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Research Article

DESIGN AND DEVELOPMENT OF SPRAY DRIED TELAPREVIR FOR IMPROVING THE DISSOLUTION FROM TABLETS

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ABSTRACT

Telaprevir acts against the virus that causes hepatitis C infection and is used to treat chronic hepatitis C infection in adult patients (aged 18–65 years) in combination with peginterferon alfa and ribavirin. Telaprevir is available as tablet at the dose of 375 mg in the market under the brand name of incivik. The primary aim of the study was to develop a pharmaceutically equivalent, stable, robust and quality improved formulation of tablets. Telaprevir is having very low solubility, which will reduce the bioavailability of the dosage form hence premix of telaprevir was prepared by spray drying using combination of hypromellose acetate succinate (HPMC-AS) and different surfactants sodium lauryl sulphate (SLS), Polysorbate-80, Docusate sodium as carriers. Further the spray dried telaprevir was formulated into tablets and evaluated. Among the tablets formulation F3 containing HPMC-AS and SLS as carrier demonstrated better drug release comparable to that of the innovator. Hence the present study clearly indicated usefulness of spray drying technology in improving the dissolution rate of telaprevir.

Keywords: Telaprevir, Hepatitis C, Spray Drying, Sodium Lauryl Sulphate and Polysorbate.

INTRODUCTION

Hepatitis C is a complex liver disease. Its medical importance and the need to rapidly identify new therapeutic approaches has resulted in intensive study of its causative agent, hepatitis C virus (HCV). The hepatitis C virus (HCV) is a single-stranded RNA virus of the Hepacivirus genus in the Flaviviridae family. Humans are the only known natural hosts of HCV. Even after two decades since its discovery, HCV continues to be major cause of concern and a huge burden on public health systems worldwide. The WHO estimates that a minimum of 3 per cent of the world's population is chronically infected with HCV[1, 2]. HCV is a prototype member of the Hepacivirus genus (from the Greek hepar, hepatos, liver) and is further classified into at least seven major genotypes that differ by about 30 per cent in their nucleotide sequence. These genotypes (1, 2, 3, 4, 5, 6 & 7) show differences with regard to their worldwide distribution, transmission and disease progression[3, 4]. These genotypes have been further classified into sub-types (a, b, c, d, etc). In fact, HCV circulates in infected individuals as a population of diverse but closely related variants referred to as "quasispecies". HCV is most commonly spread by direct contact with infected blood and blood products.

According to the Centers for Disease Control and Prevention, 21% of all acute viral hepatitis in the United States may be attributed to hepatitis C viral infection. Infection with hepatitis C almost always results in chronic infection. Sixty-seven percent of all cases develop chronic liver disease with accompanying elevation of liver enzymes. Hepatitis C viral infection is also thought to be a major contributing factor to hepatocellular carcinoma. Discovered in 1990 as a causative agent for post-transfusion non-A, non-B hepatitis, ~3% of the U.S. population is now infected with hepatitis C (between 4–5 million seropositive individuals). There are approximately 30,000 new cases of acute hepatitis C diagnosed each year in the United States. Neutralizing antibodies appear to be produced during the course of a natural infection, yet the virus mutates to escape surveillance[5]. When liver fails to clear the virus, the individuals become chronic carriers. However, within this chronically infected population the disease outcomes vary, it can be

mild (minimal inflammation of the liver) or severe and can lead to scar tissue formation. Chronic infection eventually causes cirrhosis leading to hepatocellular carcinoma (HCC) and ultimately death. Currently, there is no vaccine to prevent hepatitis C. Availability of injectable therapies and a drug has had a remarkable influence on HCV epidemiology. The incubation period of HCV, though ranging up to several months, averages 6-8 wk. HCV infection is often asymptomatic, making it a very difficult to detect it at an early stage. This is the major reason why early treatment is difficult. Therefore, hepatitis C is often referred to as a "silent disease". In a majority of infected people, virus infection does not resolve naturally.

Telaprevir acts against the virus that causes hepatitis C infection and is used to treat chronic hepatitis C infection in adult patients (aged 18–65 years) in combination with peginterferon alfa and ribavirin. Telaprevir belongs to a group of medicines called 'NS3-4A protease inhibitors'. The NS3-4A protease inhibitor reduces the amount of hepatitis C virus in your body. Telaprevir must not be taken alone and must be taken in combination with peginterferon alfa and ribavirin to be sure your treatment works. Telaprevir can be used for patients with chronic hepatitis C infection who have never been treated before or can be used in patients with chronic hepatitis C infection who have been treated previously with an interferon-based regimen.

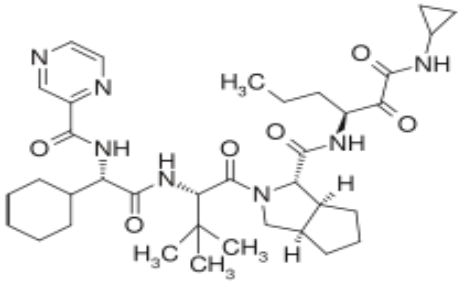

Fig. 1: Chemical Structure of Telaprevir

Solid dispersions have been widely used to enhance the solubility, dissolution rate, and bioavailability of poorly soluble drugs. Telaprevir is a poorly soluble drug to enhance dissolution rate spray drying technology was used [6, 7].

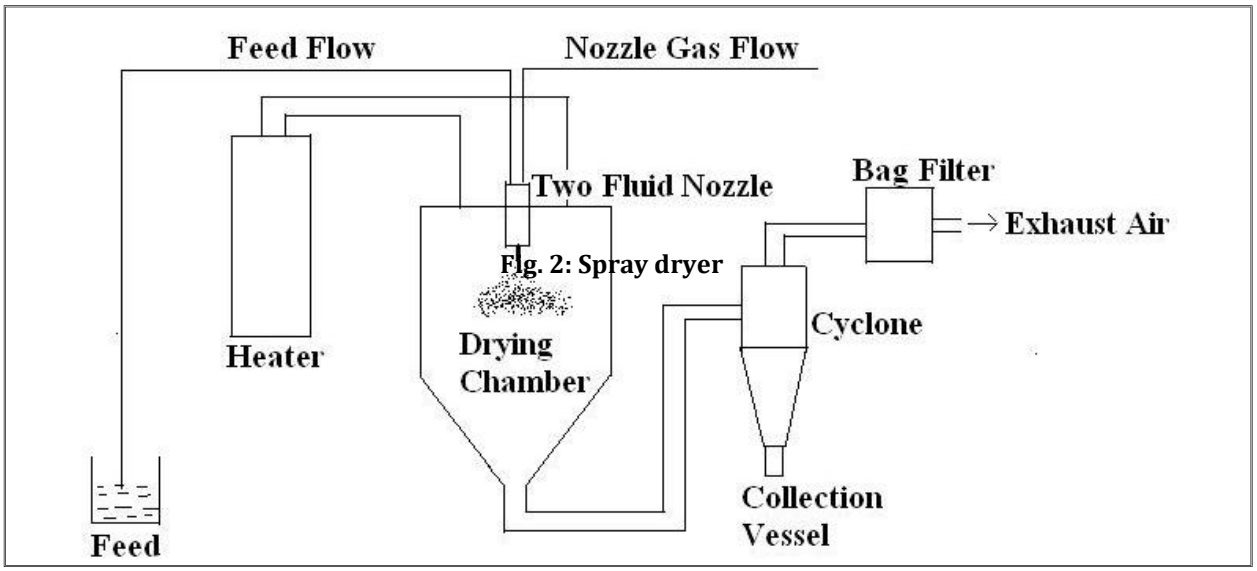

Fig. 2: Spray dryer

The objective of this study is to prepare a pharmaceutically equivalent, stable robust formulation using Hypromellose acetate succinate, Sodium lauryl sulfate, Polysorbate 80, Docusate sodium, Di calcium phosphate, Microcrystalline cellulose, croscarmellose sodium, Colloidal silicon dioxide, Megnisium stearate and Opadry white by using spray dry technology. Telaprevir drug substance is a white to off-white powder with solubility in water of 0.0047 mg/mL. Because of its low aqueous solubility we used spray dry technology to enhance its solubilty. The prepared batches of different tablets were evaluated for uniformity of weight, thickness, hardness, friability, disintegration test and in vitro dissolution study with tablets.

MATERIALS AND METHODS

Telaprevir was obtained as free gift sample from M/s Hetero labs ltd, Excipients used were Hypromellose acetate succinate – Shin-Etsu, Sodium lauryl sulfate - Stepan.co, Polysorbate 80 – Croda Singapore Pvt ltd, Docusate sodium – Cytec Industries, Di calcium phosphate - Innophos, Microcrystalline cellulose – FMC international, croscarmellose sodium – DFE Pharma, Colloidal silicon dioxide – Evonik Degussa, Megnisium stearate – Peter Greven, Opadry white - Colorcon.

Pre-compression Parameters

All pre-compression parameter including bulk density, tapped density, compressibility index, Hausner's ratio and angle of repose were evaluated.

Preformulation Studies

Preformulation involves the application of bio pharmaceutical principles to the physical chemical parameters of the drug with the goal of designing an optimum drug delivery system [8]. Preformulation studies are an important tool in the development of drug products. The interaction between the drug components and the excipient used in the formulation are generally included in the study, resulting in intelligent selection of excipients.

Flow Property Studies

Flow property of lubricated blend can be determined by angle of repose, compressibility index and hausner ratio.

Angle of Repose

The angle of repose is a characteristic related to interprticulate friction or resistance to movement between particles. A funnel was kept vertically in a stand at a specified height with bottom closed and a paper was placed below on a horizontal surface. Twenty grams of lubricated blend was added to the funnel. The funnel was then opened slowly to release the sample to form a conical heap. Radius and height of the heap was measured. The angle of repose was determined using the formula [Angle of repose (tan θ) = (Height of the heap) / (Radius of the heap)]. Flow property of the angle of repose can be done using table 1. (Table 1: Flow properties of Angle of repose).

Compressibility Index and Hausner Ratio

The compressibility index and the hausner ratio are determined by measuring both bilk volume and the tapped volume of a powder. Compressibility index was determined using formula [Compressibility Index = (Tapped Density - Bulk Density)/ (Tapped Density) X 100] and Haussner's ratio was determined using formula [Haussner ratio = (Tapped Density) / (Bulk Density)]. However, bulk density of the sample was determined by pouring a known quantity of sample into a measuring cylinder and measured the volume. Calculate the bulk density using formula [Bulk Density = Mass of the sample / Bulk volume of the sample]. Whereas, tapped density of the sample was determined by tapping the cylinder containing sample from a specific height in a given time. Calculate the tapped density using formula [Tapped Density = Mass of the sample / Tapped volume of the sample]. Interpretation of flow property of the sample was done using table 2. (Table 2: Scale of Flowability).

Preparation of Telaprevir Tablets

Weighed quantity as shown in table 3 of telaprevir was taken and dissolved in methylene chlorine and add Acetone. Weighed quantity of Hypromellose acetate succinate and surfactant (SLS, Polysorbate 80 and Docusate sodium) was dissolved in above solution. Both the solution was mix together and the resultant mixture was spray-dryed. Spray-dryed material was collected and added sifted material of A-tab, MCC, CCS and Aerosil loaded to suitable blender and blend for 10 min. finally added Mg.stearate in to blender and blend for 5 min. (Table 3: Formulae for Preparation of Telaprevir Tablets).

Evaluation of Telaprevir Tablets

Post Compression Parameters

The prepared tablets were evaluated as per standard procedure to various quality control tests such as uniformity of weight, thickness (vernier caliper), hardness (Pfizer hardness tester), friability (Roche friabilator), drug content and in vitro dissolution studies.

Uniformity of Weight

For uniformity of weight, 20 tablets were selected at random, weighed together and then individually [9]. The mean and standard deviation were determined.

Hardness

Five tablets were selected at random and the hardness of each tablet was measured using Monsanto hardness tester [10].

Friability

The friability test was carried out in Roche Friabilator [11]. Twenty tablets were weighed (wo) initially and put in a rotating drum. Then, they were subjected to 100 falls of 6 inches height (25 rpm for four minutes). After

completion of rotations, the tablets were dedusted by using camel hair brush and weighed (w). The percent loss in weight or friability (f) was calculated by the formula given below.

Friability = [(W1-W2)100]/W1

Where,

W1= Weight of tablet before test, W2 = Weight of tablet after test.

Drug Content Estimation

Telaprevir content of all the prepared tablets was estimated by the following procedure. Weigh the single tablet of each batch was taken and transferred into a 100 ml volumetric flask. 50 ml of purified water was added and vigorously shaken for 15 minutes. The solution was then sonicated for 15 minutes. After this the solution was kept aside for 15 min for equilibration and made up to volume with water. The resulted solution was filtered through 0.45 µm filter paper and suitably diluted and the drug content was estimated spectrometrically by measuring the absorbance[12, 13].

Dissolution Studies

Dissolution studies were carried out using a USP dissolution apparatus type II with 900ml dissolution mediums at 37 °C ± 0.5 and 50 rpm in 1% SLS in water. Fresh media (10 ml), which was pre-warmed at 37 °C, was replaced into the dissolution medium after each sampling to maintain its constant volume throughout the test. Dissolution studies were performed in three replicates (n = 6), and calculated mean values of cumulative drug release were used while plotting the release curves.

Drug Release Kinetics

The analysis of the mechanism of drug release from pharmaceutical dosage form is an important but complicated problem and is practically evident in case of multi particulate dosage form. The dissolution data obtained was fitted to zero order [14-16] first order [17], Higuchi [18] to understand the order and mechanism of Telaprevir release from prepared tablets.

Zero Order Release Kinetics

It defines a linear relationship between the fraction of drug released versus time. It is caluculated using equation Q = kot; where, Q is the fraction of drug released at time t and ko is the zero order release rate constant. A plot of the fraction of drug released against time will be linear if the release obeys zero order release kinetics.

First Order Release Kinetics

Exposed surface area of a tablet decreased exponentially with time during dissolution process, suggested that drug release from most slow release tablets could be described adequately by apparent first-order kinetics. The equation used to describe first order kinetics is**,** ln (1-Q) = –k1t where, Q is the fraction of drug released at time, (t) and k1 is the first order release rate constant. Thus, a plot of the logarithm of the fraction of drug remained against time will be linear if the release obeys first order release kinetics.

Higuchi Equation

It defines a linear dependence of the active fraction released per unit of surface (Q) on the square root of time. Q = k2t½; where, k2 is the release rate constant. A plot of the fraction of drug released against square root of time will be linear if the release obeys Higuchi equation.

Erosion Equation

This equation defines the drug release based on erosion alone. Q = 1-(1-k3t)3**;** where, Q is the fraction of drug released at time t, k3 is the release rate constant. Thus, a plot between [1-(1-Q)1/3] against time will be linear if the release obeys erosion equation.

Stability Studies

The purpose of stability study is to provide evidence on the quality of a drug substance or drug product which varies with time under the influence of a variety of environmental factors such as temperature, humidity and light [19, 20]. The Telaprevir tablets of F4 were packed in High-density Polyethylene bottles with Child Resistance Caps (CRC) and induction sealed. These bottles were charged for stability study at 40^0C/75% RH. Sampling time was done at initial, 1st, 2nd and 3rd month and evaluated for appearance, water content, in-vitro dissolution and assay.

RESULTS AND DISCUSSION

Drug – Excipient Compatibility Study

Compatibility studies by Accelerated and stress studies showed that there was no physical change or interaction between drug and selected excipients (Table 3). Based on the physical compatibility results and the innovator product composition the above excipients were selected for formulation development. (Table 4: Results of Drug Excipients Compatibility studies).

Flow Properties

Lubricated blends were subjected to various flow property tests such as Compressibility index, Hausner's ratio, angle of repose and results are tabulated in Table 5. Blend showed improved flow property than its pure drug. (Table 5: Flow properties of drug and lubricated blend).

Post Compression Evaluation Parameters

Assay

The prepared formulations of telaprevir tablets were done for assay studies and the results as showed in table 6 were found to be in the range from 97.50 % to 99.58 %. (Table 6: Comparative assay profile from F1 – F7).

Weight Variation, Thickness, Friability, Hardness and Disintegration

There was no difficulty in the preparation of the telaprevir tablets by using spray dry technology. Quality control tests such as weight variation, thickness, friability, hardness and disintegration for all the formulations were carried out and the results are given in Table 7. The tablets prepared in each batch showed uniformity of weight, thickness and the weight variation of the tablets was within the limits (as per IP Not more than two of the individual weights deviate from the average weight by more than 5% for the tablets with average weight more than 250 mg and 7.5% for the tablets with average weight more that 80 mg but less than 250 mg and none deviates by more than twice the stated percentage). All prepared tablets showed good strength. The hardness for Telaprevir tablets was in the range of 12-14 KP. The friability values were found to be less than 1% for all the prepared batches of tablets. The results from prepared formulations showed that all tablets were disintegrated in less than 40 seconds. (Table 7: Post Compression Evaluation Parameters).

Dissolution Studies

The results of *in vitro* dissolution studies as shown in fig. 4 and indicated that release of telaprevir was uniform for a period of 30 min from the tablets prepared by using spray drying technology. In case of F-1, F-2 and F-3 tablets prepared by using sodium lauryl sulfate showed drug release of 57.0 %, 93.0 % and 96.0 % in 30 minutes; and 91.0 %, 92.0 % drug was released from formulations F-4, F-5 prepared with polysorbate 80. The formulations F-6 and F-7 prepared with docusate sodium showed 92.0 % of telaprevir release in 30 minutes and innovator showed 95.0 % drug release in same 30 minutes. Among all prepared formulation F-3 i.e. prepared with 10 mg of sodium lauryl sulfate (SLS) showed highest percentage of drug relase of 96.0 % in 30 minutes when compared with innovator.

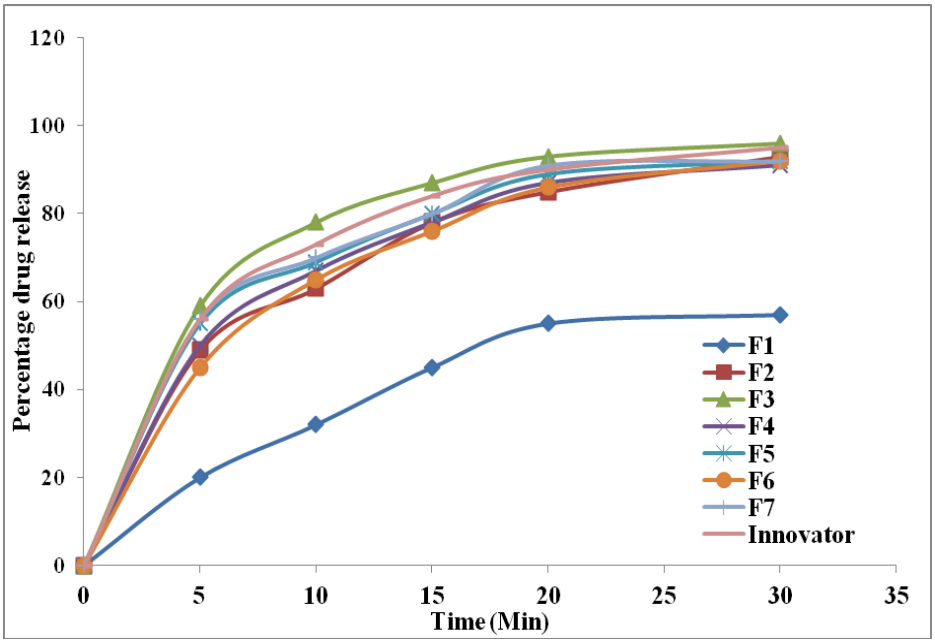

Fig. 4: Dissolution profiles of prepared telaprevir tablets

The kinetics of dissolution release profile of telaprevir tablets formulations was subjected for zero order, first order, Hixson-Crowell equation Higuchi diffusion and erosion equation and the correlation coefficient (r) values are given in Table 8. The results showed that telaprevir tablet formulations followed first order release kinetics as indicated by the correlation coefficient 'r' values (r = 0.920 to 0.990). The results also indicated that the release best fits to Higuchi diffusion (r=0.923 to 0.974) showing the particulate dissolution nature of telaprevir tablets. (Table 8: Different release kinetics of telaprevir tablets).

Stability Studies

Stability studies of F3 demonstrated no significant changes in physical parameters, water content, assay and dissolution profile after 40^0C / 75% RH 3 months. (Table 9: Results on Stability Studies).

Table 1: Flow properties of Angle of repose

Flow Property	Angle of repose (degrees)
Excellent	25 - 30
Good	31 - 35
Fair	36 - 40
Passable	41 - 45
Poor	46 – 55
Very poor	56 -65
Very very poor	>66

Table 2: Scale of Flowability

Compressibility Index (%)	Flow character	Hausner Ratio
≤10	Excellent	1.00 – 1.11
11 - 15	Good	1.12 – 1.18
16 - 20	Fair	1.19 – 1.25
21 - 25	Passable	1.26 – 1.34
26 - 31	Poor	1.35 – 1.45
32 - 37	Very poor	1.46 – 1.59
>38	Very very Poor	>1.60

Table 3: Formulae for Preparation of Telaprevir Tablets

Ingredients	F1	F2	F3	F4	F5	F6	F7
Spray Drying							
Telaprevir (mg)	375	375	375	375	375	375	375
Hypromellose Acetate Succinate (mg)	187.5	375	375	375	375	375	375
Sodium Lauryl Sulfate (mg)	10	10	15	**	**	**	**
Polysorbate 80 (mg)	**	**	**	10	15	**	**
Docusate Sodium (mg)	**	**	**	**	**	10	15
Methylene Chloride (mg)	qs	qs	qs	qs	qs	qs	qs
Acetone	qs	qs	qs	qs	qs	qs	qs
Extra granulation							
Di calcium phosphate anhydrous (mg)	50	50	50	50	50	50	50
Microcrystalline celllose (pH102) (mg)	327.5	140	135	140	135	140	135
Croscarmellose sodium (mg)	20	20	20	20	20	20	20
Collodial silicon dioxide (mg)	10	10	10	10	10	10	10
Lubrication							
Mg.stearate (mg)	20	20	20	20	20	20	20
Film coating							
Opadry white	30	30	30	30	30	30	30

Table 4: Results of Drug Excipients Compatibility studies

S.No	Composition Details	Initial	*30 days	#30 days
1	Telaprevir	White to off-white	@NCC	NCC
2	Telaprevir + Hypromellose acetate succinate	White to off-white	NCC	NCC
3	Telaprevir + Sodium lauryl sulfate	White to off-white	NCC	NCC
4	Telaprevir + Polysorbate 80	White to off-white	NCC	NCC
5	Telaprevir + Docusate sodium	White to off-white	NCC	NCC
6	Telaprevir + Di calcium phosphate anhydrate	White to off-white	NCC	NCC
7	Telaprevir + Microcrystalline cellulose (pH 102)	White to off-white	NCC	NCC
8	Telaprevir + Croscarmellose sodium	White to off-white	NCC	NCC
9	Telaprevir + Colloidal silicon dioxide	White to off-white	NCC	NCC
10	Telaprevir + Mg.stearate	White to off-white	NCC	NCC
11	Telaprevir + Opadry white	White to off-white	NCC	NCC

@ NCC = No Characeristic change ; * 30 days at 40°C/75% RH ; # 30 days at 60°C

Table 5: Flow properties of drug and lubricated blend

S.NO	Formulation	Compressibility index (%)	Hausner's ratio	Angle of repose (°)
1	Drug	27.78	1.38	47.21
2	F1	13.79	1.16	33.20
3	F2	11.44	1.13	32.17
4	F3	14.02	1.16	34.47
5	F4	12.16	1.14	32.83
6	F5	12.63	1.14	34.65
7	F6	13.33	1.15	31.18
8	F7	13.56	1.16	31.93

Table 6: Comparative assay profile from F1 – F7

Formulation batch no	F1	F2	F3	F4	F5	F6	F7
Assay (%)	97.50	98.21	99.58	99.21	98.12	98.84	98.53

Table 7: Post Compression Evaluation Parameters

Batch Code	Weight Variation Test (n=5)	Thickness (mm) (n=5)	Friability test (<1%) (n=6)	Hardness (KP) (n=5)	Disintegration (Sec)
F1	1002 ± 5.23	6.98 ± 0.07	Pass	14.87 ± 0.7	30
F2	1000 ± 4.13	6.96 ± 0.06	Pass	13.27 ± 0.9	29
F3	1001 ± 4.73	6.95 ± 0.08	Pass	14.83 ± 0.8	25
F4	1003 ± 5.22	6.97 ± 0.05	Pass	12.57 ± 0.9	37
F5	1002 ± 4.87	6.94 ± 0.07	Pass	14.31 ± 0.8	29
F6	1004 ± 5.29	6.94 ± 0.09	Pass	13.83 ± 0.9	34
F7	1002 ± 5.73	6.97 ± 0.06	Pass	14.81 ± 0.8	32

Table 8: Different release kinetics of telaprevir tablets

Formulation	Correlation coefficient (r2)				
	Zero Order	First order	Hixson Crowel's	Higuchi	Peppas
F-1	0.8777	0.922	0.909	0.969	0.925
F-2	0.7895	0.990	0.947	0.974	0.853
F-3	0.6791	0.962	0.883	0.923	0.827
F-4	0.7525	0.958	0.905	0.959	0.846
F-5	0.7218	0.947	0.888	0.945	0.835
F-6	0.7961	0.984	0.941	0.975	0.862
F-7	0.7119	0.920	0.870	0.939	0.833
Innovator	0.7145	0.977	0.908	0.942	0.834

Table 9: Results on Stability Studies

Test parameters	Initial Value	40°C / 75% RH		
		1 month	2 months	3 months
Appearance	White to off white convex film coated tablets	White to off white convex film coated tablets	White to off white convex film coated tablets	White to off white convex film coated tablets
Water by KF	2.87	3.12	3.43	3.64
Dissolution in 30 min (%)	97	97	95	94
Assay (%)	99.58	98.93	98.53	98.14

CONCLUSION

The primary aim of the study was to develop a pharmaceutically equivalent, stable, robust and quality improved formulation of Telaprevir tablets. Telaprevir was having very low solubility, hence to improve its dissolution rate spray drying technique was selected. Hypromellose acetate succinate was selected as a carrier polymer with different surfactants like SLS, polysorbate-80, docusate sodium. From the results it was concluded that the spray dried telaprevir formulated as tablets formulation F3 by using hypromellose acetate succinate and sodium lauryl sulfate showed better dissolution profile comparable to the innovator. The formulation also showed promising results during accelerated stability studies. Hence, the tablet formulation (F3) with spray dried hypromellose acetate succinate and SLS of telaprevir was best formulation.

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