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# FORMULATION DEVELOPMENT AND EVALUATION OF FAST DISSOLVING FILM OF CINNARIZINE

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**Abstract**: Cinnarizine is a $H_1$-anti histaminic drug which is used in motion sickness, vertigo, vomiting and in menier's disease. These conditions require a delivery system capable of delivering the drug rapidly for immediate relief without the need of water. The films were prepared by solvent casting technique. The $3^2$ factorial design was applied for optimization of concentration of polymer HPMC $E_5$ and plasticizer PEG 400. The prepared films were evaluated for various parameters related to delivery system like thickness, tensile strength, % elongation, folding endurance, disintegration time, drug content, *In vitro* release study and stability study. From design statistical analysis, the film (batch F5) with HPMC $E_5$ (3%) and plasticizer PEG 400 (30%) was giving low disintegration time(18 sec), sufficient strength(189±3.25) and high drug release(98.46±2.31) and better %elongation(4.32±0.82). Thus, cinnarizine film was formulated giving fast release and immediate action for motion sickness.

**Keywords:** Fast dissolving film, Cinnarizine, Motion sickness, *In vitro* drug release, Disintegration time.

***PAPER-QR CODE***

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## INTRODUCTION

Oral route of drug administration has been one of the most convenient and accepted route of drug delivery and amongst it the intraoral route is the most preferred due to its convenience and rapid onset of action. Intraoral dosage forms have evolved as an alternative to conventional tablets, capsules and liquid preparations. Various types of intraoral dosage forms used to deliver drug systemically or locally include- Liquids (solution sprays, syrups), Semi-solids (ointments, pastes), Solid dosage forms (quick dissolve and slow dissolve tablets, sublingual tablets, lozenges, films, filaments, gums, patches, lollipops).New dosage forms such as sprays, mucoadhesive patches or rapid dissolving solid matrices using advanced manufacturing processes (i.e. lyophilized wafers, solvent cast films) have been introduced recently. Of the intraoral dosage forms, rapid dissolving dosage forms have gained much attention due to improved patient compliance and ease of administration. Fast dissolving dosage forms include orally disintegrating tablets (ODTs), oral thin films.[1, 2]

## FAST DISSOLVING DRUG DELIVERY SYSTEM[2,3]

These dosage forms are intended to disintegrate, dissolve or release the drug in the oral cavity, where it has opportunity to be locally absorbed, in part or whole and alternatively may be swallowed and subsequently absorbed along the gastro-intestinal tract. Fast dissolving drug delivery system are designed to meet the needs of special patients like geriatric, paediatric, mentally ill patients and dysphasic patients having difficulty in swallowing or chewing solid dosage forms. [2]

## FAST DISSOLVING FILMS[4]

Fast dissolving film consists of fast dissolving polymer film embedded with drug. Which Quickly hydrated and dissolves when placed on the tongue or in the oral cavity(i.e., ducal, Palatal, gingival, lingualor sublingual)to provide rapid local or systemic drug delivery without need of water. The fast dissolving film is also known as rapid dissolving film, quick dissolving film, mouth dissolving film or oral thin film. Basically the rapid dissolving film can be consider as an ultra thin film of postage stamp size with an active agent or active pharmaceutical ingredient (API) and other excipients. The advantages of convenience of dosing and portability of fast dissolving film have led to wider acceptability of this dosage form by pediatric as well as geriatric population equally.

The film reportedly incorporates soluble, insoluble or taste masked drug substance. The film is manufactured as a large sheet and then cut into individual dosage unit for packaging in a range of pharmaceutical acceptable formats.

These films generally dissolve rapidly (within seconds), to release the active agents, but can be tailored to release the drug more slowly as well, depending upon their thickness, and selection of the polymer matrix.

***Advantages of fast dissolving film.***[5, 6]

This dosage form enjoys some distinct advantages over other oral formulations such as-

- Availability of larger surface area that leads to rapid disintegrating and dissolution in the oral cavity.

- The disadvantage of most ODTs is that they are fragile and brittle which warrants special package for protection during storage and transportation. Since the films are flexible they are not as fragile as most of the ODTs. Hence, there is ease of transportation and during consumer handling and storage.

- As compared to drops or syrup formulations, precision in the administered dose is ensured from each of the films.

- Pharmaceutical companies and consumers alike have embraced fast dissolving film as a practical and accepted alternative to traditional over the counter (OTC) medicine forms such as liquids, tablets, and capsules. Fast dissolving film offer fast, accurate dosing in a safe, efficacious format that is convenient and portable, without the need for water or measuring devices.

- The oral or buccal mucosa being highly vascularised, drugs can be absorbed directly and can enter into the systemic circulation without undergoing first-pass hepatic metabolism. This advantage can be exploited in preparing products with improved oral bioavailability of molecules that undergo first pass effect.

- Since the first pass effect can be avoided, there can be reduction in the dose which can lead to reduction in side effects associated with the molecule.

- Patients suffering from dysphasia, repeated emesis, motion sickness, and mental disorders prefer this dosage form as they are unable to swallow large quantity of water.

***Ideal characteristics of a suitable drug candidate***

- The drug should have pleasant taste.
- Dose should be low as possible.
- The drugs with smaller and moderate molecular weight are preferable.
- Good stability in water and saliva.
- It should be partially unionized at the pH of oral cavity.

- It should have the ability to permeate oral mucosal tissue.[6]

The drug selected for present work is Cinnarizine. The drug is used in motion sickness, vomiting, vertigo and in meniers disease. It is white powder which is practically insoluble in water, Soluble in chloroform, ethanol (3mg/ml), DMSO, dimethyl formamide.

Cinnarizine has as half life of 3-4 hr and the bioavailability is 15 to 40%. The drug is extensively metabolised via CYP2D6. Therefore to improve bioavailability fast dissolving film is a good choice of drug administration.

## MATERIALS AND METHODS

Cinnarizine was received as a gift sample from Hikal labortary Ltd,Banglore .HPMC E5, PEG-400, Aspartame were received from S.D Fine Chemicals, Mumbai. The materials and reagents used in the study were of analytical grade.

### Drug excipient compatibility study

FTIR absorption spectra of pure drug and physical mixture were recorded in the range of 400 to 4000 cm-1 by KBr disc method using FTIR spectrophotometer. FTIR study was carried out individually for drug and polymers and physical mixture of drug with all polymers. FTIR spectra of physical mixture of drug with all polymers were compared with FTIR spectra of pure drug and polymers.[9]

### Preparation of fast dissolving film of cinnarizine

The composition of fast dissolving film was optimized by using $3^2$ full factorial design (table 1). In this study, two factors were evaluated each at three levels and experimental trials were performed at all nine possible combinations. The amounts of HPMC E5 (X1) and PEG-400 (X2) were selected as independent variables. These nine formulations were studied and optimized for disintegration time and % drug release.

### Solvent casting method

Polymer HPMC E5 (2%, 3%, 4%) were weighed accurately and dispersed in water Then calculated quantity of plasticizer (20%,30%,40%) was added and mixed well till clear solution was obtained. Then the drug was added to the polymeric solution. Then solution was poured into a clean and dry glass petri dish and allowed to dry. The dried films were carefully removed from the petri dish, checked for any imperfections or air bubbles and cut in to pieces of 4 $cm^2$.[6]

**Evaluation of fast dissolving film of cinnarizine**

***Thickness***

The thickness of the film was determined using a vernier calliper at three separate points of each film. From each formulation, three randomly selected films were tested for their thickness.[10]

***Tensile strength and % Elongation***

A tensile strength of film is total weight, which is necessary to break or rupture the dosage form and this was done by a device has rectangular frame with two plates made up of iron. The 4 $cm^2$ film equivalent to 25 mg drug from each formulation was taken. One end of the film was sandwiched between the iron plates and fixed. Other end was connected to a freely movable thread over a pulley. The weights were added gradually to the pan attached with the hanging end of the thread. The force needed to fracture the film was determined by measuring the total weight loaded in the pan. The weight corresponds to break the films were taken as tensile strength.[10]

The following equation was used to calculate the tensile strength (TS)

$$\boldsymbol{Tensile\ strength} = \frac{\text{Load X 100}}{\text{Thickness of film X Width}}$$

For determination of % elongation, the initial length of the film was measured on scale and a pointer is attached to freely movable thread. Increase in length at the time of break of the film was recorded and % elongation was calculated by following formula.[10]

$$\%\mathbf{Elongation} = \frac{\text{Increase in length}}{\text{Initial length}} \text{X 100}$$

Experiments were performed in triplicate and average value was reported.

***Folding endurance***

Folding endurance is determined by repeated folding of the strip at the same place till the strip breaks. The number of times the film is folded without breaking is computed as the folding endurance value.[11]

***In vitro disintegration studies***

Disintegration time gives an indication about the disintegration characteristics and dissolution Characteristics of the film. The film as per the dimensions (4 $cm^2$) required for dose delivery

was placed on a stainless steel wire mesh placed in a petridish containing 10 ml distilled water. Time required for the film to break was noted as *In vitro* disintegration time.[11]

***Drug content***

Three films were taken from each formulation and dissolved in 100ml isotonic phosphate buffer pH6.8. Then the solution was filter through whatman filter paper (0.45 µm). From the filtrate 1ml solution was taken and suitably diluted with isotonic phosphate buffer pH 6.8 and analyzed at 252 nm using a UV visible spectrophotometer. The experiments were performed in triplicate and average values were reported.[11]

***Percentage moisture absorption* (PMA)**

The PMA test was carried out to check the physical stability of the mouth dissolving film at high humid conditions. Three films were taken, weighed accurately and placed in a desiccator containing saturated solution of aluminium chloride, keeping the humidity inside the desiccators at 79.5 %. After 72 hours the films were removed, weighed and percentage moisture absorption was calculated by using the following formula.[12]

$$\mathbf{PMA} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \text{X100}$$

***Percentage Moisture Loss* (PML)**

Percentage moisture loss was calculated to check the integrity of films at dry condition. Three 1cm square films was cut out and weighed accurately and kept in desiccators containing fused anhydrous calcium chloride. After 72 hours the films were removed and weighed. The percentage moisture loss was calculated by using the following formula.[12]

$$\boldsymbol{PML} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \text{X100}$$

***In vitro* dissolution studies**

The in-vitro dissolution studies were conducted using dissolution media phosphate buffer (500 ml). The dissolution studies (n=3) were carried out using USP dissolution apparatus XXIV (Electrolab, Mumbai, India) at 37 ± 0.5 °C and at 50 rpm using specified dissolution media. Each film with dimension (2 x 2 $cm^2$) was placed on a stainless steel wire mesh (700 µm). The film sample was placed on the sieve and submerged into dissolution media. Samples containing 5 ml volume were withdrawn at 0, 2, 5, 10, 15, 20, 25 and 30 min time intervals and filtered through 0.45 µm Whatman filter paper and were analyzed spectrophotometrically at 252 nm. To maintain the volume, an equal volume of fresh dissolution medium, maintained at same

temperature was added after withdrawing samples. The absorbance values were converted to concentration using standard calibration curve previously obtained by experiment.[13]

***Stability study***

Stability testing of promising formulation was done by subjecting the films from optimized formulation at 40 °C temperature and 75% RH for one month. After 1 month samples were withdrawn and evaluated for physical appearance, drug content, tensile strength, % elongation, folding endurance, % drug release study as discussed earlier.[10]

**RESULT AND DISCUSSION**

**Drug Excipient Compatibility**

Drug- Excipient interaction study Infrared spectroscopy was used as means of studying drug-excipients interactions. It was found that there was no chemical interaction between cinnarizine and excipients used because there were no changes in the characteristic peaks of cinnarizine in the IR spectra of mixture of drug and excipients as compared to IR spectra of pure drug.(Figure no.1 and 2)

**EVALUATION OF FACTORIAL DESIGN FORMULATIONS (F1 TO F9)**

***Uniformity of Thickness***

Results of uniformity of thickness are given in table 2. Results indicate that thickness increases as the polymer concentration increases. The thickness of prepared films was in the range of 0.090 ± 0.03 to 0.210 ± 0.02 mm. In all the cases the calculated standard deviation values were very low suggesting the prepared films were uniform in thickness and ensuring suitability of solvent casting method for the preparation of fast dissolving films.

***Tensile Strength***

The results of tensile strength from various formulations (F1 to F9) are given in table 2.Tensile strength of all the films was in the range of 152±4.53 to 230±4.52 gm/cm$^2$ with very low values of standard deviation suggesting all films were having good mechanical strengths to withstand mechanical damage during, production and application.

***% Elongation***

The results of % elongation from various formulations (F1 to F9) are given in table 2. The results revealed that % elongation was in the range of 3.52±2.09 to 4.75±3.12. This represents the elasticity of the film. Increase in concentration of HPMC E5 results in enhancement of elasticity of films.

***Folding Endurance***

The results of folding endurance of various formulations (F1 to F9) are given in table 2.All the films were showing folding endurance in the range of 94±2.08 to 117±0.12. Results revealed that as the concentration of polymers increases folding endurance increases.

***Disintegration Time***

The results of disintegration time of various formulations (F1 to F9) are given in table 2. All the films were showing disintegration time in the range of 16.03±0.15 to 20.12±1.02. Results revealed that as the concentration of polymers increases disintegration time increases.

***Uniformity of Weight***

The results of uniformity of weight are given in table 3.The weight of prepared films (F1 to F9) was in the range of 59.31±0.07 to 68.19±0.02 mg. In all the cases the calculated standard deviation values were very low which suggest that the prepared films were uniform in weight.

***% Moisture Absorption***

The results of % moisture absorption of various films are given in table 3. The results indicate that % moisture absorption of films were in the range of 1.52 ± 0.549 to 1.99± 0.031. The standard deviation values were very less suggesting that the drug absorbed low moisture content.

***% Moisture Loss***

The results of % moisture loss of various films are given in table 3. The results indicate that % moisture loss of films were in the range of 1.01 ± 0.015 to 1.53± 0.517. The standard deviation values were very less suggesting that the drug lost low moisture content.

***In Vitro Drug Release Study***

It can be seen from the table 4 and figure 3 that the cumulative % drug release from the formulations F1, F2, F3, F4, F5, F6, F7, F8 and F9 was found to be 93.41±0.96, 97.03±1.09, 96.38±0.89, 96.11±1.09, 98.46±2.31, 96.88±0.99, 95.46±1.10, 95.83±0.83, 94.53±1.06 at the end of 30 min respectively. The results suggest that HPMC E5 plays an important role in the release of drug from the films. Films having lower concentration of HPMC E5 showed higher values of drug release as compared to films having higher amount of HPMC E5. Formulation F5 showed the highest value of drug release of 98.46 ± 2.31%.

***Stability study***

The promising formulation F5 was subjected at 40 ± 0.5 °C temperature and 75 ± 5 % RH for 1 month to check the stability. The results of physical appearance, drug content, disintegration time and other parameters after 1 month storage of prepared fast dissolving films are shown in table 5 and % drug release is shown in table 6.

**CONCLUSION**

The formulation F5 satisfied all pharmaceutical parameters of fast dissolving films and appears to be promising would be able to offer benefits such as rapid drug release, good disintegration time, tensile strenght and promising % elongation and thereby may help to improve the bioavailability of drug.

**Table 1: Composition of factorial design formulations of cinnarizine**

| Batch | Drug (mg) | HPMC E5 (%w/v) | PEG 400 (%w/w of Dry polymer) | Citric Acid (mg) | Aspartame (mg) | Orange (ml) | Water (ml) |
|---|---|---|---|---|---|---|---|
| F1 | 208.17 | 3% | 20% | 30 | 20 | 0.5 | 10 |
| F2 | 208.17 | 4% | 20% | 30 | 20 | 0.5 | 10 |
| F3 | 208.17 | 5% | 20% | 30 | 20 | 0.5 | 10 |
| F4 | 208.17 | 3% | 30% | 30 | 20 | 0.5 | 10 |
| F5 | 208.17 | 4% | 30% | 30 | 20 | 0.5 | 10 |
| F6 | 208.17 | 5% | 30% | 30 | 20 | 0.5 | 10 |
| F7 | 208.17 | 3% | 40% | 30 | 20 | 0.5 | 10 |
| F8 | 208.17 | 4% | 40% | 30 | 20 | 0.5 | 10 |
| F9 | 208.17 | 5% | 40% | 30 | 20 | 0.5 | 10 |

**Table 2: Physicochemical evaluation of fast dissolving film of cinnarizine**

| Batch | Thickness (mm)* | Tensile Strength ($gm/cm^2$)* | % Elongation* | Folding Endurance* | Disintegration Time(sec)* |
|---|---|---|---|---|---|
| F1 | 0.090±0.03 | 152±4.53 | 3.52±2.09 | 94±2.08 | 16.03±0.15 |
| F2 | 0.100±0.09 | 164±3.52 | 3.71±0.39 | 95±0.03 | 20.12±1.02 |
| F3 | 0.105±0.14 | 172±1.41 | 3.87±0.52 | 97±0.11 | 17.77±0.49 |
| F4 | 0.102±0.01 | 180±1.74 | 4.09±3.12 | 99±0.01 | 18.23±0.92 |
| F5 | 0.109±0.17 | 189±3.52 | 4.32±0.82 | 109±0.23 | 18.00±1.11 |
| F6 | 0.116±0.27 | 196±2.52 | 4.45±1.11 | 112±0.15 | 17.33±0.29 |
| F7 | 0.123±0.10 | 209±2.43 | 4.59±0.87 | 114±0.15 | 17.8±0.19 |

| | | | | | |
|---|---|---|---|---|---|
| F8 | 0.140±0.07 | 220±3.87 | 4.69±3.52 | 116±0.11 | 20.08±0.51 |
| F9 | 0.210±0.02 | 230±4.22 | 4.75±2.12 | 117±0.12 | 19.02±0.30 |

*Values are means ± SD, (n=3).

**Table 3: Evaluation of prepared film**

| Batch | Uniformity of Weight (mg)* | Drug Content* | %Moisture Absorption* | %Moisture Loss* |
|---|---|---|---|---|
| **F1** | 59.31±0.07 | 94.71±0.03 | 1.70 ± 0.590 | 1.37 ± 0.598 |
| **F2** | 61.67±0.18 | 96.32±0.25 | 1.66 ± 0.554 | 1.01 ± 0.015 |
| **F3** | 62.11±0.24 | 95.29±0.06 | 1.99 ± 0.031 | 1.34 ± 0.592 |
| **F4** | 65.58±0.19 | 97.45±0.11 | 1.60 ± 0.572 | 1.29 ± 0.580 |
| **F5** | 66.42±0.01 | 97.32±0.12 | 1.87 ± 0.930 | 1.25 ± 0.537 |
| **F6** | 68.27±0.32 | 96.57±0.03 | 1.82 ± 0.025 | 1.22 ± 0.525 |
| **F7** | 65.43±0.18 | 94.28±0.21 | 1.52 ± 0.549 | 1.53 ± 0.517 |
| **F8** | 66.39±0.05 | 96.39±0.02 | 1.85 ± 0.528 | 1.30± 0.514 |
| **F9** | 68.19±0.02 | 97.99±0.34 | 1.88± 0.509 | 1.44 ± 0.508 |

*Values are means ± SD, (n=3).

**Table 4: In vitro cumulative % drug release in phosphate buffer pH 6.8**

| Time (min) | F1 | F2 | F3 | F4 | F5 |
|---|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 | 0 |
| 2 | 24.47±0.98 | 23.59±1.01 | 28.3±1.70 | 27.08±3.21 | 29.70±1.12 |
| 5 | 52.72±1.12 | 49.50±2.87 | 47.31±1.03 | 52.70±1.24 | 54.45±1.36 |
| 10 | 65.5±0.93 | 62.63±2.36 | 60.20±2.46 | 64.98±2.11 | 65.51±1.97 |
| 15 | 76.67±1.03 | 72.39±1.78 | 66.85±2.11 | 76.32±2.00 | 78.35±0.87 |
| 20 | 89.76±2.04 | 83.26±3.21 | 79.97±0.68 | 89.50±1.94 | 89.62±0.93 |
| 25 | 95.39±1.34 | 89.44±0.54 | 88.31±0.98 | 94.86±1.08 | 96.28±1.02 |
| 30 | 93.41±0.96 | 97.03±1.09 | 96.38±0.89 | 96.11±1.09 | 98.46±2.31 |

| Time(min) | F6 | F7 | F8 | F9 |
|---|---|---|---|---|
| **0** | 0 | 0 | 0 | 0 |
| **2** | 26.4±0.98 | 20.10±1.06 | 19.82±0.79 | 17.48±1.09 |
| **5** | 49.03±1.03 | 47.31±1.23 | 48.92±3.10 | 48.36±1.36 |
| **10** | 60.77 ±1.39 | 59.60±0.79 | 62.3±2.54 | 59.43±2.67 |
| **15** | 72.12±1.86 | 66.62±1.84 | 71.92±1.36 | 66.86±2.00 |
| **20** | 81.04±2.54 | 79.55±0.87 | 81.10±2.03 | 79.73±1.90 |
| **25** | 88.06±0.72 | 88.01±0.90 | 87.81±0.86 | 86.81±0.86 |

| | | | | |
|---|---|---|---|---|
| **30** | 96.88±0.99 | 95.46±1.10 | 95.83±0.83 | 94.53±1.06 |

*Values are means ± SD, (n=3).

**Table 5: Stability study of promising batch F5**

| Parameter | At 0 day | After 30 days |
|---|---|---|
| Appearance | Good | No change |
| Drug content | 97.32 ± 0.12 | 97.05 ± 0.27 |
| Disintegration time (min.) | 18.00± 1.11 | 18.69 ± 2.32 |
| Tensile strength (gm/cm$^2$) | 189± 3.52 | 188.67 ± 1.53 |
| % elongation | 4.32 ± 1.11 | 4.44± 2.12 |
| Folding endurance | 109± 0.23 | 109± 3.06 |
| Weight uniformity | 66.42± 0.01 | 66.30±1.23 |

The results of % cumulative drug release of promising formulation (F5) after 1 month of storage is shown in table 6.

**Table 6: *In vitro* % drug release of F5 at 0 day and after 30 days**

| Time (min.) | %Cumulative Release | |
|---|---|---|
| | **At o day** | **After 30 days** |
| **0** | 0.00 ± 0.000 | 0.00 ± 0.000 |
| **2** | 29.70±1.12 | 27.02± 0.137 |
| **5** | 54.45± 1.36 | 53.23± 0.896 |
| **10** | 65.51± 1.97 | 63.14± 1.067 |
| **15** | 78.35± 0.87 | 76.12± 0.936 |
| **20** | 89.62± 0.93 | 86.56± 1.009 |
| **25** | 94.86± 1.08 | 92.75± 0.861 |
| **30** | 98.46±2.31 | 96.21±0.012 |

*Values are means ± SD,(n=3).

**IR Spectroscopy of drug**

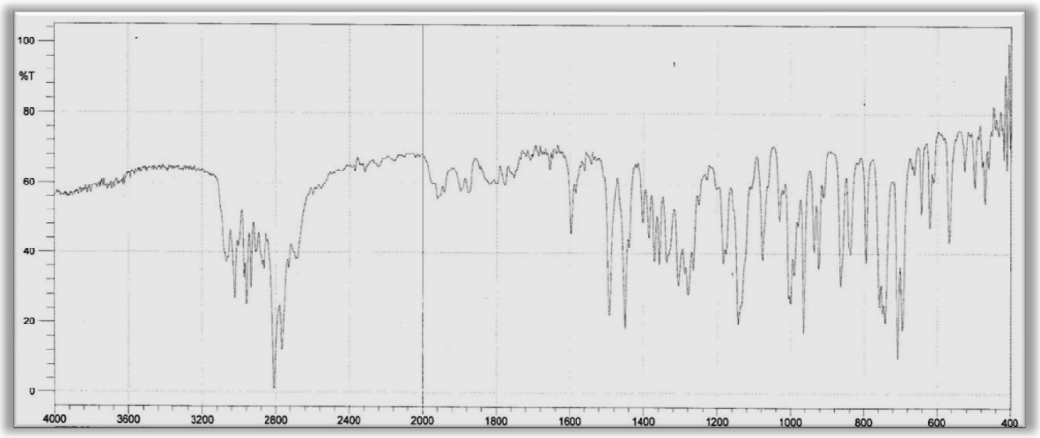


**Figure 1: FTIR Spectra of cinnarizine**

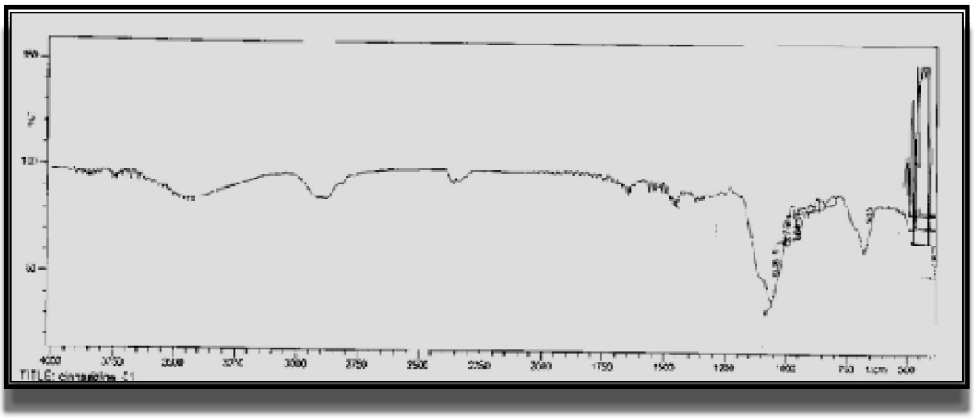

**Figure 2: Comparison of interpretation of FTIR spectra of cinnarizine and physical mixture**

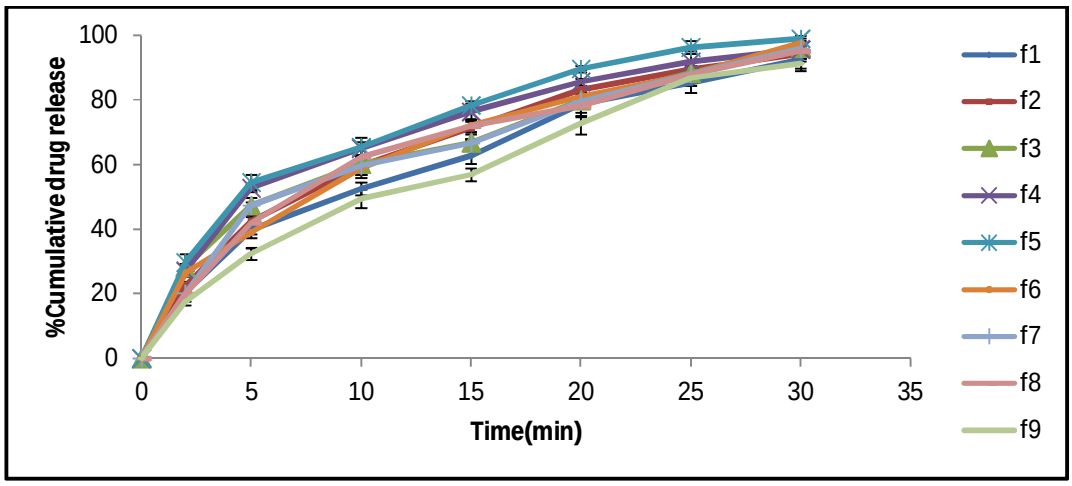


**Figure 3: *In vitro* dissolution of cinnarizine from formulation F1 to F9**

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