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Research Article

FORMULATION AND EVALUATION OF DOLUTEGRAVIR SODIUM SOLID DISPERSIONS AND FAST DISSOLVING TABLETS USING POLOXAMER-188 AND JACK FRUIT SEED STARCH AS EXCIPIENTS

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ABSTRACT

Objective: The current work mainly focuses on solubility enhancement of dolutegravir which is a biopharmaceutical classification system Class-II drug using jack fruit seed starch (JFS2) as excipient which improves the drug release.

Materials and Methods: Starches were extracted using aqueous and alkali methods (sodium hydroxide at 0.1%, 0.25%, and 0.5% concentrations) from jack fruit seed powder. These starches were evaluated for phytochemical and physicochemical parameters. Fast dissolving tablets were prepared using dolutegravir sodium solid dispersion, JFS2, and croscarmellose sodium (CCS) in various concentrations using wet granulation technique. Various pre- and post-compression parameters were evaluated along with *in vitro* drug release studies; characterization studies such as Fourier transform infrared (FTIR) spectroscopy, differential scanning calorimetry (DSC), scanning electron microscopy, X-ray diffraction (XRD), and stability studies.

Results: Phytochemical tests revealed the presence of only starch in all extracts. Starch prepared from 0.1% sodium hydroxide (JFS2) showed best physicochemical properties. From *in vitro* dissolution studies, it was observed that solid dispersion formulation DF3 containing dolutegravir sodium and poloxamer-188 in 1:1.5 ratios showed a better dissolution rate. From *in vitro* dissolution studies, tablet formulations DFT6 and DFT9 containing 12.5% w/w of JFS2 and 12.5% w/w of CCS showed enhanced dissolution rate compared with other formulations. FTIR and DSC studies revealed that there were no major interactions between drug and excipients. XRD studies revealed the nature of formulations. Accelerated stability studies showed that all tablets were stable.

Conclusion: The tablets prepared using jack fruit starch seed starch revealed the superdisintegrant property of starch.

Keywords: Jack fruit seed starch, Dolutegravir, Poloxamer-188, Solid dispersions, Fast dissolving tablets.

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INTRODUCTION

Solubility is an important physicochemical factor affecting the absorption of the drug and its therapeutic effectiveness. Nowadays, scientists are focusing on the development of oral dosage forms of poor aqueous solubility drugs through various solubility enhancing approaches. Among these approaches, preparation of solid dispersions is one of the widely used approaches. The term solid dispersion refers to a group of solid products consisting of at least two different components, a hydrophilic matrix and a hydrophobic drug [1,2].

The present study is aimed to develop dolutegravir sodium fast dissolving tablets using solid dispersion technique to improve the solubility and dissolution rate. Dolutegravir sodium is an antiretroviral agent which mainly acts by inhibiting the enzyme human immunodeficiency virus integrase which is needed for the viral replication process. According to the Biopharmaceutical Classification Scheme, dolutegravir can be considered as Class II drug, i.e., water-insoluble, lipophilic, and highly permeable compound. Therefore, it is possible to improve its bioavailability by increasing apparent solubility in water through solid dispersion technology [3-5]. Fast dissolving tablet is a solid dosage form containing a medicinal substance or active ingredient which disintegrates rapidly usually within a matter of seconds when placed on the tongue. It helps in faster drug release and better effect of formulation. Although several synthetic carriers have been developed, natural carrier development is gaining focus in recent days due to their easy availability [6].

A novel solid dispersion formulation of dolutegravir sodium was prepared by fusion method using poloxamer 188 as a carrier. Dolutegravir sodium tablets were prepared by wet granulation method with the best solid dispersion along with jack fruit seed starch (JFS2), employing a neoteric method which could prove the superdisintegrant property of JFS2.

MATERIALS AND METHODS

Procurement of materials

Dolutegravir sodium was a gift sample from Dr. Reddy's Lab (Hyderabad, India). Poloxamer 188 was a gift sample from Pellets Pharma Ltd. (Hyderabad, India). Sodium hydroxide, magnesium stearate, and talc were procured form S. D Fine Chem. Ltd. (Mumbai, India). Croscarmellose sodium (CCS) was a gift sample from NATCO Pharma Ltd. (Hyderabad, India) and jackfruit seeds were procured from the local market (Guntur, Andhra Pradesh, India).

Extraction of jackfruit seed starch using alkali method

JFS2 was isolated using aqueous and alkali extraction methods [7]. Jack fruit seed flour (5 gm) was added in water, 0.1%, 0.25%, and 0.5% of sodium hydroxide (100ml) and soaked (6 h or 8 h) at room temperature with occasional stirring. The slurry was filtered through 120 mesh stainless sieve. The filtrate solution was kept in a refrigerator for overnight and then removed, and the supernatant was discarded. The crude starch was washed with distilled water for 3 times, and the starch cake was dried at 40°C for 24 h in tray dryer. The starch was grounded

into a fine powder using mortar and pestle. The obtained starches were packed in a plastic bag and kept at room temperature until further use.

Phytochemical tests for jack fruit seed powder and extracted starches

The raw jackfruit powder and starch extracts were subjected to phytochemical tests for the identification of carbohydrates, proteins, alkaloids, glycosides, and steroids by various tests [8]. The results are given in Table 1.

Evaluation of physicochemical properties of jack fruit seed powder and extracted starch

Various physicochemical properties such as gelatinization temperature, pH, viscosity, swelling index, and water absorption index were evaluated using suitable methods [9]. All the results are indicated in Table 2.

Total microbial load of isolated JFS2

The total microbial load is an important parameter which decides the suitability of a substance for use as an excipient in the pharmaceutical dosage form. The agar medium was prepared and placed in an autoclave for 1 h. To this, bacterial culture like *Escherichia coli* was added, mixed well and poured into Petri plates and allowed to solidify for 10 min. After solidification, the starch powder was sprinkled and kept in an incubator for 24 h. According to many pharmacopeias, in case of excipients from natural origin, the total aerobic count should not be >1000 cfu/g and total fungal count should not exceed 100 cfu/g.

Acidity

About 1 g of starch was added to 100 ml of ethanol (70%) which was previously neutralized to phenolphthalein solution. This solution was shaken for 1 h, filtered and 50 ml of the filtrate was titrated with 0.1 M sodium hydroxide.

Table 1: Phytochemical tests for JFSP and extracted starches

Test	JFSP	JFS1	JFS2	JFS3	JFS4
Carbohydrates	+	+	+	+	+
Polysaccharides	+	+	+	+	+
Proteins	–	–	–	–	–
Alkaloids	+	–	–	–	–
Glycosides	–	–	–	–	–
Steroids	+	–	–	–	–
Flavonoids	+	–	–	–	–
Saponins	+	–	–	–	–

+ve indicates positive and –ve indicates negative. JFSP: Jack fruit seed powder, JFS1: Jack fruit seed powder extracted with water, JFS2: Jack fruit seed powder extracted with 0.1% sodium hydroxide, JFS3: Jack fruit seed powder extracted with 0.25% sodium hydroxide, JFS4: Jack fruit seed powder extracted with 0.5% sodium hydroxide

Fluorescence

About 500 mg of starch powder was dissolved in an organic solvent and placed on a glass slide. The slide was examined under ultraviolet (UV) cabinet for the presence of any fluorescent material.

Oxidizing substances

To 5.0 g of sample, 10 ml of water and 1 ml of acetic acid were added and stirred until a homogeneous suspension was obtained. 0.5 ml of a freshly prepared saturated solution of potassium iodide was added, mixed and allowed to stand for 5 min.

Sulfated ash

About 1–2 g of the starch was placed in an accurately weighed crucible and ignited until thoroughly charred. Then, it is cooled and the residue was moistened with 1 ml of sulfuric acid. It was heated gently until white fumes are no longer evolved and ignited at 800°C until black particles have disappeared. The crucible was cooled and few drops of sulfuric acid were added and heated. Then, it was weighed. This procedure was repeated until two successive weighing does not differ by >0.5 mg.

Loss on drying

Loss on drying is widely used to determine the moisture content of a sample, although occasionally it may refer to the loss of any volatile matter from the sample. Not >15% (for all starches except potato starch) and not >20% (for potato starch) of weight loss should be obtained. It was determined by drying 0.2 g of starch in an oven at 105°C.

Test for amylose content

About 100 mg of isolated starch sample was taken, and to it, 1 ml of ethanol and 9 ml of 1 N sodium hydroxide were added and kept aside for overnight. The suspension was thoroughly mixed. The dispersed sample was transferred to a 100 ml volumetric flask and diluted to the mark with distilled water. 5 ml of test starch solution was pipetted into a 100 ml volumetric flask and 1 ml of 1 N glacial acetic acid and 2 ml of iodine solution (0.02 N) were added. The volume was made up to 100 ml with distilled water and the absorbance was measured at 620 nm.

Preparation of dolutegravir sodium solid dispersions by fusion method

Solid dispersions of dolutegravir sodium were prepared using Poloxamer-188 in different ratios by fusion method. Poloxamer-188 was placed in a China dish and heated at 40°C until it gets melted, and then dolutegravir sodium was added to it. After vigorous stirring in normal temperature, the mixture gets solidified. The solid mass was crushed, pulverized, and sieved. The granules obtained were stored in a desiccator for further studies. The results are given in Table 3.

Table 2: Evaluation of physicochemical properties for jack fruit seed powder and extracted starches

Parameters	JFSP	JFS1	JFS2	JFS3	JFS4
Gelatinization temperature	218–221°C	220–223°C	210–215°C	224–227°C	226–229°C
pH	6.32	6.50	7.10	6.78	6.98
Viscosity	1.856 cps	2.089 cps	2.578 cps	2.265 cps	2.312 cps
Swelling index	58	63	83	76	78
Water absorption index	250	270	290	260	280
Microbial growth	Absent	Absent	Absent	Absent	Absent
Loss on drying (%)	9.0	9.2	8.0	8.5	8.8
Oxidizing substances	No brown (or) blue color was observed	No brown (or) blue color was observed	No brown (or) blue color was observed	No brown (or) blue color was observed	No brown (or) blue color was observed
Fluorescence	No fluorescence observed	No fluorescence observed	No fluorescence observed	No fluorescence observed	No fluorescence observed
Acidity	Non acidified	Non acidified	Non acidified	Non acidified	Non acidified
Sulphated ash	0.09%	0.08%	0.1%	0.2%	0.1%
Amylose content	16.36	14.28	20.25	18.36	17.69

JFSP: Jack fruit seed powder, JFS1: Jack fruit seed powder extracted with water, JFS2: Jack fruit seed powder extracted with 0.1% sodium hydroxide, JFS3: Jack fruit seed powder extracted with 0.25% sodium hydroxide, JFS4: Jack fruit seed powder extracted with 0.5% sodium hydroxide

Evaluation of pre-formulation parameters

The prepared solid dispersions were evaluated for various pre-formulation parameters such as angle of repose, Carr's index, Hausner's ratio, and particle size [10,11]. The results are indicated in Table 4.

Drug content uniformity for solid dispersions

Solid dispersions of dolutegravir sodium equivalent to 50 mg was weighed and transferred into a 100 ml volumetric flask. To this, a small quantity of methanol was added to dissolve. It was shaken occasionally for about 15 min, and the volume was made up to 100 ml by methanol. The solution was filtered using Whatman filter paper. The filtrate was subsequently diluted with 6.8 pH phosphate buffer, and the absorbance was measured at 258 nm using 6.8 pH phosphate buffer as blank.

Table 3: Composition of dolutegravir sodium solid dispersions prepared by fusion method

Composition	Drug: Polymer ratio (Dolutegravir sodium*: Poloxamer-188)
DF1	1:0.5
DF2	1:1.0
DF3	1:1.5
DF4	1:2.0
DF5	1:3.0
DF6	1:4.0

*One part is equal to 50 mg

***In vitro* dissolution studies**

Dissolution studies for all solid dispersions were performed in a calibrated eight station dissolution test apparatus (LABINDIA DS8000) equipped with paddles employing 900 ml of 6.8 pH phosphate buffer as a dissolution medium. The paddles were operated at 50 rpm, and the temperature was maintained at 37±1°C throughout the experiment [12]. The samples were withdrawn at 5, 10, 15, 20, 30, 45, and 60 min and replaced with an equal volume of same dissolution medium to maintain the sink conditions throughout the experiment. Samples withdrawn were suitably diluted with same dissolution medium, and the amount of the drug dissolved was estimated by Lab India Double Beam UV spectrophotometer (UV 3000+) at 258 nm. The dissolution profiles were indicated in Table 5 and the parameters in Table 6.

Preparation of dolutegravir sodium tablets

Dolutegravir sodium tablets were prepared from the optimized solid dispersions using wet granulation technique. The drug concentration was maintained constant, while jackfruit seed starch and CCS concentrations were increased. The raw materials were individually weighed, passed through sieve 80 and blended for 15 min using double cone blender. The powder mixture of lactose, half amount of jackfruit starch was then converted into damp mass using sucrose solution. The damp mass was passed through sieve 20 to obtain granules and they were kept in tray dryer for drying at 60°C for 1 h. The optimized solid dispersion was added to lactose granules and blended for 15 min using double cone blender. Flavoring agent was added to powdered mass and blended with 1% talc and magnesium stearate and compressed as

Table 4: Pre-formulation parameters of dolutegravir sodium solid dispersions

Solid dispersion	Angle of repose (°)	Carr's index (%)	Hausner's ratio	Average particle size (μm)	Drug content (mg) (Mean±SD)
DP	32	19	1.22	35	-
DF1	25	14	1.19	174	46.22±0.54
DF2	23	13	1.20	171	44.85±0.41
DF3	21	12	1.16	168	49.62±0.77
DF4	25	13	1.18	175	48.54±0.81
DF5	24	14	1.17	176	47.87±0.59
DF6	24	15	1.21	174	47.11±0.17

*DP indicates Dolutegravir sodium pure drug, n=3, SD: Standard deviation

Table 5: Drug release profiles of dolutegravir sodium solid dispersions prepared by fusion method

Time (in min)	Cumulative % drug released (Mean±SEM)						
	DP	DF1	DF2	DF3	DF4	DF5	DF6
5	5.35±1.17	35.41±1.20	39.95±0.14	72.59±1.08	71.87±1.88	70.95±0.25	67.38±1.08
10	7.08±1.78	36.81±1.87	45.27±2.01	78.82±1.55	80.71±1.40	76.67±0.86	76.00±1.69
15	9.67±0.15	41.74±0.64	56.71±1.28	83.5±0.19	82.28±2.11	79.51±1.03	79.03±2.04
20	10.9±2.07	48.76±0.33	61.35±0.61	90.22±2.31	90.33±0.65	81.61±1.66	80.33±0.48
30	11.64±1.07	51.92±1.96	70.40±1.81	99.76±0.47	94.53±0.31	88.57±2.05	86.53±0.23
45	12.22±1.88	54.33±1.14	84.23±0.34	99.89±0.85	98.57±1.22	95.93±1.81	91.10±1.26
60	13.34±1.64	58.82±1.01	88.31±2.14	99.90±1.04	98.87±1.77	95.97±1.11	91.43±1.09

n=3, SEM: Standard error of mean

Table 6: *In vitro* dissolution parameters of dolutegravir sodium solid dispersions

Formulation	% drug released at 60 min	T_{50} (min)	T_{90} (min)	DE_{20}%	First order rate constant		Hixson-Crowell cube root plot	
					K (min^{-1})	R^2	K ($min^{-1/3}$)	R^2
DP	26.86	>60	>60	12.5	0.007	0.448	0.004	0.732
DF1	58.82	28	>60	35.0	0.024	0.906	0.008	0.895
DF2	88.31	13	>60	42.5	0.033	0.912	0.020	0.906
DF3	99.90	3.0	20	72.5	0.078	0.938	0.039	0.960
DF4	98.87	2.5	20	67.5	0.068	0.922	0.029	0.940
DF5	95.97	2.5	35	65.0	0.048	0.901	0.022	0.950
DF6	91.43	3.0	40	62.5	0.053	0.912	0.015	0.927

tablets using CLIT 10 station mini press. The compositions of various tablet formulations are given in Table 7.

Evaluation of post-compression parameters

The compressed tablets were further evaluated for post-compression parameters such as weight uniformity, hardness, friability, wetting time, dispersion test, and drug content [13]. The results are given in Table 8.

Drug content uniformity

Fast dissolving tablets of dolutegravir sodium from a batch were taken at random and were crushed to a fine powder. The powdered material was transferred into a 100 ml volumetric flask and few ml of methanol was added to it. It was shaken occasionally for about 30 min and the volume was made up to 100 ml by adding methanol. The resulting solution was set aside for few minutes and the supernatant solution was collected, filtered by Whatman filter paper. Then, the filtrate was subsequently diluted with phosphate buffer pH 6.8 and the absorbance was measured at 258 nm.

***In vitro* dissolution studies of dolutegravir sodium fast dissolving tablets**

The dissolution test was carried out in United States Pharmacopoeia (USP) apparatus Type II (paddle) with 900ml of 6.8 pH phosphate buffer as a dissolution medium. The samples were drawn at 5, 10, 15, 20, 30, 45, and 60 min. The fresh volume of the medium was replaced with the withdrawn volume to maintain the sink conditions and constant volume throughout the experiment. Samples withdrawn were suitably diluted with same dissolution medium, and the amount of drug dissolved was estimated by ELICO SL UV – 210 at 258 nm and subsequently analyzed for the cumulative percentage of drug released. The dissolution studies on each formulation were conducted in triplicate. The drug release profiles for all the formulations are given in Tables 9-11.

Reverse-phase high-performance liquid chromatography (RP-HPLC) studies

The dissolution studies for the optimized formulations were further analyzed by RP-HPLC method to achieve the concurrency [14]. The dissolution test was carried out in USP Apparatus Type II (paddle) with 900 ml of 6.8 pH phosphate buffer as the dissolution medium. The samples were drawn at 5, 10, 15, 20, 30, 45, and 60 min. The fresh volume of the medium was replaced with the withdrawn volume to maintain the sink conditions and constant volume throughout the experiment. Samples withdrawn were suitably diluted with the same dissolution medium, and the amount of drug dissolved was estimated by RP-HPLC. 40 µL of the respective concentration solution is injected to HPLC using a syringe. The sample was run for 10 min. The retention time and peak area were noted.

Table 7: Composition of dolutegravir sodium fast dissolving tablet formulations

Ingredient (mg/tablet)	Formulations									
	DFT1	DFT2	DFT3	DFT4	DFT5	DFT6	DFT7	DFT8	DFT9	DFT10
DF3 solid dispersion	125	125	125	125	125	125	125	125	125	125
Lactose	157	149.5	142	134.5	127	119.5	112	127	119.5	112
JFS2	-	7.5	15	22.5	30	37.5	45	-	-	-
CCS	-	-	-	-	-	-	-	30	37.5	45
Sucrose	15	15	15	15	15	15	15	15	15	15
Pineapple flavor	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Talc	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Magnesium stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Total weight	300	300	300	300	300	300	300	300	300	300

Q.S: Indicates quantity sufficient, CCS: Croscarmellose sodium , JFS2: jack fruit seed starch

Table 8: Post-compression parameters of various dolutegravir sodium fast dissolving tablet formulations

Formulation	Weight uniformity (mg)	Hardness (kg/cm^2) (Mean±SD)	Friability (% loss)	Wetting time (s)	Dispersion test	Drug content (mg/tablet) (Mean±SD)
DFT1	298±2	3.0±0.5	0.3	180	Passed	45.64±0.5
DFT 2	300±2	3.5±0.3	0.2	135	Passed	48.90±0.4
DFT 3	299±1	3.0±0.5	0.2	100	Passed	48.82±0.3
DFT 4	300±3	3.2±0.4	0.2	75	Passed	47.79±0.6
DFT 5	300±3	3.5±0.2	0.4	21	Passed	49.52±0.2
DFT 6	299±2	3.2±0.4	0.1	20	Passed	49.76±0.6
DFT 7	300±2	3.0±0.5	0.3	15	Passed	45.34±0.3
DFT 8	300±1	3.2±0.8	0.4	36	Passed	47.74±0.4
DFT 9	299±3	3.2±0.4	0.3	19	Passed	49.90±0.2
DFT 10	300±2	3.5±0.1	0.2	50	Passed	48.10±0.2

n=3, SD: standard deviation

Table 9: Dissolution profiles of dolutegravir sodium fast dissolving tablet formulations (DFT1–DFT6)

Time (min)	Cumulative % drug released (Mean±SEM)						
	DP	DFT1	DFT2	DFT3	DFT4	DFT5	DFT6
5	10.73±0.28	23.67±1.77	27.83±2.04	36.34±0.45	39.31±0.58	42.85±1.07	48.72±1.22
10	14.16±1.12	38.42±0.41	42.75±1.72	49.75±0.19	50.70±0.63	56.66±1.98	58.42±1.54
15	19.35±0.97	46.66±0.93	56.45±0.09	58.03±0.24	62.18±0.17	73.01±1.72	77.60±0.47
20	21.81±1.02	58.21±1.08	67.20±0.35	70.89±0.38	75.19±1.45	86.90±0.54	91.84±0.83
30	23.28±0.55	69.66±1.88	74.54±1.66	79.51±0.75	80.36±1.68	92.90±0.33	99.00±0.97
45	24.44±0.26	80.16±0.81	93.90±1.87	93.69±1.22	96.03±1.99	98.90±0.04	99.69±1.11
60	26.86±1.26	87.28±0.44	97.21±2.01	99.47±1.09	97.47±0.43	99.80±1.47	99.77±1.05

n=3, SEM: Standard error of mean, DP: Doultegravir sodium pure drug

The runs were continued for all concentrations. The dissolution profiles were drawn using method as described earlier. Peak area versus time chromatogram and data are given in Table 12 and shown in Fig. 1. The comparative drug release profile of optimized formulation DFT6 using RP-HPLC and UV spectrophotometric analysis is given in Table 13.

Statistical analysis

The results obtained were statistically evaluated. As the procedures performed and the results obtained were in triplicates, the mean along with their standard deviations was calculated for drug content, and standard error of mean was calculated for drug dissolution profiles.

Characterization studies

Based on the dissolution studies, the optimized formulations were selected, and Fourier transfer infrared (FTIR), and differential scanning calorimetry (DSC) studies were performed to observe the drug-polymer interactions. X-Ray diffraction (XRD) studies were performed to detect the nature of formulations. Scanning electron microscopy (SEM) analysis was performed on JFS2, dolutegravir sodium, poloxamer-188, CCS, optimized solid dispersion, and fast dissolving tablet formulations to know surface characteristics. The results are shown in Figs. 2-5.

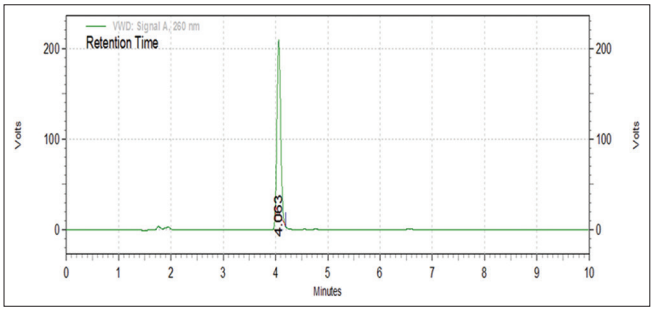

Fig. 1: Reverse-phase high-performance liquid chromatography chromatogram of dissolution sample (DFT6) at 20 min time interval

Accelerated stability studies

Accelerated stability studies were carried out on optimized formulations as per International Council for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines. After the stability studies, the formulations were evaluated for physical parameters, drug content, and drug release studies. The results are indicated in Tables 14-16.

RESULTS AND DISCUSSION

Extraction of starch from jack fruit seeds

The starches extracted from jack fruit seeds were crisp, slightly granular, free-flowing and stable in nature.

Phytochemical screening of jack fruit seed flour and starch extracts

The raw jack fruit seed powder and starches extracted were screened for the presence of various phytochemical constituents.

Evaluation of physicochemical properties of jack fruit seed powder and extracted starch

All the parameters evaluated for jack fruit seed powder and extracted starches were within specified Indian Pharmacopoeial limits. Of all the starches, JFS2 with high swelling and water absorption index was selected for preparation of fast dissolving tablets.

Preparation of dolutegravir sodium solid dispersions by fusion method

Solid dispersions of dolutegravir sodium were prepared using Poloxamer-188 in different ratios by fusion method. The composition of dolutegravir sodium solid dispersions prepared by the fusion method is given in Table 3.

Evaluation of pre-formulation parameters

Various pre-formulation parameters of dolutegravir sodium solid dispersions were evaluated. The obtained results are indicated in Table 4.

Table 10: Dissolution profiles of dolutegravir sodium fast dissolving tablet formulations (DFT7–DFT10)

Time (min)	Cumulative % drug released (Mean±SEM)					
	DP	DFT7	DFT8	DFT9	DFT10	DMT
5	10.73±0.47	24.43±1.19	41.51±0.57	46.7±1.22	65.96±0.44	12.47±0.78
10	14.16±0.81	36.26±1.08	55.75±1.44	58.29±0.96	67.27±0.72	29.26±0.11
15	19.35±1.16	46.78±0.40	71.94±1.65	75.96±2.14	76.98±1.70	41.68±1.25
20	21.81±1.78	79.12±1.66	87.91±2.11	92.7±1.07	91.41±1.93	56.35±1.71
30	23.28±1.94	91.62±1.54	91.64±1.08	98.2±1.42	93.73±2.04	72.89±2.55
45	24.44±0.65	94.55±0.70	97.36±0.37	98.79±0.90	95.23±1.62	85.16±1.33
60	26.86±0.83	95.80±0.21	97.66±0.82	99.69±0.14	98.09±0.81	89.72±0.90

n=3, SEM: Standard error of mean, DP: Dolutegravir sodium pure drug, DMT: Dolutegravir marketed tablet

Table 11: Dissolution parameters of dolutegravir sodium fast dissolving tablets

Formulation	% drug released at 60 min	T_{50} (min)	T_{90} (min)	DE_{20}%	First order		Hixson crowell	
					K (min^{-1})	R^2	K ($min^{-1/2}$)	R^2
DP	26.86	>60	>60	12.5	0.007	0.448	0.004	0.732
DFT1	87.28	17	>60	30	0.033	0.977	0.028	0.961
DFT2	97.21	12.5	44	42.5	0.059	0.929	0.041	0.860
DFT3	99.47	11	43	45	0.071	0.960	0.045	0.860
DFT4	97.47	10	40	50	0.062	0.976	0.041	0.955
DFT5	99.80	7	40	50	0.082	0.960	0.051	0.947
DFT6	99.77	6	20	57.5	0.082	0.982	0.053	0.980
DFT7	95.80	16	30	35	0.058	0.918	0.042	0.880
DFT8	97.66	8	27	55	0.004	0.822	0.042	0.869
DFT9	99.69	7	20	47.5	0.111	0.990	0.050	0.985
DFT10	98.09	45	20	60	0.059	0.898	0.036	0.891
DMT	89.72	17	>60	15	0.055	0.943	0.033	0.970

DP: Dolutegravir sodium pure drug, DMT: Dolutegravir marketed tablet

Table 12: Drug release profiles of optimized formulation (DFT6) by RP-HPLC analysis

Time (min)	Cumulative % drug released (Mean ± SEM)
5	40.56 ± 1.08
10	50.86 ± 1.64
15	73.25 ± 0.87
20	89.36 ± 1.17
30	96.32 ± 2.13
45	98.10 ± 1.77

n = 3, SEM: Standard error of mean

Table 13: Comparative drug release profiles of optimized formulation (DFT6) by RP-HPLC and UV spectrophotometry analysis

Time (min)	Cumulative % drug released (Mean±SEM)	
	DFT6 (UV)	DFT6 (HPLC)
5	48.72±1.22	40.56±1.08
10	58.42±1.54	50.86±1.64
15	77.60±0.47	73.25±0.87
20	91.84±0.83	89.36±1.17
30	99.00±0.97	96.32±2.13
45	99.69±1.11	98.10±1.77
60	99.77±1.05	98.45±1.24

n=3, SEM: Standard error of mean, RP-HPLC: Reverse-phase high-performance liquid chromatography chromatogram, UV: Ultraviolet

***In vitro* dissolution studies of dolutegravir sodium solid dispersions**

Formulation DF3, prepared in 1:3 ratios of dolutegravir sodium and Poloxamer-188 showed maximum drug release proving that solid dispersion technique enhances drug release as suggested by earlier studies [15]. The fusion technique used for the formulation of solid dispersions was also proved to be most advantageous as suggested earlier [16]. Employment of hydrophilic polymer was proved to be effective in dissolution enhancement [17]. The dissolution profiles of dolutegravir sodium solid dispersions are given in Table 5.

Formulation of dolutegravir sodium fast dissolving tablets

Dolutegravir sodium fast dissolving tablets with various concentrations of JFS2 and CCS were prepared by wet granulation technique. Formulations DFT2 to DFT7 were prepared using 2.5–15% of JFS2. Formulations DFT8 to DFT10 were prepared using 10–15% of CCS. Formulation DFT1 does not contain any superdisintegrant. The compositions are given in Table 7.

Evaluation of post-compression parameters

The wet granulation process was found to be suitable for compressing prepared granules as fast dissolving tablets [18,19]. All the batches of tablets were compressed under identical conditions to minimize processing variables. Then, the compressed tablets were further evaluated for post-compression parameters. The results are given in Table 8. Weight uniformity, hardness, and friability loss of all tablet formulations were within the specified limits. Thus, all the batches of tablet formulations were found to be stable and suitable for further studies.

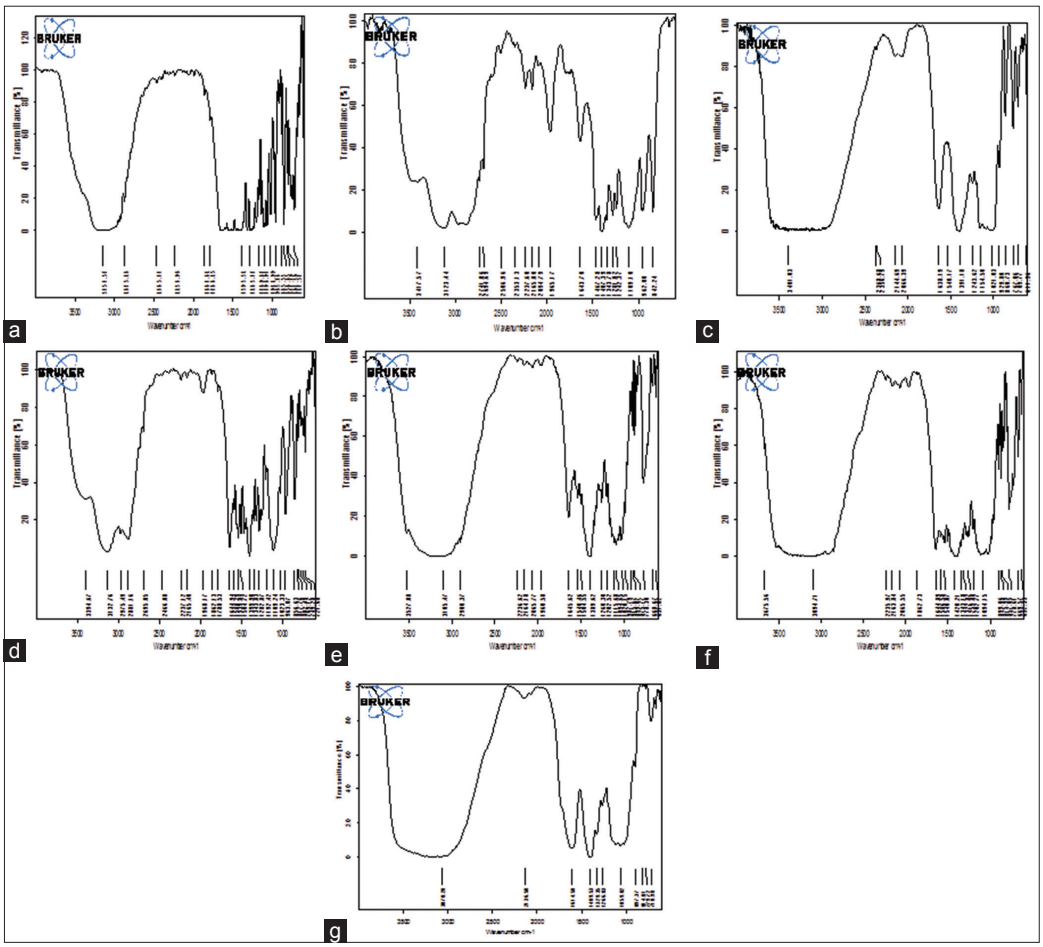

Fig. 2: Fourier transfer infrared spectra: (a) Dolutegravir sodium pure drug (b) Poloxamer-188 (c) DF3 solid dispersion (d) JFS2 (e) DFT6 Formulation (f) CCS (g) DFT9 formulation. JFS2: Jack fruit seed starch extracted with 0.1% sodium hydroxide, CCS: Croscarmellose sodium, DF3: Solid dispersion of dolutegravir±Poloxamer-188 in 1:3 ratio, DFT6: Solid dispersion of DF3 with 12.5% JFS2, DFT9: Solid dispersion of DF3 with 12.5% CCS

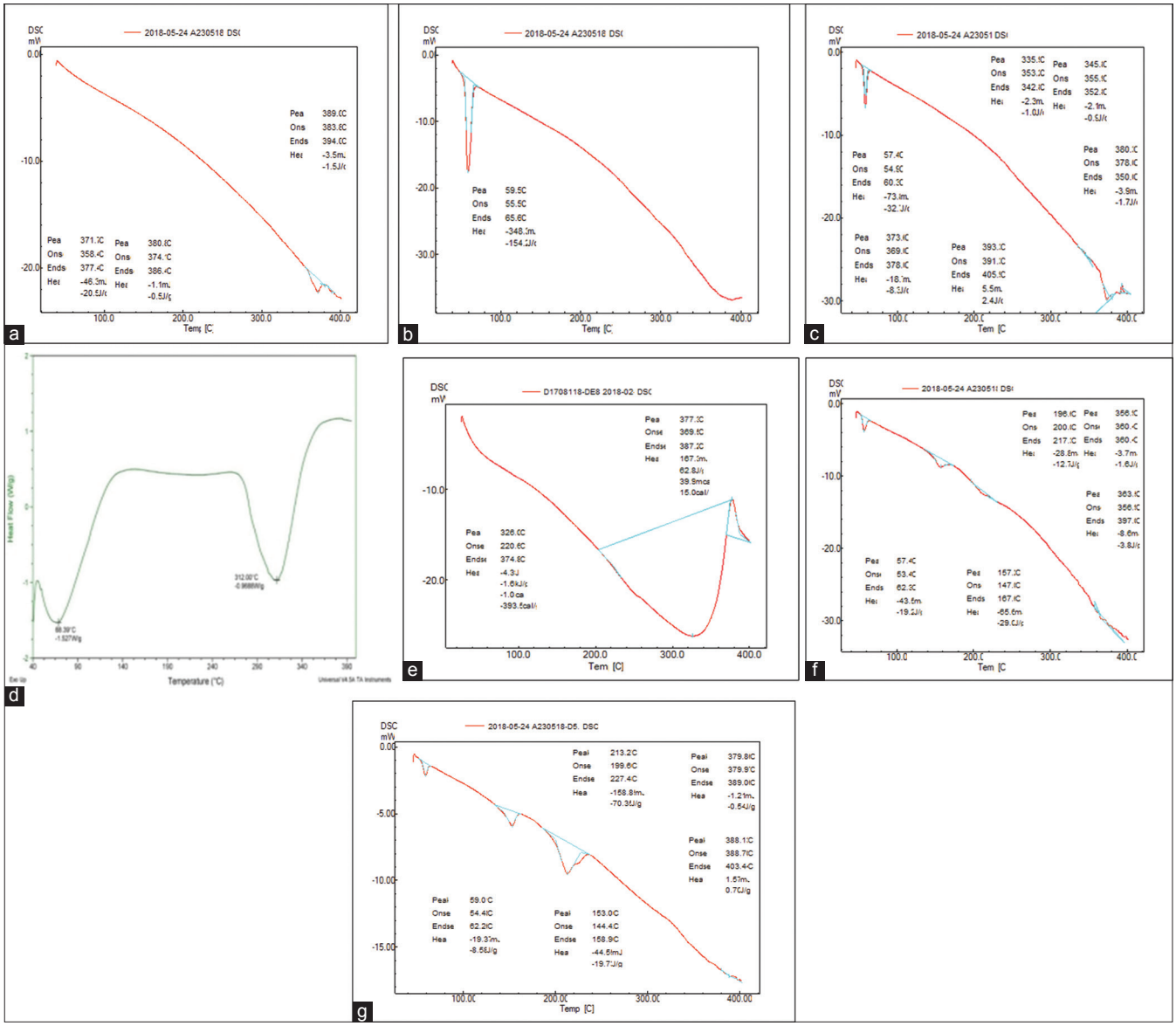

Fig. 3: Differential scanning calorimetry thermograms: (a) Dolutegravir sodium pure drug (b) Poloxamer-188 (c) DF3 Solid Dispersion (d) JFS2 (e) DFT6 formulation (f) CCS (g) DFT9 formulation. JFS2: Jack fruit seed starch extracted with 0.1% sodium hydroxide, CCS: Croscarmellose sodium, DF3: Solid dispersion of dolutegravir±Poloxamer-188 in 1:3 ratio, DFT6: Solid dispersion of DF3 with 12.5% JFS2, DFT9: Solid dispersion of DF3 with 12.5% CCS

***In vitro* dissolution studies of dolutegravir sodium fast dissolving tablets**

Dissolution studies were carried on all fast dissolving tablet formulations using USP paddle method (Apparatus II) with phosphate buffer pH 6.8 as dissolution medium by maintaining the bath temperature at 37±1°C and the paddles were operated at 50 rpm. The dissolution profiles of all the fast dissolving tablets are given in Tables 9 and 10.

It was observed that the type of starch as superdisintegrant and its proportion in the formulation have greatly influenced the dissolution parameters of various formulations. Formulation DFT6 containing 12.5% w/w of JFS2 as superdisintegrant exhibited similar dissolution profile with that of the formulation DFT9 prepared by 12.5% w/w CCS. Several studies have been conducted earlier indicating the effect of superdisintegrants over solubility enhancement [20]. They suggest the usage of a mixture of superdisintegrants rather than single. Solid dispersions were already proved to be effective in dissolution rate enhancement [21]. Along with this, if starch was also incorporated, it could increase the dissolution rate more. Natural derivatives are nowadays playing an important role in solubility enhancement [22]. Recent studies suggest the application of natural starches as superdisintegrants. They also prove the equal efficacy of natural starches and already established superdisintegrants.

RP-HPLC studies

The dissolution studies for the optimized formulations were further analyzed by RP-HPLC method. The dissolution profiles obtained from RP-HPLC technique showed almost similar dissolution profile as that of UV spectrophotometric analysis which indicated the accuracy of data.

Characterization studies

Based on the dissolution studies performed on all the formulations, the optimized formulations were selected, and the following studies were done.

FTIR spectroscopic analysis

The FTIR spectral investigations were conducted on dolutegravir pure drug, poloxamer-188, solid dispersion DF3, JFS2, CCS, DFT6, and DFT9

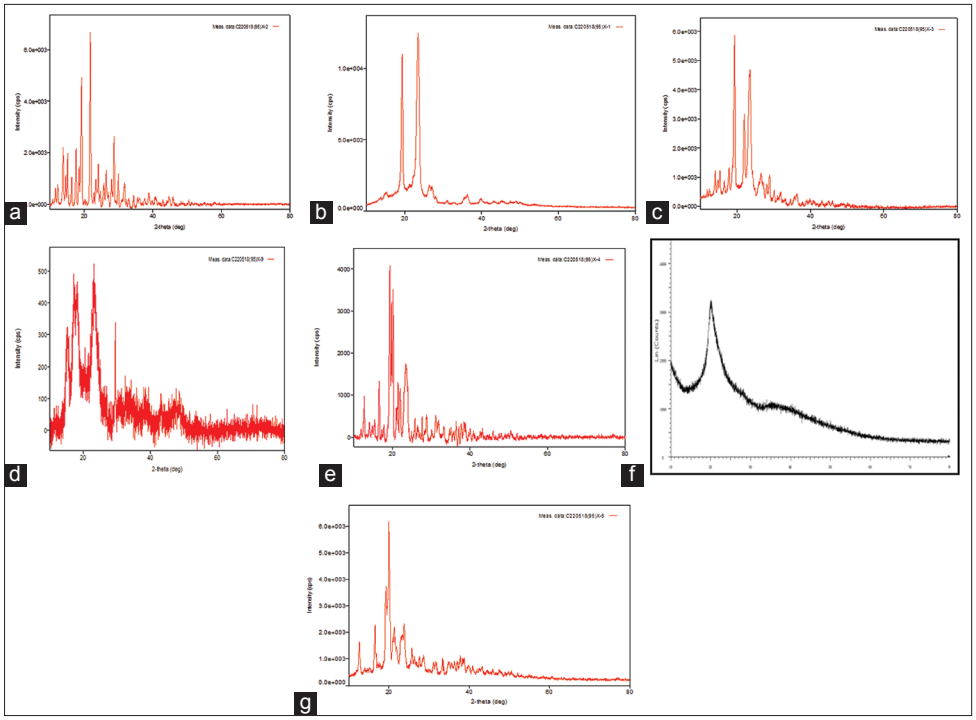

Fig. 4: X-ray diffraction diffractograms: (a) Dolutegravir sodium pure drug (b) Poloxamer-188 (c) DF3 solid dispersion (d) JFS2 (E) DFT6 formulation (f) CCS (g) DFT9 formulation. JFS2: Jack fruit seed starch extracted with 0.1% sodium hydroxide, CCS: Croscarmellose sodium, DF3: Solid dispersion of dolutegravir±Poloxamer-188 in 1:3 ratio, DFT6: Solid dispersion of DF3 with 12.5% JFS2, DFT9: Solid dispersion of DF3 with 12.5% CCS

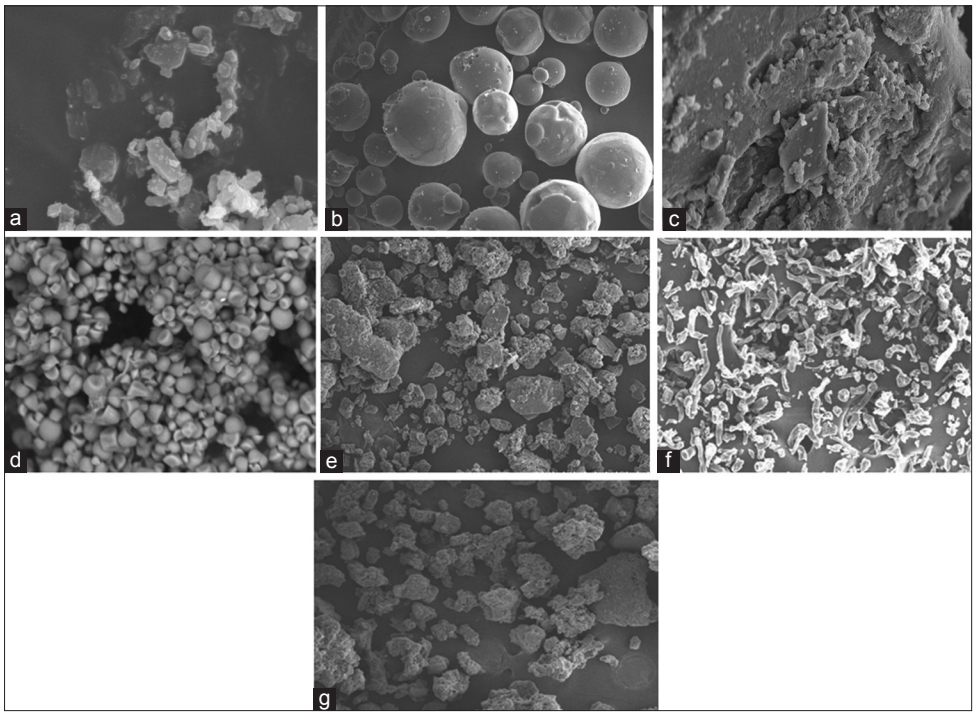

Fig. 5: Scanning electron microscopy images: (a) Dolutegravir sodium pure drug (b) Poloxamer-188 (c) DF3 solid dispersion (d) JFS2 (e) DFT6 Formulation (f) CCS (g) DFT9 formulation. JFS2: Jack fruit seed starch extracted with 0.1% sodium hydroxide, CCS: Croscarmellose sodium, DF3: Solid dispersion of dolutegravir±poloxamer−188 in 1:3 ratio, DFT6: Solid dispersion of DF3 with 12.5% JFS2, DFT9: Solid dispersion of DF3 with 12.5% CCS

formulations. The pure drug dolutegravir sodium exhibited sharp peak at 2234.96 cm^{-1}, 1393.32 cm^{-1}, 856.65 cm^{-1}, and 885.53 cm^{-1} indicating the presence of C-N stretching, C≡C stretching, C-O-C stretching, C-H bending, and Ar-H bending. For Poloxamer sharp peaks at 2237.60 cm^{-1}, 2165.00 cm^{-1}, and 842.24 cm^{-1} indicated C-N stretching, C≡C stretching, and C-H bending. For DF3 solid dispersion, sharp peaks at 2237.12 cm^{-1}, 2165.40 cm^{-1}, 1391.18 cm^{-1}, and 842.24 cm^{-1} indicated C-N stretching, C≡C stretching, C-O-C stretching, and Ar-H bending. For JFS2 sharp

Table 14: Post-compression parameters of formulations DFT6 and DFT9 under accelerated stability conditions

Formulation	Storage condition	Hardness (kg/cm²)	Friability (% loss)	Dispersion test	Wetting time (s)	Drug content (mg/tablet)
DFT6	Before Storage	3.2±0.4	0.2	Passed	20	49.76±0.6
	25±2°C, 60±5% RH	3.1±0.2	0.3	Passed	21	49.00±0.2
	40±2°C, 75±5% RH	3.2±0.4	0.2	Passed	19	48.86±0.2
DFT9	Before Storage	3.2±0.1	0.2	Passed	19	49.90±0.6
	25±2°C, 60±5% RH	3.2±0.4	0.3	Passed	20	49.50±0.6
	40±2°C, 75±5% RH	3.1±0.2	0.3	Passed	19	49.80±0.6

Table 15: Accelerated stability studies dissolution profiles of formulation (DFT6)

Time (min)	Before storage	25±2°C, 60±5% RH	40±2°C, 75±5% RH
5	48.72±1.22	48.69±1.20	45.90±0.74
10	58.42±1.54	58.40±1.48	55.58±1.11
15	77.60±0.47	77.58±1.52	74.23±2.04
20	91.84±0.83	91.82±1.71	87.65±1.99
30	99.00±0.97	99.00±0.54	95.09±1.73
45	99.69±1.11	99.65±0.87	95.41±1.25
60	99.77±1.05	99.74±0.33	96.22±1.81

n=3, RH: Relative humidity

Table 16: Accelerated stability studies dissolution profiles of formulation (DFT9)

Time (min)	Before storage	25 ± 2°C, 60 ± 5% RH	40 ± 2°C, 75 ± 5% RH
5	46.7 ± 1.22	46.69 ± 1.19	46.65 ± 1.07
10	58.29 ± 0.96	58.26 ± 1.78	58.23 ± 2.88
15	75.96 ± 2.14	75.93 ± 1.44	75.30 ± 1.44
20	92.7 ± 1.07	92.68 ± 1.05	92.63 ± 0.79
30	98.2 ± 1.42	98.18 ± 2.11	98.14 ± 0.23
45	98.79 ± 0.90	98.75 ± 0.53	98.70 ± 0.15
60	99.69 ± 0.14	99.65 ± 1.73	99.61 ± 0.09

n = 3, RH: Relative humidity

peaks at 1391.18 cm^{-1} and 860.73 cm^{-1} were observed indicating the presence of C-O-C stretching and Ar-H bending. For DFT6 tablet formulation, sharp peaks at 2236.62 cm^{-1}, 2164.18 cm^{-1}, 1389.62 cm^{-1}, and 875.77 cm^{-1} indicated the presence of C-N stretching, C≡C stretching, C-O-C stretching, C-H bending, and Ar-H bending. For CCS, a sharp peak at 2136.50 cm^{-1} and 897.37 cm^{-1} indicated the presence of C≡C stretching and Ar-H bending. For DFT9 formulation, a sharp peak at 2163.84 cm^{-1}, 857.05 cm^{-1}, and 899.06 cm^{-1} indicated the presence of C≡C stretching, C-H bending, and Ar-H bending. The remaining peaks were unaltered indicating that there was no drug and excipients interaction. The detailed spectral elucidations are shown in Fig. 2.

DSC

A differential scanning calorimeter (DSC 200F3, Shimadzu) was used to obtain the DSC curves of dolutegravir sodium pure drug, poloxamer-188, solid dispersion DF3, CCS, DFT6, and DFT9 formulations representing the rates of heat uptake. The DSC results revealed that a sharp peak for dolutegravir sodium was observed at 371.78°C, 380°C, and 389°C. A sharp endothermic peak for poloxamer-188 was observed at 59.5°C. Sharp and broad peaks for DF3 were observed at 57.47°C, 345.80°C, and 373.68°C. Broad endothermic peaks for jack fruit seed starch were observed at 68.39°C and 312.00°C. For DFT6, a broad peak and sharp peak were observed at 57.47°C, 356.96°C, and 363.59°C. Sharp endothermic peaks for CCS were observed at 326.00°C and 377.3°C. A broad and sharp peak for DFT9 was observed at 59.01°C, 153.00°C, and 379.86°C. These studies revealed that there were no drug and excipient interactions which were confirmed by obtaining similar thermographic peaks at respective temperatures. The detailed thermographs are shown in Fig. 3.

Powder XRD (PXRD)

PXRD patterns were traced employing X-ray diffractometer Shimadzu and DSC-60, Germany for all the samples using Nickel filter, CuK (α) radiation, a current of 20 mA and receiving slit of 0.2 inches. PXRD studies of dolutegravir sodium showed several sharp peaks from 10 to 40 θ°. The PXRD studies for poloxamer 188 showed only two sharp peaks at 20–30 θ°. The solid dispersion prepared by dolutegravir sodium and polaxmer-188 revealed that sharp peaks corresponding to the polymer were observed at 20–30 θ°. This indicated that the crystallinity of the pure drug was greatly reduced by solid dispersion formulation having poloxamer 188. PXRD studies of JFS2 showed sharp peaks at 17–33 and CCS at 20.3 θ°. DFT6 and DFT9 formulations exhibited peaks at 3–30 θ°. The PXRD patterns are shown in Fig. 4.

SEM

SEM images were taken for Dolutegravir sodium pure drug, poloxamer-188, solid dispersion DF3, JFS2, CCS and a blend of DF3 and jack fruit starch. SEM photographs of dolutegravir sodium exhibited high crystallinity of drug with several planes of the surface. Poloxamer-188 exhibited a spherical shaped granular form of beads. Solid dispersion DF3 showed that the drug was absorbed on to the spherical beads and thereby the crystallinity of the drug is greatly reduced. The Jack fruit starch, JFS2 exhibited spherical free flowing with a low dense form of starch grains without having any intact resinous or mucilaginous mass and CCS exhibited crystallinity. The SEM image of a blend of Dolutegravir DF3 and Jack fruit starch (DFT6 formulation) exhibited the well-distributed spherical shaped intragranular spaces and bead-like crystals were clearly observed. The SEM image of a blend of DF3 and CCS (DFT9 tablet formulation) exhibited the well distributed spherical-shaped bead-like crystals. The SEM images were clearly shown in Fig. 5.

Accelerated stability studies of dolutegravir sodium fast dissolving tablets

The fast dissolving tablets DFT6 and DFT9 containing dolutegravir sodium which showed good *in vitro* performance were subjected to accelerated stability studies. These studies were carried out by investigating the effect of temperature on the physical properties and drug release from fast dissolving tablets. The results of these studies are given in Tables 14-16. The results thus indicated that there were no visible and physical changes observed in the frequency-discrimination thresholds (FDTs) even after storage. Weight uniformity, hardness, friability, wetting time, dispersion test, and drug content were found to be uniform before and after storage at different conditions. It was also observed that there was no significant change in drug release from the FDTs. Thus, the drug release characteristics of FDTs designed were found to be quite stable.

CONCLUSION

The starch JFS2 extracted from jack fruit seeds with 0.1% sodium hydroxide is found to be the best and is used as superdisintegrant for preparation of fast dissolving tablets. Dolutegravir sodium solid dispersions were prepared using various concentrations of JFS2 and poloxamer-188 and were subjected to *in vitro* dissolution studies. From these studies, it was observed that the proportion of starch as superdisintegrant has influenced the dissolution parameters of various formulations. Dolutegravir sodium fast dissolving tablets were prepared using various concentrations of JFS2 and CCS and were subjected to *in vitro* dissolution studies. From these studies, it was observed that the

proportion of starch as superdisintegrant has influenced the dissolution parameters of various formulations. Similar dissolution profiles were observed for formulations, DFT6 containing 12.5% w/w of JFS2 and DFT9 containing 12.5%w/w of CCS as superdisintegrants. The possible mechanism of superdisintegrant effect of these starches might be the rapid uptake of water, followed by swelling which causes the elevation of hydrostatic pressure in a tablet that leads to faster disintegration of tablets. The optimized formulations when subjected to FTIR and DSC analysis showed no drug-excipient interactions. Similarly, XRD studies were conducted to know the crystalline and amorphous nature of the samples. The optimized formulations DFT6 and DFT9 were also subjected to accelerated stability studies, which revealed that there were no significant changes in physical parameters and drug content even after the stability studies at various storage conditions which indicated that these formulations were stable.

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AUTHOR'S CONTRIBUTIONS

Dr. Vidyadhara Suryadevara the guarantor of this study has designed and supervised the experimental process. Mr. Sundeep Mupparaju and Ms. Sailaja Yallam have carried out the experiments and analyzed the results. Mr. Sandeep Doppalapudi has contributed in preparation and revision of the manuscript. Dr. Sasidhar Reddyvallam L C and Dr. Ramu Anne have reviewed the manuscript.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

REFERENCES

1. Saharan VA, Kukkar V, Kataria M, Gera M, Chowdhury PK. Dissolution enhancement of drugs, Part I: Technologies and effect of carriers. Int J Health Res 2009;2:107-24.
2. Dhirendra K, Lewis S, Udupa N, Atin K. Solid dispersions: A review. Pak J Pharm Sci 2009;22:234-46.
3. Clotet B, Feinberg J, van Lunzen J, Khuong-Josses MA, Antinori A, Dumitru I, *et al.* Once-daily dolutegravir versus darunavir plus ritonavir in antiretroviral-naive adults with HIV-1 infection (FLAMINGO): 48 week results from the randomised open-label phase 3b study. Lancet 2014;383:2222-31.
4. Elzi L, Erb S, Furrer H, Cavassini M, Calmy A, Vernazza P, *et al.* Adverse events of raltegravir and dolutegravir. AIDS 2017;31:1853-8.
5. Raffi F, Rachlis A, Stellbrink HJ, Hardy WD, Torti C, Orkin C, *et al.* Once-daily dolutegravir versus raltegravir in antiretroviral-naive adults with HIV-1 infection: 48 week results from the randomised, double-blind, non-inferiority SPRING-2 study. Lancet 2013;381:735-43.
6. Chauhan V, Kumar K, Teotia D. Fast dissolving tablets: A promising approach for drug delivery. Univ J Pharm Res 2017;2:58-4.
7. Fateatun N, Jiaur RM, Sultan MM, Sorifa A, Aminul IT, Ahmed M. Physicochemical properties of flour and extraction of starch from Jack Fruit seed. Int J Nut Food Sci 2014;3:347-54.
8. Menaka T, Nagaraja G, Yogesh DB, Sunil Kumar US, Prakash L. Physicochemical properties of flour and isolated starch from Jackfruit seeds (Artocarpus Heterophyllus). Res J Pharm Sci 2011;1:14-8.
9. Vidyadhara S, Sasidhar RL, Lakshmi HD, Vijetha P, Vijetha K. Studies on jack fruit seed starch as a novel natural superdisintegrant for the design and evaluation of Irbesartan fast dissolving tablets. Int Med Res 2017;6:280-91.
10. Okunlola A, Odeku OA. Comparative evaluation of starches obtained from *Dioscorea* species as intragranular tablet disintegrants. J Drug Del Sci Technol 2008;18:445-7.
11. Sharda S, Bishambar S, Kirtika M, Monalisha N, Neha K, Shalini M. Solid dispersions: A tool for improving the solubility and dissolution of metronidazole. Int J Drug Del 2013;5:94-8.
12. Appa RB, Shivalingam M, Kishore RY, Somesekhara R, Rajesh K, Sunitha N. Formulation and evaluation of aceclofenac solid dispersions for dissolution rate enhancement. Int J Pharm Sci Drug Res 2010;2:146-50.
13. Sreenivas SA, Gadad A, Patil M. Formulation and evaluation of Ondansetron hydrochloride directly compressed mouth dissolving tablets. Indian Drugs 2006;4:35-7.
14. Bhavar GB, Pekamwar SS, Aher KB, Thorat RS, Chaudhari SR. High-performance liquid chromatographic and high-performance thin-layer chromatographic method for the quantitative estimation of dolutegravir sodium in bulk drug and pharmaceutical dosage form. Sci Pharm 2016;84:305-20.
15. Dharna A, Neelam S, Sukhbir S, Sandeep A. Solid dispersions: A review on drug delivery system and solubility enhancement. Int J Pharm Sci Res 2013;4:2094-105.
16. Shashikumar Y, Veena M, Srinivas M. Solid dispersion technique to enhance the solubility and dissolution rate of Aripiprazole by fusion method. Int J Pharm Pharm Sci 2016;8:187-92.
17. Pratik SD, Sushma V, Puja S. Fast dissolving tablet using solid dispersion technique: A review. Int J Curr Pharm Res 2017;9:1-4.
18. Sharma A, Jain CP. Preparation and characterization of solid dispersions of carvedilol with PVP K30. Res Pharm Sci 2010;5:49-56.
19. Shukla D, Subhashis C, Sanjay S, Brahmeshwar M. Mouth dissolving tablets II: An overview of evaluation techniques. Sci Pharm 2009;77:327-41.
20. Venkatarao M, Vidyadhara S, Sandeep D. Formulation and evaluation of Telmisartan solid dispersions using *Entada* scandens seed starch and Poloxamer-188 as superdisintegrants. Asian J Pharm Clin Res 2018;11:474-81.
21. Rubendra K, Dinesh KM, Dinesh KJ. Solid dispersion: A novel means of solubility enhancement. J Crit Rev 2016;3:1-8.
22. Emmanuel OO, Musiliu OA, Ekaete IA. Evaluation of callinectes chitosan as a superdisintegrant in metronidazole tablet. Int J Pharm Pharm Sci 2017;9:111-8.