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DEVELOPMENT AND EVALUATION OF FAVIPIRAVIR AGGLOMERATES FOR DIRECT COMPRESSION BY CRYSTALLO-CO-AGGLOMERATION TECHNIQUE

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Keywords:

Crystallo-co-agglomerates, Favipiravir, Solubility, Direct compression, Dissolution

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ABSTRACT: During the severe worldwide pandemic caused due to SARS COV-2 Corona virus, Favipiravir has been used for the treatment. It is a water insoluble anti-viral drug with poor dissolution and poor flow properties, resulting in poor oral absorption and less bioavailability. For a long time, the phrase "direct compression" was used to describe the compression of a single crystalline component into a compact without the addition of any other materials. Using excipients and solvents, the crystallo-co-agglomeration process aggregates drug crystals in the form of small spherical particles to create an intermediate product with better micromeritic and mechanical characteristics, solubility, and dissolution. Crystallo-co-agglomeration is a unique approach in which the pharmaceuticals or excipients are crystallized and agglomerated concurrently from a good solvent and/or bridging liquid by adding a non-solvent. The present study aims to formulate crystallo-co-agglomerates of Favipiravir to improve its physicochemical and mechanical properties. Results obtained during the evaluation showed that CCA technique could be successfully employed as an alternative to conventional wet agglomeration.

INTRODUCTION: Until the late 1950s, the bulk of tablets were made using a procedure that required granulation of powdered ingredients before tableting. The granulation step's primary goal is to create a free-flowing, compressible mixture of active substances and excipients. The discovery of new tablet technology and the availability of new excipients or novel kinds of excipients, particularly fillers and binders, have enabled the production of tablets using the considerably simpler direct compression process [1].

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Compared to the more typical granulation technique, there has been increasing interest in studying the possibility of direct compression tableting in recent years. Simple mixing and compression of powders are used to make tablets, which has a variety of advantages, including savingin both time and money. Numerous medications have been successfully tested using this technique [2].

Moreover, some drawbacks limit direct compression's practical applicability to a few products. Problems involving relative density and flow qualities are included. To solve the aforementioned challenges, the particle size should be increased. To solve these issues, Kwashima *et al* devised a new technology called "Spherical crystallization." This method can also be used to change the crystalline form of medicines. However,

it was only used to increase the size of the drug particles. Kadam *et al.* developed Crystallo-co-Agglomeration in 1997 as an outgrowth of spherical crystallisation.

C CCA, or crystallo-co-agglomeration, is a unique approach in which a medication, pharmaceuticals, or excipients are crystallised and agglomerated concurrently from a good solvent and/or bridging liquid by adding a non-solvent. This one-step procedure was carried out with one, two, or more medicines in tiny or high doses, with or without diluents. The resulting spherical agglomerates were formed into complete beads (encapsulated spensules), which acts as transitional stage for direct compression with enhanced micromeritic (flowability), mechanical (friability), crushing, and compressional (compressibility, compactability) characteristics. The drug release properties were influenced by the polymer composition chosen. CCA's key advantages are its ease of use and cheaper production costs due to its single-step operation [3].

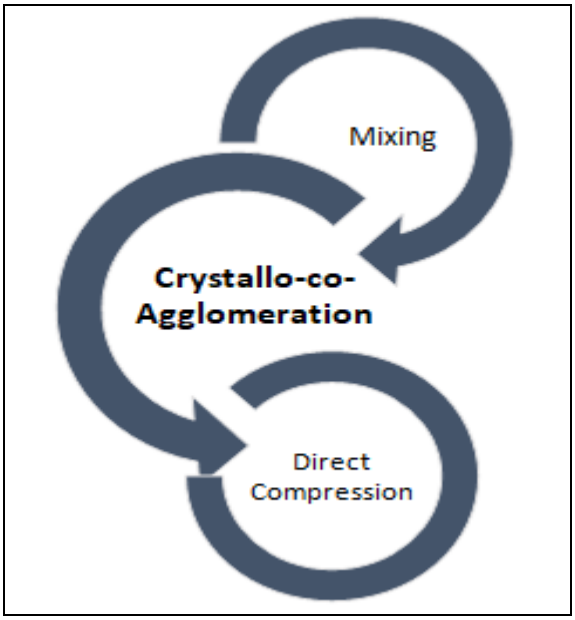

FIG. 1: STEPS IN TABLET MANUFACTURING USING CRYSTALLO-CO-AGGLOMERATION

Drug Profile [4, 5]: Favipiravir is an approved drug for new and re-emerging pandemic influenza. Favipiravir has proven efficacy against a broad range of influenza viruses and may halt the replication of several other RNA viruses. Favipiravir is a water insoluble anti-viral drug with poor dissolution and poor flow properties which results in poor oral absorption and less bioavailability. The choice of drug was made based on the above-mentioned problems associated with the drug. In the present study to improve the solubility, dissolution, compressibility, and flow properties of favipiravir, crystallo-co-agglomerates of favipiravir has been developed using Crystallo-co-Agglomeration technique and evaluated to check its enhanced properties. CCA of Favipiravir prepared in the presence of polymer PEG 6000 for overall enhancement of physicochemical properties. In this FVP was crystalized from acetone as good solvent and simultaneously agglomerated with excipients in the presence of DCM as bridging solvent.

Physicochemical properties of raw FVP and its agglomerates were characterized in the solid-state using techniques such as SEM, FTIR, DSC, XRD, HS-GC, Drug Content, Solubility studies and dissolution tests. The improvement in micromeritic properties was determined by calculating the angle of repose, Haussner's ratio, Carr's Index of FVP and its agglomerates respectively.

MATERIALS AND METHOD:

Material: Favipiravir was obtained as gift sample from PEG 6000, Dichloromethane (DCM) and all other chemicals and reagents used were of analytical grade.

Selection of Solvent System: Based on solubility studies, acetone was selected as good solvent, and water was selected as antisolvent. For selecting bridging liquid trials were conducted at a preliminary level using chloroform, hexane, toluene, and Dichloromethane (DCM) for the agglomeration behaviour. By considering the best result obtained, DCM is selected as bridging solvent for the preparation of FVP agglomerates.

Method:

Development of FVP Agglomerates by CCA: Favipiravir agglomerates were prepared using three solvent system comprising Acetone-Dichloromethane-Water (Good solvent, Bridging solvent and bad solvent). The drug Favipiravir was dissolved in acetone. This solution was added slowly to a solution of polymer PEG 6000 in distilled water. The resultant mixture was kept for continuous stirringon magnetic stirrer (300 rpm)at room temperature. With constant stirring bridging

solvent DCM was added drop wise to obtain the agglomerates, which were then filtered and dried overnight. Different agglomerates were prepared for the compositions shown in **Table 1** with the help of Design of Expert software (DOE).

TABLE 1: COMPOSITION OF DEVELOPED BATCHES OF FVP AGGLOMERATES WITH DOE

Sr. no.	Factor (%)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	PEG 6000 (gm)	1.9	0.1	**1**	**1**	2.27	1	1.9	0.1	1
2	DCM (ml)	1	5	**3**	**3**	3	5.82	5	1	0.17
3	ACETONE (ml)	5	5	5	5	5	5	5	5	5
4	Distilled Water (ml)	40	40	40	40	40	40	40	40	40
5	Favipiravir (gm)	1	1	1	1	1	1	1	1	1

Optimization of CCA Process: Variables such as mode of addition of bridging solvent, agitation speed (rpm), agitation time (min) and temperature (^{o}C) were optimized [6].

Characterization of Favipiravir Crystallo-co-Agglomerates:

Production Yield: The dried agglomerates were collected and weighed. The measured weight was divided by the total amount of all non-volatile compounds used for the formulation *i.e*. drugs and excipients [7].

Production yield (%) = Practical Mass (CCA / Theorotical Mass (Polymer + drug) × 100

Drug Content: In a 100 mL volumetric flask, 10 mg of agglomerates were accurately weighed and the volume was adjusted to 100 mL with methanol (100 g/mL), which served as a test solution. A UV spectrophotometer was used to analyse the standard solution after it had been sonicated for 5 minutes [8].

Drug Content (%) = Practical drug concentration / Theorotical drug concentration × 100

Fourier Transformation Infrared Spectroscopy (FTIR): The study aimed to determine the compatibility of polymers such as PVA, PEG-6000, and PVP with Favipiravir. It also includes determining the suitability of a polymer for agglomerate preparation. The samples of pure drug and physical mixture, such as Favipiravir and PVA, PEG-6000, were prepared. The scanning range was kept from 4000 to 400 cm^{-1}. FTIR spectra were obtained using a Shimadzu FTIR spectrometer [9].

Field Emission Scanning Electron Microscopy (FE-SEM): The surface morphology of the optimized formulations was studied using a FE-SEM operated at an accelerating voltage of 10 kV and obtained micrographs were examined at different magnifications [10].

Differential Scanning Calorimetry (DSC): The thermal behaviour of the drug-loaded agglomerates was studied using a differential scanning calorimeter at a heating rate of 10°C/min. The measurements were performed at a heating range of 20-250°C under a nitrogen atmosphere [11].

Determination of Residual Solvent by Head Space Gas Chromatography (HS-GC): Accurately weighed optimized agglomerates were suspended in acetone and shaken in orbital shaking incubator for 24 hrs at 100 rpm. Subsequently, the dispersion was filtered, and the filtrate was analyzed using HS-GC and Helium as carries gas. The reference solution (1000 ppm) and sample solution were injected alternatively to HS-GC and area of peak obtained was used to calculate the solvent concentrate in agglomerates [12].

X-ray Diffraction Study (XRD): The X-ray diffraction spectra of Favipiravir and prepared agglomerates were recorded with an x-ray diffraction meter using a voltage of 45 Kv and a current of 40 mA. The instrument was operated in continuous scan mode over 2θ range at 20°-80°. The relative intensity $\boldsymbol{I/I_0}$ and interplanar distance (d) corresponding to the 2θ values were reported and compared [13].

Dissolution Studies: Using a USP Type II dissolution apparatus paddle technique, dissolution rate evaluation of Favipiravir alone and produced agglomerates were done in triplicate. Dissolution tests were performed with 900 ml of phosphate buffer (pH 6.8) at 37±0.5°C and 50 rpm per minute.

By replacing each 5 ml aliquot extracted with 5 ml of fresh phosphate buffer, the volume of the dissolving medium was increased to 900 ml (pH6.8). The solutions were suitably diluted and the concentrations of favipiravir in samples were

determined spectrophotometrically at 235nm. The results of dissolution studies were statistically analysed [14, 15].

RESULTS AND DISCUSSION:

Micromeritic Properties: The results for micrometric properties of pure Favipiravir and drug agglomerates were shown in **Table 2**. The agglomerates showed improvement in flow property when compared to pure Favipiravir. Among different agglomerates prepared, formulation batch F4 showed maximum flow ability as evidenced by low values of angle of repose (12.22±0.32), Haussner's ratio (0.42±0.04) and Carr's index (18±0.66 %).

TABLE2: MICROMERITIC PROPERTIES CHARACTERIZATION OF FAVIPIRAVIR AND AGGLOMERATES

Formulation	Bulk density (gm/cc)	Tapped density(gm/cc)	Carr's Index (%)	Hausner's Ratio	Angle of Repose (θ)
FVP	0.28 ± 0.003	0.58 ± 0.004	22.48 ± 0.11	1.14 ± 0.05	24.56 ± 0.21
FVP-PEG 6000 Agglomerates	0.36 ± 0.006	0.74 ± 0.024	18 ± 0.66	0.42 ± 0.04	12.22 ± 0.32

Production Yield and Drug Content: The practical yield for the batch F3 and F4 was found to be 82.78± 0.08% which indicated that polymer at the concentration 1% had better productive results. Similarly, drug content for batches F3 and F4 were found to be 92.09±0.98%.

TABLE 3: PRODUCTION YIELD AND % DRUG CONTENT OF FVP AGGLOMERATES

Sr. no.	% Production Yield	% Drug Content
F1	70.78 ± 0.28	90.19 ± 0.18
F2	62.98 ± 0.14	89.78 ± 0.26
F3	82.78 ± 0.08	92.29 ± 0.18
F4	82.78 ± 0.08	92.29 ± 0.18
F5	76.68 ± 0.10	84.78 ± 0.08
F6	72.48 ± 0.48	88.88 ± 0.18
F7	80.68 ± 0.18	89.78 ± 0.28
F8	78.18 ± 0.38	90.18 ± 0.8
F9	72.38 ± 0.28	86.28 ± 0.18

Fourier Transformation Infrared Spectroscopy (FTIR): The potassium bromide pellet containing Favipiravir and optimized agglomerates were prepared separately to record the spectrum in the range of 4000 to 400 cm^{-1} by using FT-IR spectrophotometer. The FTIR spectrum of Favipiravir spherical crystals batch F3 and F4 exhibited characteristics band consistent with pure Favipiravir which indicated that no chemical interaction occurred between the drug and excipients used in the formulation. The peaks with observed frequencies and standard frequency range are as shown in **Table 4.**

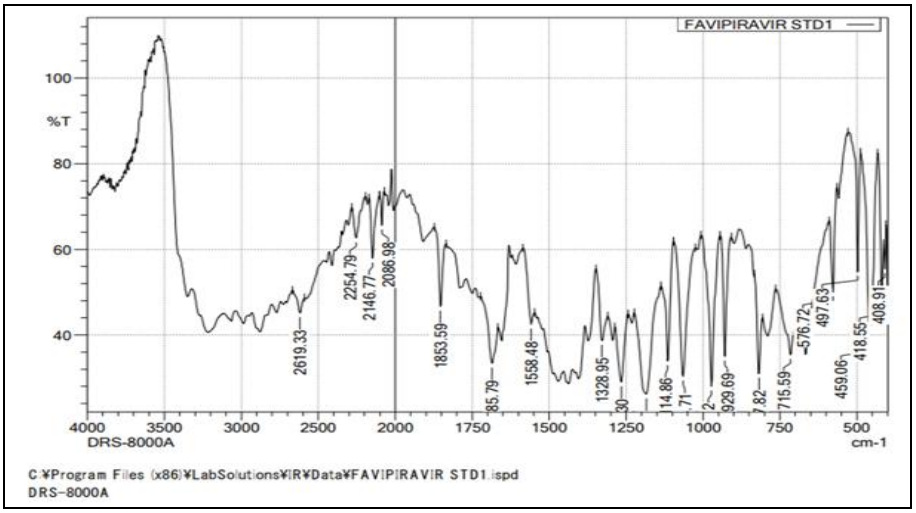

FIG. 2: FT-IR SPECTRUM OF PURE FAVIPIRAVIR

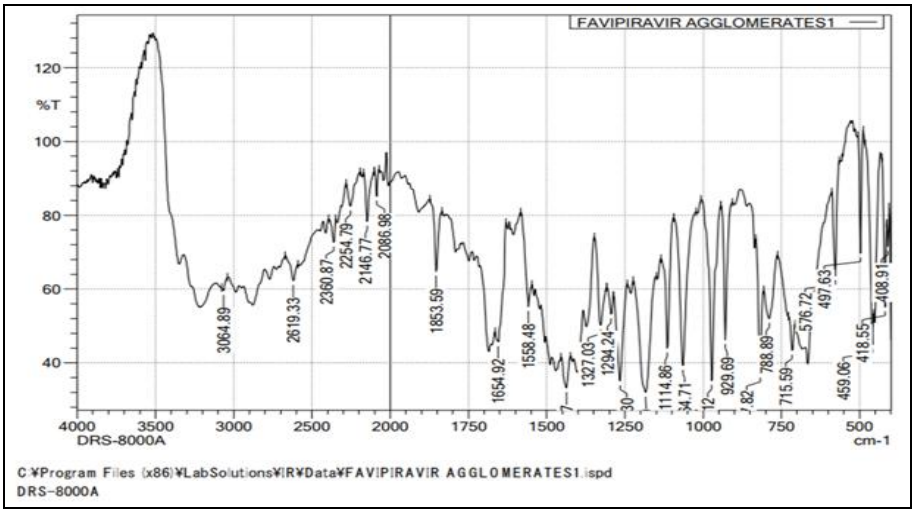

FIG. 3: FT-IR SPECTRUM OF PURE FAVIPIRAVIR AGGLOMERATES

TABLE 4: FT-IR SPECTRAL ANALYSIS FOR PURE FVP AND FVP-PEG 6000AGGLOMERATES

Sr. no.	Functional Group	Standard Frequency (cm^{-1})	FVP pure drug (cm-1)	FVP CCA agglomerates (cm-1)
1.	C-F stretching	1400-1000	1265.3	1265.3
2.	O-H bending	1390-1310	1328.95	1327.03
3.	C=O stretching	1880-1770	1853.69	1853.59
4.	N-H stretching	3000-3550	3064.89	3167.42
5.	C=N stretching	1690-1640	1685.79	1654.92

Field Emission Scanning Electron Microscopy (FE-SEM): The shape and surface morphology were observed using FE-SEM. The agglomerates were observed at various magnifications to analyse the effect of additives on surface morphology and agglomeration efficiency. An examination of the FE-SEM of FVP as shown in **Fig. 4** confirmed that the pristine FVP was significantly smaller in particle size and blade, or plate shaped elongated crystals with fines which hindered the flowability and compressibility. Improved flowability of agglomerates was mainly because of good sphericity of modified crystals obtained by CCA as evident by the cylindrical shape of crystals/agglomerates **Fig. 5**. FE-SEM of FVP revealed no evidence of porosity with smooth surface whereas agglomerated FVP have shown cylindrical crystals with clear evidence of rough surface and porosity.

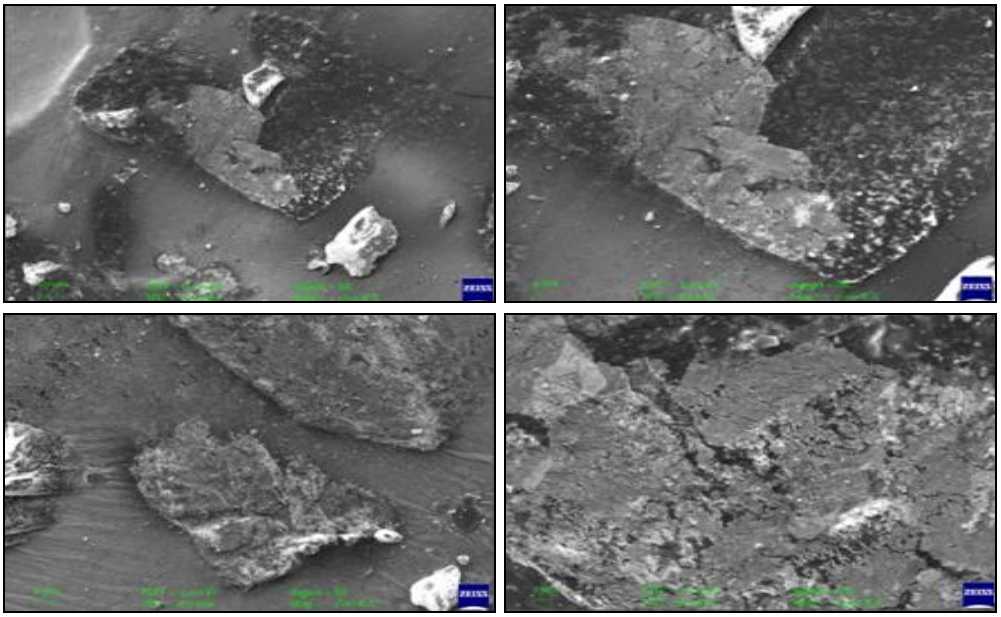

FIG. 4: FE-SEM OF FAVIPIRAVIR AT 1KX, 2KX, 5KX AND 10KX

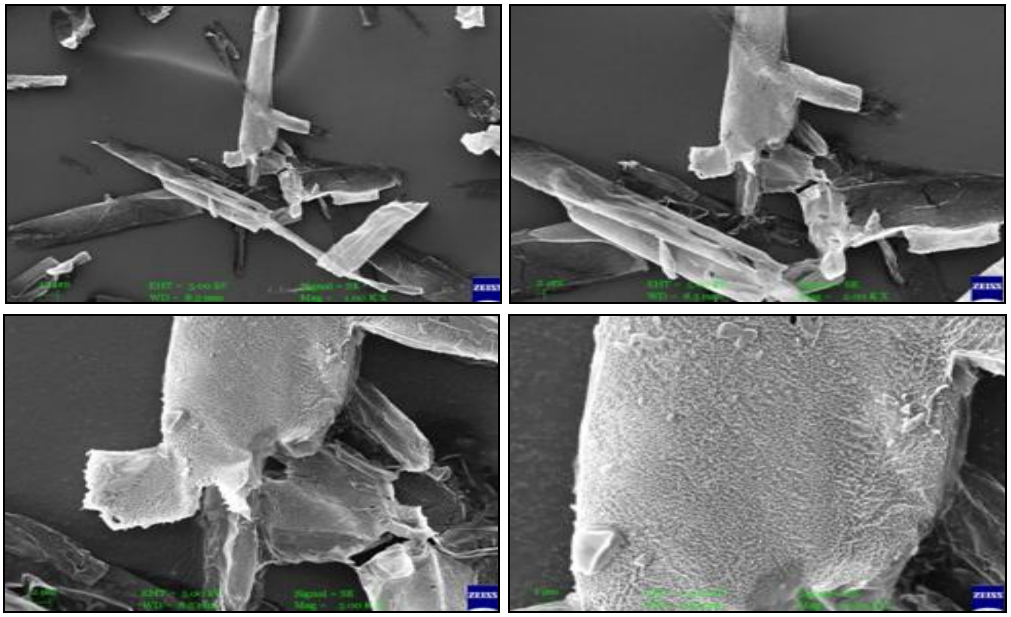

FIG. 5: FE-SEM OF FVP-PEG6000 OPTIMIZED AGGLOMERATES AT 1KX, 2KX, 5KX AND 10KX

Differential Scanning Calorimetry (DSC): Favipiravir showed a prominent endothermic peak in differential scanning calorimetry (DSC) thermograms of pure drug and spherical crystals, indicating its crystalline form.

When the enthalpies were examined, it was discovered that when agglomerates were formed in the presence of PEG 6000, partial amorphization occurred, and the reduction in enthalpy was not due to any incompatibility with polymers.

DSC thermogram of FVP showed a sharp characteristic endothermic peak at 193.16°C corresponding to its melting point, indicating its crystalline nature as shown in **Fig. 6**. This sharp peak confirmed the purity of FVP with no noticeable impurities present. In the DSC thermogram of agglomerates, endothermic peak corresponds to FVP at 192.65°C.

This occurrence might be attributed to the dispersion of crystalline ATS into amorphous polymer PEG 6000.Partial amorphization of drug might provide comparatively more stability than their complete amorphous counterparts.

These findings from DSC clearly indicated transformation of crystalline form of FVP to its amorphous form in agglomerates which might be responsible for improved dissolution.

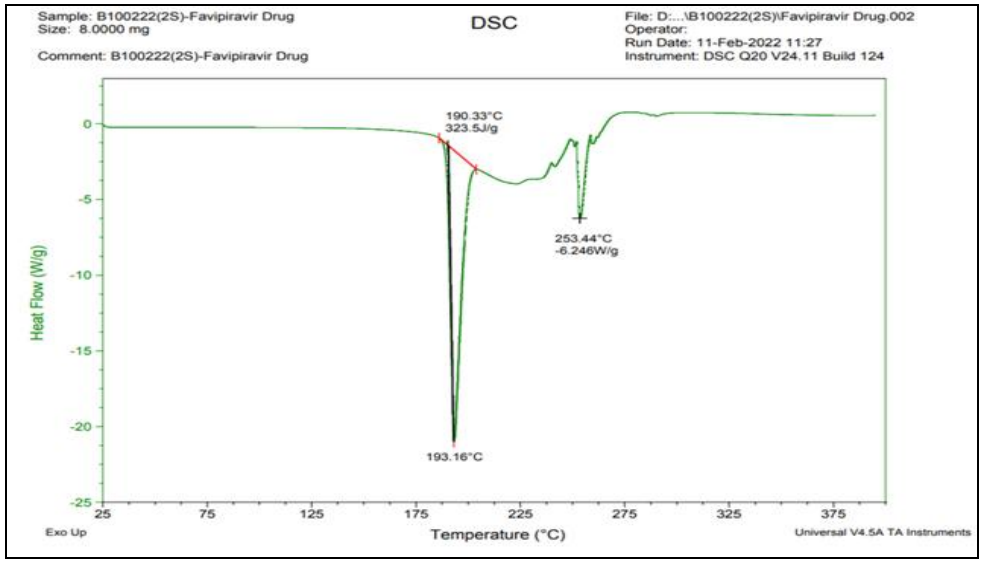

FIG. 6: DSC THERMOGRAM OF PURE FAVIPIRAVIR

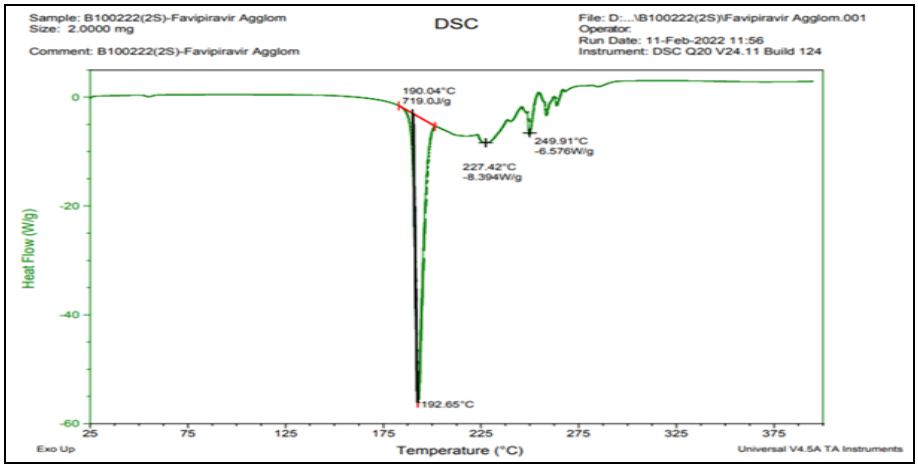

FIG. 7: DSC THERMOGRAM OF FAVIPIRAVIR CRYSTALLO-CO-AGGLOMERATES

Determination of Residual Solvent by Head Space Gas Chromatography (HS-GC): Residual solvents are critical impurities in excipients, drug substances and ultimately drug products, because they may cause toxicity and safety issues and effect physicochemical properties of drug substances and drug products.

A HS-GC chromatogram of standard solvent i.e DCM, Acetone and agglomerate, are shown in **Fig. 8, 9** & **10**. A residual solvents peaks of optimized FVP agglomerates were observed at same retention times as that of standard (1.45 min and 1.0 min for DCM and Acetone respectively with extremely low intensity, as shown in **Tables 5** and **6**. It depicted that most of the solvents were evaporated and very small amount of solvents retained in agglomerates.

Furthermore, the amount of DCM and acetone was determined by the area covered by peak at same retention time, and it was found to be 6.03 ppm and 11.09 ppm respectively as shown in **Table 7**. According to ICH, the permitted daily exposure (PDE) for DCM and acetone was 150 ppm and 5000 ppm respectively. The results of this study revealed that both the solvents were entrapped in agglomerates at insignificant extent; hence, it does not produce toxicity in humans.

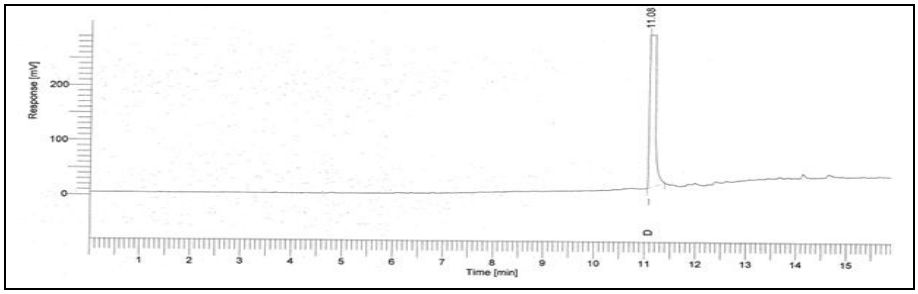

FIG. 8: RESIDUAL SOLVENT DETERMINATION FOR DCM

TABLE 5: RESULTS OF RESIDUAL SOLVENT DETERMINATION FOR DCM

Peak	Component name	Time [min]	Area [uVsec]	Height [uV]	Area [%]	Rel. RT
1	DCM	11.08	6884247	974488.55	100	1.45
2		11.08	6884247	974488.55	100	

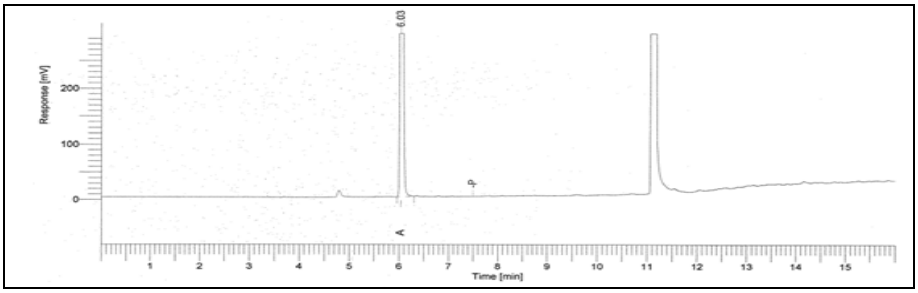

FIG. 9: RESIDUAL SOLVENT DETERMINATION FOR ACETONE

TABLE 6: RESULTS OF RESIDUAL SOLVENT DETERMINATION FOR ACETONE

Peak	Component name	Time [min]	Area [uVsec]	Height [uV]	Area [%]	Rel. RT
1	Acetone	6.03	4080668.30	987824.18	100	1.00
2		6.03	4080668.30	987824.18	100	

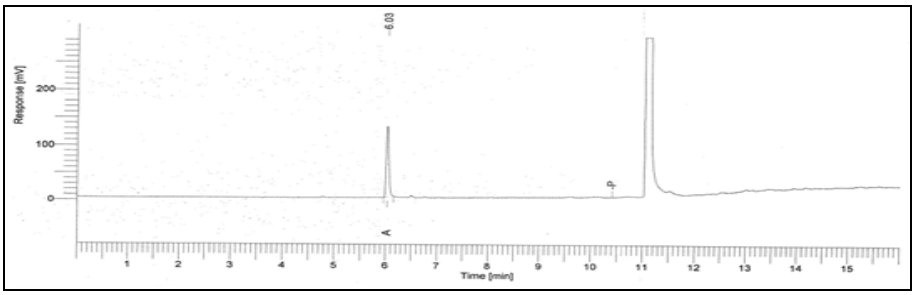

FIG. 10: RESIDUAL SOLVENT DETERMINATION FOR OPTIMIZED AGGLOMERATES

TABLE 7: ANALYSIS REPORT OF RESIDUAL SOLVENT DETERMINATION

Sr. no.	Sample	Injection	Peak Area	%RSD	DCM (ppm)	Acetone (ppm)
1	FVP Agglomerates	Injection-1	4080668.3	**0.545**	**6.03**	**11.09**
2		Injection-2	4037364.19			
3		Injection-3	4066913.34			
		Average	4061648.61			

X-ray Diffraction Study (XRD): When compared to pure Favipiravir, the XRD pattern of the agglomerates showed a halo pattern with less strong and more dense peaks, indicating a loss in crystallinity or partial amorphization of the drug in its agglomerated form. Intensities of drug characteristics peaks were decreased in agglomerates which might be due to differences in crystallinity of FVP in agglomerate as illustrated in **Fig. 11** & **12.**

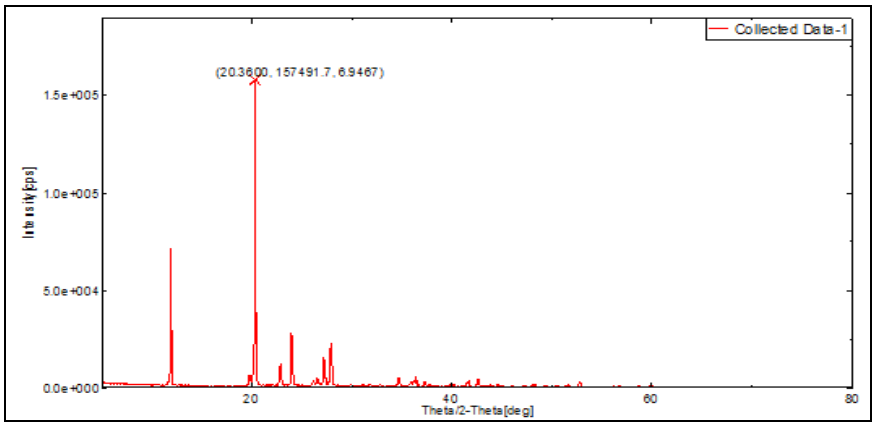

FIG. 11: X-RAY DIFFRACTOGRAM OF FAVIPIRAVIR

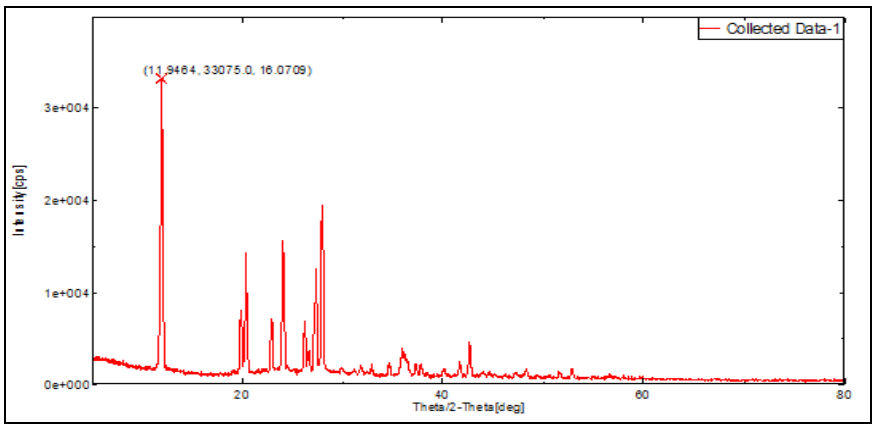

FIG. 12: XRD PATTERN OF OPTIMIZED BATCH OF FVP-PEG 6000 AGGLOMERATES

Dissolution Studies: The dissolution profile of PEG 6000 containing agglomerates showed drug release in the range of 53.33%- 61.02%. Results are given in **Table 8**. Dissolution profiles are illustrated in **Fig. 13** and **14**. From the above discussion, it was concluded that agglomerates of batches F3 and F4 containing PEG 6000 had a higher dissolution rate than the agglomerates of other batches. Hence, batch F4is considered an optimized batch, and agglomerates were selected for further evaluation.

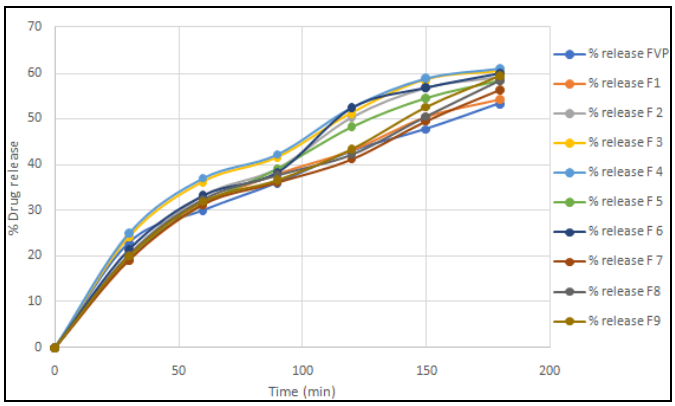

FIG. 13: DISSOLUTION PROFILE OF PURE FAVIPIRAVIR AND BATCHES OF AGGLOMERATES

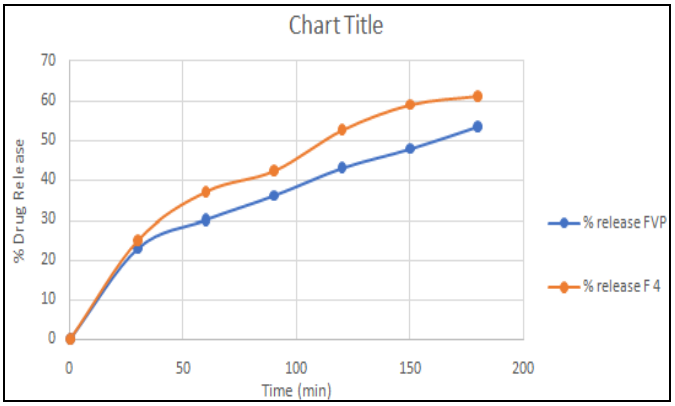

FIG. 14: DISSOLUTION PROFILE OF PURE FAVIPIRAVIR AND OPTIMIZED AGGLOMERATES

TABLE 8: PERCENTAGE DRUG RELEASE OF PEG 6000 CONTAINING AGGLOMERATES

Time (min)	% release FVP	% release F1	% release F 2	% release F 3	% release F 4	% release F 5	% release F 6	% release F 7	% release F8	% release F9
0	0	0	0	0	0	0	0	0	0	0
30	22.95	19.17	20.42	24.24	25.04	19.82	21.42	19.17	20.22	20
60	30.01	31.36	33.17	36.26	37.06	31.31	33.19	31.32	32.36	31.9
90	36	37.99	39.11	41.54	42.24	38.99	38.22	36.1	37.62	36.5
120	42.9	43.14	50.25	51.2	52.48	48.14	52.25	41.14	42.14	43.3
150	47.71	50.44	56.68	58.47	58.84	54.44	56.68	49.44	50.44	52.4
180	53.33	54.31	59.1	60.28	61.02	58.31	59.8	56.31	58.32	59.3

CONCLUSION: FVP-polymer agglomerates were successfully prepared by the crystallo-co-agglomeration technique. CCA technique can be successfully employed as analternative to conventional wet agglomeration. This study showed that, the micromeritics of the agglomerates such as flowability, packability and compatibility were dramatically improved. The dissolution rate of agglomerate was increased in the presence of PEG 6000.

From the above investigation, it can be concluded that this method is proficient for creating spherical agglomerates with enhanced micromeritics, mechanical and conventional properties.

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CONFLICTS OF INTEREST: Nil

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