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Formulation and evaluation of antiviral drug sofosbuvir fast dissolving tablets using natural super disintegrants

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Abstract: The main objective of this study to formulate of fast dissolving tablets of sofosbuvir, an antiviral drug used for hepatitis C virus. The direct compression method was employed for the formulation of sofosbuvir FDT and optimized for weight variation test, thickness, hardness, friability, wetting time, water absorption ratio, in-vitro disintegration test, and in-vitro dissolution studies, assay identification by using HPLC and stability studies. Master formulation of F4, Sofosbuvir showed promising results compared to others formulations and selected as the most suitable and best formulation among them. It also has better efficacy, disintegration and dissolution time. F4 was fabricated with both super disintegrants like croscarmellose sodium and sodium starch glycolate that lead to its required features. This formulation would be a good alternate for the management of viral diseases with better dissolution profile, stability and improved bioavailability for the patients.

Keywords: Sofosbuvir, natural super disintegrants, croscarmellose sodium, sodium starch glycolate, fast dissolution profile.

INTRODUCTION

Sofosbuvir was discover in 2007 and use for the treatment of constant viral hepatitis, genotypes 1, 2, 3, 4, 5 and 6 in U.S in 2013. Sofosbuvir used with different other antiviral drugs (Tran, 2012).

Fast dissolving tablets

A fast dissolving tablet dissolves or disintegrates within seconds in the oral cavity with or without organization of water. Fast dissolving tablet directed orally because oral organization of medication is simple helpful and safe, the most usually utilized course. Not less than 90% of medications used to make systemic impacts were controlled orally. United State Pharmacopeia, Food and Drug Administration FDA characterizes as solid dose form containing helpful material, that dissolve rapidly inside seconds once set over tongue (Bhardwaj *et al.,* 2010). According to European pharmacopoeia, these were the tablets which get dissolved quickly in mouth within a time span of less than 3 minutes in the oral cavity before it gets swallowed (Bhardwaj *et al.,* 2010).

Advantages

Good feeling of mouth property helps to change the basic view of medication as bitter taste tablets for pediatric. It is convenient to administration due to its precise dosing, rapid dissolution and absorption of drug as contrast to other liquids. No need of water for swallowing. Easy to administration of patients who deny to swallows tablets patients such as pediatric, gastric and psychiatric patients. Marked increase the bioavailability of drug due to its pre-gastric absorption via mouth followed by pharynx and esophageal area, thus avoid first pass effect by liver (Bandari *et al*., 2008; Bi *et al*., 1999; Indurwade *et al*., 2002; Manivannan, 2009; Patel and Patel, 2008; Song *et al*., 2004; Wilson *et al*., 1987).

Objectives

To prepare fast dissolving tablets of sofosbuvir that till not available in market. Identification of API by FTIR. Percentage solubility studies of Sofosbuvir by HPLC. Preformulation studies of sofosbuvir a. Angle of Repose b. Bulk Density c. Tapped Density d. Compressibility Index e. Hausner Ratio post formulations studies of fast dissolving tablets of sofosbuvir a. Weight Variation test b. Thickness c. Hardness d. Friability e. Wetting Time f. Water absorption ratio g. In vitro Disintegration test h. Content uniformity *in vitro* dissolution studies. Dissolution Studies with the other available formulation of sofosbuvir. Assay identification by use of HPLC. Stability studies of fast dissolving tablet of sofosbuvir.

MATERIALS AND METHODS

Materials

Sofosbuvir, Sodium starch glycolate, aspartame, magnesium stearate, talc powder and lactose monohydrate taken from Searle i.v solutions Pvt Ltd Lahore Pakistan as gift. Croscarmellose sodium and mannitol from Seoul technology. Chemicals used in assay identification like methanol, potassium dihydrogen phosphate,

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orthophosphoric acid were taken from Wilshire Labs Lahore Pakistan.

Pre-compression studies

It's necessary to verify that the active pharmaceutical ingredient meets the specified standards and also assess that which kind of excipients required for the manufacturing of tablet before the preparation of fast dissolving tablets of sofosbuvir. For such purpose, conduct pre formulation studies (Kalia *et al.,* 2009).

IR spectroscopic examination

Identification as well as considerate the possible special effects of API and other ingredients of formulation over each other which may influence the position of peaks in spectra, was examined by using IR technique. FTIR method was employed to obtain spectra's, which get saved in library. Wave number selected ranged from 4000 - 400cm while using BRUKUR FTIR spectrophotometer. IR spectral studies of pure Sofosbuvir as well as formulation were carried out (Sarfraz *et al.,* 2016).

Melting point of API

Melting point apparatus was used to performed melting point test by filled the capi1lary tube with the drug apparatus was strongly monitored when drug started to melt the temperature of the drug noted (Giordano *et al.,* 2003).

Particle size of blend

Particles usually categorized as very Coarse (08), Coarse (20), moderately coarse (40), fine and very fine. To determine the average particle size by different techniques can be used, like sedimentation rate or microscopy. Sieving technique used for particle size analysis because of most common and simple method. Sieve analyses were performed by use of nest or stack of sieves where each lower sieve has a smaller aperture size than that of the sieve above it. Put the final mix of powder the most upper sieve and on the vibrator (Bandari *et al.*, 2008).

Moisture content of blend

Moisture content of the granules should be evaluated, as an important for moisture effects the physicochemical properties of drug, and compressibility of powder also dependent on it. The granules should have certain moisture level depending on the drug as well as the procedure adopted to manufacture the tablets it can be examine by digital moisture analyzer took the final mix on aluminum foil, place in the digital moisture analyzer and determined the (LOD) loss on drying percentage (Bandari *et al.*, 2008).

Angle of repose

Angle of repose determined flow property of the final bland. It's also predicting movement of powder via hopper. In this technique, use funnel and adjust its height in a conduct to on tripod iron stand. Sample was permitted to pass through the funnel and cone formed at the bottom of funnel. The diameter of cone calculated. Angle of repose calculated by following equation (Bandari *et al.*, 2008).

$$\text{Angle of repose} = \frac{1}{\tan}\left(\frac{h}{r}\right)$$

Here, h = height and r = radius

20g of final mix taken then final mixed powder was passed through the funnel slowly to form a sharp heap. The height of the powder heap formed was measured with scale. Circumference formed was drawn with a pencil on the graph paper. The radius was measured and the angle of repose was determined (Mahmood *et al.,* 2016).

Bulk density

Bulk density ratio of given mass of power and its bulk volume. Weighed amount of power poured in a measure cylinder and volume (Vb) to be noted. Bulk density calculated through the following equation (Mahmood *et al.,* 2016).

$$\text{Bulk density} = \frac{M}{V_b}$$

Here M = Mass of the power Vb = Bulk volume of the powder

Tapped density

Tapped density was the percentage mass of powder over tapped volume. Tapped the powder filled cylinder for about 50 times. After tapping its volume measured (Mahmood *et al.,* 2016).

$$\text{Tapped density} = \frac{M}{V_b}$$

Compressibility index and Hausner ratio

Measure the unsettle volume of powder "Vo" than final tapped volume "Vf" of the powder even that no further volume changes of powder. Find out the finally Compressibility index and Hausner ratio by following expressions (Mahmood *et al.,* 2016).

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

$$\text{Compressibility index} = \frac{\text{TD - BD}}{\text{BD}} \times 100$$

Here, TD= Tapped density BD= Bulk density

Hausner ratio by divided the bulk density of the powered with the tapped density. Compressibility index also determined the flow properties of the final mixed powdered by subtracted the tapped density to the bulk density and divided with bulk density (Mahmood *et al.,* 2016).

Procedure for formulation

Weight all ingredients and pass through the mesh # 40 separately. After passing through sieve geometrically mixed at least 10min except magnesium stearate. At the end finally add the magnesium stearate to above blend and mix it for 5min. After this compressed the blend by

use of 6mm round punch ZP-07 compression machine (Kalia *et al.,* 2009)

After successive mixing of the powder this powder mingle was then compressed by mean of 6mm punch with filled weight 700mg per tablet on 07 punch station rotary machine (Wilshire labs, Lahore, Pakistan). Batches of 50 tablets were prepared for each of the designated formulations.

Post compression parameters

Weight variation of tablets

Twenty tablets from all formulations were weighted separately by mean of digital electronic balance (Shimadzu). The 10 tablets average weights as well as their percentage deviation were calculated (Sarfraz *et al.,* 2015).

Tablet thickness

For the identification of thickness (mm) of tablets were separately measures each tablet from all formulations by digital Vernier caliper. Average thickness and standard deviation were determined (Mahmood *et al.,* 2015).

Hardness testing

Hardness or tablet infraction force of six tablets from each of the four designed formulations was tested by Monsanto hardness tester. First, zero adjustment by placing tablet in contact with the lower plunger. After this initiatory step the upper plunger was hardly pressed alongside the spiral by means of spiraling the threaded attachment around that central axis until the tablet was fractured. A cursor travelled by the side of a measuring device inside the barrel for indicating the amount of strength as the spring got compressed. After documenting the power of breakage, the zero reading of force was then subtracted from it. It measured the tablet breaking force in Kg/cm^2 (Mahmood *et al.*, 2016).

Friability

Weight the 25 tablets (W_1) Put in the friabilator then run at the speed of 25 rotations per minute (rpm) for a time lapse of 4 minutes or in other terms operated at the frequency of 100 revolutions and once again weight of the tablets was noted (W_2). The %age friability is determined by this formula (Sarfraz *et al.,* 2015).

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

W_1 = Weight of tablets before revolution W_2= Weight of tablets after revolution

Invitro disintegration time

For this test use calibrated disintegration test apparatus (Pharm test D-63512) to evaluate the disintegration process of formulated tablets. Individually tablet unit was put inside the tubes that were present in disintegration apparatus containing 1 liter distilled water which was kept at 37±2Ċ temperature. The accurate time required by our formulations to disintegrate totally and to become a clear mass was recorded. This procedure was done for each formulation. Hence for each sample 18 tablets were tested and for each test the resulting time in minutes were recorded (Sameer *et al.,* 2009).

In-vitro dissolution time

Dissolution tests were performed by use of 6.8 pH buffer solutions. About 900mL of dissolution media was added in each of 6 vessels of dissolution apparatus separately and stabilized on 37±0.5 at 50 rpm. Took the sample between the dilution medium from the surface by 3ml of disposable syringe make up the dilution if necessary according to the standard and find the percentage dissolution of sofosbuvir by HPLC method samples were collected three times with the interval of 5minute (Sarfraz *et al.,* 2015).

Assay identification

Reagents distilled water, methanol, potassium dihydrogen phosphate, orthophosphoric acid used in HPLC for the case of sofosbuvir HPLC injector with loop volume of 10µl, pump, programmed changeable wavelength UV detector used. Prepared buffer solution that accurately weigh 1.75g of potassium dihydrogen phosphate and dissolve it in 1000 ml of HPLC Grade water, orthophosphoric ac1d used to adjust the pH to 4 with dilute, filter through 0.45µm membrane filter of nylon and buffer degas. mobile phase used that prepared from the above 50% buffer and mix with 500ml of methanol 50% degas in ultrasonic water bath for 5min and filter through 0.45µ filter under vacuum filtrate (Hassouna *et al*., 2017). To prepared stock solution of SFS (1mg/mL) was manufacture by weighing 10mg and dissolving in the mobile phase phosphate buffer (pH4.0): methanol (50:50%v/v). Standard solutions of SFS were prepared in the range of 5µg/mL to 30µg/mL by diluting the stock solution with mobile phase. The elated monitored at 262nm. Each solution was then injected into the column and chromatograms were recorded (Hassouna *et al*., 2017).

Kinetic release

Kinetic re1ease studies were the most necessary fraction for the development of formulation that described the release pattern of a drug from the formulation. The kinetic model describes the release mechanism of drug from the formulations in term of quantitative as well as qualitative change. Different approaches were used to analyze the dissolution data and to study release pattern of drug from the four formulations that were formulated. Commonly three different methods were used to analyze the dissolution data. To inspect kinetic release of the drug and evaluate dissolution profile of all formulations Statistical method used (ANOVA).

Table 1: Master formulations of API sofosbuvir

Code	Ingredients	F1	F2	F3	F4
1	Sofosbuvir	400	400	400	400
2	Croscarmellose sodium	-	130	-	29
3	Starch sodium glycolate	-	-	130	46.4
4	Lactose anhydrous	10	10	10	30
5	Mannitol	10	10	10	33.6
6	Aspartame	60	60	60	10
7	Magnesium stearate	20	20	20	50
8	Talc	200	70	70	101
	Total weight (mg)	700	700	700	700

Table 2: Flow properties of the final mixed powder that used in fast dissolving tablet

Code	Bulk Density (g/mL)	Tapped Density (g/mL)	Angle of Repose (θ)	Carr's Index (%)	Hausner's Ratio	Moisture Content (%)
F1	0.59	0.71	26.00	13.73	1.26	0.63
F2	0.58	0.65	28.00	15.77	1.14	0.57
F3	0.59	0.71	26.00	13.73	1.26	0.63
F4	0.56	0.65	25.00	11.74	1.12	0.36

All parameters' values are average of three determinants.

Table 3: HPLC Optimized method parameters for the assay identification of sofosbuvir

Parameters	Method
Column	C18(250×4.6MM,5µm)
Mobile phase	Phosphate buffer: methanol (50: 50)
Flow rate	0.8ml/min
Run time	8min
Column temperature	Ambient
Volume of injection loop	10µl
Detector wavelength	262nm
Drug RT	1.01min
Linearity range	5-30 µg/ml

Following parameter and methods implemented on HPLC for the detection of API sofosbuvir assay from the designed formulated tablets.

Table 4: Post compression parameters of fast dissolving tablets of sofosbuvir

Code	Water absorption ratio (%)	Thickness (mm)	Friability* (%)	Hardness (Kg/cm^2)	Wetting* Time (Sec)	Disintegration* Time (Sec)	Weight Variation (mg)	Assay (%)
F1	56.71±0.00	4.70	0.597±0.001	5.80	144±0.03	74±1.00	700.30	98.90
F2	67.73±0.01	4.69	0.592±0.01	5.75	482±0.04	66±1.00	699.00	97.86
F3	75.35±0.01	4.66	0.696±0.02	5.96	76±0.03	24±1.53	701.00	97.95
F4	85.55±0.03	4.71	0.706±0.00	4.98	24±0.03	07±1.00	701.00	98.02

*n= 5 ± S.D. (Standard deviation)

Table 5: Dissolution profile of fast dissolving tablets of sofosbuvir in 6.8 pH phosphate buffer

Code	Cumulative percentage of drug release (sofosbuvir fast dissolving tablets) (%)			
	0	5mins	10mins	15mins
F1	0	55.1	75.6	98.9
F2	0	55.7	75.2	97.9
F3	0	55.8	76.6	97.9
F4	0	59.8	80.9	98.03

Table 6: Three-month stability results of post-compression parameters

Parameters	F1	F2	F3	F4
Initial Color	Nearly white	Nearly white	Nearly white	Nearly white
Color after 3 months	Nearly white	Nearly white	Nearly white	Nearly white
Initial wt. (mg)	700.30	699.00	701.00	701.00
Wt. after 3 months (mg)	700.00	699.00	701.00	699.00
Initial thickness (mm)	4.70	4.69	4.66	4.71
Thickness after 3 months (mm)	4.70	4.69	4.66	4.71
Initial Hardness (Kg/cm^2)	3.80	3.75	5.96	4.98
Hardness after 3 months (kg/cm^2)	3.84	3.81	5.76	4.54
Initial Friability* (%)	0.597±0.01	0.592±0.01	0.696±0.02	0.706±0.00
Friability* after 3 months (%)	0667±0.02	0.598±0.00	0.701±0.01	0.722±0.04
Initial Disintegration* Time (sec)	74±1.00	66±1.00	24±1.53	7±1.00
Disintegration* Time (sec) after 3 months	69±0.03	68±0.01	27±1.00	6±0.00
Initial Wetting* Time (sec)	144±0.03	82±0.04	76±0.03	24±0.03
Wetting* Time after 3 months (sec)	147±0.05	79±0.01	81±0.01	23±0.02
Initial Assay %	98.90	97.86	97.95	98.02
Assay (%) after 3 months	98.90	96.60	97.95	98.00

*n = 5±S.D. (Standard deviation)

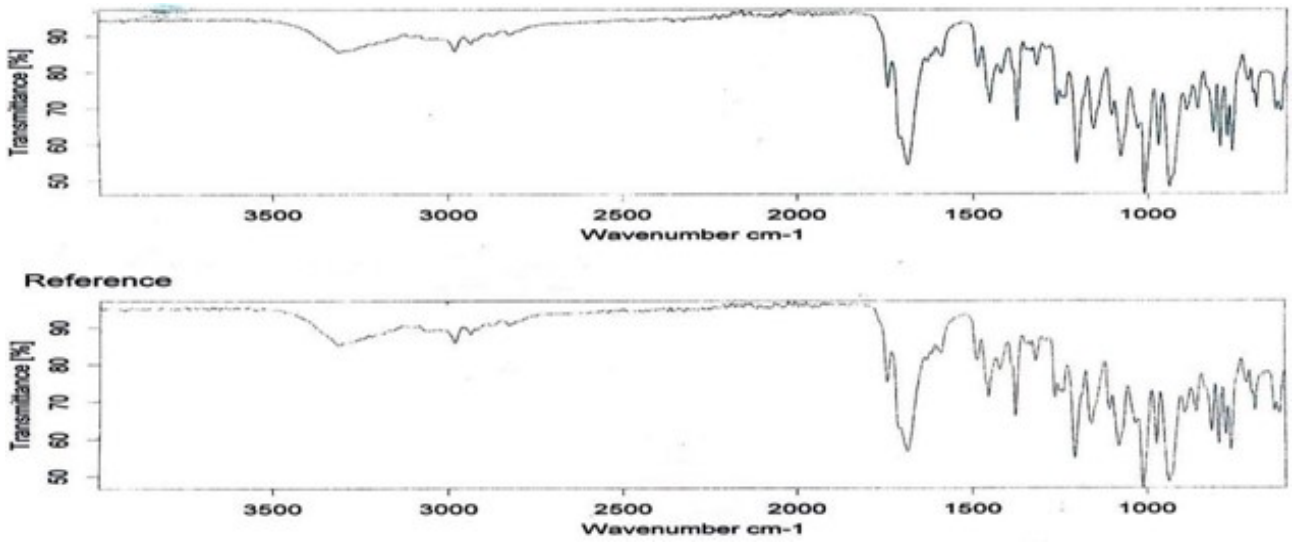

Fig. 1: FTIR spectrum of pure sofosbuvir with the standard that present in the FTIR library

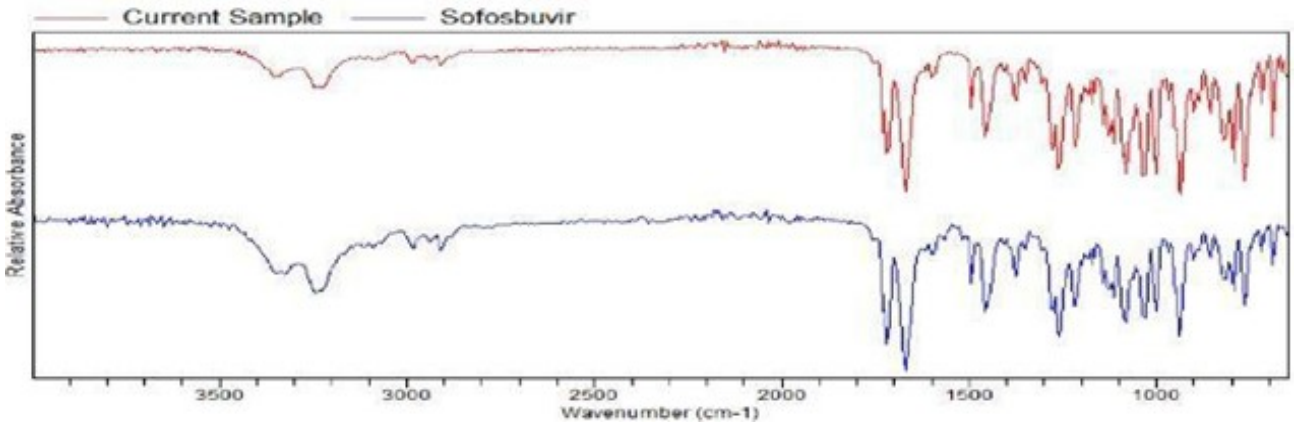

Fig. 2: FT1R spectra of formulation F4 against reference standard of sofosbuvir

In vitro dispersion time

In this test took a tablet, put inside a beaker pre-filled with solution (Approx. 10-15mL), buffered solution with pH 6.8. Determined the total time that take to disperse tablet completely it was carefully noted (Sarfraz *et al.,* 2015).

Accelerated stability studies

For the period of three-month stability studies were adopted for tablets (60±2ċ, RH 75±5%) (Marshal *et al.,* 1987). Pharmaceutical prepared stability can be explained as the ability for some particular formulation in a particular container or closure that to stay remain within its own physical condition, microbiological, chemical, specific therapeutic and toxicological effect during its shelf life. The accelerated stability studies have huge concern; as adequate outcome it could be documented under harassed conditions. It prepared information on which proposed drug shelf life and it depends upon their storage conditions (Suresh *et al.,* 2007).

Water absorption ratio and wetting time

Wetting time test basically used to predict that how the tablet disintegrates in presence of a suitable medium. To perform this test took 5 tissue papers and cut them in circular shape so that a diameter of about 10 centimeters. After that, positioned these tissues in a Petri dishes and poured 10ml of water miscible dye solution in each Petri dish. Then these tablets took in each Petri dish and cautiously positioned it over these tissue papers. The water moistened the tablet and reached to the upper surface of the tablet within few minutes. The time noted called wetting time. Water absorption ratio, simply a fraction within initial weight of the tablet W_b noted prior to place in petri plate to that of wetted tablet weight W_a (Gohel *et al.,* 2005). It calculated by

$$\text{Water absorption ratio} = \frac{W_a - W_b}{W_b} \times 100$$

STATISTICAL ANALYSIS

The results of the analysis and stability studies were analyzed through one-way analysis of variance (ANOVA) Minitab 11 software. Data were expressed as a mean ± standard deviation (SD). The value of $p<0.05$ was considered significantly different.

RESULTS

Bulk density of all formulations was between 0.564 to 0.599g/mL, Tapped density 0.651 to 0.717g/mL. Other parameters like Angle of repose, Hausner ratio, Carr's index and Moisture content percentage values were 25 to 28θ, 1.12 to 1.26, 11.74 to 15.77%, 0.36 to 0.63%. Pre-compression parameters results mentioned in (table 2) that was under specification.

Post compression parameters like Weight variation, Hardness, Thickness, Friability, in between 699.00 to 701.00mg, 4.98 to 5.96kg/cm^2, 4.66 to 4.71mm, 0.592±0.01 to 0.706±0.00% the official limit of limit of friability must be less than 1% these results mentioned in (table 2) which were under limit. Disintegration time of four formulations in between 74±1.00 to 7±1.00sec, Wetting time 144±0.03 to 24±0.03sec, Water absorption ration 85.55 to 56.71, and tablet assay in between 97.85 to 98.90% pharmacopeial limit of tablet assay 95 to 105%. All post compression parameters results mentioned in (table 4) these were present in pharmacopeial limit. Cumulative release drug profile mentioned in (table 5) 98.03% drug release with 15min.

Stability study determined that all the post compression parameters within limit after performing three month stability so fast dissolving tablet of antiviral drug stable and that F4 formulation would be used for future purpose.

DISCUSSION

Flow properties

Flow properties of all the four formulations were showed better results due to use of 2.82% magnesium stearate and 9.86 % talc in formulations. Flow properties also depends upon the particle size of the final blend uniform particle size obtained by pass through the mesh number 42 and also on LOD loss on drying less must be less than 3% and moisture contents in the final mixture. The use of magnesium stearate as lubricant improved the flow rate of final blend excellently (Mehmood *et al.,* 2016).

Weight variation

Each of the formulation showed best and uniform weight result of tablets because of their absent of sticking between the material and the powder between punches of machine. Such weight variation manually controlled by ZP-07 compression machine with control of compression forces of upper and lower punches lengths weight checked with the intervals of time (Sarfraz *et al.,* 2015).

Thickness

Thickness of each formulation was controlled by manual adjustment of the compression machine punches. It can also control by of compression machine room environment. Like control moisture of the room and also temperature. Humidity of the compression machine area must be 45% and temperature 25ċ that control the tablets related problems. Standard thickness of the single solid dosage form could be variate in between ± 0.005mm (Mehmood *et al.,* 2016).

Hardness

Hardness of 6 tablets was checked by digital Monsanto hardness tester of each formulation. Results of hardness for the formulation showed in limit. Hardness of each the

formulation is controlled by the addition talc and lactose in the formulation lactose in these formulation acts as dry binder (Mehmood *et al.,* 2016).

Friability

Friability of the F4 formulation was low as compare to the other formulations but that were within range the friability was less in this formulation due to the addition of two natural super disintegrants as compare to the other formulation. Such super disintegrants improve the dispersion and breaking capacity of the tablets also decrease the internal tablet forces (Sarfraz *et al.,* 2015).

Invitro disintegration time

Disintegration time of F2, F3 and F4 were less in 1min even F4 formulation disintegration time just 7sec because use of double super disintegrants like croscarmellose sodium and sodium starch glycolate. F1 formulation showed higher disintegration time as compare to others because in F1 formulation did not used any dispersing agent (Sarfraz *et al.,* 2015).

In-vitro dissolution time

Invitro dissolution time F4 formulation lesser as compare to other it dissolves in buffer solution with pH 6.5 in 0.75min cause of two super disintegrants sodium starch glycolate and croscarmellose sodium such super disintegrants have fibers of cellulose that have high absorption intensity that enhance the dissolution release profile of sofosbuvir (Sarfraz *et al.,* 2015).

Formulation assay by HPLC

Addition of 100% API sofosbuvir in each formulation therefore final assay result of tablets observed similar.

Stability studies

According to the ICH guidelines the stability study of formulations was done for three months of compressed blistered tablets placed in the stability chamber. Check the physical appearance of the tablets like colour, thickness, disintegration time, dissolution time and hardness. Then perform the chemical test of the formulation that were kept under stability chamber chemical test includes that assay identification must be stable throughout shelf life. International conference of harmonization provides the instruction to maintain temperature 60±1 ºC and relative humidity 75%±5 for accelerated stability studies.

Wetting time and water absorption ratio

Water absorption ratio of fast dissolving tablets enhanced due to natural super disintegrants fibers of sodium starch glycolate and croscarmellose sodium have high ability to absorb water and remain inside the tablet such water absorption enhance disintegration and also dissolution profile of the tablets (Jagdale *et al.,* 2010).

CONCLUSION

Concluded from this project the formulations of F4 showed good results as compare to the others because in this formulation added the two super natural disintegrants like croscarmellose sodium and sodium starch glycolate that enhance the disintegration and dissolution of the tablets F4 formulation of fast dissolving tablets of sofosbuvir recommended for future use due to that good disintegration, dissolution, and release profile.

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