Research Article

Formulation and *In Vitro* Evaluation of Mouth Dissolving Tablets of Venlafaxine Hydrochloride

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ABSTRACT

The purpose of the present investigation is to formulate mouth dissolving tablets of venlafaxine HCl, a novel antidepressant by direct compression method using microcrystalline cellulose as directly compressible filler. The drug-excipients compatability was ruled out through FTIR studies. Nine formulations of mouth dissolving tablets of venlafaxine HCl were prepared using sodium starch glycolate, crospovidone and croscarmellose sodium as superdisintegrants in different concentrations of 2, 3.5 and 5% w/w. The prepared tablets were evaluated for thickness, hardness, friability, weight variation, drug content *and in vitro dispersion time, wetting time, water absorption ratio, in vitro* drug release and stability. All the evaluation parameters were found to be within the limits of IP specifications. The disintegration time was found to be linearly decreases with the increase in the amount of superdisintegrant, where as the dissolution rate linearly increases. One amongst nine promising formulations, the formulations prepared by using of crospovidone emerged as overall the best formulation. This optimized formulation showed good release profile with complete drug release within 20 min. The release profile and drug content were remained unchanged after stability studies. It was concluded that mouth dissolving tablets of venlafaxine HCl can be successfully formulated by superdisintegrant addition method with improved patient compliance.

Keywords: Mouth dissolving tablets, Venlafaxine HCl, Superdisintegrants, Direct compression, Stability studies

INTRODUCTION

Oral routes of drug administration have wide acceptance up to 50-60% of total dosage forms. Solid dosage forms are popular because of ease of administration, accurate dosage, self-medication, pain avoidance and most importantly the patient compliance[1]. The most popular solid dosage forms are being tablets and capsules; one important drawback of this dosage forms for some patients, is the difficulty to swallow[2]. Drinking water plays an important role in the swallowing of oral dosage forms.

Often times people experience inconvenience in swallowing conventional dosage forms such as tablet when water is not available, in the case of the motion sickness (kinetosis) and sudden episodes of coughing during the common cold, allergic condition and bronchitis[3]. For these reasons, tablets that can rapidly dissolve or disintegrate in the oral cavity have attracted a great deal of attention.

Mouth dissolving tablets are not only indicated for people who have swallowing difficulties, but also are ideal for active people. Mouth dissolving tablets are also called as fast dissolving tablets, melt-in mouth tablets, orodispersible tablets, rapimelts, porous tablets, quick dissolving etc. Fast dissolving tablets are those when put on tongue disintegrate instantaneously releasing the drug which dissolves or disperses in the saliva[4]. The faster the drug into solution, quicker the absorption and onset of clinical effect. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach[5]. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablets dosage form. The advantage of mouth dissolving dosage forms are increasingly being recognized in both, industry and academics. The basic approach in development of Mouth dissolving tablet is the use of superdisintegrants like cross linked carboxymethyl cellulose (croscarmellose), sodium starch glycolate (primogel, explotab), polyvinylpyrollidone (polyplasdone) etc, which provide instantaneous disintegration of tablet after putting on tongue, their by release the drug in saliva. The bioavailability of some drugs may be increased due to absorption of drug in oral cavity and also due to pregastric absorption of saliva containing dispersed drugs that pass down into the stomach. More ever, the amount of drug that is subjected to first pass metabolism is reduced as compared to standard tablet[6].

Selected drug venlafaxine HCl is not available as mouth dissolving formulation in market. The type of formulation play very important factor for the patients, who really in need of this type of the formulation. Especially these formulations are designed with using sweetening agents (aspartame) and flavors (vanilla, pineapple) which still make more compliance with taste and smell. These products are indicated for the treatment of depressive illness including depression accompanied by anxiety. Following an initial response venlafaxine is indicated for the prevention of relapses of the initial episode of depression or for the prevention of the recurrence of new episodes. Venlafaxine tablets contain the active ingredient venlafaxine, as venlafaxine HCl, which is an anti-depressant. Usually the mouth dissolving tablets are

formulated by various techniques like freeze drying technique, WOW technique, Durasolv technique, etc. But in the design of the formulation of mouth dissolving tablets of venlafaxine HCl is majorly focused on direct compression which is cost effective when compared to other technologies.

Advantages of Mouth Dissolving Tablets[7]

- Patient's compliance for disabled bedridden patients and for travelling and busy people who do not have ready access to water.
- Good mouth feel property of MDDS helps to change the basic view of medication as "bitter pill", particularly for paediatric patients due to improved taste of bitter drugs.
- Convenience of administration and accurate dosing as compared to liquid formulations.
- Benefit of liquid medication in the form of solid preparation.
- More rapid drug absorption from the pre-gastric area i.e. mouth, pharynx and esophagus which may produce rapid onset of action.
- Pregastric absorption can result in improved bioavailability, reduced dose and improved clinical performance by reducing side effects.

Disadvantages of Mouth Dissolving Tablets

In most cases the fast dissolving tablets lack the mechanical strength common to traditional tablets. Many products are very lightweight and fragile requiring them to be individually packaged. Patients should be advised not to push these tablets through the foil film, but instead, peel the film back to release the fast-dissolving tablet.

Due to the formulation of fast dissolving tablets, which are also more susceptible to degradation via temperature and humidity, some of the newer fasts dissolving tablet formulations are dispensed in a conventional stock bottle. Pharmacists are advised to take care when dispensing such formulations to ensure they are not exposed to high levels of moisture or humidity.

Excess handling of tablets can introduce enough moisture to initiate dissolution of tablet matrix.

Ideal Properties of Mouth Dissolving Tablets[8,9]

- Not require water to swallow and should dissolve or disintegrate in the mouth within a few seconds.
- Allow high drug loading.
- Be compatible with taste masking and other excipients.
- Have a pleasing mouth feel.
- Leave minimal or no residue in the mouth after oral administration.
- Have sufficient strength to withstand the rigors of the manufacturing process and post manufacturing handling.
- Exhibit low sensitivity to environmental conditions such as humidity and temperature.
- Be adaptable and amenable to existing processing and packaging machinery.
- Allow the manufacture of tablets using conventional processing and packaging equipments at low cost.

MATERIALS AND METHODS

Materials

Venlafaxine HCl, Croscarmelose sodium, Sodium starch glycolate, Crospovidone, Microcrystalline cellulose, Talc, Magnesium stearate, Aspartame and Pineapple flavor.

Optimization of dose of Venlafaxine HCl for the preparation of Mouth Dissolving Tablets

In this work, superdisintegrant method was attempted for the formulation development. The venlafaxine tablets are available in 25, 37.5, 75, and 150 mg doses in the market. Dose of 25 mg is selected for the present study.

Dose was calculated by considering the molecular weight which indicates that 25 mg of venlafaxine base is equivalent to 28.2 mg of venlafaxine HCl.

Development of the formulation in the present study was mainly based on the type and concentration of polymers and the properties of the drug.

Various polymers in different combinations were used so as to get tablets with good physical properties. The direct compression technique is preferred for making tablets. Therefore, a pharmaceutical composition containing venlafaxine HCl suitable for generating tablets using direct compression would be much appreciated.

Drug–polymer Compatibility Studies

In the preparation of tablets formulation, drug and polymer may interact as they are in close contact with each other, which could lead to the instability of drug. Preformulation studies regarding the drug-polymer interaction are therefore very critical in selecting appropriate polymers.

FT-IR spectroscopy was employed to ascertain the compatibility between venlafaxine HCl and the selected polymers. Potassium bromide, pure drug, and the polymers were heated to 105°C for one hour to remove the moisture content if present in a hot air oven.

Then in presence of IR lamp, potassium bromide was mixed with drug and/or polymer in 9:1 ratio and the spectra were taken. FT-IR spectrum of venlafaxine HCl was compared with FT-IR spectra of venlafaxine HCl with polymers.

Formulation of Venlafaxine HCl Mouth Dissolving Tablets

Venlafaxine HCl tablets were manufactured for the nine batches F-I to F-IX using the ingredients mentioned in the materials and methods section keeping the total weight (150 mg) of the tablet constant in all the formulations. The direct compression technique was used to manufacture the tablets. The drug and the excipients were passed through #60-sieve. Weighed amount of drug and excipients except magnesium stearate were mixed in a polybag by geometric addition method for 20 minutes manually. The blend was then lubricated by further mixing with magnesium stearate (#60-sieve). All the above ingredients were subjected for drying to remove the moisture content at 40 to 45°C, the mixture was blended with flavor and the powder blend was then compressed on 10-station rotary punching machine using flat faced punches. Round punches measuring 8 mm diameter were used for compression of tablets.

Evaluation of Venlafaxine HCl Mouth Dissolving Tablets

The tablets after punching of every batch were evaluated for in-process and finished product quality control tests i.e thickness, weight uniformity test, hardness, friability, drug content, *in vitro* dispersion, water absorption ratio, wetting time, *in vitro* drug release and stability studies.

Thickness

Thickness of the tablets was measured using Digimatic micrometer (Mitutuyo, Japan). The values of thickness were used to adjust the initial stages of compression.

Weight Variation Test

Twenty tablets were weighed individually and all together. Average weight was calculated from the total weight of all tablets. The individual weights were compared with the average weight.

The percentage difference in the weight variation should be within the permissible limits (±7.5%). The percent deviation was calculated using the following formula:

$$Percentage\ Deviation = \frac{Individual\ weight - Average\ weight}{Average\ weight} \times 100$$

Any variation in the weight of tablet (for any reason) leads to either under medication or over medication. So, every tablet in each batch should have a uniform weight. Deviation within the IP permissible limits of ±7.5% is allowed as the tablet weighs 150 mg. Corrections were made during the compression of tablets to get uniform weight[10,11].

Hardness Test

Hardness is a force required to break a tablet across the diameter. The hardness of a tablet is an indication of its strength. The tablet should be stable to mechanical stress during handling and transportation.

The degree of hardness varies with the different manufactures and with the different types of tablets. The hardness was tested using Monsanto tester. The force was measured in Kg/cm^2.

Friability Test

Friability is the loss of weight of tablet in the container/package, due to removal of fine particles from the surface. This in process quality control test is performed to ensure the ability of tablets to withstand the shocks during processing, handling, transportation, and shipment. Permitted friability limit is 1.0 %. Roche friabilator (Electrolab, Mumbai) was used to measure the friability of the tablets. Ten tablets were weighed collectively and placed in the chamber of the friabilator. In the friabilator, the tablets were exposed to rolling, resulting free fall of tablets (6 inches) within the chamber of the friabilator. It was rotated at a rate of 25 rpm. After 100 rotations (4 minutes), the tablets were taken out from the friabilator and intact tablets were again weighed collectively[12]. The percent friability was determined using the following formula:

$$Friability = \frac{W_1 - W_2}{W_1} \times 100$$

where, W1 = weight of the tablet before test, W2 = weight of the tablets after test

Percentage Drug Content

Three tablets were selected randomly and average weight was calculated. Tablets were crushed in a mortar and accurately weighed amount of tablet powder was taken from the crushed blend. Then the samples were transferred to three 100 ml volumetric flasks and were diluted up to the mark with phosphate buffer (pH 6.8) solution. The contents were shaken periodically and kept for 24 hours for solvation of drug completely.

The mixtures were filtered, appropriately diluted and absorbance was measured at 224.8 nm against blank reference. The drug content in each tablet was calculated[13].

In vitro Dispersion Time

In vitro dispersion time was measured by dropping a tablet into a Petri dish containing 10 ml of phosphate buffer solution, pH 6.8 (simulated saliva fluid). Three tablets from each formulation were randomly selected and tested. *In vitro* dispersion time was found and expressed in seconds.

Wetting Time and Water Absorption Ratio

Wetting time of dosage form is related with the contact angle. Wetting time of the mouth dissolving tablets is another important parameter, which needs to been assessed to give an insight into the disintegration properties of the tablets; a lower wetting time implies a quicker disintegration of the tablet. The wetting time of the tablet can be measured using a simple procedure.

Two circular tissue papers of 10 cm diameter are placed in a petridish having the same inner diameter. Ten ml of

phosphate buffer solution, 6.8 pH containing Eosin, a water soluble dye, is added to petridish.

A tablet is carefully placed on the surface of the tissue paper so that complete tablet was not immersed in the solution. Then, the time required for buffer to reach upper surface of the tablet is noted as wetting time[13].

Water absorption ratio (R) is calculated using the formula:

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

where, Wa = weight of tablet after absorption, Wb = weight of tablet before absorption

In vitro Drug Release

In vitro drug release of the samples was carried out using USP – type II dissolution apparatus (paddle type). The dissolution medium, 900 ml of phosphate buffer (pH 6.8) solution, was placed into the dissolution flask maintaining the temperature of 37±0.5°C and rpm of 50. One Venlafaxine HCl tablet was placed in each flask of dissolution apparatus. The apparatus was allowed to run for 30 min. Samples measuring 5 ml were withdrawn after every 5 minutes and continued for 30 minutes. Samples were filtered through 10 µm filter.

The fresh dissolution medium was replaced every time with the same quantity of the sample. The collected samples were analyzed at 224.8 nm using dissolution medium as blank. The cumulative percentage drug release was calculated[14].

Stability Studies

Stability is defined as the ability of a particular drug or dosage form in a specific container to remain within its physical, chemical, therapeutic, and toxicological specifications.

Drug decomposition or degradation occurs during storage, because of chemical alteration of the active ingredients or due to product instability, lowering the concentration of the drug in the dosage form. The stability of pharmaceutical preparation should be evaluated by accelerated stability studies. The optimized formulation of venlafaxine HCl tablets was selected for the stability studies.

The accelerated stability studies were carried out according to ICH guidelines by storing the samples at 40 ± 2°C and 75 ± 5% RH for 1 month. The tablets were evaluated for hardness, drug content, and dissolution study and compared with tablets which were evaluated immediately after manufacturing[15].

RESULTS AND DISCUSSION

Mouth dissolving tablets of venlafaxine HCl were developed with a view to deliver the drug in a rapid manner. The Drug-polymer compatibility was ruled out from FTIR studies.

The peaks obtained indicated that there was no interaction of drug with polymers used. A total of nine formulations (FI-FIX) were prepared with three different superdisintegrants in different concentrations. The formulation of venlafaxine HCl tablets is shown in Table 1.

All the formulated tablets were examined for evaluation parameters thickness, friability, hardness, weigh variation, content uniformity, *in vitro* dispersion time, wetting time, water absorption ratio and *in vitro* drug release studies.

The results of evaluation parameters were found to be within the standard specifications. The results of the evaluation parameters are shown in Table 2 and Table 3. The thickness of all the formulated tablets was found to be 2.48-2.53mm.

The hardness of formulated tablets was found to be 2.3-3.3 kg/cm^2. The friability of all the tablets was found to be 0.31- 0.71%, which is less than 1 %.

The weigh variation of all the formulated tablets was within the limit of ± 7.5%. The % drug content of all the formulated tablets was found to be 99-101.80 %. The wetting time of tablets was found to be 34.30-159.6 seconds and water absorption ratio was 47.37-108.22 seconds.

Table 1: Formulation of mouth dissolving tablets of Venlafaxine HCl

Ingredients (mg)	F-I	F-II	F-III	F-IV	F-V	F-VI	F-VII	F-VIII	F-IX
Venlafaxine HCl	28.2	28.2	28.2	28.2	28.2	28.2	28.2	28.2	28.2
Sodium starch glycolate	3	5.25	7.5	---	---	---	---	---	---
Croscarmelose sodium	---	---	---	3	5.25	7.5	---	---	---
Crospovidone	---	---	---	---	---	---	3	5.25	7.5
Talc	12	12	12	12	12	12	12	12	12
Aspartame	5	5	5	5	5	5	5	5	5
Flavour	3	3	3	3	3	3	3	3	3
Magnesium sterate	4	4	4	4	4	4	4	4	4
Microcrystalline cellulose (q.s)	150	150	150	150	150	150	150	150	150

Table 2: Results of thickness, hardness, friability, weight variation and drug content for Venlafaxine HCl tablets

Formulation code	Thickness (mm)*	Hardness (kg/cm^2)*	Friability* (%)	Weight variation (mg)	Drug content (%)
F-I	2.52 ± 0.06	3.2 ± 0.2	0.30 ± 0.04	150.47	99.65
F-II	2.51 ± 0.05	2.8 ± 0.3	0.36 ± 0.03	149.64	99.43
F-III	2.53 ± 0.01	3.0 ± 0.2	0.44 ± 0.06	150.36	101.80
F-IV	2.50 ± 0.05	3.1 ± 0.5	0.31 ± 0.03	148.60	99.73
F-V	2.49 ± 0.07	3.3 ± 0.3	0.37 ± 0.02	149.30	99.74
F-VI	2.48 ± 0.07	3.2 ± 0.3	0.31 ± 0.04	149.45	100.70
F-VII	2.51 ± 0.02	3.1 ± 0.6	0.67 ± 0.03	149.80	99.00
F-VIII	2.52 ± 0.04	3.1 ± 0.3	0.43 ± 0.04	150.40	99.64
F-IX	2.50 ± 0.05	2.3 ± 0.3	0.71 ± 0.05	149.87	99.20

***** Each value is a mean ± SD of three trials

Table 3: Results of *In vitro* dispersion time, wetting time and water absorption ratio of Venlafaxine HCl tablets

Formulation code	*In vitro* dispersion time* (seconds)	Wetting time* (seconds)	Water absorption* ratio (%)
F- I	128.50 ± 0.90	133.26 ± 1.40	75.82 ± 2.42
F- II	83.93 ± 1.77	90.06 ± 1.61	101.95 ± 2.06
F- III	56.50 ± 0.82	58.06 ± 0.82	108.22 ± 3.40
F- IV	154.13 ± 1.41	159.60 ± 1.85	47.37 ± 2.50
F- V	113.60 ± 2.06	117.56 ± 2.11	54.73 ± 0.42
F- VI	77.27 ± 2.67	82.00 ± 1.85	60.19 ± 3.26
F- VII	73.55 ± 1.80	129.60 ± 1.90	66.71 ± 2.86
F- VIII	35.57 ± 1.01	58.20 ± 2.41	95. 13 ± 2.39
F- IX	26.65 ± 0.83	34. 30 ± 1.88	99. 31 ± 2.32

***** Each value is a mean ± SD of three trials

Table 4: Results of *In vitro* drug release studies for Venlafaxine HCl tablets

Time (min)	% Cumulative drug release								
	F-I	F-II	F-III	F-IV	F-V	F-VI	F-VII	F-VIII	F-IX
0	0	0	0	0	0	0	0	0	0
5	21.13± 2.62	44.17± 2.07	46.00± 1.95	26.72± 0.53	31.36± 1.19	46.67± 0.78	44.81± 0.84	47.06± 0.63	65.94± 0.74
10	30.37± 1.02	54.94± 1.21	58.96± 1.56	31.26± 0.33	39.71± 1.19	53.55± 0.66	57.68± 2.58	61.00± 0.88	73.12± 1.20
15	36.83± 2.92	72.65± 1.49	70.97± 1.27	40.49± 0.54	44.64± 1.90	60.02± 1.19	72.85± 1.00	74.68± 0.65	84.57± 1.90
20	46.40± 1.17	74.93± 1.25	74.12± 0.53	53.56± 1.08	50.84± 1.11	66.65± 0.18	80.87± 1.38	82.21± 1.22	100.24± 1.53
25	49.54± 2.07	79.60± 0.66	83.18± 0.80	60.94± 0.43	57.10± 0.84	72.14± 0.59	87.06± 1.03	88.02± 1.53	---
30	58.40± 0.38	86.54± 0.61	90.53± 0.84	70.98± 1.28	73.87± 1.22	76.64± 1.34	91.80± 0.28	91.80± 0.28	---

Table 5: Results of parameters of stability studies for optimized formulation of Venlafaxine HCl tablets (F-IX)

Evaluation parameter	On zero day	After 10 days	After 20 days	After 30 days
Thickness* (mm)	2.4±1.12	2.3±1.45	2.4±2.08	2.5±2.54
Hardness* (kg/cm^2)	3.1±0.65	3.2±1.22	3.0±0.34	3.1±0.43
In vitro dispersion time* (sec)	32.83±1.33	31.11±2.76	30.80±1.98	33.74±1.87
Wetting time* (sec)	28.43±0.67	26.61±1.09	26.35±0.32	24.38±0.43
Water absorption ratio*(sec)	99.12±1.43	100.55±2.03	98.93±0.78	99.48±1.65
Drug content (%)	98.87	99.03	99.76	99.12

***** Each value is a mean ± SD of three trials

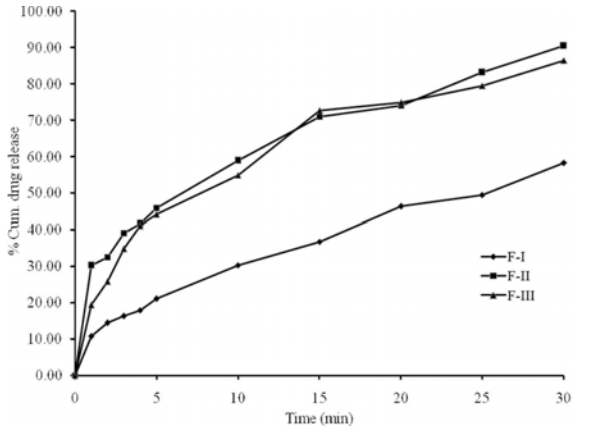

Figure 1: Dissolution profile of Venlafaxine HCl tablets formulated with sodium starch glycolate (F-1, F-II & F-III)

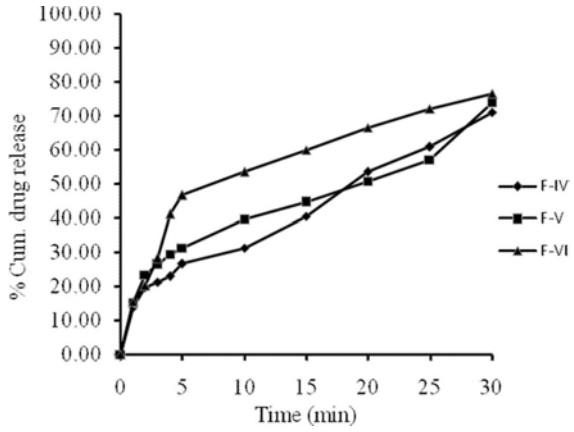

Figure 2: Dissolution profile of Venlafaxine HCl tablets formulated with croscarmelose sodium (F-IV, F-V & F-VI)

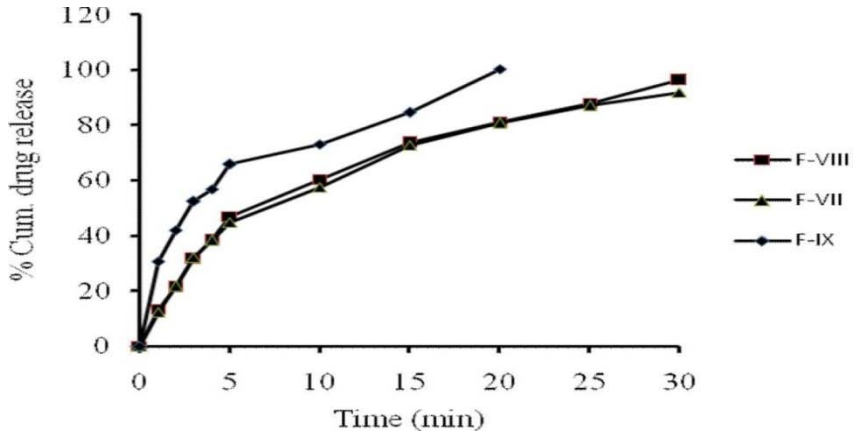

Figure 3: Dissolution profile of Venlafaxine HCl tablets formulated with crospovidone (F-VII, F-VIII & F-IX)

In vitro Drug Release Studies

The tablets formulated with sodium starch glycolate (F-I, F-II and F-III) showed 58.40, 86.54 and 90.53 % of drug release in 30 min, respectively. Drug release profile of all these formulations did not show 100 % drug release within 30 minutes.

The tablets formulated with Croscarmellose Sodium (F-IV, F-V and F-VI) showed 70.98, 73.82 and 76.64 % of drug release in 30 minutes respectively. Drug release profile of all these formulations did not show 100 % drug release within 30 minutes.

The tablets of F-VII and F-VIII have shown 91.80 and 96.31% of drug release in 30 min, respectively. However, the tablets of F-IX have shown complete drug release in 20 minutes.

Drug release profile of F-IX of the formulations mentioned above closer to the 100 % drug release.

As F-VII showed 91.80 % in 30 min, F-VIII showed 96.31 % in 30 min and F-IX showed 100.24 % of drug release in 20 min.

The data of *in vitro* drug release for all the formulations is shown in Table 4 and the dissolution profiles of the formulations were shown in Figure 1,2 and 3 respectively.

Stability Studies

Mouth dissolving tablets of F-IX were kept for accelerated stability study at 40 ± 2°C and 75 ± 5 %RH for 1 month using desiccator and hot air oven. After a period of one

month, the samples were observed for any change in physical parameters. The drug content of the formulations was found 99.30% for tablets of F-IX, which shows that, there is no decrease in drug content and difference is insignificant. The tablets of F-IX were subjected for the thickness, friability, hardness, *in vitro* dispersion, wetting time, weight variation, % drug content and dissolution studies are carried out during stability testing. The parameters were found to be within the limits. The data for the results of valuation parameters is shown in Table 5.

CONCLUSION

From all the above observations, it was concluded that the formulation F-IX containing 5% of Crospovidone was found to be better formulation in terms of rapid disintegration and maximum percentage drug release when compared with all other formulations. This optimized formulation also showed all the parameters without any variation after subjecting to stability studies for a period of 30 days. Prepared tablets disintegrate within few seconds without need of water; thereby enhance absorption leading to increase bioavailability. Thus, the present study demonstrated potentials for rapid absorption, improved bioavailability, effective therapy and increased patient compliance.

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