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RESEARCH ARTICLE

Formulation and Evaluation of Orodispersible Tablet of Dolutegravir - Methionine Cocrystal

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Formulation and Evaluation of Orodispersible Tablet of Dolutegravir - Methionine Cocrystal

SUMMARY

Dolutegravir, a newly approved anti-HIV drug, is insoluble in the normal gastric pH range, resulting in a slow onset of action. The research proposes cocrystallization process to increase the solubility of the drug and hence dissolution. The cocrystals of dolutegravir were formulated using methionine as coformers by solvent evaporation method. The cocrystals were evaluated for solubility, in vitro drug release, and solid-state characterization, study. The orodispersible tablets of dolutegravir cocrystal were successfully prepared by direct compression method. The solid-state characterization study showed the compatibility and amorphization of the drug in the cocrystal form. The cocrystal of drug: methionine (1:2) was found to enhance dissolution in pH 1.2 by 1.88 times compared to the pure drug. The orodispersible tablets disintegrated at 10.05±0.5 secs and 90±0.64% of the drug was released in 20 min. Hence, it can be concluded that the methionine-dolutegravir cocrystal can be a promising means to improve the solubility of the drug.

Key Words: *Dolutegravir, methionine, solubility enhancement, orodispersible tablet, dissolution.*

Dolutegravir - Metionin Kokristalinin Ağızda Dağılabilen Tabletinin Formülasyonu ve Değerlendirilmesi

ÖZ

Yeni onaylanmış bir anti-HIV ilaç olan dolutegravir, normal gastrik pH aralığında çözünmez ve bu da etkisinin geç başlamasına neden olur. Araştırma, ilacın çözünürlüğünü ve dolayısıyla çözünmesini artırmak için birlikte kristalleşme işlemi önermektedir. Dolutegravirin kokristalleri, çözücü buharlaştırma yöntemiyle koformer olarak metiyonin kullanılarak formüle edildi. Kokristaller çözünürlük, in vitro ilaç salınımı ve katı hal karakterizasyonu çalışmaları açısından değerlendirildi. Dolutegravir kokristalinin ağızda dağılabilen tabletleri doğrudan basım yöntemiyle başarılı bir şekilde hazırlandı. Katı hal karakterizasyon çalışması, ilacın kokristal formunda uyumluluğunu ve amorfizasyonunu gösterdi. İlacın kokristali : metiyoninin (1:2), pH 1.2'de çözünürlüğü saf ilaca göre 1.88 kat artırdığı bulundu. Ağızda dağılabilen tabletler 10.05±0.5 saniyede dağıldı ve ilacın %90±0.64'ü 20 dakikada salındı. Dolayısıyla, metiyonin-dolutegravir kokristalinin ilacın çözünürlüğünü iyileştirmede umut verici bir araç olabileceği sonucuna varılabilir.

Anahtar Kelimeler: *Dolutegravir, metiyonin, çözünürlük artışı, ağızda dağılabilen tablet, çözünme.*

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INTRODUCTION

Dolutegravir is an integrase strand transfer inhibitor (INSTI), recommended to be used in conjunction with other antiretroviral agents in the management of HIV-1 (Mattevi & Tagliari 2017). It is a newly approved BCS Class II drug and is insoluble over the gastric pH range (Yu et al., 2017).The poor solubility of the drug results in delayed onset of action and less oral bioavailability (Buchanan *et al*., 2017). Therefore, the requirement for a new form of the drug with refined physicochemical properties is highly desirable.

Pharmaceutical co-crystals are composed of two or more ionic or molecular compounds mixed with a specific stoichiometric ratio with the active pharmaceutical ingredient (API) to yield a neutral single-phase system. They are a new and promising method for enhancing the performance of pharmaceuticals by modulating their mechanical, optical, release profile, and chemical stability, thereby improving bioavailability, and therapeutic efficacy (Guo *et al*., 2021).

Tesson *et al*, researched cocrystals of lorcaserin, and patented the finding on the improvement of stability of the drug (Tesson *et al* 2017). Nanubolu *et al* summarized the findings on the solubility improvement of aripiprazole in their study (Nanubolu *et al* 2016).

Co-crystal components combine via non-covalent interactions including hydrogen bonds, van der Waals interactions, ionic bonds, or π-π interactions (Bhattacharyya & Manjunath, 2023). The co-crystallization process arises from the molecular interaction between similar molecules/homomers, and heteromers /different molecular structures (Qiao *et al*., 2011).

Following USFDA regulations, an API and counter molecule must have a lower proton transfer potential to be categorized as cocrystals. Therefore, to restrict the salt formation, the difference in pKa between the two components must be less than 1(Food and Drug Administration 2018).

The presence of polar groups in the structure of amino acids capable of forming hydrogen bonds characterizes them as novel coformer in the cocrystallization procedure. They support the "green method" co-crystallization of active molecules. The zwitterionic nature of the amino acids allows them to create hydrogen bonds with the API that strengthens the contacts and increases stability (Nugrahani & Jessica, 2021). They are also considered to be generally recognized as safe (GRAS), because of their low toxicity. Therefore, amino acids can be a good choice and potential co-former for co-crystallization of dolutegravir.

The research work plans to use methionine as a coformer for improving the solubility of dolutegravir and formulate an orodispersible tablet of high effectivity.

MATERIALS AND METHODS

Materials

Dolutegravir was procured as a gift sample from Strides Arcolab, Bangalore. The amino acid methionine was purchased from Sigma-Aldrich. Methanol, hydrochloric acid, and other analytical grade chemicals used for the analysis and preparation of tablets were purchased from SD Fine Chemicals, Bangalore, India.

Method of preparation of Dolutegravir cocrystal

Cocrystals of dolutegravir were prepared by solvent evaporation method using methionine, as coformers. The drug and the coformer solutions were prepared separately using methanol and water. Both the solutions were mixed on a magnetic stirrer poured into the petri dish, and dried in the hot air oven at 50˚C for 30 min. It was then allowed to cool at room temperature, weighed, and stored for further studies. Methionine was screened at two different ratios, drug: coformer 1:1, 1:2 (Raheem Thayyil *et al*., 2020).

Determination of drug content

A known quantity (5 mg) of the sample was dissolved in a specific volume of diluting solution consisting of phosphate buffer solution pH 3.0, acetonitrile, and methanol at a ratio of 50:20:30. An aliquot

of 1 ml was withdrawn and diluted suitably and estimated spectrophotometrically at 322 nm. The same process was repeated for the pure drug of the same quantity (Bhattacharyya *et al*., 2022). A standard graph was constructed previously in the range of 5-35 µg/ml using the diluting solution at 322 nm with an accuracy of 99.98%, a regression coefficient of 0.9998, and a linearity equation of Y=0.0174X. Experimentation was carried out in triplicates. Using the following formula the drug content was determined

$$\%Drug\ content = \frac{Absorbance}{Standard\ absorbance} \times 100$$

Determination of solubility in different pHs

The solubility of cocrystals of dolutegravir was determined in three different pH buffers (pH 1.2, pH 4.5, and pH 6.8). Cocrystal equivalent to the maximum dose of the drug was dissolved in 250 ml of three different buffers. The flasks were shaken in a mechanical shaker for 24 h at room temperature, after 24 h a known volume of solution was transferred to a centrifuge tube, and was centrifuged at 3000 rpm for 15 min, filtered, diluted, and assayed spectrophotometrically at 322 nm. All the tests were carried out in triplicates (Baka, Comer & Takács-Novák, 2008).

Tukey's test to select the best drug coformer ratio

Dolutegravir cocrystals were compared with the pure drug and among themselves Tukey's multiple comparison tests (at a significance level of $P < 0.05$) were used to identify the best combination of drug coformer ratio of the selected amino acid.

Selection of dissolution media based on solubility at different pHs

The solubility of the best cocrystal of methionine and dolutegravir was determined in entire GI pH range buffers (pH 1.2, pH 3.0, pH 4.5, pH 5, pH 6.8, and pH 7.5). A maximum dose of the drug in its cocrystals was dissolved in 250 ml conical flasks containing different buffers. The solubility was determined by the same method as described earlier. The solubility data was used to calculate the Gibbs free energy and dose solubility ratio that helped to select the dissolution media (Baka *et al*., 2008). The Gibbs free energy of transfer (ΔG) was calculated using the following equation

$$\triangle G = -2.303RT \log \frac{So}{Ss}$$

where S_0 and Ss are the solubilities of the drug in water and dolutegravir cocrystal in the respective media respectively (Bhattacharyya *et al*, 2022).

Drug release study

USP paddle-type II apparatus was used to conduct the dissolution study for the best cocrystal of dolutegravir. Dissolution media was selected after the solubility study using the concept of Gibbs free energy calculation and dose solubility ratio and was carried out in 900 ml of pH 1.2 HCl buffer. Cocrystal equivalent to 50 mg of dolutegravir was used for the drug release study stirring at a speed of 75 rpm, at 37±0.5°C for 60 min. The sampling was done at regular intervals (10 min) and was analyzed spectrophotometrically at 322 nm (Panzade P & Shendarkar G 2019). Three trials were carried out for each measurement

Fourier Transform Infrared (FTIR) spectroscopy study

The sample was analyzed using BRUKER FTIR Spectrometer Alpha II using the ATR technique from a range of 3500 cm^{-1} to 1000 cm^{-1}. The pure drug dolutegravir and the selected cocrystal were subjected to the analysis (Raheem Thayyil *et al*., 2020).

Powder X-ray Diffraction (PXRD)

PXRD was used to identify the crystallinity of the drug in pure drug and best cocrystal. The data instrument used to analyze PXRD patterns was Rigaku Smartlab 3kW Japan. The powder X-ray diffraction study was carried out for pure drug and best cocrystal using Cu Ka radiation at 25˚C and scanned from 2 to 80, 2θ diffraction angle (Manjunath & Bhattacharyya, 2023).

Differential Scanning Calorimetry (DSC) study

The best cocrystal and reference standard drug are maintained at constant temperature and subjected to thermal analysis using the DSC Perkin-Elmer- 4000

series. Test samples were placed in aluminum pans and thematically sealed. Samples were heated from 20-400°C at an accelerating rate of 10°C per minute under nitrogen atmosphere. The thermograms were recorded.

Scanning electron microscopy (SEM)

The surface morphology of pure drug and the best cocrystal was imaged by a scanning electron microscope (Hitachi SU 3500) performed at an accelerating voltage of 10 kV. The powder in a few µg was fixed onto the stub, gold was sputtered, samples were adhered with a double-sided sticky carbon tape and images were taken (Raheem Thayyil *et al*., 2020).

Nuclear Magnetic Resonance (NMR)

^{1}H-NMR measurements were performed at ambient temperature Bruker NMR spectrometer, USA. The solid-state CP/MAS ^{1}H-NMR spectra of pure drug and DOLMET 1:2 were performed in DMSO solvent system using the cross-polarization magic angle spinning pulse sequence at measurement conditions of spinning 100 MHz, pulse delay 5s, contact time 10 minutes, and 24 h analysis time per sample. The signals were recorded (Kumar *et al*., 2019).

Preparation of orodispersible tablets

Precompression characteristics of the powder blend of best cocrystal and method of preparation of tablet

Orodispersible tablets of Dolutegravir cocrystals were prepared by direct compression method. Each orodispersible tablet of 250 mg contains cocrystal of 30 mg equivalent dolutegravir, cross carmellose sodium (4%w/v), microcrystalline cellulose (46%w/v), mannitol (22%w/w), and lubricant (0.01%).

The angle of repose, bulk density, tapped density, Carr's index, and % porosity were carried out to get the precompression characteristics of the powder blend of best cocrystal before compression to tablets. All the tests were performed in triplicates (Martha *et al*., 2017).

The drug and excipients were subjected to milling followed by sieving, mixing, and compression into a tablet using Rimek mini press-1 tablet punching machine with a compression force of 38±5 kN (Panzade *et al*.,2017).

Post compression evaluation

Physical evaluation of tablets

The thickness of the tablets was determined using vernier calipers for randomly selected 30 tablets. Hardness was determined using a Monsanto hardness tester for 6 tablets selected randomly. Each of the 20 tablets was individually weighed using an electronic balance and the average weight of the tablets was checked. The % deviation of each tablet weight from the average weight was also estimated (Martha *et al*., 2017).

Wetting time

The wetting test was performed using amaranth solution and cotton. The cotton was placed on the petri dish containing amaranth solution and the tablet was placed on top of the cotton. The time taken for the tablet to turn completely red was noted.

Disintegration test

The disintegration test was carried out for 6 tablets in 900 ml of distilled water using LAB-HOSP tablet disintegration test machine. The time taken for the tablet to disintegrate completely was noted. The test was performed in triplicates (Dey & Maiti, 2010).

Friability test

The friability test was carried out for 10 tablets using Electrolab friabilator (USP) EF-1W. The tablets were rotated at 25 rpm for 4 min. Initial and final weights were noted and % friability was calculated after the test (Pawar *et al*., 2014). % Friability was calculated using the following equation

$$Friability(\%) = \frac{(W1 - W2)}{W1} * 100$$

Where, W_1 is the weight of tablets before tumbling, and $W2_1$ is the weight of tablets after tumbling.

Drug release study of the orodispersible tablets

The same dissolution conditions as described prior were kept for the study of the dissolution of orodispersible tablets. The dissolution was carried out for 20 min. 1 ml of the sample was withdrawn at 5 min intervals and replaced with 1 ml of the fresh dissolution media. The diluted samples were analyzed spectrophotometrically at 322 nm. The analysis was carried out in triplicates (Panzade & Shendarkar, 2019).

Stability studies of orodispersible tablets

The orodispersible tablets were stored at 40°±2°C at a relative humidity of 75% ±5% for 3 months in sealed glass vials. The samples were observed for appearance, wetting, friability, disintegration, and *in vitro* drug release every month (Panzade & Shendarkar, 2017).

RESULTS AND DISCUSSION

Determination of solubility of cocrystals in different pH

Solubility studies of pure drug and Dolutegravir cocrystals (DOLMET 1:1 and DOLMET 1:2) in different pH (pH 1.2, pH 4.5, and pH 6.8) were carried out where the solubility of DOLMET 1:2 cocrystal was found to be the highest at pH1.2 compared to the pure drug and DOLMET 1:1 cocrystal as shown in Figure 1.

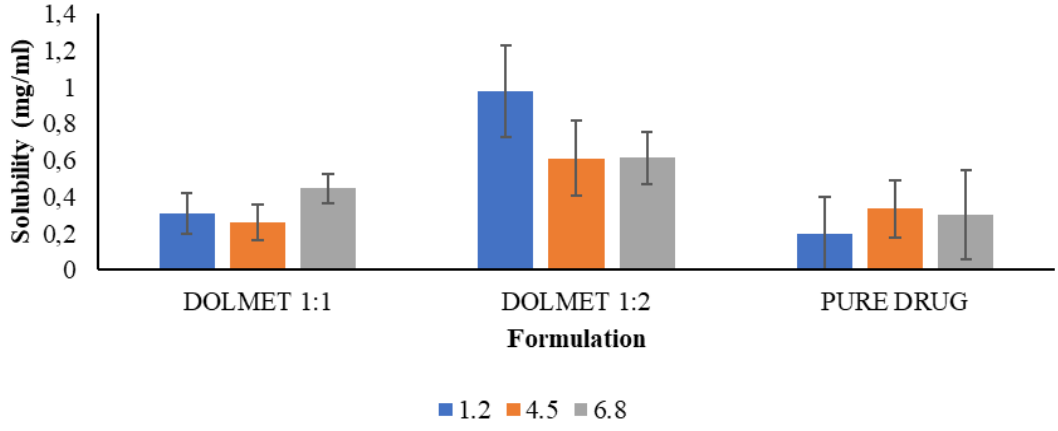


Figure 1. Comparative solubility of cocrystals of DOLMET 1:1, DOLMET 1:2, and pure drug in different pH (1.2, 4.5, and 6.8)

Dolutegravir is a weak acid and has a pka of 8.2. As per pH partition theory, the drug with pKa>8, will remain essentially unionized at all pHs, the entire gastrointestinal tract (GIT) thus serves as the absorption site for such molecules. Hence solubility improvement in the entire GIT is preferred for promoting absorption. The calculation of Gibb's Free energy gives an understanding of the improvement of solubility. A negative Gibb's free energy depicts the spontaneity of the solution process. The calculated Gibbs free energy of cocrystal DOLMET 1:2 predicted the dissolution can be spontaneous in all the media, but the highest might be in pH 1.2. The Gibbs free energy calculation was minimal for DOLMET 1:2 at pH 1.2 as shown in Table 1. Dose solubility ratio was lowest at a value of 51.32. Hence considering the solubility parameters of DOLMET 1:2, pH 1.2 was selected as the dissolution media for the cocrystal.

Table 1. Thermodynamic solubility analysis of DOLMET 1:2

pH	Solubility (mg/ml)	Gibs's Free energy	Dose solubility ratio
1.2	0.97±0.25	-10.54	51.32
3	0.66±0.15	-5.67	75
4.5	0.609±0.20	-7.19	82.07
5	0.51±0.04	-8.99	96.66
6.8	0.61±0.14	-6.87	81.69
7.4	0.88±0.18	-6.89	56.49

Tukey's multiple comparison test ($p < 0.05$) revealed that DOLMET 1:2 was significantly better than pure drug and DOLMET 1:1 as shown in Table 2. Hence DOLMET 1:2 was selected as the best cocrystal for further evaluations.

Table 2. Tukey's Multiple Comparison Test

Tukey's Multiple Comparison Test	Mean Diff.	Significant? P < 0.05?	Summary	95% CI of diff
DOLMET 1:2 vs DOLMET 1:1	0.6657	Yes	***	0.6657 to 0.6657
DOLMET 1:2 vs PURE DRUG	0.7787	Yes	***	0.7787 to 0.7787
DOLMET 1:1 vs PURE DRUG	0.1130	Yes	***	0.1130 to 0.1130

Determination of solubility of best cocrystal in the entire GI pH range

Solubility of the pure drug and best cocrystal (DOLMET 1:2) in the entire GI pH range (pH 1.2, to pH 7.4) was carried out where DOLMET 1:2 cocrystal showed improved solubility than the pure drug in the entire GI pH range with maximum solubility at pH 1.2 as shown in Figure 2.

***In vitro* drug release study**

In vitro drug release of pure drug and DOLMET 1:2, cocrystal was carried out for 60 min and graphically represented as % CDR v/s time profile. DOLMET 1:2 cocrystal showed remarkable improvement in dissolution compared to pure drugs. The *in vitro* dissolution rate of DOLMET 1:2 was more than 80 % in 60 min as shown in Figure 2.

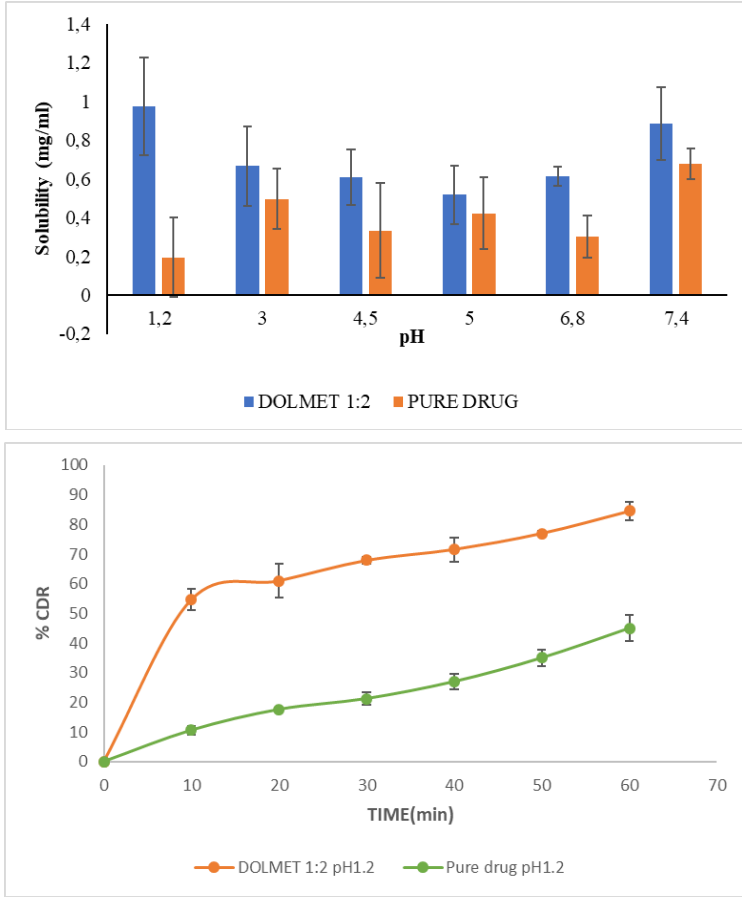


Figure 2. Solubility of DOLMET 1:2 and pure drug in the entire GI pH range (A)

In vitro drug release of DOLMET 1:2 and pure drug (B)

FTIR

The compatibility of the drug and coformer was established through the FTIR study, Major peaks were found to be retained in the sample at a lower intensity indicating the formation of H bond with the coformer. The presence of peaks at 1640.73 cm^{-1}(C=C), 1363.95 cm^{-1}(C=F), 1318.18 cm^{-1}(C=N), 1271.48 cm^{-1}(C-O), 854.50 cm^{-1}(C-H) and 3064.96 cm^{-1}(O-H) of the pure drug was observed in the cocrystal of DOLMET 1:2 as shown in Figure 3 (Mupparaju *et al*., 2021).

PXRD

The PXRD diffraction pattern of the pure drug demonstrated high-intensity peaks, confirming the crystalline nature of the pure drug. The major peaks of the drug at 2Θ 6.4, 14.62, 19.25, 23.38, and 29.96 were significantly lowered in DOLMET 1:2 indicating amorphization of the drug in its cocrystal and supporting the dissolution enhancement. The presence of new peaks at 2Θ 20.69, 23.10, 23.22,33.15, etc. confirms the formation of the cocrystal of dolutegravir. The PXRD patterns of pure drug and DOLMET 1:2 are shown in Figure 3 (Mupparaju *et al*., 2021). The reduction in the intensity of the peaks in the cocrystals confirmed the amorphization of the drug which supported the high solubility of the cocrystals compared to the pure drug.

DSC

A broad endothermic peak of the pure dolutegravir at its melting point of 368.83 ˚C indicated the crystalline nature of the drug. The thermogram of cocrystal DOLMET 1:2 showed a reduced peak at 231˚C that suggested the formation of the cocrystal. The reduced intensity of the peak depicts its amorphization. The DSC thermograms are presented in Figure 3 (Mupparaju *et al*., 2021). These observations also supported the findings of PXRD studies and the improvement of solubility.

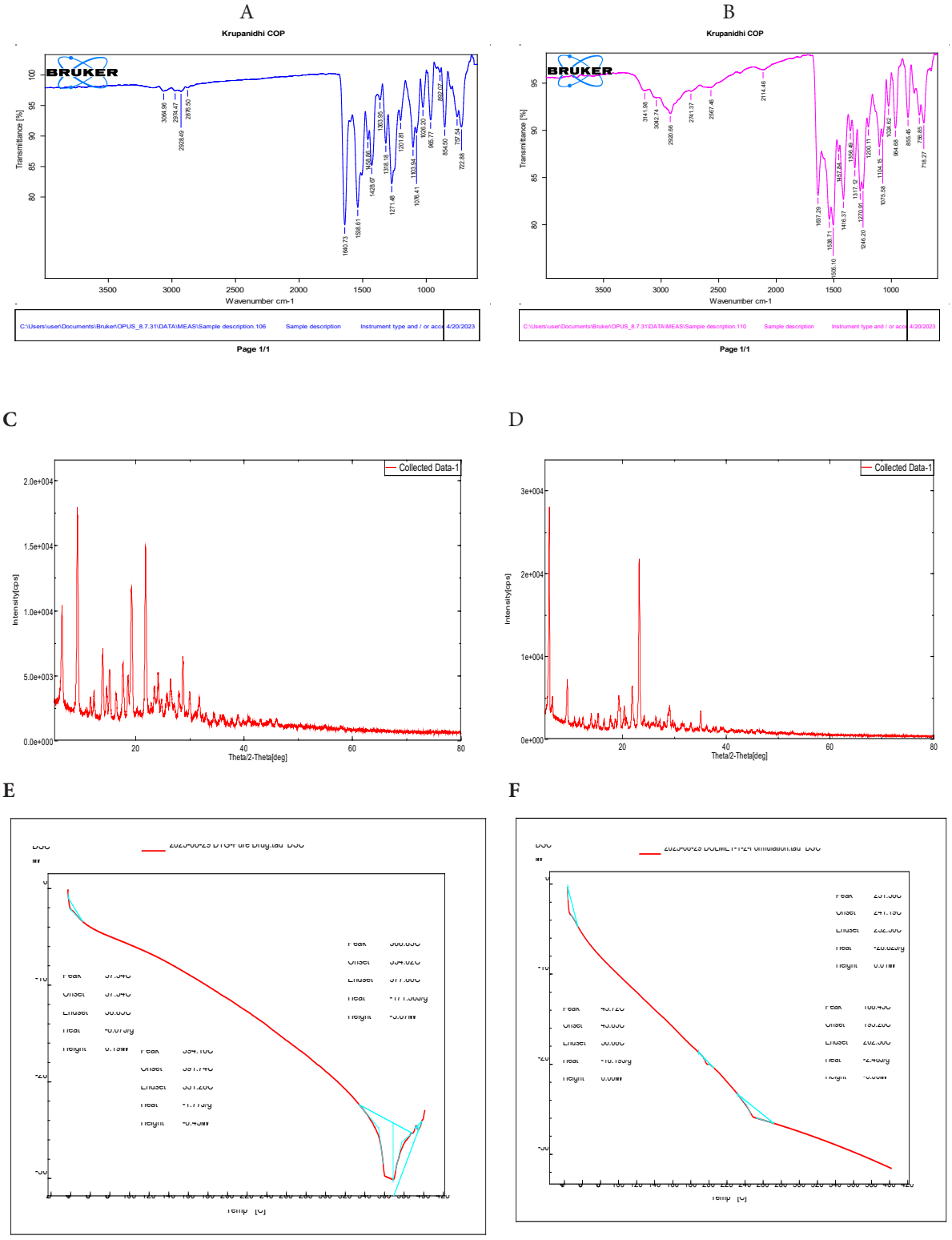


Figure 3. FTIR of Pure drug (A) and DOLMET 1:2 (B), PXRD of Pure drug (C) and DOLMET 1:2 (D), DSC of Pure drug (E) and DOLMET 1:2 (F).

SEM

The surface morphology study of the pure drug and DOLMET 1:2 at the same magnifications is shown in Figure 4. The crystalline nature of the pure drug was observed in the images and the cocrystals were found to be discrete nano-sized particles. A significant change in shape and surface topography was observed in the cocrystal. The crystallinity of the drug was transformed into fine dispersed particles attached to the coformers. These changes might have contributed to the flow properties of the cocrystals (Reham AK *et al*., 2019).

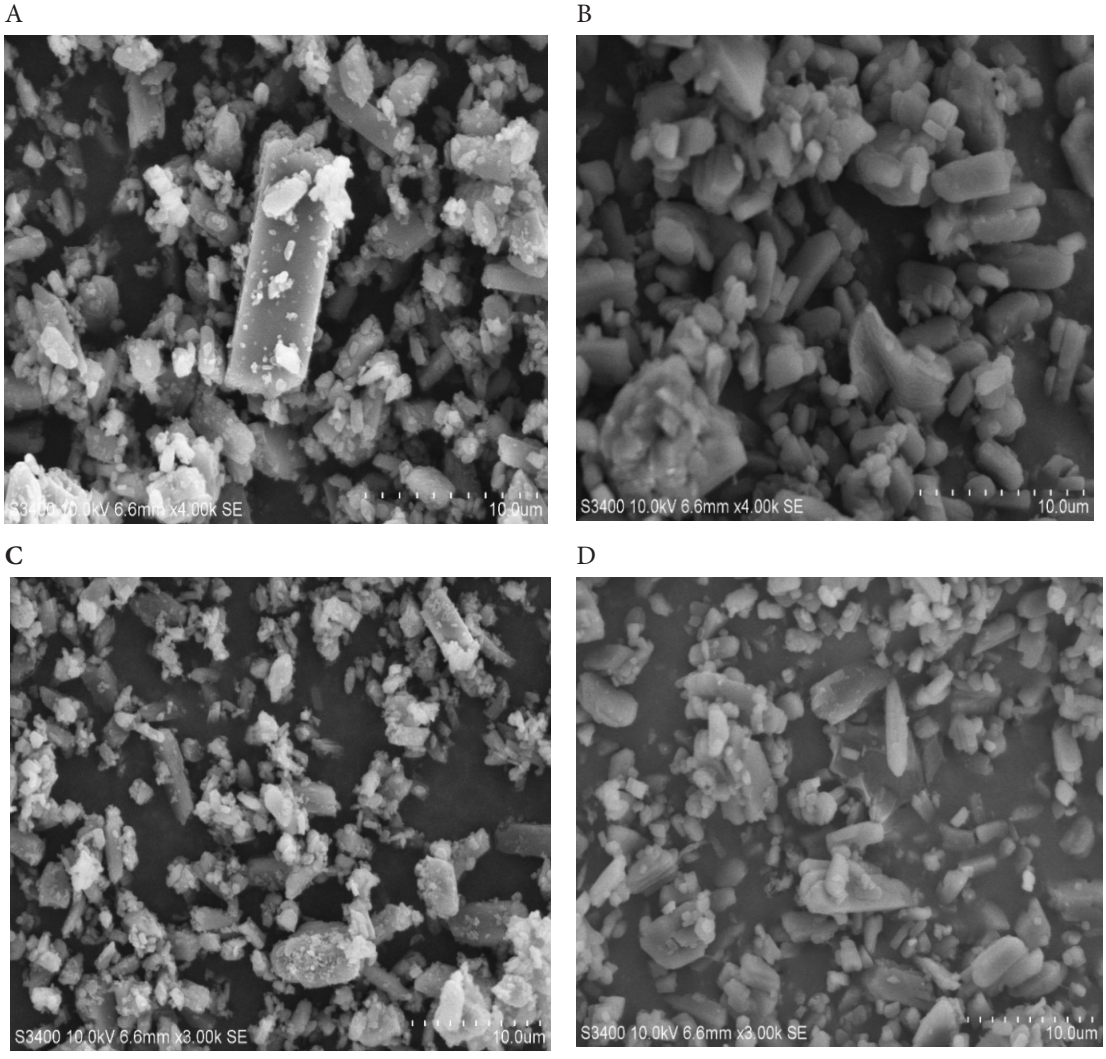
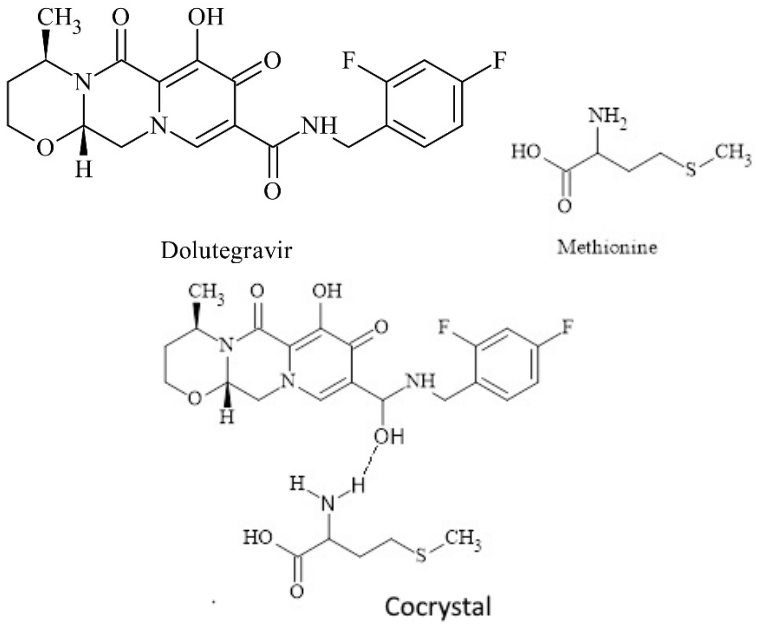


Figure 4. SEM images of Pure drug (A, B) and DOLMET1:2(C, D)

NMR

The formation of hydrogen bonds in dolutegravir cocrystals was verified through NMR, which showed peak broadening at 3.321 for DOLMET 1:2. As depicted in Figure 5, this interaction involves the amino group and dioxo groups, confirming cocrystal formation and excluding salt formation.



Scheme 1. Structure of drug, coformer, and cocrystal

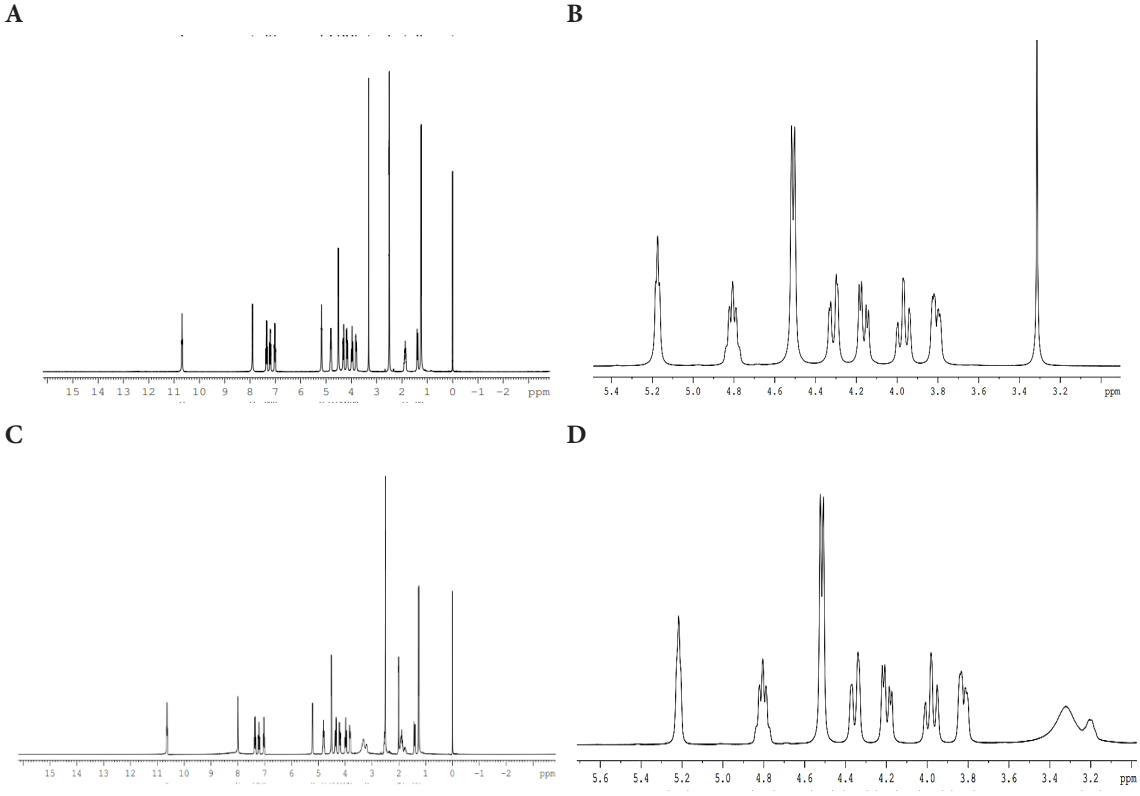
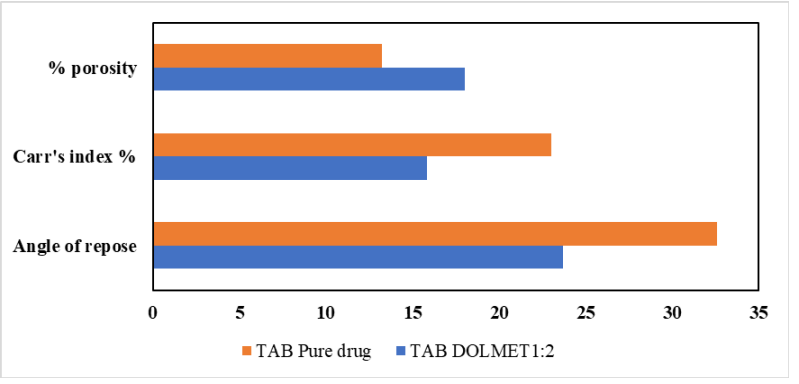


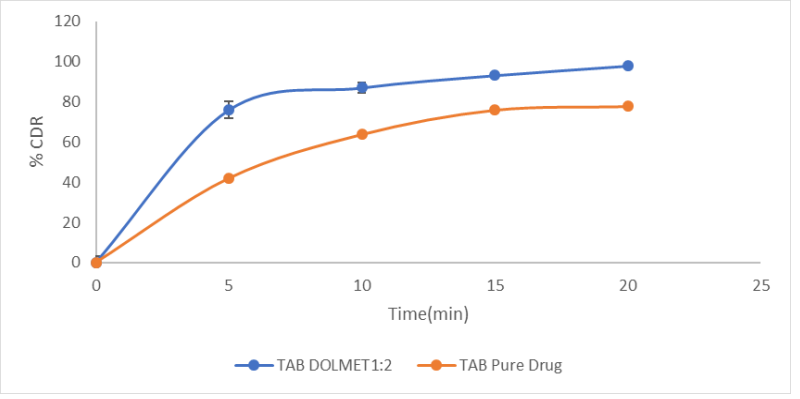
Figure 5. NMR of Pure drug (A, B) and DOLMET 1:2 (C, D)

Precompression evaluation of the powder blend of cocrystal

The particle size, size distribution, shape, density, and surface area influence precompression properties and flow of powder. Precompression evaluation was carried out for the pure drug and powder blend of the cocrystal before compressing into tablets. It was observed that the powder blends of the cocrystal possessed good flow properties and acceptable compressibility index compared to the pure drug as shown in Figure 6. An angle of repose of less than 25 was observed for the cocrystals, which is indicative of the excellent flow of the powder blend. Carr's index was found to be around 15, which indicated the compressibility of the cocrystal was good compared to the pure drug powder blend. % porosity was increased as it was calculated from the bulk density and particle density measurement. This might be the reason for the improvement in the dissolution (Sujitha *et al*., 2014).



A



B

Figure 6. Precompression characteristics of the powder blend of DOLMET 1:2 and pure drug (A), *In vitro* drug release of orodispersible tablets of DOLMET 1:2 and pure drug

Post-compression evaluation of orodispersible tablets

Post-compression studies such as weight variation, friability, disintegration, hardness, and wetting were carried out for orodispersible tablets. Weight variation was limited to the range of ±0.5%, and friability was found to be 0.00855 %. The tablets were disintegrated at 10.05±0.5 seconds. The hardness and wetting time were found to be 3±0.87 kg/cm^2 and 13.62±0.05 seconds respectively. All the findings supported the requirements of the orodispersible tablets. Hence the suitability of cocrystals of dolutegravir for developing fast-dissolving orodispersible tablets with excellent transportability was established.

***In vitro* drug release study of orodispersible tablets**

The *in vitro* drug release studies unequivocally demonstrated the superior dissolution performance of orodispersible tablets compared to pure drug tablets. Orodispersible tablets showed promising results in dissolution compared to pure drug tablets and the % CDR for orodispersible tablets was found to be more than 90% in 20 min as shown in Figure 6. This rapid and enhanced drug release profile suggested the potential of orodispersible tablets to improve bioavailability and accelerate therapeutic onset. The optimized formulation and cocrystal technology employed in these tablets successfully addressed the limitations of pure drug tablets, paving the way for a more efficacious and patient-compliant treatment option.

Stability studies of orodispersible tablets

Stability studies for the pure drug and orodispersible tablet were carried out for 3 months (temperature of 40° ± 2°C and relative humidity of 75% ± 5%) and it was found that there was no significant change in the appearance, weight, hardness, and friability. The critical stability parameters are listed as shown in Table 3. There were no significant differences ($p<0.05$) observed in the tablets kept for stability study for 3 months.

Table 3. Stability studies of orodispersible tablets of DOLMET 1:2

Storage time(months)	Wetting time (Sec)	Disintegration time (Sec)	%CDR
0	13.62±0.05	10.05±0.5	97.95±0.02
1	13.7±0.09	10±0.3	97.8±0.05
2	13.7±0.06	10.1±0.4	97.76±0.04
3	13.71±0.05	10±0.5	97.7±0.06

CONCLUSION

The cocrystallization process of dolutegravir in the presence of different amino acids was experimented out and revealed that a new improved physiochemical form of dolutegravir was obtained at a stoichiometric ratio of 1:2 of the drug: methionine. Methionine was found to be more effective in improving the solubility of the drug as evidenced from the dissolution studies. The solid-state characterization and surface morphology of the cocrystal showed amorphization of the pure drug. The orodispersible tablet formed with the crystal showed good precompression, post-compression, disintegration, and drug release. Hence the process of cocrystallization of dolutegravir with amino acids was found to be promising in overcoming the poor solubility of the drug.

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AUTHOR CONTRIBUTION STATEMENT

All authors contributed to data collection, processing, writing, revision of the draft, reading and approval of the final manuscript.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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