is used as superdisintegrant in given formulation to achieve fast disintegration of tablet and patient compliance and convenience[13].

MATERIALS AND METHODS:

Materials:

Cinnarize and Soluplus were obtained as gift sample from Glenmark pharma Nasik, and BASF, The chemical company Germany respectively. Kyron T-314 was obtained as gift sample from Corel Pharma, Ahmadabad. All other ingredients are of pharmaceutical and analytical grades.

Methods:

Preparation of solid dispersion of Cinnarizine with Soluplus:

Preparation of physical mixtures (PMs):

The physical mixtures were prepared by mixing the required amount of Cinnarizine and Soluplus in the ratio of 1:1, 1:2, 1:3 for 15 min in a mortar with pestle until a homogeneous mixture was obtained. This resulting mixture was sieved through a 40 mesh screen. The powder was stored in a dessicator until further evaluation.

Preparation solvent evaporation method dispersions (SDs)[14]:

Accurately weighed quantities of Cinnarizine and Soluplus in the ratio of 1:1 1:2, 1:3 by weight were dissolved in acetone in a porcelain dish. The solvent was evaporated by occasional stirring and wet mass was kept in hot air oven at 50ºC for

drying. The dried mass was sieved through 40 mesh screen. The solid dispersion was stored in a dessicator until further evaluation.

Characterization of solid dispersion

Saturation solubility studies[15]:

Excess quantity of pure Cinnarizine and its all prepared physical mixtures and solid dispersions with Soluplus were added in a 50 ml of glass stoppered volumetric flasks containing 25 ml of solvent (pH 1.2 buffer solution and phosphate buffer pH 6.8 separately). The flasks were sealed, placed on mechanical shaker and agitated for 24 hrs at $28^0C \pm 0.2^0C$. After 24 hrs, the samples were then filtered through Whatman filter paper, diluted suitably and absorbance was measured at 254 nm.

Drug content [15]:

The content of Cinnarizine in each physical mixture and solid dispersions was determined using by UV spectroscopy. Accurately weighed physical mixture or solid dispersion equivalent to 25 mg of Cinnarizine was transferred to 100 ml volumetric flask containing 10 ml of methanol and dissolved. The volume was made up to 100 ml with methanol. The solution was filter through Whatman filter paper. 1 ml of this solution was diluted 10 times with methanol to achieve 25 µg/ml and the absorbance was measured at 254 nm.

Infrared spectroscopy[16,17]:

IR spectra were obtained by KBr disk method using Fourier- transform infrared (FTIR) spectrometer (8400 S Shimadzu). KBr disks prepared using hydrostatic press a thrust of 5 tons/cm^2 for 5 min. The scanning range was 400 to 4000 cm^{-1}.

Differential scanning calorimetry[16,17]:

The DSC measurements were performed on a Differential Scanning Calorimetry (Shimadzu-DSC 60) with a thermal analyzer. All accurately weighed samples (5 mg) were placed in sealed aluminum pans, before heating under nitrogen flow (10 ml/min) at a scanning rate of 10˚C/min. from 35˚C- 300˚C. An empty aluminum pan was used as reference.

Dissolution studies[15,18]:

The pure drug, physical mixtures and solid dispersions equivalent to 25 mg of Cinnarizine were subjected to the dissolution study using USP dissolution apparatus type II (Paddle) maintained at 37 ± 0.5ºC and 50 rpm. Dissolution medium used is pH 1.2 buffer 900ml.

Samples of 5 ml were withdrawn at regular interval of 3 min. The volume withdrawn was replaced by fresh volume of dissolution medium to maintain constant volume of medium. The filtered samples were analyzed spectrophotometrically at 254 nm.

Formulation of tablets using Solid dispersion of Cinnarizine

Tablets containing equivalent to 25 mg of Cinnarizine solid dispersion were prepared by direct compression. The blend was compressed on a 10 station rotary machine using round shaped, concave punches. The composition of tablet is given in following table.

Table 1: Composition of tablet

Ingredients	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)
Solid Dispersion	100	100	100	100
Kyron T 314	2	4	6	8
Aspartame	1.2	1.2	1.2	1.2
Magnesium stearate	0.6	0.6	0.6	0.6
Talc	0.6	0.6	0.6	0.6
Microcrystalline cellulose pH 102	95.6	93.6	91.6	89.6
Total	**200**	**200**	**200**	**200**

Evaluation

Physical evaluation of tablet blend

Angle of repose[19]:

The angle of repose of each powder blend was determined by glass funnel method by using the following equation

$$\tan\theta = h/r$$

Where,

h = height of cone

r = radius of powder cone

Bulk density[19]:

Bulk density of solid dispersion granules were determined by pouring gently 25 gm of sample through a glass funnel into a 100 ml graduated cylinder. The powder was carefully leveled without compacting it and the apparent volume was measured (V_o). Bulk density was calculated as below-

$$\text{Bulk density} = M/Vo$$

Where,

M = mass of powder

V_o = apparent unstirred volume

$$\text{Bulk Density (g/ml)} = \frac{\text{Mass of powder (M)}}{\text{Bulk volume of the powder (Vo)}}$$

Tapped density[19]:

The tapped density was determined by pouring 25 gm sample (solid dispersion with excipients) through a glass funnel into a 100 ml graduated cylinder. The cylinder was tapped from height of 2 inches until a constant volume obtained. Volume occupied by the sample after tapping was recorded and tapped density was calculated.

$$\text{Tapped Density (g/ml)} = \frac{\text{Weight of powder}}{\text{Tapped volume of the powder}}$$

Carr's index[19]:

It is also one of the simple method to evaluate flow property of a powder by comparing the bulk

density and tapped density. Carr's index is also known compressibility index and which was calculated.

$$\text{Carr's index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

Hausner's ratio[19]:
It provides an indication of the degree of densification that could result from vibration of feed hopper. Lower the hausner ratio better is the flowability.

$$\text{Hausner ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Evaluation of tablets
The tablets were evaluated for the following test parameters,

Weight variation test[18]:
Twenty tablets of each formulation were weighed individually using an electronic balance. The average weight was calculated and individual tablet was compared with the average value and the deviation was recovered.

Content uniformity of tablets[15]:
Ten tablets were weighed and crushed in a small mortar. The fine powder equivalent to 25 mg of Cinnarizine was transferred to 100 ml volumetric flask containing 10 ml of methanol and dissolved. The volume was made up to 100 ml with methanol. The solution was filter through Whatman filter paper. 1 ml of this solution was diluted 10 times with methanol to achieve 25 µg/ml and the absorbance was measured at 254 nm.

Thickness:
Twenty tablets were randomly selected from formulations and thickness was measured individually. It was expressed in millimeter and average was calculated.

Friability test[18]:
Friability test is performed to assess the effect of friction and shocks, which may often cause tablet to chip, cap or break. Roche friabilator was used for the purpose. (according to USP monograph 1216 - tablets with a unit weight equal to or less than 650 mg, take a sample of whole tablets corresponding as near as possible to 6.5 gm.) Pre weighed sample of tablets was placed in the friabilator, which was then operated for 100 revolutions/min. Tablets were dusted and reweighed. The percentage friability was calculated by,

$$F = \frac{W_{initial} - W_{final}}{W_{final}} \times 100$$

Percentage weight loss was calculated. A loss of less than 0.5 to 1 % in weight was generally acceptable.

***In-vitro* disintegration study[18,20]:**
The process of breakdown of a tablet into smaller particles is called as disintegration.
The *in-vitro* disintegration time of a tablet was determined using disintegration test apparatus. The disintegration test was carried out using USP disintegration test apparatus-II. Tablets were placed individually in each tube of disintegration test apparatus and discs were placed over each tablet. Distilled water (900 ml) was used as the medium which is maintained at 37 ± 2°C and the time taken for each tablet to disintegrate completely was recorded.

Hardness[20]:
Tablet hardness and resistance to powder and friability are necessary requisites for acceptance. The Pfizer hardness tester was used for hardness testing. Generally 4 kg/cm^2 hardness is considered as acceptable for uncoated tablets.

Wetting time[21,22]:
A piece of tissue paper folded twice was kept in petri dish (internal diameter 5.5 cm) containing 10 ml of distilled water. A tablet having a small amount of amaranth powder on the upper surface was placed on the tissue paper. The time required to develop a red color on the upper surface of the tablet was recorded as wetting time.

Water absorption ratio[21,22]:
A piece of tissue paper folded twice was placed in a small Petri dish (5 cm diameter) containing 6 ml of water. A tablet was put on the tissue paper and allowed to wet completely. The wetted tablet was then weighed and the water absorption ratio 'R' was determined by using following equation.

$$R = \frac{W_b - W_a}{W_a} \times 100$$

Where,
W_a= weight of tablet before water absorption
W_b = weight of tablet after water absorption.

***In-vitro* dispersion time[23]:**
In-vitro dispersion time of prepared tablet was done by dropping the tablet in 10 ml measuring cylinder containing 6 ml of simulated salivary fluid (pH 6.8). Time required for complete dispersion of tablet was measured.

Dissolution study[18]:
In order to study prepared tablet subjected to the dissolution study using USP dissolution apparatus type II (Paddle) maintained at 37 ± 0.5ºC and 50 rpm. Dissolution medium used is pH 1.2 buffer 900ml. Samples of 5 ml were withdrawn at regular interval of 3 min. The volume withdrawn was replaced by fresh volume of dissolution medium to maintain constant volume of medium. The filtered

samples were analyzed spectrophotometrically at 254 nm.

Stability studies[24]:

In the present study, the stability studies were carried out as per ICH guidelines at 40°C ± 2°C/75 % ± 5% RH for the selected formulation (F4) for 3 month. After specified time intervals, parameters like hardness, dispersion time, disintegration time, drug content, and *in-vitro* dissolution were evaluated according to the procedure described as above.

RESULTS AND DISCUSSIONS:

Characterization of solid dispersion system

Saturation solubility studies:

Table.2: Saturation solubility of PD (Cinnarizine), PMs and SDs in pH 1.2 buffer

Formulation code	Saturation Solubility(mg/ml)
PD	0.63261±1.51
PM1:1	1.5765±1.79
PM1:2	2.351±1.74
PM1:3	2.8352±0.658
SD1:1	3.70014±1.31
SD1:2	3.99324±1.084
SD1:3	4.84606±1.08

Mean, ±SD, n= 3

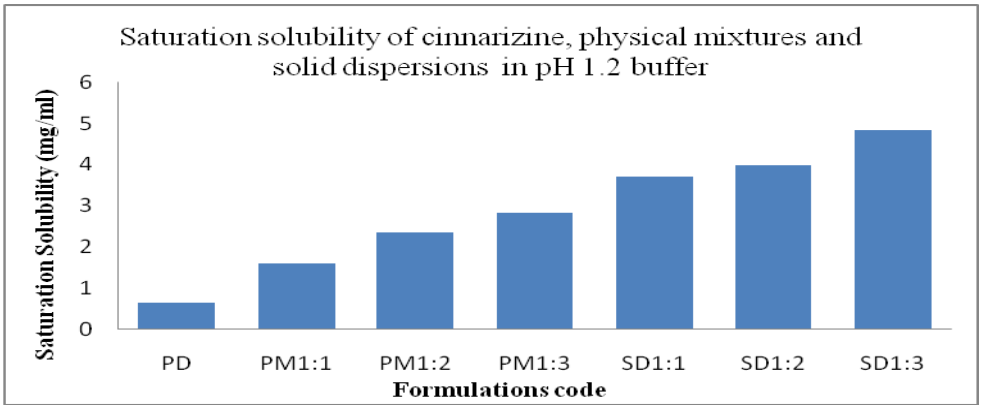

Fig 1: Saturation solubility of PD, PMs and SDs in pH 1.2 buffer

Table 3: Saturation solubility of PD, PMs and SDs in pH 6.8 phosphate buffer

Formulation Code	Saturation Solubility(mg/ml)
PD	0.003975±0.135
PM1:1	0.00672±0.3400
PM1:2	0.009963±0.2064
PM1:3	0.015639±0.4745
SD1:1	0.020549±0.2064
SD1:2	0.028793±0.3400
SD1:3	0.030684 ±0.2813

Mean, ±SD, n= 3

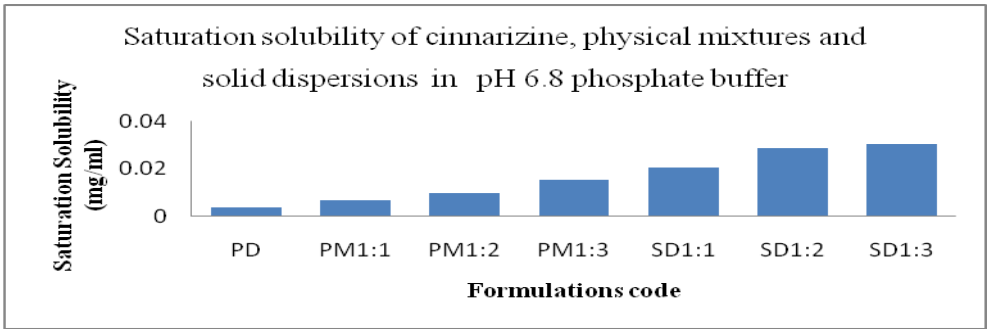

Fig 2: Saturation solubility of PD, PMs and SDs in pH 6.8 phosphate buffer

The saturation solubility profile for the pure Cinnarizine and its all prepared physical mixture and solid dispersion is shown in figure no.6.5 and 6.6. These figures indicate that Cinnarizine is having very low solubility i.e. 0.6326 mg/ml and 0.0039 mg/ml in pH 1.2 buffer solution and pH 6.8 phosphate buffer respectively. Physical mixture and solid dispersion with Soluplus shows increase in solubility respectively as concentration of polymer is increases.

The ratio 1:3 of solid dispersion gives the maximum saturation solubility among all the physical mixture and solid dispersions i.e. 4.8460 mg/ml and 0.030684 mg/ml in pH 1.2 buffer solutions and pH 6.8 phosphate buffer respectively.

Analysis of drug content

The percentage drug content of PMs and SDs are shown in table no 4.

Table 4: Results of drug content with Soluplus.

Methods	Ratio	Drug Content (%)
Physical Method (PMs)	1:1	98.78±.8050
	1:2	99.19±.8798
	1:3	99.20±.9814
Solvent Evaporation Method (SDs)	1:1	99.23±.3098
	1:2	99.13±.9226
	1:3	100.04±.4000

Mean, ±SD, n= 3

The drug content of Cinnarizine physical mixtures and solid dispersions was found to be in range 98.78 % to 100.04 % and these values are within the acceptable range. Low values of standard deviation with respect to drug content indicate uniformity of drug distribution in all the physical mixtures and solid dispersions of Cinnarizine.

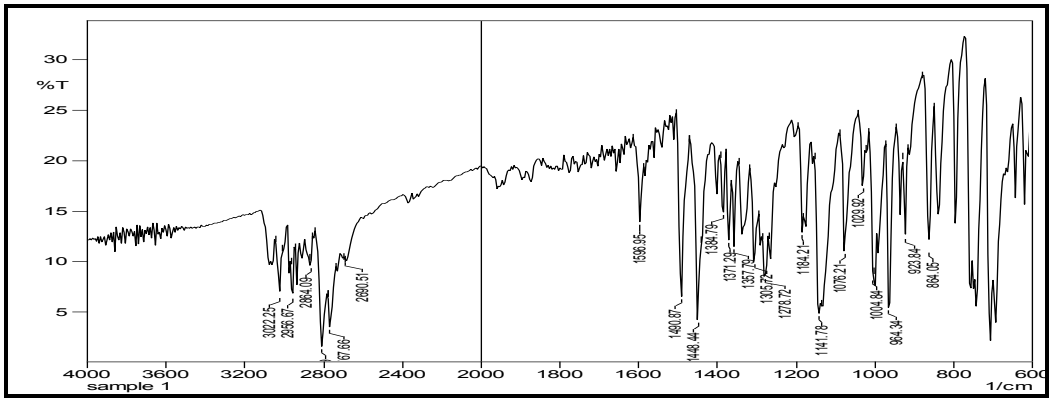

Fig .3: FTIR spectrum of Cinnarizine

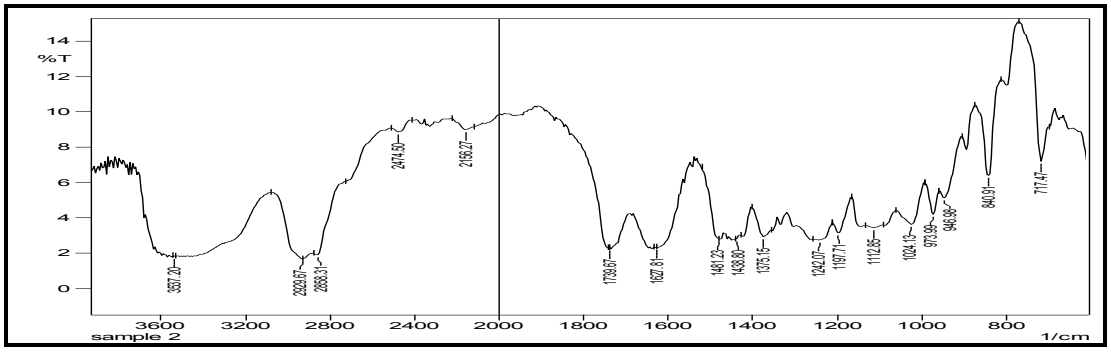

Fig 4: FTIR spectrum of Soluplus

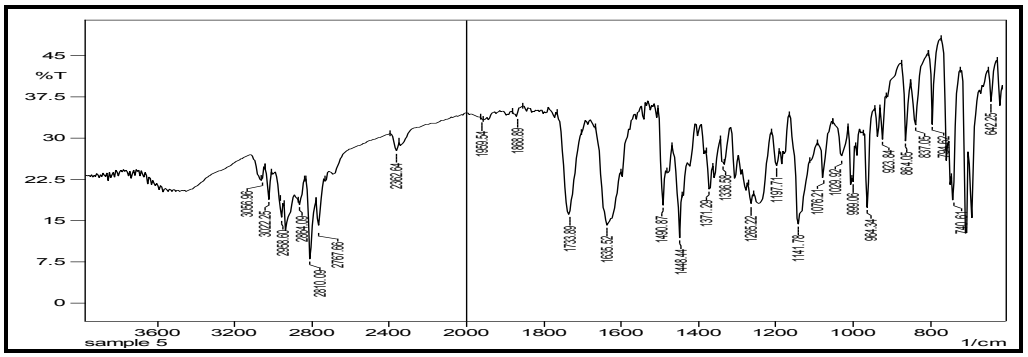

Fig 5: FTIR spectra of solid dispersion (1:3)

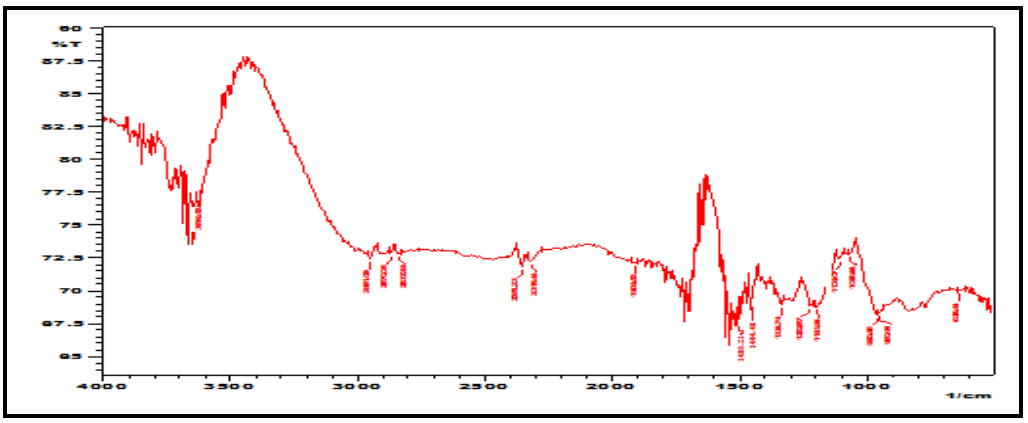

Fig 6: FTIR spectra of Kyron T-314

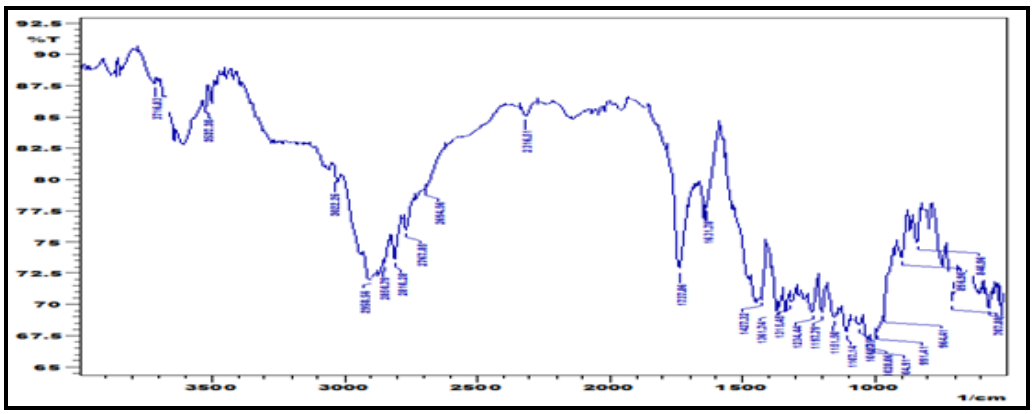

Fig 7: FTIR spectrum of orodispersible tablet (F4)

Fourier Transform Infra Red (FTIR) Spectroscopy:

Fourier transform infrared spectroscopy has been used to assess the interaction between carrier and drug molecule. The FTIR spectrum of Cinnarizine, Soluplus and solid dispersion prepared by solvent evaporation method are as shown in figure no.6&7.

The FTIR studies were performed to detect the molecular interaction between drug and polymers. The FTIR spectra of Cinnarizine, Soluplus and their solid dispersion are shown in the figure no. 3, 4 and 5 respectively. In FTIR spectra of Cinnarizine the characteristic absorption peaks, aromatic C-H bending occurs at 3022.25 cm^{-1}, aliphatic C-H stretching occurs at 2956.67 cm^{-1}, the C=C stretching occurs at 1490.87 cm^{-1}, C-N stretching occurs at 1141.78 cm^{-1}. Soluplus shows the characteristic peaks O-H stretching at 3537.20 cm^{-1} , C-H stretching at 2929.67 cm^{-1} C=O stretching at 1627.81 cm^{-1}, C-N at C-N stretching 1197.71 cm^{-1} The peaks of solid dispersion of Cinnarizine with Soluplus shows one additional peak at 3537.20 cm^{-1} indicative of intermolecular hydrogen bonding between Cinnarizine and Soluplus.

The IR spectra of Kyron T 314the characteristic peak C=C stretching occur at 1480.34 cm^{-1} , C-H stretching occur at 2870 cm^{-1}, and CH_2 bending occur at 1465.45 cm^{-1}. The IR spectra of F4

formulation blend show all characteristic peaks Cinnarizine and solid dispersion and it indicates that there is no interaction between solid dispersion and Kyron T 314.

Differential scanning calorimetry study

The DSC thermo gram of Cinna rizine, Soluplus, solid dispersion prepared by solvent evaporation method and it's overlapped as shown in figure no.8-11 respectively

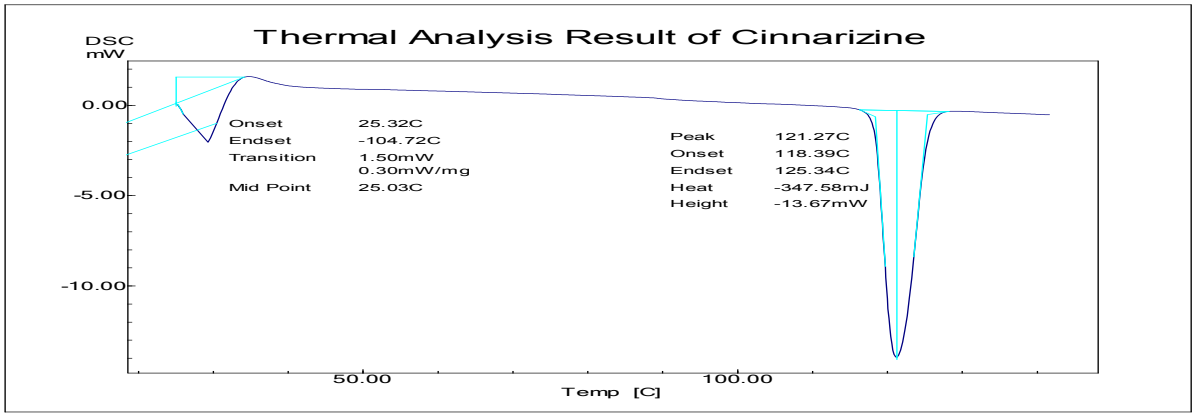

Fig 8: DSC Thermogram of Cinnarizine

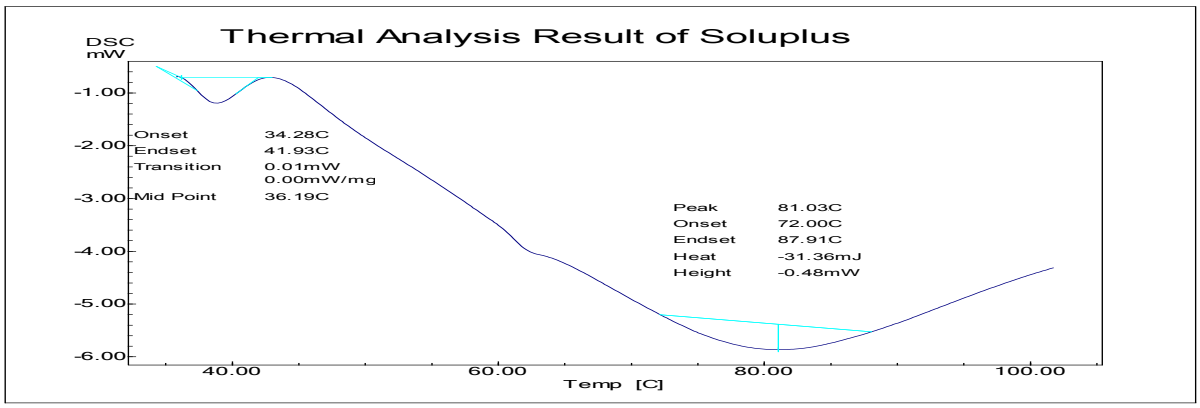

Fig 9: DSC Thermogram of Soluplus

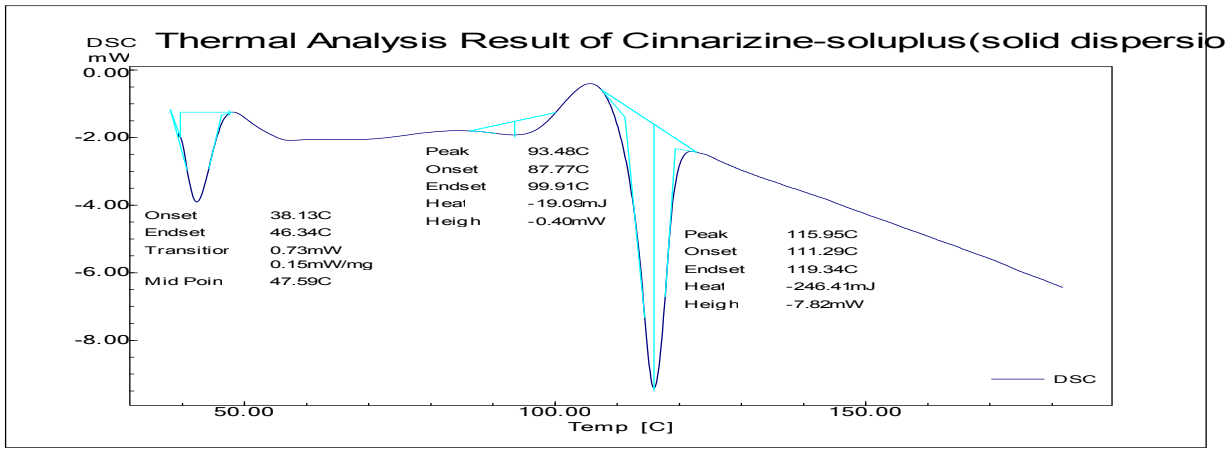

Fig 10: DSC Thermogram of solid dispersion (1:3)

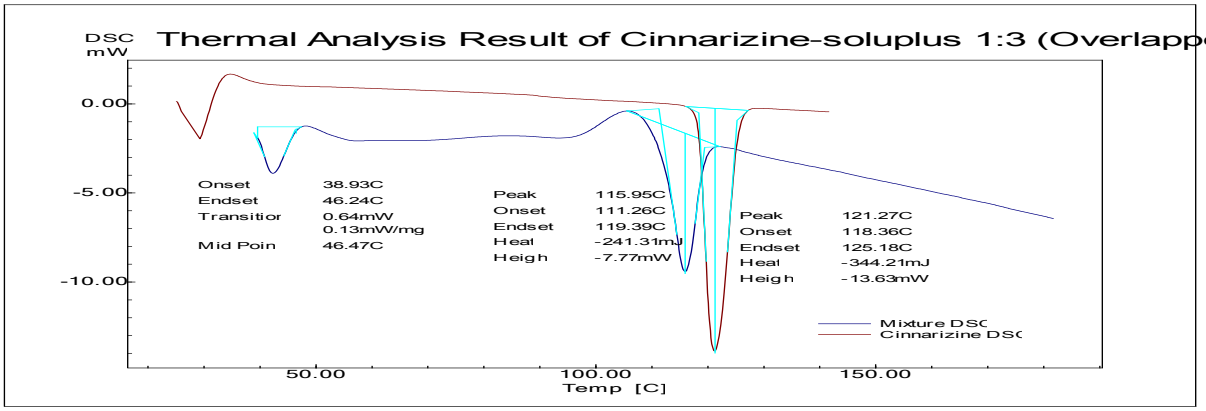

Fig 11: DSC Thermogram of Cinnarizine and solid dispersion (1:3) overlapped

From the figure no.8 the Cinnarizine showed the melting point at 121ºC, from figure no.9 Soluplus showed the melting point at 81ºC, from figure no.10 the solid dispersion showed the melting point reduced to 115ºC from 121ºC and the intensity of the peak in pure drug is reduced. From the figure no.11 it can be concluded that there is a formation of solid dispersion with conversion of drug crystalline to amorphous form.

Dissolution study

In order to investigate the release rate of PD, PMs and SDs with Soluplus in the ratio 1:1, 1:2 and 1:3 were subjected to dissolution study in USP type II dissolution apparatus at 50 rpm in 900 ml pH 1.2 buffer solution as a dissolution medium. Temperature of dissolution medium was maintained at 37 ± 0.5^0C. PD 25 mg and PMs and SDs equivalent to 25 mg of Cinnarizine were added in each vessels. 5ml sample withdrawn at regular time interval of 3 min and filtered through Whatman filter paper. An equal volume of fresh dissolution medium was added in order to kept total volume of dissolution medium constant. Filtered samples absorbance was measured at 254 nm and results are shown in table no 5-6and figure no12-13.

Table 5: Results of percentage cumulative drug release of PD, PMs with Soluplus

Time (min)	PD	PM 1:1	PM 1:2	PM 1:3
0	0	0	0	0
3	10.546±0.5339	10.7223±0.1555	11.4465±0.3905	12.6361±0.4741
6	14.8164±0.4123	16.9371±0.3236	18.5963±0.4970	19.9994±0.3558
12	17.0359±0.8688	20.7269±0.4764	23.5303±0.5437	26.8015±0.3210
15	20.9066±0.6491	26.0106±1.1239	28.3172±0.8966	32.5863±1.118
18	25.7801±0.5563	33.5502±0.7962	34.8559±0.4669	38.6662±1.1249
21	31.1403±0.4715	39.7343±0.3302	40.6832±0.7665	44.6682±1.1813
24	35.9184±0.0784	44.8656±1.655	47.1413±1.5349	52.0503±1.2690
27	44.6076±1.005	55.5306±1.312	60.5688±1.1986	67.4507±0.6648
30	49.432±0.4227	61.0257±0.9124	66.6699±0.8894	75.9167±0.4513

Mean, ±SD, n= 3

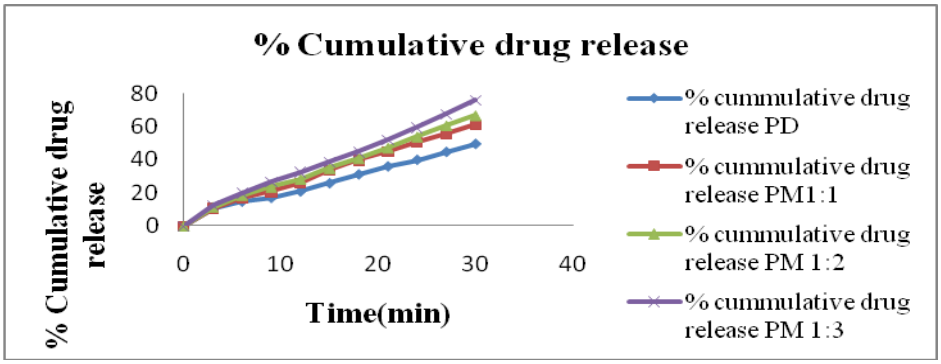

Fig 12: *In-vitro* dissolution profile of PD and PMs with Soluplus

Table 6: Results of percentage drug release of PD, SDs with Soluplus

Time (min)	PD	SD 1:1	SD 1:2	SD 1:3
0	0	0	0	0
3	10.5460±0.533	13.2091±0.268	21.7396±0.2687	26.3430±0.498
6	14.8164±0.412	20.3647±0.238	30.2396±0.5382	34.5066±1.092
9	17.0359±0.868	27.274±0.544	38.8587±0.8584	45.0113±0.829
12	20.9066±0.649	33.2693±0.392	46.7799±0.9484	58.2940±0.689
15	31.1403±0.471	40.1764±0.698	58.6232±0.5696	72.4766±1.335
18	31.1403±0.471	47.276±0.414	69.2896±0.2302	84.9260±1.235
21	35.9184±0.078	54.4139±0.235	79.5995±0.9607	96.9768±0.418
24	39.8905±0.454	61.2796±0.353	91.9330±1.0698	99.8296±0.399
27	44.6076±1.005	70.199±0.564	98.8932±0.2632	-
30	49.4320±0.422	78.7834±0.366	-	-

Mean, ±SD, n= 3

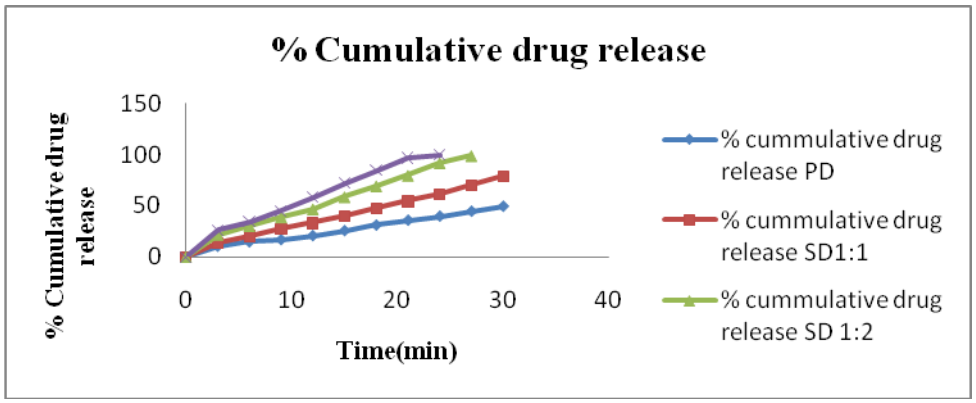

Fig 13: *In-vitro* dissolution profile of PD, SDs with Soluplus

From the table no.5 and figure no.12, it is observed that the physical mixture of 1:3 shows the higher percent cumulative drug release after 30 min as compared to the other physical mixture of 1:1, 1:2 ratio and pure drug. This is 75.9167 ± 0.4513 % as compared to other physical mixture of 1:1, 1:2 ratio and pure drug, which is 61.0257 ± 0.9124 %, 66.6699 ± 0.8894 % and 49.43 ± 0.4227 % respectively after 30 min.

From the table no.6 and figure no.13, it is observed that the solid dispersion of 1:3 shows the higher percent cumulative drug release after 24 min as compared to the other solid dispersion of 1:1, 1:2 ratio and pure drug. This is 99.82 ± 0.3998 % as compared to other solid dispersion of 1:1, 1:2 ratio and pure drug, which is 78.78 ± 0.366 %, 98.89 ± 0.2632 %, and 49.43 ± 0.4227 % respectively after 30 min.

In order to investigate the drug release from the prepared solid dispersion, *in-vitro* dissolution study carried out in pH 1.2. The better dissolution performance of solid dispersions was increased as compared to the pure drug and physical mixture in pH 1.2 in a particular time course. This may be attributed to the higher solubility of Soluplus in dissolution medium and improved wetability of the drug particles, significant reduction particle size during the formation of the solid dispersion and intrinsically higher rate of dissolution of the selected soluble polymer, which could pull insoluble but finely mixed drug into the bulk of dissolution medium.

The Cinnarizine solid dispersion prepared with Soluplus by solvent evaporation method in ratio 1:3 showed better percent cumulative drug release as compared to other solid dispersions, physical mixtures and pure drug. The percent cumulative drug release rate of solid dispersion with ratio 1:3 was 99.82 ± 0.399 % in 24 min. and solid dispersion 1:1, 1:2, physical mixture 1:1, 1:2, 1:3 and pure drug was 75.91 %, 98.89 %, 61.02 %, 66.66 %, 75.91 ± 0.957 % and 49.43 ± 0.422 % in 30 min. in pH 1.2 buffer respectively. Among all these formulation solid dispersion with 1:3 ratios is best due to percent cumulative drug release that is 100.19 % in 24 min.

From the results of dissolution studies, the solid dispersion with 1:3 ratio prepared by using Soluplus was selected for tablet formulation.

Evaluation of solid dispersion tablet

Pre compression evaluation of tablet blend.

Formulations ready for compression containing solid dispersion of Cinnarizine and various excipients were subjected for pre-compression parameters to study the flow properties of granules angle of repose, mean bulk density, mean tapped density, carr's index, hausner's ratio as shown in table no.7

Table 7: Evaluation of precompression parameters of orodispersible tablets containing Cinnarizine solid dispersion.

Formulation Code	Angle of Repose(^{0})	Bulk Density (g/cm^2)	Tapped Density (g/cm^2)	Carr's Index (%)	Hausner's Ratio
F1	25.1033 ±0.9042	0.8048 ±0.0108	0.9260 ±0.0102	13.08 ±0.3592	1.1506 ±0.0047
F2	24.73 ±0.4430	0.8217 ±0.0232	0.9460 ±0.0180	13.14 ±0.7950	1.1514 ±0.0104
F3	23.9733 ±0.9957	0.7954 ±0.0113	0.9158 ±0.0135	13.04 ±0.2655	1.1500 ±0.035
F4	23.7833 ±1.008	0.7997 ±0.0157	0.9158 ±0.0134	12.68 ±0.5167	1.1452 ±0.0067

Mean, ±SD, n= 3

Formulation design:

The present study was carried out to develop orodispersible tablets of Cinnarizine solid dispersion (1:3) in order to improve patient compliance and also to prepare user-friendly formulations. In this case, four formulations of orodispersible tablets were prepared by direct compression method using superdisintegrant Kyron T 314. The detailed composition of each formulation is given in the table no.1.

Post compression parameters:

The tablets prepared by direct compression technique were subjected for evaluation according to various official specifications and other parameters like shape and color, thickness, diameter, hardness, friability, weight variation, *in-vitro* disintegration time, wetting time, water absorption ratio, dispersion time, drug content and *in- vitro* dissolution studies as shown in table no.8 to 10 and figure no.14.

Table 8: Evaluation of post compression parameters of orodispersible tablets containing Cinnarizine solid dispersion.

Formulation Code	Hardness (kg/cm^2) n=5	Thickness (mm) n=20	Diameter (mm) n=20	Friability (%)	Weight Variation (mg) n=20	Drug Content (%) n=3
F1	3.90 ±0.100	4.94 ±0.0228	7.49 ±0.0058	0.5616	199.7 ±1.1742	99.10 ±0.6100
F2	3.78 ±0.0836	4.96 ±0.0329	7.49 ±0.0044	0.4117	200.25 ±1.4823	99.44 ±0.5086
F3	3.84 ±0.1341	4.94 ±0.0290	7.5 ±0.0064	0.4723	200.15 ±1.3518	99.60 ±0.4000
F4	3.86 ±0.1140	4.96 ±0.0372	7.49 ±0.0075	0.4419	200 ±1.0760	99.81 ±3987

Table 9: Evaluation of post compression parameters of orodispersible tablets containing Cinnarizine solid dispersion.

Formulation code	Wetting time (sec)	Dispersion time (sec)	Water absorption ratio (%)	Disintegration time (sec)
F1	31.33±0.5773	34.33±0.01	88.16±0.7636	26.16±0.7527
F2	24.66±1.1547	28.33±0.04	90.00±0.5000	21.5±0.8366
F3	19.66±0.5773	23.33±0.01	90.83±1.0408	16.83±0.7527
F4	14.0±1.000	19.33±0.01	94.66±1.0408	13±0.8944

Mean, ±SD, n=3

Dissolution study of formulated tablet

The formulated tablets were subjected to dissolution study in USP type II dissolution apparatus at 50 rpm in 900 ml pH 1.2 buffer solution as a dissolution medium. Temperature of dissolution medium was maintained at 37 ± 0.5^0C. Orodispersible tablet equivalent to 25 mg of Cinnarizine were added in each vessels. 5 ml sample withdrawn at regular time interval of 3 min, filtered through Whatman filter paper. An equal volume of fresh dissolution medium was added in order to kept total volume of dissolution medium constant. Filtered samples absorbance was measured at 254 nm and results are shown in table no 10 and figure no14.

The orodispersible tablet containing Cinnarizine solid dispersion prepared with Soluplus by solvent evaporation method in ratio 1:3 showed better percent cumulative drug release in less than 30 min. The percent cumulative drug release rate of formulation F1 was 99.14 ± 0.4240 % in 24 min. F2 was 99.49 ± 0.4672 %in 21 min, 99.4461 ± 0.2273 % in 18 min and F4 was 99.7582 ± 0.6297 % in 15 min. Among all these formulations F4 is best due to percent cumulative drug release that is 99.7582 % in 15 min.

From the results of dissolution studies, the formulation F4 is selected as a final formulation and compared with marketed tablet.

Table 10: Results of percentage cumulative drug release of orodispersible tablet formulations F1-F4 Mean, ±SD, n=3

Time (min)	F1	F2	F3	F4
0	0	0	0	0
3	27.4525±0.2688	28.7741±0.3583	31.981±0.4655	34.9465±0.3905
6	35.6479±0.4756	36.4859±0.2682	44.1586±0.7357	49.6523±0.2358
9	46.6262±0.2366	47.9843±0.6224	57.4283±0.4733	70.9995±0.4751
12	59.7627±0.9956	60.8696±0.3233	71.848±0.4733	88.6855±1.013
15	73.0741±0.6237	76.1174±0.6058	84.7574±0.7862	99.7582±0.6297
18	86.4059±0.8609	88.001±0.2340	99.4461±0.2273	-
21	96.6027±0.8748	99.498±0.4672	-	-
24	99.1475±0.4240	-	-	-

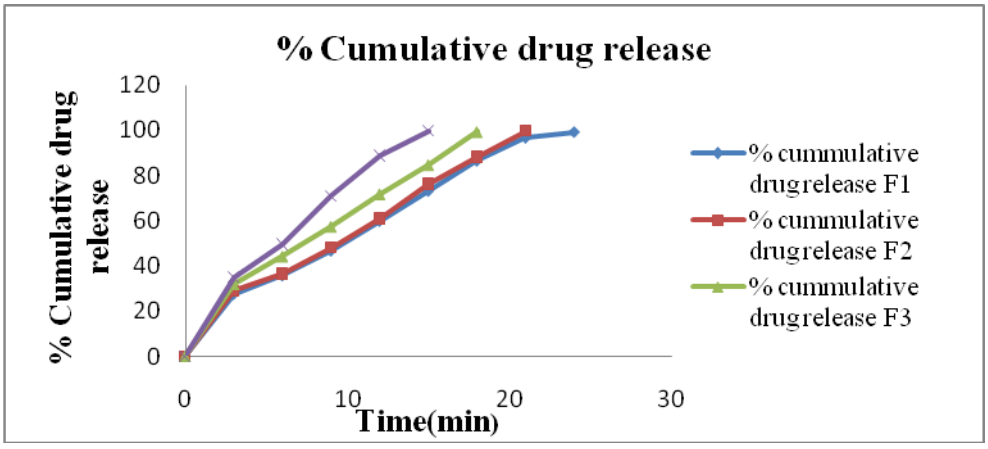

Fig 14: *In-vitro* dissolution profile of orodispersible tablet formulations F1-F4

Comparison between marketed Cinnarizine tablet (conventional) and selected formulation F4

Table 11: Comparative result of marketed Cinnarizine tablet and formulation F4

Parameter	Marketed Tablet	Formulation F4
Weight Variation(n=20)	198.21±1.5301	200.00±1.0760
Hardness (Kg/cm^2)(n=5)	4.31 ±0.7524	3.86 ±0.1140
Wetting Time (Sec.)	176.2±0.231	14.0 ±1.000
Friability (%)	0.7525	0.4419
Disintegration Time (Sec.)	305.5±3.526	13.00± 0.894
Drug Content (%)	97.72±0.2350	99.81±0.3987

Mean, ±SD, n=3

Table 12: Results of percentage cumulative drug release of marketed tablet and formulation F4

Time (min)	Marketed Tablet	Formulation F4
0	0	0
3	24.4293±0.2370	34.9465±0.3905
6	36.2029±0.6258	9.6523±0.2358
9	44.7516±1.0082	70.9995±0.4751
12	56.0673±1.3602	88.6855±1.013
15	66.9272±0.2321	99.7582±0.6297

Mean, ±SD, n=3

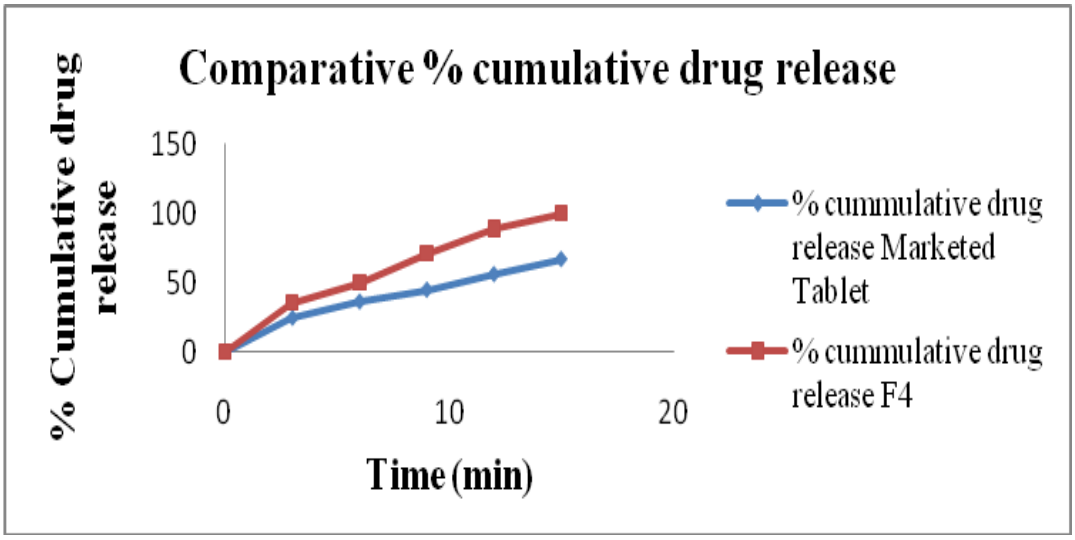

Fig 15: *In-vitro* dissolution profile of marketed tablet and formulation F4

Comparative results between marketed Cinnarizine tablet (conventional) and formulation F4 are reported in table no 11-12 and figure no 15. Mouth dissolving tablet of Cinnarizine is not available in market. Percent cumulative drug release of marketed formulation in 15 min was 66.9272 ± 0.2321 % and F4 formulation was 99.7582 ± 0.6297 %.

From the comparative study between marketed tablet and formulation F4, it was concluded that F4 formulation show better results than conventional marketed Cinnarizine tablet.

Stability study

The physical appearance of the samples kept for stability studies were checked each month and found that there was no difference in the appearance.

Table 13: Stability studies for orodispersible tablets (F4)

Parameter	40°C ± 2°C/75% ± 5% RH		
	30 Day	60 Day	90 Day
Hardness (Kg/cm ^{2})	3.89 ± 0.4370	3.94±0.7590	4.93±0.2743
Dispersion time (sec)	19.63±0.4211	20.17±0.3871	20.18±0.1835
Disintegration time (sec.)	13.47±0.1457	13.64±1.3804	14.20±0.2752
Drug content (%)	99.44±0.2758	99.50±0.3620	98.98±0.1552
***In-vitro* Dissolution**	99.32±0.5387	99.29±0.1575	98.92±0.1560

Mean, ±SD, n=3

After completion of three month stability study there was no any significance change occurred in formulation F4.

SUMMARY AND CONCLUSION:

The enhancement of the oral bioavailability is currently one of the greatest challenge in the development of poorly water soluble drugs. To increase the solubility and hence the bioavailability it is important to increase the dissolution of the poorly water soluble drugs. One of the possible way to overcome this limitation is the use of solid dispersion technique. Cinnarizine is a H_1 receptor antagonist is mostly prescribed in treatment of motion sickness, vomiting and vertigo. It is BCS class II drug having low solubility and high permeability, and shows variable bioavailability and delay in onset of action. It is well established fact that, dissolution is the rate limiting step in the absorption process. Conventional tablet of Cinnarizine is available in markets which are not suitable where fast onset of action is needed.

In order to overcome above problems, the present study was carried out to develop orodispersible tablets containing Cinnarizine solid dispersion. Solid dispersions of Cinnarizine were prepared by using novel polymer Soluplus in different ratios by physical mixture and solvent evaporation method. The drug and polymer ratio of 1:1, 1:2, 1:3 were used in order to enhance solubility and dissolution rate. After formulation completed Cinnarizine, physical mixture and solvent evaporation method dispersions were proceeds for its evaluation study

Saturation solubility of Cinnarizine was found to be 0.6326 mg/ml and 0.0039 mg/ml in pH 1.2 buffer solution and pH 6.8 phosphate buffer respectively. Physical mixture and solid dispersion with Soluplus shows increase in solubility respectively. The ratio 1:3 of solid dispersion gives the maximum saturation solubility among all the physical mixture and solid dispersions i.e. 4.8460 mg/ml and 0.030684 mg/ml in pH 1.2 buffer solution and pH 6.8 phosphate buffer respectively. Drug content was found to be in range 98.78 ± 0.8050 % to 100.04 ± 0.4000 % and these values are within the acceptable range. Low values of standard deviation with respect to drug content indicate uniformity of drug distribution in all the physical mixtures and solid dispersions of Cinnarizine.

In FTIR study were peaks of SD1:3 shows one additional peak at 3537.20 cm^{-1} than pure Cinnarizine peaks, which is indicative of intermolecular hydrogen bonding between Cinnarizine and Soluplus. In DSC study thermogram of Cinnarizine shows sharp endotherm at 121ºC indicating melting point of Cinnarizine. The thermogram of Soluplus shows change in heat capacity at 81ºC indicating melting point of Soluplus. In SD 1:3 thermogram shows the reduction in melting point from 121^{0}C to 115^{0}C and intensity of peak also reduced. This decrease in melting point of Cinnarizine may attribute to crystalline to amorphous nature in solid dispersion.

In order to investigate *in-vitro* release of pure drug, physical mixtures and solid dispersions with Soluplus were subjected to dissolution study in USP type II dissolution apparatus. PD, PM1:1, 1:2 and 1:3 shows 49.432 ± 0.4227 %, 61.025 ± 0.9124 %, 66.669 ± 0.8894 % and 75.916 ± 0.4513 % drug release respectively in 30 min. Solid dispersion SD1:1, SD1:2 and 1:3 shows 75.916 ± 0.9570 %, 98.893 ± 0.2632% and 99.829 ± 0.3998 % drug release in 30 min, 27 min and 24 min respectively. It indicate that SD1:3 shows higher drug release 99.82 ± 0.3998 % within 24 min compared to PD, PMs and SD1:1, 1:2. From the results of dissolution studies SD1:3 is selected as best formulation for tablet formulation.

Orodispersible tablets of SD1:3 were prepared by using Kyron T-314 as a superdisintegrant in different concentration 1 %, 2 %, 3 % and 4 % by direct compression method. These formulations are coded as F1, F2, F3 and F4. In order to establish

compatibility study, the FTIR spectra of formulation blend shows all characteristic peaks of Cinnarizine and SD1:3 and it indicates that there is no any significance interaction between SD1:3 and Kyron T 314.

The blends of all the formulations were evaluated for pre-compression parameters like angle of repose, bulk density, tapped density, carr's index and housner's ratio. The results that are obtained for formulation F1-F4 shows good compression and flow property. The prepared tablets were subjected for post-compression parameters. The results for all formulations possessed good mechanical strength with sufficient hardness in the range of 3.78 to 3.90 kg/cm^2. The percent friability was found to be 0.4117 to 0.5616 which is less than 1m% indicating tablets were mechanically stable. All formulations show 199.7 to 200.25 mg/tablet weight, which complies with pharmacopeias limit. Drug contents were found to be within pharmacopeias limit. The wetting time, dispersion time, disintegration time for all formulations was found to be 14.0 to 31.33 sec., 19.33 to 34.33 sec. and 13.0 to 26.16 sec. It is decreasing wetting, dispersion and disintegration time with increasing concentration of Kyron T-314.

The *in-vitro* dissolution profiles were indicates faster and maximum drug release from all formulations F1 to F4. F1 shows 99.1475 ± 0.4240 % in 24 min., F2 shows 99.498 ± 0.4672 % in 21 min., F3 shows 99.4461 ± 0.2273 % in 18 min and F4 shows 99.7582 ± 0.6297 % in 15 min. Based on obtained results, the formulation F4 is selected as a best formulation and which is compared with marketed formulation. Percent drug release of marketed formulation in 15 min was 66.9272 ± 0.2321 % and F4 formulation was 99.7582 ± 0.6297 %.

The prepared orodispersible tablet of Cinnarizine solid dispersion has shown better release and stability as compared to marketed formulation.

The conclusions from present research work are as follows:

The use of Soluplus for obtaining solid dispersion of Cinnarizine proved successful.

The significance increase in solubility and dissolution was observed from solid dispersion containing Cinnarizine and Soluplus in 1:3 ratio prepared by solvent evaporation method as compared to pure drug, physical mixtures and other solvent evaporation method dispersions.

Soluplus as a solid dispersion carrier imparts good surface adsorbent property and leaves drug in amorphous state that increases the surface area, due to enhances the dissolution rate.

Formulation of orodispersible tablet of Cinnarizine solid dispersion (1:3) by using Kyron T- 314 showed rapid *in-vitro* disintegration and dispersion time.

Formulation of orodispersible tablet by using solid dispersion of Cinnarizine is unique technique by which solubility and bioavailability of drug can be enhanced with improving patient compliance and convenience.

It can be concluded that combination of solid dispersion and superdisintegrant is a promising approach to prepare efficient orodispersible tablet of BCS class II drug (low solubility, high permeability).

Standardized orodispersible tablet formulation F4 was found to be stable after three month accelerated stability study.

Thus, the objectives of the research work were successfully achieved.

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