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To study the efficacy of co-crystallization technique in enhancing the bioavailability of oral hypoglycemic agents

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ABSTRACT

The bioavailability of the drug is mainly governed by factors like partition coefficient, solubility Pka, etc. The modification of these physicochemical properties can be done to enhance the bioavailability and thus effective therapy can be achieved. This research deals with the advantages of co-crystals over salts, solvates (hydrates), solid dispersions and polymorphs. A pharmaceutical co-crystal is a single crystalline solid that incorporates two neutral molecules, one being an active pharmaceutical ingredient (API) and the other a co-crystal former. In the present study co-crystals of Metformin Hydrochloride and Glimepiride were prepared using different co-formers. Different ratio of urea, succinic acid and tartaric acid were used to design the co-crystals. They were formulated by two different methods- cooling crystallization and solvent evaporation. The prepared co-crystals were evaluated for microscopic characters, product yield, Fourier Transform Infrared Spectroscopy, Micromeretic properties, drug content, dissolution study of co-crystals, stability studies. The results indicated that co-crystals prepared by using a suitable co-former can definitely enhance the dissolution rate ultimately leading to enhanced bioavailability. Out of three co-formers used to design the co-crystals, succinic acid is found to be more effective. Moreover the bioavailability of Glimepiride is more enhanced as compared to Metformin Hydrochloride as it belongs to BCS class II.

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INTRODUCTION

Limited aqueous solubility of active pharmaceutical ingredients (APIs) presents a tremendous challenge in the development process of new drug products. The fraction of BCS class II and IV drugs among new molecular entities has even been estimated as being as high as 90% (Vishweshwar *et al.*, 2006). A crystal of an organic compound is the ultimate supermolecule, and its assembly, governed by chemical and geometrical factors, from individual molecules is the perfect example of solid-state molecular recognition. A pharmaceutical cocrystal is said to be composition of an drug (API) and an suitable conformer (Desiraju, 1995). They not only enhance the bioavailability but can also enhance the permeability, physical and chemical stability and even processability (Sohrab and S, 2015). Sometimes this effect is attributed to a reduction in particle size which results in an enhanced surface area (Cho *et al.*, 2010). Metformin hydrochloride, a BCS class III drug, is an antihyperglycemic agent, which improves glucose tolerance in type II diabetes. It

has been reported that the absolute bioavailability of metformin hydrochloride when given orally is 50–60% (Hajare and Patil, 2012). The challenge with Metformin Hydrochloride is the poor bioavailability due to less permeability. Glimepiride is an orally active hypoglycemic substance belonging to the sulphonylurea group (Al-Madhagi *et al.*, 2017). Glimepiride is classified under class II according to biopharmaceutical classification system (Frick *et al.*, 1998). The challenge with Glimepiride is the poor bioavailability due to less solubility. Hence taking in considerations the challenges, co-crystals were developed to access the efficacy of technique for BCS class II and III drugs.

MATERIALS AND METHODS

Metformin Hydrochloride and Glimepiride were obtained as gift samples from MSN Labs, Hyderabad. All other chemicals were procured from SD Fine chemicals.

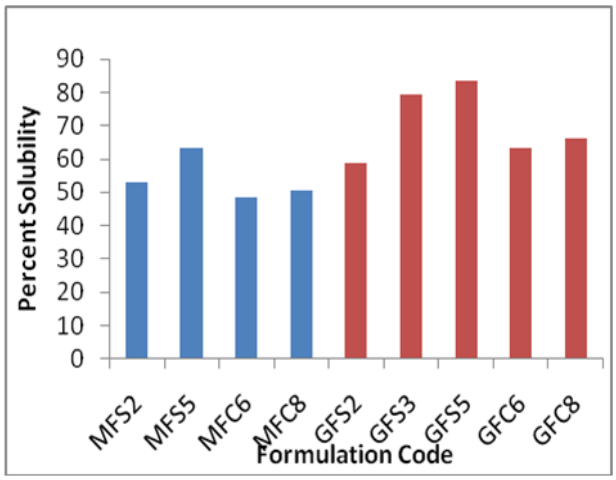

Figure 1: Solubility analysis

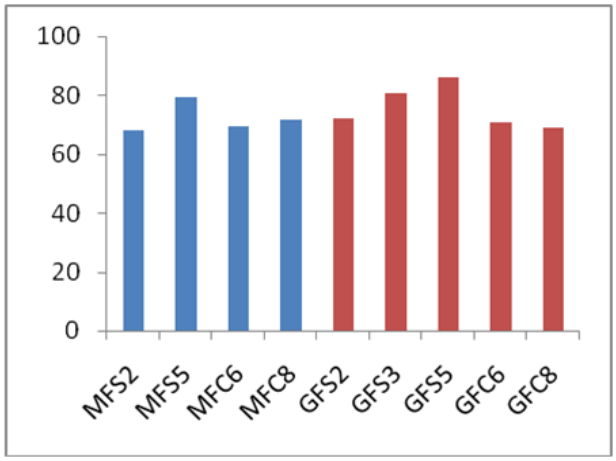

Figure 2: % Drug content

Pre-formulation testing is the first step in the rational development of dosage forms of a drug. FTIR

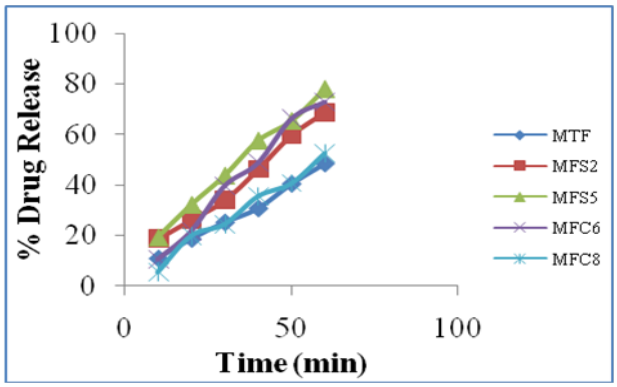

Figure 3: Drug release profile from MTF co-crystals

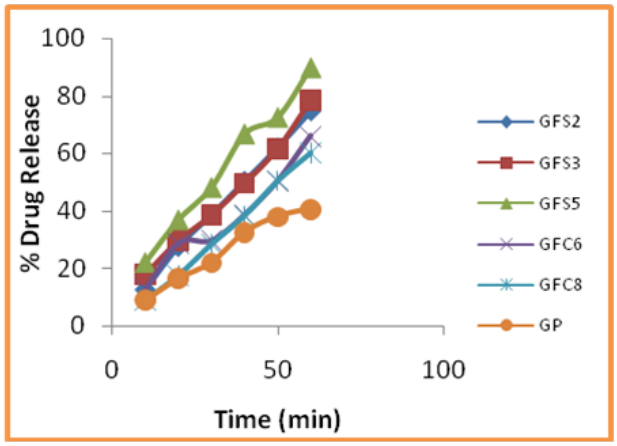

Figure 4: Drug release profile from GP co-crystals

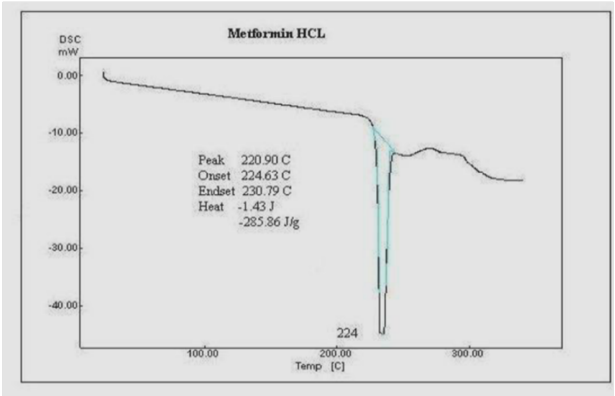

Figure 5: DSC of MTF

studies were done by using KBr pellet method. Calibration curve was plotted using standard solution. The co-crystals were designed using two techniques (Blagden *et al.*, 2007)

Solvent evaporation method

Drug and the co-former were dissolved in 10ml of methanol & stirred for some time. The solvent was evaporated & the co-crystals were obtained.

Cooling Crystallization method

Table 1: Formulation table of Metformin Hydrochloride (MTF) co-crystals

Ingredients (In ratio)	Metformin Hydrochloride	Tartaric acid	Succinic acid	Urea	Solvent in ml
MFS1	1	1			10
MFC1	1	1			10
MFS2	1		1		10
MFC2	1		1		10
MFS3	1			1	10
MFC3	1			1	10
MFS4	1	1.5			10
MFC4	1	1.5			10
MFS5	1		1.5		10
MFC5	1		1.5		10
MFS6	1			1.5	10
MFC6	1			1.5	10
MFS7	1	2			10
MFC7	1	2			10
MFS8	1		2		10
MFC8	1		2		10
MFS9	1			2	10
MFC9	1			2	10

Table 2: Formulation table of Glimepiride (GP)co-crystals

Ingredients (In ratio)	Glimepiride	Tartaric acid	Succinic acid	Urea	Solvent in ml
GFS1	1	1			10
GFC1	1	1			10
GFS2	1		1		10
GFC2	1		1		10
GFS3	1			1	10
GFC3	1			1	10
GFS4	1	1.5			10
GFC4	1	1.5			10
GFS5	1		1.5		10
GFC5	1		1.5		10
GFS6	1			1.5	10
GFC6	1			1.5	10
GFS7	1	2			10
GFC7	1	2			10
GFS8	1		2		10
GFC8	1		2		10
GFS9	1			2	10
GFC9	1			2	10

Table 3: Physical attributes

Formulation	Yield Obtained (Yes/No)	% yield
MFS2	Yes	60
MFC2	Yes	72.12
MFS3	Product was sticky	
MFC3	Yes	78.64
MFS5	Yes	80.01
MFC5	Yes	68.92
MFC6	Yes	52.26
MFS7	Product was sticky	
MFC7	Product was sticky	
MFS8	Yes	74.34
MFC8	Yes	65.93
GFS2	Yes	68.19
GFC2	Yes	70.12
GFS3	Yes	38.26
GFC3	Yes	70.11
GFS5	Yes	95.01
GFC5	Yes	73.21
GFC6	Yes	60.48
GFS7	Product was sticky	
GFC7	Product was sticky	
GFS8	Yes	79.16
GFC8	Yes	63.2

Table 4: Data of stability study

Formulation	% drug content	In-vitro release study
MFS5	76.39	76.84
GFS5	85.2	87.19

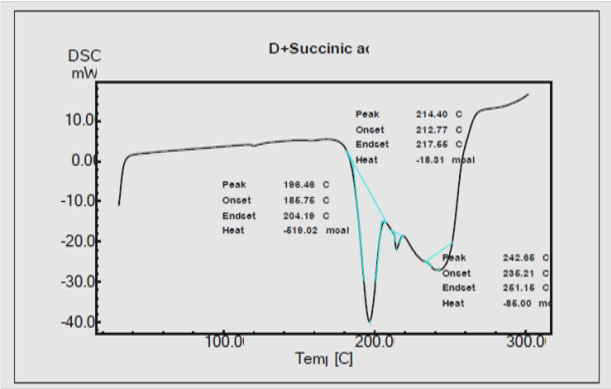

Figure 6: DSC of MTF and Succinic acid

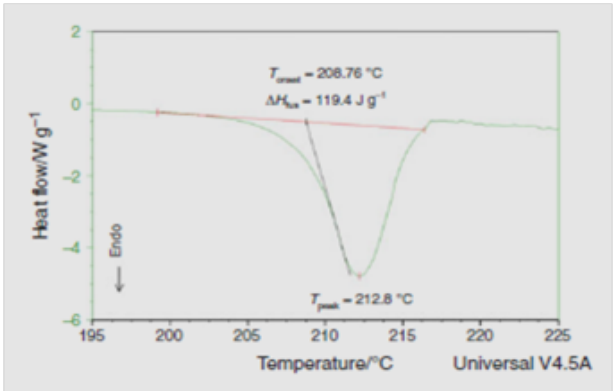

Figure 7: DSC of GP

Drug & co-former were taken in the ratio of 1:1. The drug was dissolved in 10ml of methanol & co-former was dissolved in 10ml of distilled water. Drug solution was added into the co-former solution & stirred for 5 mins. Then the solution was refrigerated overnight & filtered to obtained co-crystals.

A total of 18 formulations were designed for Metformin hydrochloride using three different co-formers. The detailed formulation is given in Table 1.

A total of 18 formulations were designed for

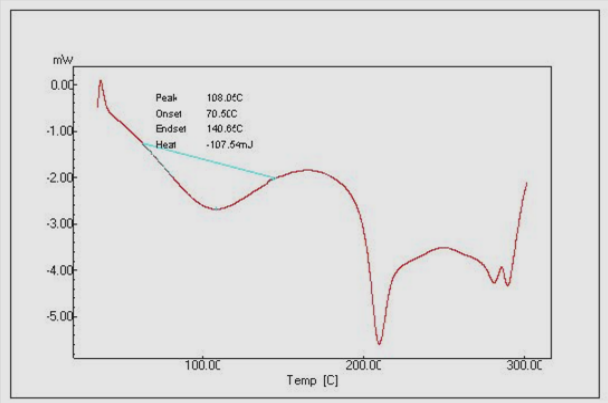

Figure 8: DSC of GP and Succinic acid

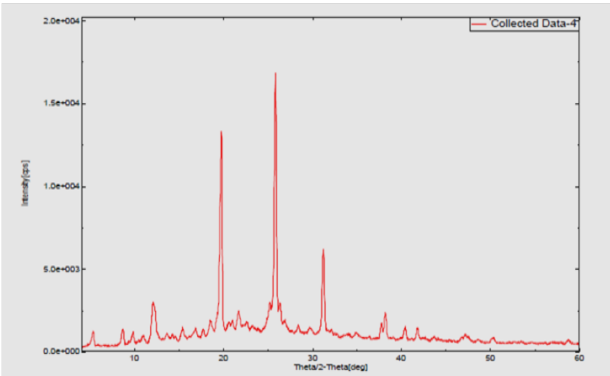

Figure 9: XRD graph of MFS5

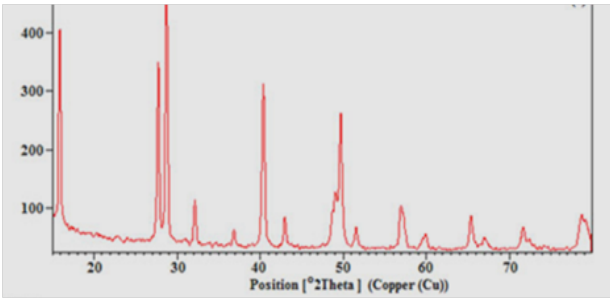

Figure 10: XRD graph of GFS5

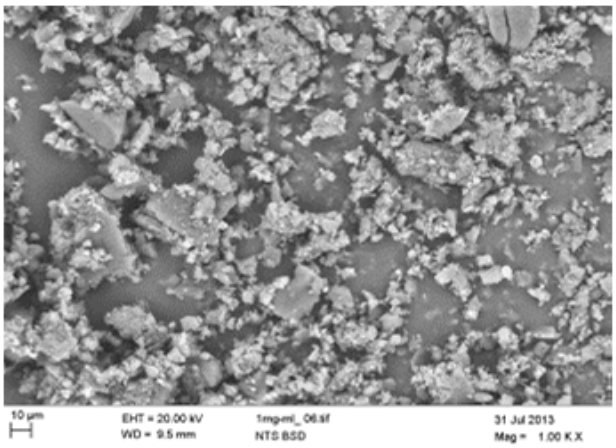

Figure 11: SEM analysis of MTF

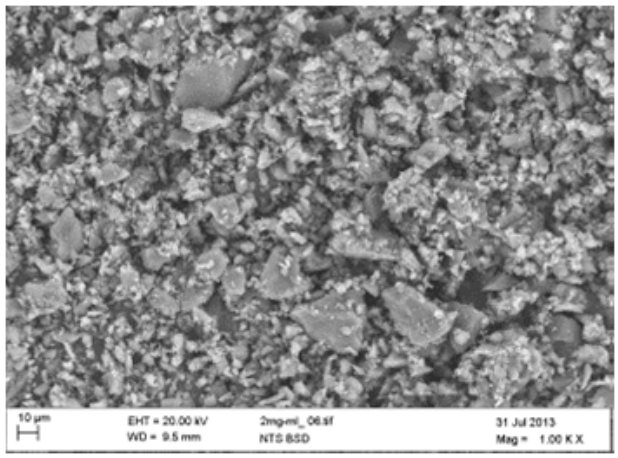

Figure 12: SEM analysis of MFS5

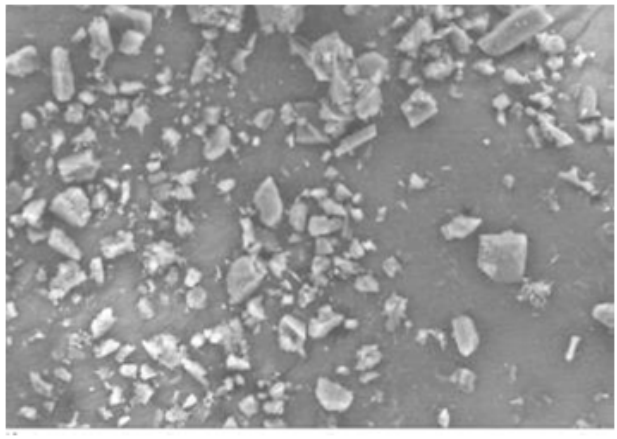

Figure 13: SEM analysis of GP

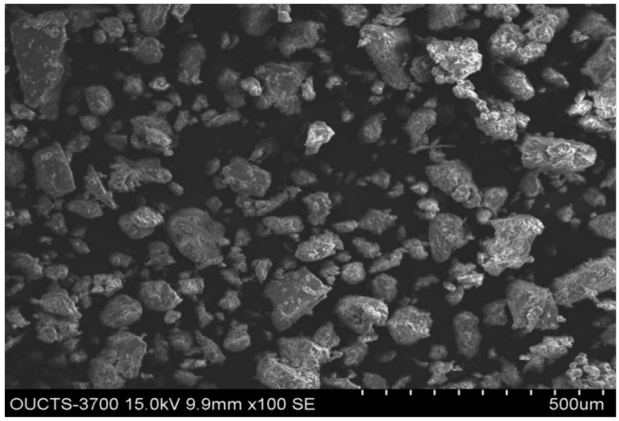

Figure 14: SEM analysis of GFS5

Glimepiride using three different co-formers. The detailed formulation is given in Table 2.

Characterization of Co-crystal

Microscopic evaluation

All the prepared co-crystals were observed under Motic BA 210 microscope (Remenar *et al.*, 2003) which was used as a primary investigation tool to confirm the formation of co-crystals visually and to observe the crystal habit of the prepared co-crystals,

compare the shape of co-crystals was with the pure drug.

Drug content

Prepared co-crystals that were equivalent to about 10 mg or pure drug were dissolved in 100 ml of distil water after accurate weighing followed by solution filtration and dilution after which drug content was analysed in a UV spectrometer against blank (Sohrab and S, 2015).

% Drug Content=

$$\frac{Actual\ amt\ of\ drug\ in\ co-crystals \times 100}{The\ theoretical\ amount\ of\ drug\ in\ co-crystals}$$

In vitro drug release

The in vitro release of pure drug Metformin Hydrochloride and Glimepiride and their cocrystals were tested in a USP XXII dissolution apparatus.

DSC studies

Differential scanning calorimetry was performed using DSC-60, Shimadzu Japan. The samples were placed in a sealed aluminum pan, before heating under nitrogen flow (30mL/min) at a heating rate of 5°C/min from 25°C to 250°C. The heat flow as a function of temperature was measured for the drug and the crystal former (Berry *et al.*, 2008).

XRPD studies

This method is based on an interaction of a monochromatic X-ray beam with a crystalline substance. Different planes of atoms or molecules in a crystal act as a grating for X-rays.

Scanning electron microscopy (SEM)

The surface characteristic of prepared crystal was studied by SEM (JSM 6360 LV, Joel, Japan).

FTIR studies

FTIR spectrum were generated for the prepared co-crystals using a Shimadzdu FTIR-8300 spectrophotometer and the spectrum was recorded in the region of 4000 to 400 cm-1.

Stability studies

This was performed for the optimized samples of both the drugs. Chemical stability was carried out by dissolving a known amount of sample in dissolution media and estimating the drug content. Optimized batch was stored under dry conditions in desiccator at 40 ± 2°C /75 ±5 % RH for a period of 180days. The samples were examined visually for any change of state.

RESULTS AND DISCUSSION

The formulations were prepared and the percent yield was determined. Some formulations were not successful and lost its consistency during storage. The details is mentioned in Table 3.

The formulations containing tartaric acid as the conformer were not prepared successfully. The formulations having drug: tartaric acid in ratio 1:2, were prepared but not be able to collect from the apparatus. All the formulations were sticky and adhered to the glass beaker. Formulations containing drug and succinic acid showed good percent yield. The product obtained was dry and can be stored at room temperature. The formulations containing drug and urea showed a good product for ratio 1: 1 and 1:1.5. But upon storage some of the urea formulations absorbed moisture and became sticky.

Figure 1 shows the results of solubility analysis. It showed that the prepared formulations had a good solubility profile as compared to the pure drugs. The solubility of the metformin hydrochloride co-crystals were less enhanced as compared to the glimepiride co-crystals. Figure 2 shows the results of drug content analysis. The drug content of all the formulations were found to be in the range of 62% to 89%. This shows a good practical yield.

Figures 3 and 4 shows the results of the drug release of pure drugs and the formulated co-crystals. Maximum release was obtained from the formulations containing succinic acid as the coformer. The drug release from the formulations MFS5 and GFS5 is found to be the highest. MFS5 which is formulated by solvent evaporation method and contains Metformin hydrochloride: Succinic acid in ratio 1:1.5 showed 78.05% drug release over a period of 60min. GFS5 which is formulated by solvent evaporation method and contains Glimepiride: Succinic acid in ratio 1:1.5 showed 89.86% drug release over a period of 60min. This enhancement in the drug release can be related to the BCS classification. As Glimepiride belongs to BCS Class II drug which has low solubility and high permeability, the solubility is enhanced when co-crystals are formed. But for the drug, Metformin Hydrochloride, which belongs to BCS Class III and has high solubility and low permeability, the solubility is less affected by the co-crystals technique.

Figures 5 and 6 shows the DSC data for the Metformin Hydrochloride and formulation MFS5 (MTF + Succinic acid). No significant shift in the peak is noted.

Figures 7 and 8 shows the DSC data for the Glimepiride and formulation GFS5 (GP + Succinic

acid). No significant shift in the peak is noted.

The pure drug and cocrystals are demonstrated by the diffraction patterns. The intensity of Xray diffraction pattern for pure drug, at a 2 θ angle of 12.22 was found to be 100%, whereas co-crystals showed 100% intensity of 25.82 (for MTF) and 32.80 (for GP) at θ angle. The XRD graph for formulation MFS5 is given in Figure 9 and for GFS5 is given in Figure 10. The shifting of intensity for 2 θ angle in comparison with pure drug is mainly because of interplanar distance (d angle) indicating different arrangement of molecules, hence confirms the development of new crystalline phase.

The scanning electron microscopical image of pure drug Metformin Hydrochloride is given in Figure 11 and of formulation MFS5 is given in Figure 12.

The scanning electron microscopical image of pure drug Glimepiride is given in Figure 13 and of formulation GFS5 is given in Figure 14.

The SEM of the formulations (MFS5 and GFS5) predicts that the co-crystals are formed successfully.

Stability studies were conducted for a period of 180 days and the end test results indicates that both the optimized formulations have a good stability- physically and chemically. The post stability testing data is given in Table 4.

CONCLUSIONS

The co-crystals of Metformin Hydrochloride and Glimepiride were formulated successfully. The conformer- succinic acid showed promising result as compared to tartaric acid and urea. Hence it can be concluded that succinic acid can be the co-former of choice to enhance the bioavailability of BCS class II drugs, which face challenge in solubilization. For BCS class III drugs i.e Metformin Hydrochloride, co-crystals also can enhance the bioavailability if formulated with suitable conformer.

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None.

Conflict of Interest

None.

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