



Mouth Dissolving Tablets of Favipiravir using Superdisintegrants: Preparation, Optimization and *In-vitro* Evaluation

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

To formulate and evaluate the mouth dissolving tablet dosage forms of favipiravir using various superdisintegrants by using wet granulation technique.

Batches of favipiravir Mouth dissolving tablets were formulated by using the wet granulation technique. The formulated granules were evaluated for their flow properties as a pre-compression parameter and the friability, hardness, disintegration, wetting ratio, wetting time, dissolution, and drug release parameters were evaluated as post-compression parameters. The effect of the varying concentrations of superdisintegrants on the formulation for disintegration time was ascertained and the results were compared.

The tablet had friability and hardness values ranging from 0.60 ± 0.04 to $0.68 \pm 0.04\%$ and 3.9 ± 0.057 to 4.3 ± 0.21 (kg/cm^2). Tablet weights did not vary significantly but the disintegration time varied from

44.66±0.57 to 142.66±2.51 min and the wetting time varied from 45.33±0.57 to 144±3.06 min and the optimal batch of tablets shows a drug release of 98.8% within 60 min and first-order release kinetics of the formulations are compared.

Keywords: Favipiravir; super disintegrants; crospovidone; croscarmellose sodium; sodium starch glycolate; wetting time; wetting ratio; disintegration time.

1. INTRODUCTION

The US FDA, Centre for Drug Evaluation and Research (CDER) defines an orally Disintegrating tablet as “a solid dosage form containing medicinal substances, which disintegrates rapidly, usually within a matter of seconds, when placed upon tongue” [1]. The European Pharmacopeia defines a similar term, orodisperse, a tablet that can be placed in the mouth where it disperses rapidly before swallowing [2].

Recent market studies indicate that more than half of the patients prefer ODT. As of 2020 analytics, north America is having a consumption market share value of nearly 40.5%, Europe is having a market share of 31.6%, China, South America, Asia-pacific, middle east Asia, and Africa are also major market for oral disintegrating tablets. The expected market for ODT will reach 21300 million USD by 2024 from 11200 million USD in 2019 [3].

The extent of the solubility of the drug influences the rate of absorption of the drug. The quicker the drug dissolves into the solution, the faster the absorption and faster the onset of clinical action of the drug [4,5]. The medicament should readily dissolve or disintegrate in the saliva within or less than a minute. A very little amount of saliva is sufficient for the oral disintegration of the medicament in the oral cavity and the drug is then absorbed partially or entirely into the systemic circulation from the blood vessels of the sublingual mucosa or it can be swallowed as a solution into the GIT [4]. The sublingual route produces a faster onset of action orally ingested tablets and surpasses the hepatic first-pass metabolism [6].

The fast-dissolving drug delivery system is quickly picking up acceptance in this pandemic as a significant novel drug delivery system. The fast-dissolving formulation is so popular since they are easy in administration for better patient compliance. Pediatric and geriatric patients have difficulty in swallowing the conventional dosage forms where fast dissolving tablets show great

feasibility to them in accepting the medication easily by placing the tablet on the tongue and it dissolves or disintegrates in the oral cavity [4,7].

ODT is formulated by a various process, which differs in the methodologies and finds differences in the various physical and chemical properties of the tablet such as Mechanical strength, taste, swallowability, drug dissolution, bioavailability and stability of the drug. ODT's can be formulated by various methodologies such as Freeze-Drying or Lyophilization, Cotton candy process, molding, spray drying, mass extrusion and mass extrusion and compaction (wet granulation, dry granulation, direct compression) [4].

1.1 Drug Profile

In the trend of drug repurposing for the treatment of the COVID-19 many drugs such as hydroxychloroquine, remdesivir, lopinavir, ritonavir, and some other drugs favipiravir which is previously existing drug for diseases like SARS-CoV and MERS (Middle East Respiratory Syndrome) has shown a quick service in treating the pandemic before the vaccine. The recommended dosage regimen of favipiravir is 1800 mg twice a day on day 1, followed by 800 mg twice a day for 7 days if needed continued upto maximum 14 days [8,9]. Favipiravir (T-705; 6-fluoro-3-hydroxy-2-pyrazinecarboxamide) is an antiviral agent that selectively inhibits the RNA-dependent RNA polymerase (RdRp) of RNA viruses. It is a synthetic prodrug that was initially used in the treatment of influenza infections [8-10].

It is having good bioavailability (97.6%), 54% protein binding, and a low apparent volume of Distribution (15-20L).

The C_{max} is attained after 2Hrs of administration. Both T_{max} and half-life increase after multiple doses. It is having a very short half-life of 2.5-5 h which is rapidly eliminated in the hydroxylated form. Favipiravir shows both dose-dependent and time-dependent pharmacokinetics [8].

Favipiravir undergoes ribosylation and phosphorylation intracellularly to become the active favipiravir RTP. The active form binds to and inhibits RNA dependent RNA polymerase (RdRp), which in turn prevents viral transcription and replication of the viral genome and also there are several hypotheses in the mechanism of action of favipiravir like incorporated in the viral RNA strand and preventing it from further extension and also hypothesis was that it induces lethal mutagenesis in vitro during the influenza viral infection [8,9]. In the present research work, a wet granulation method was employed in the manufacture of ODT considering the pre-compression studies of the excipients and the hardness of the tablet.

2. MATERIALS AND METHODS

2.1 Materials

Favipiravir API was received as a gift sample from Biophore limited, Hyderabad. Mannitol is used as a diluent. Starch paste has used as a binder for the granulation process. Sodium starch Glycolate, Croscarmellose sodium USP-NF (AC-Di- Sol) (from FMC biopolymer), Crospovidone (from FMC biopolymer) were used as superdisintegrants. Aspartame (Loba chemicals) is used as a sweetening agent, Magnesium stearate and talc (from Ferro industries) were used as glidants and lubricant.

Various equipment was used for the preparation of the mouth dissolving tablets such as Electronic balance (EssayDigi), UV-Visible Spectrophotometer (UV-1700 Shimadzu), Hot Air Oven (Centex), Sieve shaker (Ganson), Vernier

Callipers (Mitutoyo), Glassware (Borosil), Digital pH meter (Susima Technologies Ltd), Friabilator (EF-2, Electro lab, Mumbai, Hardness tester, Dissolution apparatus (Lab India Disso 8000), Disintegration Apparatus (Lab India), Bulk density apparatus (Electrolab) and tablet punching machine (VJ Instruments).

2.2 Formulation and Preparation of Orodispersable Tablets by Wet Granulation Method

Favipiravir, superdisintegrants (croscarmellose, sodium starch glycolate, crospovidone) in various proportions of 5%, 10%, 15%, mannitol was taken in quantity sufficient to 300 mg of the tablet and the other excipients were accurately weighed and mixed in geometric proportion as shown in Table 1. The starch paste of 5% was prepared and added to the mixture as a binder to prepare a wet mass. Granules were prepared by passing the wet mass through the sieve no.#16. Granules were dried at 60°C for 45 min. Granules were then mixed with talc, magnesium stearate as shown in the table. Granules were evaluated for the pre-compression studies.

2.3 Evaluation

2.3.1 Drug excipient compatibility

The compatibility between the excipients and the drug was done using the FTIR pellet press technique using potassium bromide and the obtained graphs were observed for their spectra wavelengths.

Table 1. Formulation table

S. No	Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
1	Favipiravir	200	200	200	200	200	200	200	200	200	200
2	Mannitol	80	65	50	80	65	50	80	65	50	56
3	Sodium Starch Glycollate	15	30	45	-	-	-	-	-	-	15
4	Croscarmellose sodium	-	-	-	15	30	45	-	-	-	15
5	Cross povidone	-	-	-	-	-	-	15	30	45	15
7	Aspartame	1	1	1	1	1	1	1	1	1	1
8	Magnesium Stearate	3	3	3	3	3	3	3	3	3	3
9	Talc	1	1	1	1	1	1	1	1	1	1
10	Starch Paste (5%w/v)	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

2.3.2 Preparation of standard graph of favipiravir

10 mg of favipiravir was dissolved in 10 ml of water using a cyclomixer. This solution is referred to as a standard solution. From the standard solution make 10 μ /ml stock solution was made and measured for the maximum wavelength obtained using UV-VIS spectrophotometer. The obtained wavelength is selected as λ_{max} . The obtained spectrum is 235nm. Different stock solutions of 3,6,9,12,15 μ g/ml were prepared and observed for their linearity. The standard curve was plotted.

2.3.3 Evaluation of the granules

2.3.3.1 The angle of repose

The angle of repose was evaluated by using the funnel method. The granules were poured through the funnel that can be raised vertically until a maximum cone height (h) was obtained. The radius of the heap (r) was measured and the angle of repose was calculated using the below formula [6].

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

Where, θ is the angle of repose.

2.3.3.2 Tapped density

Tapped density is determined by placing a graduated cylinder containing a known mass of granules and mechanical tapper apparatus, which is operated for an affixed number of times until there is no more change in the volume was attained. Using the formula, the tapped density was calculated [6].

Tapped density = Weight of the granules/ tapped volume of the granules

2.3.3.3 Carr's compressibility index

The Best way for finding out the free flow of the granules is compressibility index; it is the indication for the ease of flow of the granules it is calculated by the given formula [11].

$$\text{Carr's Index (\%)} = \frac{\text{Tapped Density} - \text{Bulk Density}}{\text{Tapped density}} \times 100$$

2.3.3.4 Hausner's ratio

It is the indirect index for the ease of powder flow. It is calculated by the following formula [11].

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

2.3.4 Evaluation of post compression parameters of tablets

The formulations were evaluated for the hardness, weight variation, tablet size and thickness, friability, disintegration time, *in-vitro* dispersion time, wetting time and water absorption ratio, assay, content uniformity and *in-vitro* dissolution.

2.3.4.1 Appearance

The general appearance characteristics of the tablet were evaluated such as tablet size, shape color, presence or absence of the odor, taste, surface texture.

2.3.4.2 Hardness

The hardness of the tablet was measured by diametric compression using a Monsanto Hardness Tester. Tablet was placed between the two anvils, force to the anvils and the crushing strength that causes the tablet to break was recorded. A tablet hardness of about 2-4 kg/cm² is taken as adequate for mechanical stability of the ODT [12].

2.3.4.3 Weight variation

Twenty tablets were selected randomly during compression and the mean weight was measured. Then individual tablets were weighed was compared with the mean weight and none of the tablets should deviate from the mean weight by more than $\pm 10\%$ [12].

2.3.4.4 Thickness

The thickness of the tablets from each of the formulation was measured using vernier calipers by placing the tablet between two arms of the vernier calipers, which is measured in mm.

2.3.4.5 Friability

It is performed to measure the effect of friction and shock, which may cause the tablet to chip, cap, or break. The friability of the tablet was measured in a Roche friabilator. This device subjects several tablets to the combined effect of abrasion and shock by using a plastic chamber that revolves at 25 rpm/min for 4 min dropping the tablet at a distance of 6 inches with each revolution. Pre weighed tablets were placed in

the friabilator and after de-dusting, the tablets are reweighted [13].

The percent friability was measured using the formula:

$$\text{Friability (\%)} = \frac{[(\text{Initial Weight}-\text{Final weight}) / (\text{Initial weight})] \times 100}{}$$

2.3.4.6 Uniformity of drug content

The drug content uniformity test was used to determine the uniform amount of active ingredient present in all formulations. The tablets are selected randomly and pulverized to a fine powder. the powder equivalent to 100mg of favipiravir was taken and dissolved in 10ml of distilled water in a volumetric flask, the volume was adjusted to 100ml with phosphate buffer pH 6.8 and the solution was filtered an aliquot of 1.0ml of solution were diluted to 10ml phosphate buffer pH 6.8 in a separate volumetric flask. The drug content in all the formulations was estimated spectrophotometrically using UV Spectrophotometer with λ_{max} at 235 nm [13-14].

2.3.4.7 *In-vitro* disintegration time

The test was performed using the disintegration apparatus. A tablet was placed in each of the six tubes of the apparatus the basket with the bottom surface made of a stainless-steel screen was immersed in a water bath at $37 \pm 2^\circ\text{C}$ and one perforated disc was placed on each of the tubes. The time in seconds was recorded for the completed disintegration of the tablet with no remnants of the palpable mass in the apparatus [15].

2.3.4.8 *In-vitro* dispersion time

In-vitro dispersion time was measured by dropping a tablet in 10 ml measuring cylinder containing 6 ml of buffer solution simulating the saliva fluid(pH 6.8) [16].

2.3.4.9 Wetting time and water absorption test

Wetting time is used to test the inner porosity of the tablet and the hydrophilicity of the excipients. The pore size decreases and the wetting time increases with an increase in the compression force. A linear relationship exists between the wetting time and the disintegration time. A piece of tissue paper folded twice was placed in a small petri dish of an internal diameter of 6.5cm containing 6ml of distilled water. A tablet was

placed on the paper, and the time for complete wetting of the tablet was measured in seconds.

The same procedure was repeated for determining the water absorption ratio. The wetted tablet was then weighed. The water absorption ratio, was determined according to the following equation [17].

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

W_a = weight of the tablet before the study

W_b = weight of the tablet after study

R = water absorption ratio.

2.3.5 10 *In-vitro* drug release studies

The release rate of favipiravir from the fast-dissolving tablet was determined by using the USP dissolution testing apparatus II (Paddle type). The dissolution test was performed using 900ml of phosphate buffer pH-6.8 as dissolution medium at 50rpm and temperature $37 \pm 0.5^\circ\text{C}$. at predetermined time intervals, 5ml of the sample was withdrawn using the syringe fitted to a free filter, the volume withdrawn at each interval was replaced with the same quantity of fresh medium. The resultant samples were filtered through watmann filter paper No.41 and analyzed for the presence of the drug release by measuring the absorbance at 235 nm (Graph 4) using UV visible spectrophotometer after suitable dilutions [18-20].

3. RESULTS AND DISCUSSION

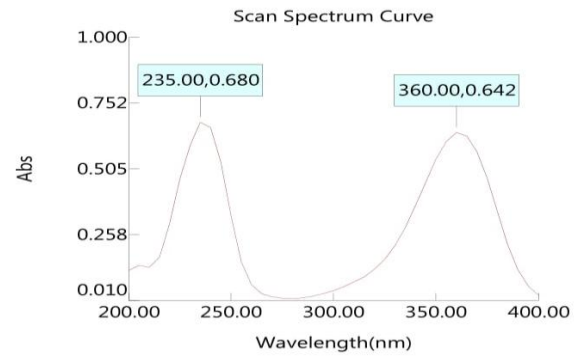
3.1 Results

3.1.1 Standard calibration graph

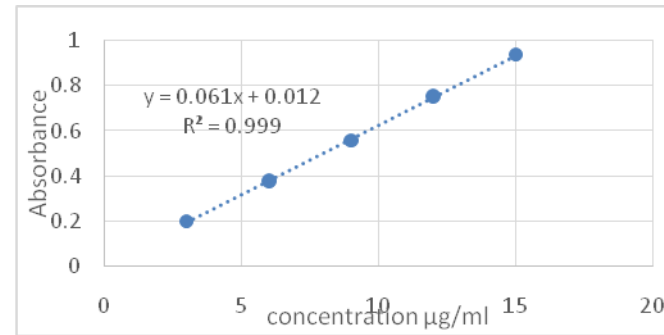
The prepared stock solutions were observed for absorbance at wavelength 235nm shown in the Graph a and Graph b was plotted using excel.

3.1.2 Granules properties

The physical properties were evaluated for the prepared granules of all the formulation from-1 to F-10 as shown in Table 2. Results of the bulk density were in the ranged of 1.17 ± 0.01 to 1.23 ± 0.02 , the tapped density ranged from 1.38 ± 0 to 1.48 ± 0.02 , the angle of repose ranged from 20.95 ± 0.71 to 29.85 ± 0.71 , Compressibility index ranged from 13.50 ± 1.42 to 17.51 ± 0.26 , and the Hausner's ratio ranged from 1.15 ± 0.02 to 1.19 ± 0.02 .



Graph a. UV spectrum Standard graph



Graph b. Standard calibration graph of favipiravir

3.1.3 Tablets properties

Table 3 shows the tablet properties of all the prepared formulations were evaluated as the post-compression parameters, the hardness of the tablet ranged from 3.9 ± 0.057 to 4.3 ± 0.21 , the thickness of the tablet ranged from 3.5 ± 0.1 to 3.73 ± 0.115 , the Percent friability ranged from 0.60 ± 0.04 to 0.68 ± 0.04 and all the formulations passed the % weight variation and % drug content. Where all the formulations are suitable for the compression of the tablet.

Table 4 shows the disintegration properties of all the formulations, disintegration time ranges from 44.66 ± 0.57 to 142.66 ± 2.51 minutes, wetting time ranges from 45.33 ± 0.57 to 144 ± 3.060 minutes and water absorption ratio ranges from 21.75 ± 2.17 to 71.5 ± 2.27 . Where F10 has shown good disintegration properties suitable for fast MDT.

3.1.4 Compatibility study

Compatibility studies were performed using IR Spectrophotometer. The FT-IR spectrum of the

pure drug and the physical mixtures of the drug and the excipients were reported in the (Figs. 1 to 5). For the compatibility studies the spectra of the pure drug is compared with the spectra of the physical mixtures.

3.1.5 Drug release studies

The Drug release data was analyzed as per the Zero order and the first order kinetics as shown in the Graphs 3 & 4.

3.2 Discussion

The FT-IR spectrum of the pure drug and the physical mixture of the drug and the excipients were studied for the compatibility studies, the peaks obtained in the spectra's of the physical mixtures (Figs. 2, 3, 4 and 5) correlates with the peaks of the drug spectrum (Fig. 1) this indicates that there are no interactions between the drug and the excipients used in the formulation.

Table 2. Pre compression parameters of the formulations; n=3

Formulation code	Angle of repose	Bulk density	Tapped density	% of compressibility	Hausner's Ratio
F1	24.54 ± 1.84	1.23 ± 0.02	1.45 ± 0.02	14.87 ± 2.85	1.174 ± 0.03
F2	23.78 ± 1.46	1.21 ± 0.03	1.40 ± 0.02	13.50 ± 1.42	1.15 ± 0.02
F3	25.68 ± 1.66	1.25 ± 0.02	1.48 ± 0.02	17.51 ± 0.26	1.19 ± 0.02
F4	28.64 ± 0.43	1.23 ± 0.02	1.45 ± 0.02	14.91 ± 0.10	1.17 ± 0.02
F5	29.85 ± 0.71	1.22 ± 0.01	1.38 ± 0.02	11.34 ± 1.66	1.12 ± 0.02
F6	29.16 ± 2.73	1.18 ± 0.01	1.36 ± 0.01	13.22 ± 1.20	1.14 ± 0.01
F7	22.63 ± 1.23	1.18 ± 0.01	1.39 ± 0.02	15.29 ± 1.33	1.17 ± 0.02
F8	22.55 ± 3.5	1.17 ± 0.01	1.34 ± 0.05	15.21 ± 1.25	1.17 ± 0.01
F9	23.14 ± 0.60	1.19 ± 0.01	1.40 ± 0.02	15.17 ± 1.67	1.17 ± 0.02
F10	20.95 ± 0.71	1.19 ± 0.01	1.39 ± 0.02	14.08 ± 1.96	1.16 ± 0.02

Table 3. Post compression parameters of the formulations; n=3

Formulation code	Hardness(kg/cm ²)	Thickness(mm)	Friability (%)	% weight variation	Drug content(%)
F1	4.0 ± 0.152	3.4 ± 0.208	0.62 ± 0.07	Pass	198.6 ± 0.76
F2	4.1 ± 0.057	3.5 ± 0.10	0.60 ± 0.04	Pass	197.8 ± 1.04
F3	4.0 ± 0.208	3.6 ± 0.152	0.65 ± 0.09	Pass	198.16 ± 1.15
F4	4.3 ± 0.210	3.73 ± 0.115	0.68 ± 0.04	Pass	199.16 ± 1.04
F5	4.2 ± 0.251	3.6 ± 0.115	0.66 ± 0.02	Pass	199.33 ± 1.15
F6	3.9 ± 0.057	3.5 ± 0.057	0.64 ± 0.01	Pass	199.66 ± 0.57
F7	3.9 ± 0.152	3.5 ± 0.057	0.64 ± 0.02	Pass	199.16 ± 1.04

Formulation code	Hardness(kg/cm ²)	Thickness(mm)	Friability (%)	% weight variation	Drug content(%)
F8	4.06±0.115	3.5±0.120	0.63±0.02	Pass	199.83±0.28
F9	4.16±0.152	3.7±0.115	0.62±0.01	Pass	199.66±0.28
F10	4.15±0.13	3.7±0.057	0.63±0.01	Pass	199.83±0.28

Table 4. Post compression parameters of the formulations; n=3

Formulation code	Disintegration time	Wetting time	Water absorption ratio
F1	75.66±1.52	77.33±2.08	52.1±0.13
F2	66.66±2.72	73.33±1.15	45.31±0.81
F3	59.66±2.08	60.66±2.30	33.21±1.52
F4	76.66±2.08	77.66±2.30	48.68±0.57
F5	71.33±1.04	73.66±1.52	43.21±1.52
F6	62.23±2.60	64.33±1.15	36.16 ± 0.56
F7	128.33±1.5	131.66±1.5	24.28±0.24
F8	138.66±2.04	134.33±2.04	22.57±1.33
F9	142.66±2.51	144.25 ± 3.06	73.75±2.17
F10	44.66±0.57	45.33±0.57	71.50 ± 2.27

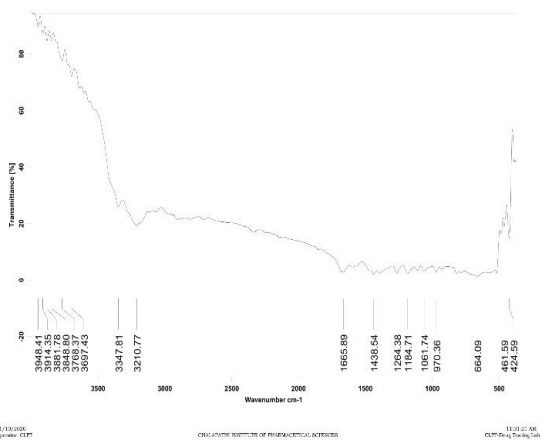


Fig. 1. FR-IR of pure drug (Favipiravir)

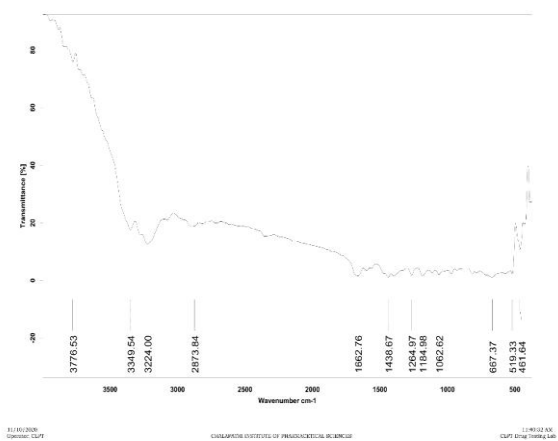


Fig. 2. FR-IR of pure drug and CCS

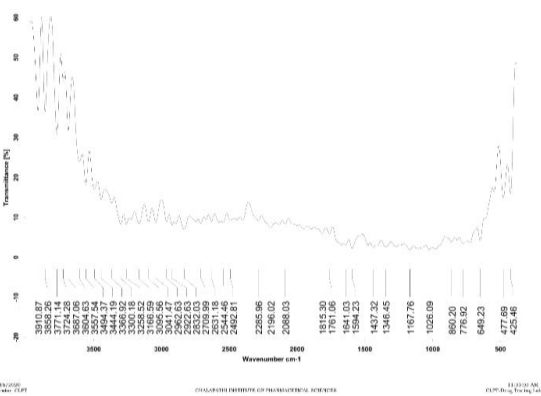


Fig. 3. FR-IR of pure drug and SSG

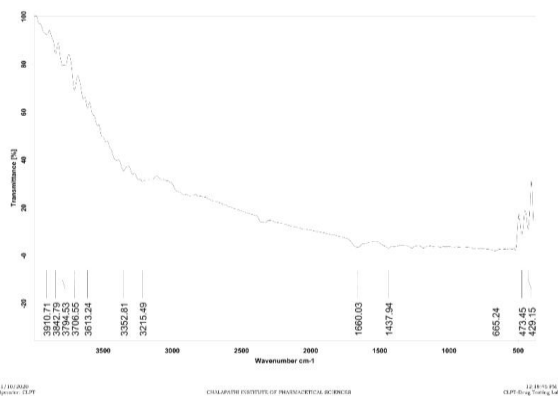


Fig. 4. FR-IR of pure drug and CPV

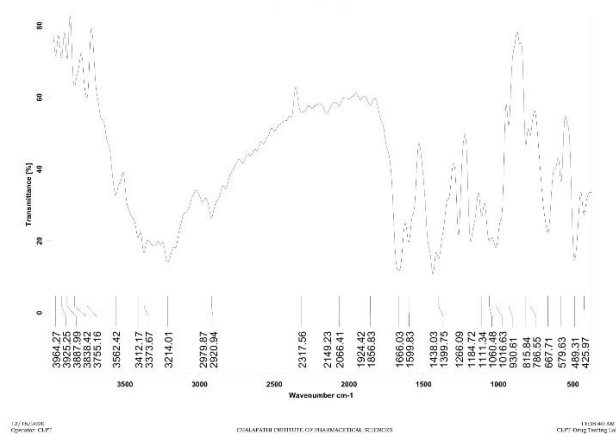
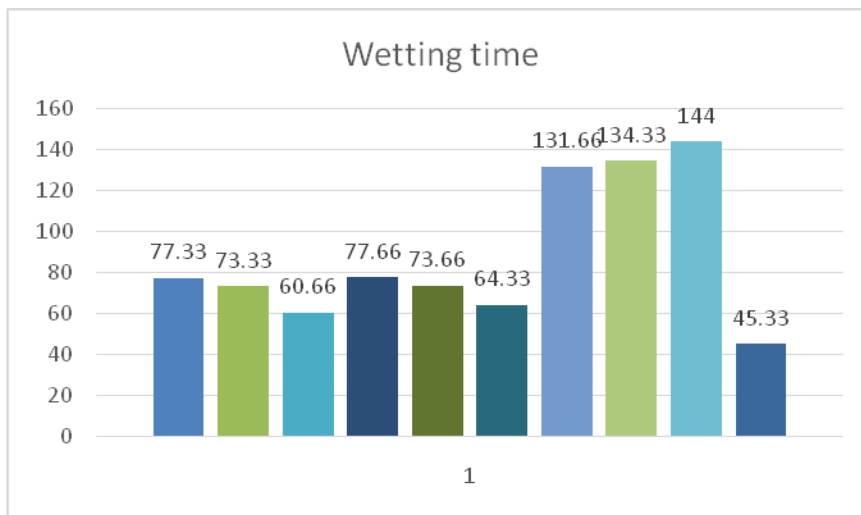
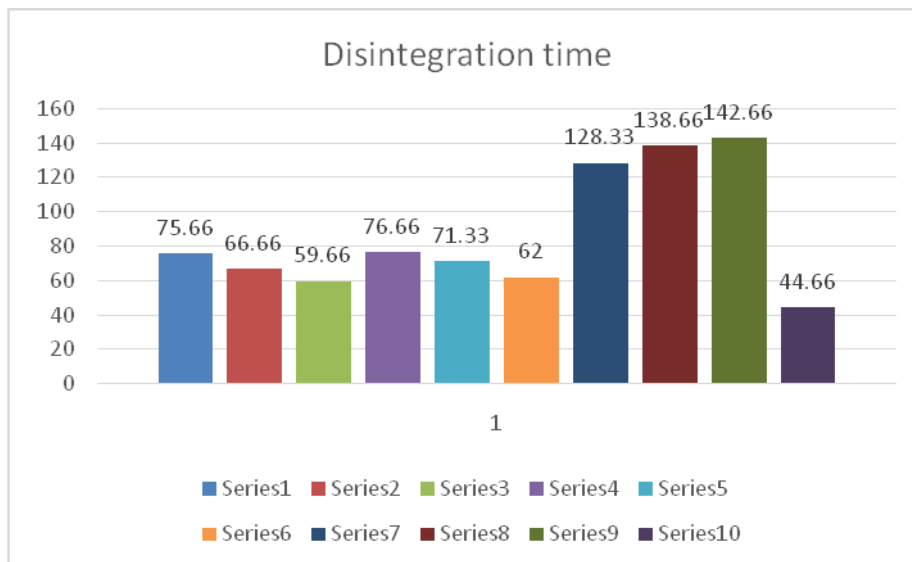


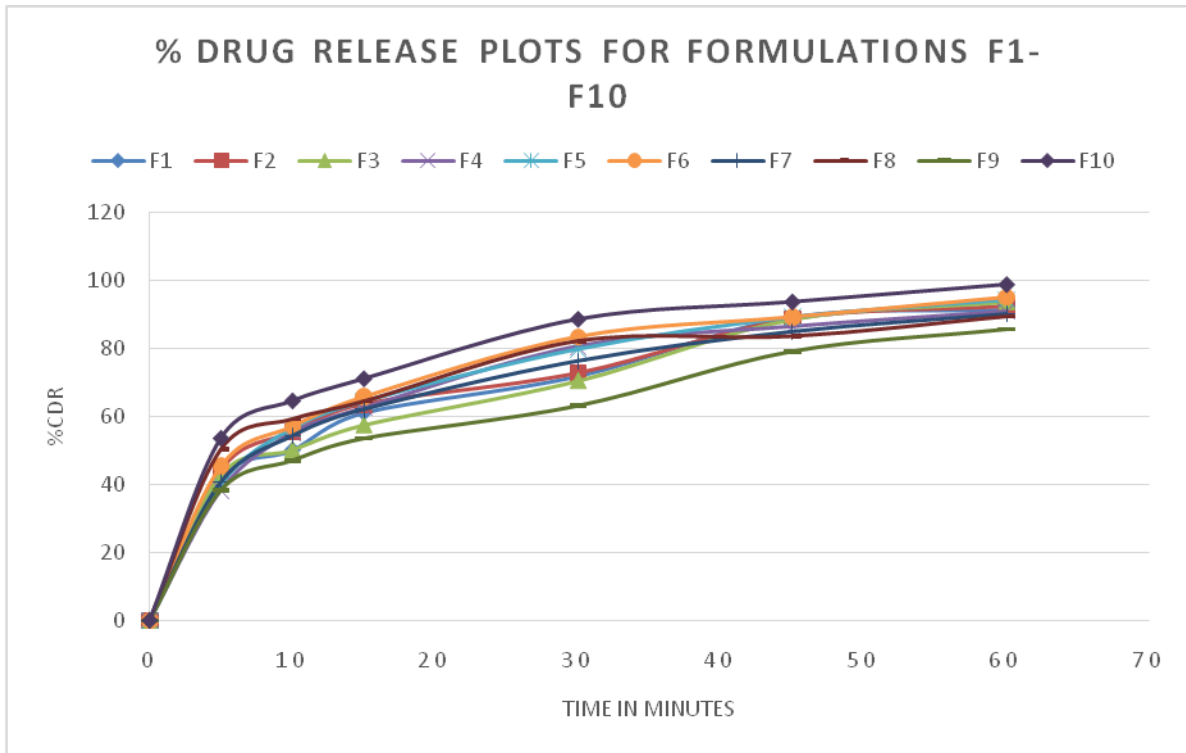
Fig. 5. FR-IR of F-10 formulation



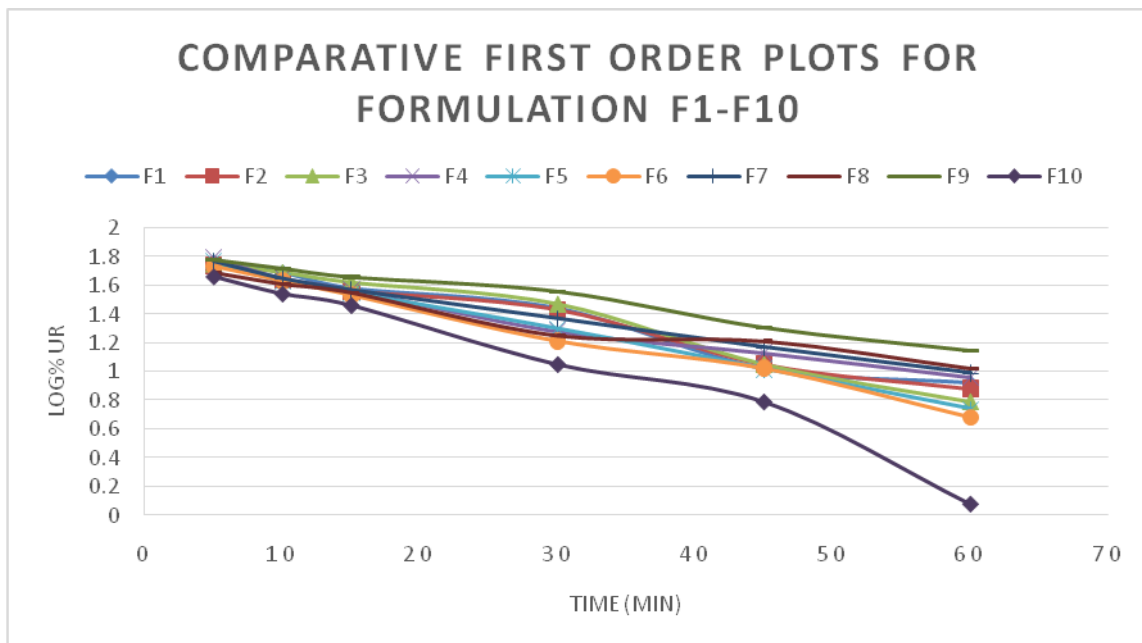
Graph 1. Comparison of the wetting time for formulations F1-F10



Graph 2. Comparison of disintegration time for formulation F1-F10



Graph 3. *In-vitro* release profile offavipiravir mouth dissolving tablets for formulation F1-F10



Graph 4. First orderkinetic release plots for formulations F1-F10

From the obtained results it was very clear that all the pre-compression parameters of the granules were suitable for the compression of the tablet which is in the good range. The hardness of the tablets are in the considerable range of which F1 shows less hardness, the thickness is

within the range, the friability of all the tablets was less than 1% which is a permissible limit.

The disintegration time is directly proportional to the wetting time, on comparison of disintegration and wetting time (Graphs 1 and 2) F10 has given

good results which get disintegrates in less than a minute and suits the pharmacopeial definition. From dissolution studies (Graph 3) F-10 have shown morethan 50% drug release within 5 minutes and 98.8% drug release in 60 minutes at pH6.8 buffer solution. The optimized formulation F10 have shown regression of 0.9714 which concludes that it follows first-order release kinetics (Graph 4).

4. CONCLUSION

The present research work predicts the applicability of various superdisintegrants such as Croscarmellose sodium, crospovidone, and sodium starch glycolate in the formulation and the development of the mouth dissolving tablet formulations of favipiravir. The tablets were successfully prepared using the wet Granulation technique using various concentrations of different superdisintegrants and from the results, it was clearly understood that the formulation containing 5% of crospovidone, 5% croscarmellose sodium and 5% Sodium starch Glycolate as superdisintegrants were found to be the best formulation in terms of the disintegration and the rate of dissolution.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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