RESEARCH ARTICLE

Formulation and Evaluation of Fexofenadine hydrochloride-Nutraceutical Cocrystal to Improve Bioavailability through Inhibition of P-Glycoprotein Mediated Drug Efflux

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ABSTRACT

Background: Pharmaceutical co-crystallization is recommended as novel approach to improve bioavailability of BCS class-III drugs. Fexofenadine HCl (FEX) is an antiallergic, exhibits low oral bioavailability (33%). FEX being a substrate of p-gp drug efflux transporter which is accountable for its poor bioavailability. Drug-Nutraceuticals co-crystallization is projected as a rationale approach to improve the permeability of FEX. Coformers having ability to inhibit p-gp were screened by molecular docking approach. Additionally, the coformers were also looked up for the nutritional value they offer. Co-crystals of FEX with Piperine (FEX-PIP) and Curcumin (FEX–CUR) were effectively developed by NG &LAG method. Molecular docking studies revealed the possibility of one hydrogen bond with -4.5 Kcal/mol binding affinity of FEX with Curcumin. FEX–CUR (1:1) cocrystals characterized by SEM, FTIR, DSC &P-XRD. Cocrystal contained O-H-O hydrogen bond amid oxygen atom of secondary -OH of FEX and hydrogen atom of para-hydroxy group on aromatic ring of CUR. The permeability of newly formed cocrystals evaluated by everted gut sac method displayed a 2.68-fold increase in permeability as matched to drug and 2.62-fold increase in dissolution profile. Results indicated usefulness of cocrystallization method to expand permeability of FEX using nutraceuticals as coformers.

Keywords: Fexofenadine HCl, Nutraceuticals, Cocrystal, Everted gut sac, p-gp efflux transporter, Molecular docking

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INTRODUCTION

Physicochemical characteristics of a molecule play a crucial role and influences how drug behaves during manufacturing and administration, impacting its bioavailability, stability, and therapeutic effectiveness. Pharmaceutical cocrystallization emerges as a feasible plan for tailoring and changing physico-chemical characteristics of pharmaceutical actives, all without any negative impact on their pharmacological activity[1]. Cocrystals, constituting of more than one neutral molecular entity within a crystal lattice with a precisely defined stoichiometric ratio, show a pivotal character in this approach. Co-crystals hinges on functional groups of actives and coformers, facilitating the establishment of -H bonds or additional interactions. Selection of appropriate coformers is crucial, primarily based on their capacity to engage in non-covalent interactions, particularly hydrogen bonding with drugs. Several methodologies have been proposed for the judicious selection of conformers. Each of these approaches provides a unique perspective on identifying suitable coformers, contributing to the versatility of cocrystallization as a pharmaceutical modification strategy[2].

FEX anti-allergic, is a substrate of p-glycoprotein which causes its efflux and might be the reason for its poor bioavailability (33%)[3]. The naturally occurring nutraceuticals are a new class of compounds with a proven safety records that can be utilized as a coformersare also reported to inhibit p-gptransporters[4,5]. Various methods are reported to improve bioavailability through enhancing solubility of drug[6]. However, improvement of permeability of FEX can be achieved through cocrystallization approach selecting multi-functional coformers having high permeability, p-gp inhibitory potential which can form hydrogen bond with drug.

Research set out to find a way to make FEX more bioavailable by forming cocrystals. Nutraceutical coformers piperine and curcumin were ground using neat grinding & liquid aided grinding techniques to create a co-crystal.

MATERIALS AND METHODS

Materials

Fexofenadine HCl was kind gift by Emcure pharmaceuticals Ltd. Piperine and Curcumin were provided by Sunpure extracts Pvt. Ltd., Delhi as gift. Research Lab

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Table 1: Fexofenadine HCl and nutraceutical conformer docking outcome

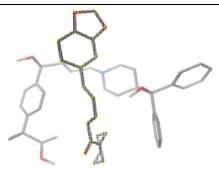
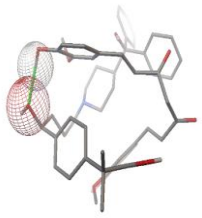
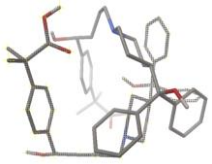
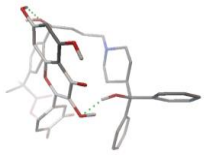
Coformer	Binding Energy (Ei) (Kcal/ mol)	Complex formed	Type of interaction
Piperine	-4.35		No hydrogen bond formation is possible
Curcumin	-4.5		1 Hydrogen bond and ∏-∏ stacking interaction possible
Pro-anthocyan-idin	-5.88		No hydrogen bond formation is possible
Quercetin	-5.0		2 Hydrogen bonds formation possible

Table 2: Summary of dissolution parameters MDT, MDR and DE from *in-vitro* dissolution study

Formulation	MDT (min)	MDR (%/min)	DE (%)
Pure FEX tablet	37.99	0.37	43.52
Marketed FEX tablet	35.14	0.85	44.97
Cocrystal tablet	31.80	1.99	59.41

Fine Chem Pvt. Ltd. of Mumbai was the source for all solvents and excipients that were needed. The program AutoDock vina was used to do molecular docking.

Methods

Nutraceutical coformers were initially shortlisted based on its inhibitory action on p-glycoprotein and further checked for their potential to create co-crystal with FEX on basis of-H bond.

Molecular Docking

Pubchem7 provided 2D structures of FEX (PubChem CID: 63002) & coformers. OpenBabelGUI 2.2.3 transformed allmol files intopdb files. AutoDock 4.2.3 opened the files and added polar hydrogen and Kollman charges to make pdbqt files. Calculating the torsion angles of the pdbqt files prepared them for docking. The kind and intensity of contacts were detected while docking with each conformer [7-9].

Preparation of FEX Cocrystal

FEX cocrystals separately with Curcumin and Piperine were formulated by two approaches; NG & LAG technique using drug:conformer molar ratios 1:1, 1:2 and 2:1.For LAG method, acetone was used as solvent[10,11].

Characterization of Cocrystals

SEM

A Nova NanoSEM 450 was used to analyze surface morphology of optimized batch, coformers & FEX. An aluminum stub coated with a thin layer of platinum (about 5 nanometers thick) & rendered to a vacuum for 100 seconds at 30 watts was used as a base for the sample powder, which was then sprinkled directly onto the double-sided sticky tape.

Infrared Spectroscopy

The potential drug-coformer interaction was investigated using infrared spectroscopy. After dispersing the samples in KBr pellet, they were scanned by a PerkinElmer IR spectrophotometer with a resolution of 4 cm-1, operating within the 4000-400 cm^{-1} wavelength range.

DSC

An instrument with software TA-60 and an empty standard aluminum pan were utilized for DSC, which was conducted on a calorimeter (DSC-60, Shimadzu, Japan). Scans were acquired within the temperature range of 30-400◦C, with a heating rate of 10◦C/min.

XRD Study

Pure FEX and FEX cocrystal powder studied with a Bruker D8 Advance Diffractometer. Each sample was mounted on a motorized goniometer head so it could spin while data was being acquired. The device also came with a precise focus X-ray tube[12,13].

Ex-vivo Permeation Study

Researchers used goat intestine segments to conduct everted gut sac tests in order to deduce how FEX and FEX cocrystal are absorbed. After identifying the small intestine with jejunum portion, the segment was separated and washed in a petri plate using phosphate buffer 6.8 media. We used a glass rod to delicately evert the cleansed intestine, and then we sliced the jejunum portion into 3 cm pieces. To make a gut sac, one end was threaded with a thread & other end was used to insert a dissected butterfly needle. The gut sac was filled with 2 mL of phosphate buffer with a pH of 6.8 using dissected butterfly needle that was inserted. It was placed in an experimental test solution with a volume of 50 ml at a time equal to zero. At 37 degrees Celsius, the experimental solution was kept with constant aeration. The sample solution (0.5 ml) was taken out of sac &diluted to 5 ml in order to conduct UV analysis at specified intervals of 0, 15, 30, 60, and 120 minutes. After each measurement at the specified intervals, volume in gut sac was kept constant at 2 ml with phosphate buffer 6.8 and the percentage of drug penetration was calculated[14].

In-vitro Dissolution Study

The USP type II dissolving device, set at 100 rpm, was used for the *in-vitro* study. Our dissolving media consisted of about 900 mL of phosphate buffer with a pH of 6.8 and a temperature of 37±0.5°C. The dissolving medium was replenished at predefined intervals with the addition of 0.5 mL of blank dissolution media after 0.5 mL of samples were extracted and strained through a 0.45 µm membrane. By

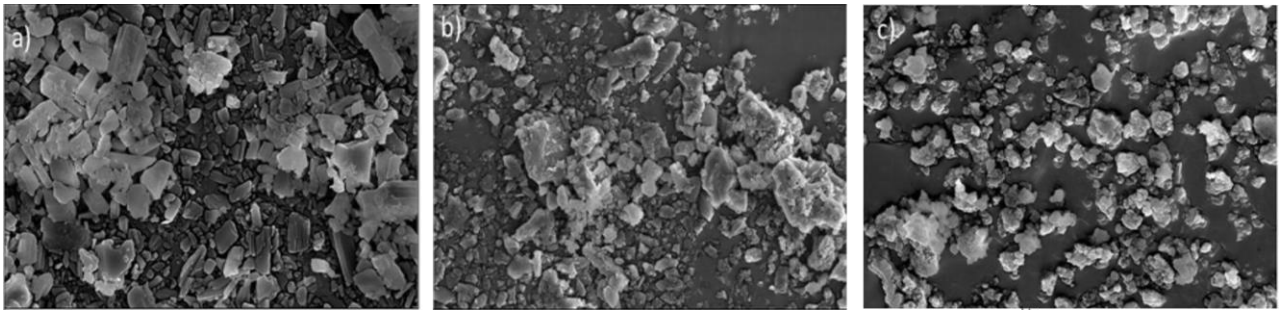


Figure 1: SEM of a) Fexofenadine HCl b) Curcumin c) FEX: CUR 2:1 cocrystals by LAG method

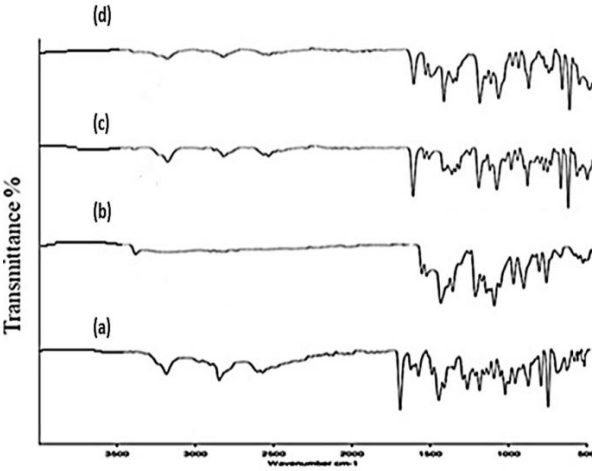


Figure 2: FTIR spectrums of a) Fexofenadine HCl b) Curcumin c) Physical mixture Fexofenadine and Curcumin d) FEX: CUR 2:1 cocrystals by LAG method

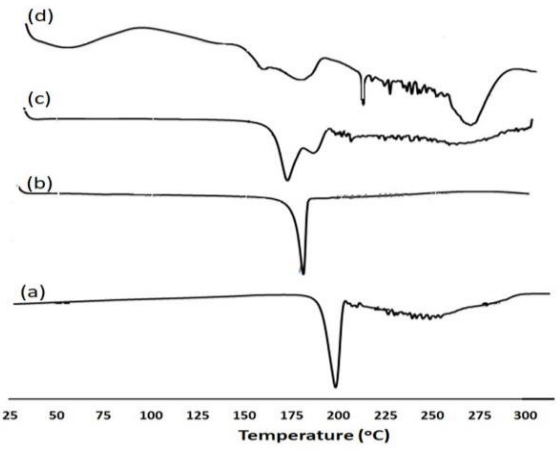


Figure 3: DSC thermograms of a) Fexofenadine HCl b) Curcumin Physical mixture Fexofenadine and Curcumin d) FEX: CUR 2:1 cocrystals by LAG method

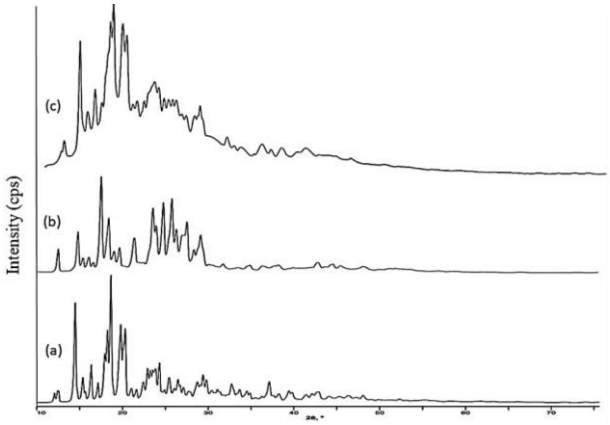


Figure 4: PXRD graphs of a) Fexofenadine HCl b) Curcumin c) FEX: CUR 2:1 cocrystals by LAG method

UV spectrophotometer, the concentration of the dissolved medication was measured at 220nm.

RESULTS

Screening of Coformers

Finding the best coformer to impart the necessary qualities to the cocrystal is an important and crucial phase in the cocrystallization process.

Molecular docking results are shown in Table 1 which revealed that Curcumin and Quercetin were the only coformers able to form non-covalent interactions with FEX. Curcumin interacts with FEX with binding energy -4.5Kcal/mol whereas Quercetin with binding energy -5.0Kcal/mol along with two hydrogen bonds.

SEM

According to the scanning electron microscopy (SEM) in Figure 1, the crystals of pure FEX were irregular in size and shape, appearing both rod-like and columnar (Fig 1a), whereas the crystals of pure Curcumin were similarly uneven in size and shape, appearing both flat and cuboidal (Fig 1b). Crystals of the produced co-crystal of FEX and Curcumin (2:1) have an uneven size and a granular or cuboidal form (Fig. 1c).

FTIR

Fig 2 shows FTIR spectra for pure FEX, Curcumin, physical mixture of FEX with Curcumin and FEX-Curcumin cocrystal. Strong absorption bands at 3293cm^{-1},in the region of 3030–3067cm^{-1} and at 2933cm^{-1} are observed in FTIR spectrum of pure FEX (Fig 2a), respectively. Curcumin showed a strong absorption band at 3506cm^{-1} (Fig 2b) whereas FTIR spectrum of physical mixture showed most of the characteristic peaks of both pure components used (Fig 2c). Moreover, as shown in Figure 2d, the produced cocrystal's FTIR spectra had a little peak shift from 3293 to 3297 cm^{-1}, which corresponds to the O-H carboxylic acid stretch of FEX.

Differential Scanning Calorimetry (DSC)

DSC thermograms for drug, curcumin, physical mixture & co-crystal are showed in Fig 3. As shown in figure intense endothermic peaks were observed at 198ºC for pure FEX (Fig 3a) and at 183ºC for pure Curcumin (Fig 3b). The

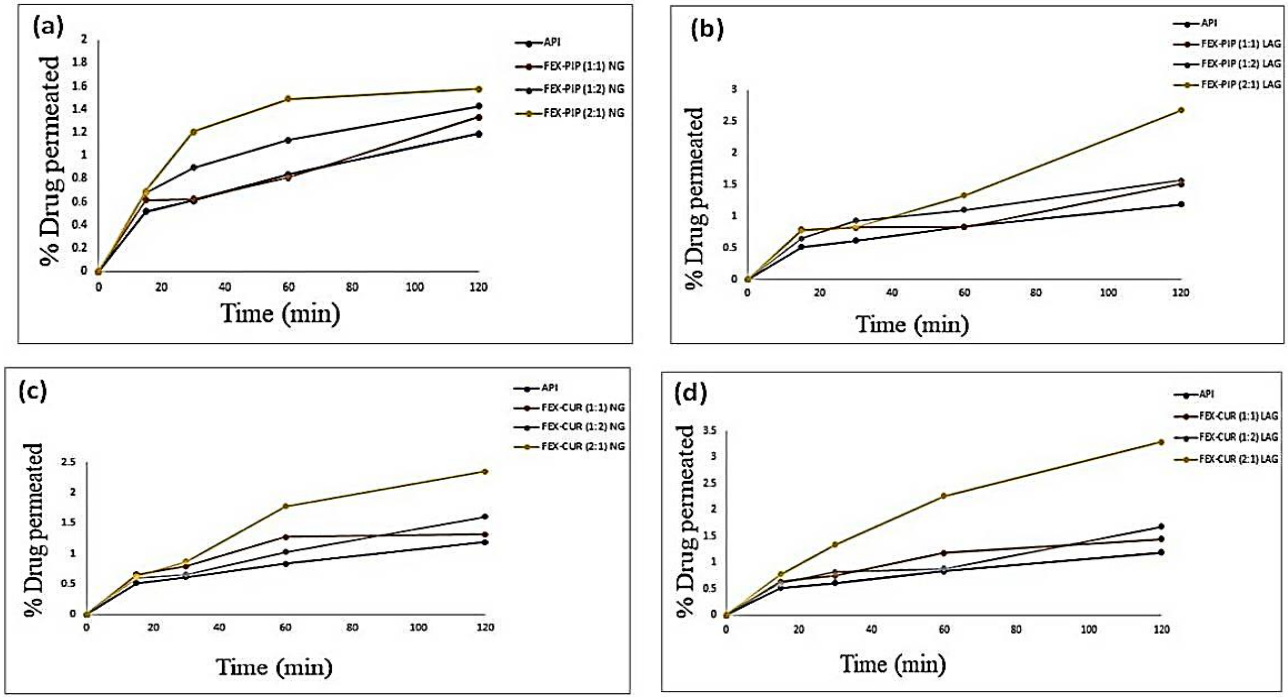


Figure 5: Ex-vivo everted gut sac permeability study for co-crystal formulations

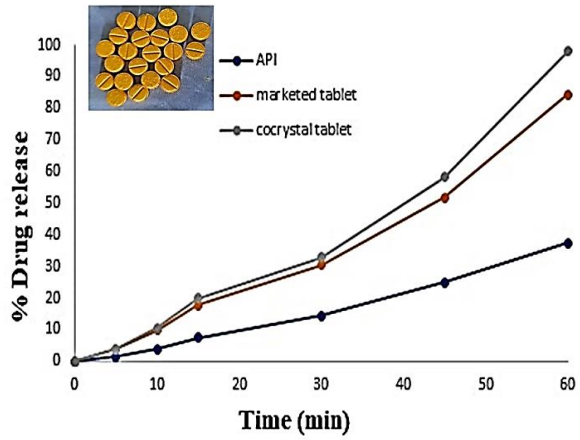


Figure 6: *In-vitro* dissolution study in Phosphate buffer pH 6.8for Pure API, Marketed Tablet and FEX: Curcumin Co-crystal tablet

physical mixture thermograms (Fig 3c) showed a complicated change in the DSC thermogram in which two endothermic peaks at 171ºC and 185ºC were observed. DSC thermogram of FEX: CUR (2:1) by LAG method showed a single sharp endothermic peak at 208ºC (Fig 3d).

PXRD

Figure 4a and figure 4b indicate that PXRD diffractograms of pure FEX and curcumin exhibit several strong, powerful peaks ranging from 10 to 40 2θ. Sharp peaks for drug whereas for pure curcumin several sharp intense peaks at 12.1, 12.26, 14.3, 14.54, 17.2, 17.24, 18.0, 21.1, 23.1, 24.4, 25.5, 27.2 and 28.8 degrees. Final fexofenadine-curcumin cocrystal displayed a number of distinct peaks, with specific peaks seen at 18.0, 18.22, 18.34, 19.30, 19.77, and 21.1 degrees (Fig 4c).

Everted Intestinal Sac Permeability Study

It governs how rapidly a dissolved form of drug will enter into the bloodstream by crossing the intestinal wall. Permeability is a complicated kinetic process that depends on the drug's physiochemical nature as well as the biophysiochemical characteristics of the gastrointestinal barrier membrane.

As depicted in Fig 5, all cocrystals developed using p-gp inhibitor nutraceutical conformers viz; piperine and curcumin demonstrated improved permeation as compared to pure drug. FEX-PIP cocrystals (2:1 ratio) showed higher permeation than 1:2 followed by 1:1. This observation was consistent with both the conformers used and methods adopted for the study.

Further, LAG method of cocrystal showed higher % drug permeation as compared to NG method (Fig 5a-d). With NG method for piperine (Fig 5a) 1.12, 1.20 and 1.33 fold increase in % permeation was seen for 1:1, 1:2 and 1:3 ratios, respectively. Furthermore, using curcumin as conformer (Fig 5c) 1:10, 1.35 and 1.97 fold increase in permeation was achieved for 1:1, 1:1, 1:2 and 1:3 ratios, respectively. With Piperine as coformer 2.25-fold higher permeation was observed (Fig 5b) whereas with Curcumin it was 2.68-fold when compared with pure drug permeation at the end of 120min for cocrystals developed using LAG method (Fig 5d).

In-vitro Dissolution Study

From permeability study observations and benefits of curcumin, FEX:CUR cocrystals (2:1 ratio) by LAG method were selected for *in-vitro* release testing. A tablet containing cocrystals was prepared utilizing the direct compression method; after 5 minutes, the tablet began to disintegrate.

In-vitro release profile (Fig 6) developed tablet was equated with pure FEX & marketed preparation. It was noted that drug release from developed cocrystal tablet was faster and higher from pure drug tablet as well as marketed tablet. At the end of 15 min, drug release from cocrystal tablet was five-times as equated to pure drug tablet & almost double

compared to marketed tablet. Percentage of drug release at the end of 60 minutes for pure FEX, marketed tablet, and manufactured cocrystal tablet was determined to be 37.33%, 84.36%, and 97.93%, respectively.
Table 2 summarizes results. As depicted in table 2, MDT was small for cocrystal tablet (31.80 min), MDR (1.99 %/min) was significantly higher (5.38-fold) and DE was 59.41%.

DISCUSSIONS

Traditional experimental methods of coformer screening often lack reliable data on the outcomes of the crystallization reaction, relying on hit-or-miss coformer selection. Unanticipated results, including solvates, hydrates, salts, and eutectics, can further complicate cocrystallization investigations. Moreover, conducting experimental techniques for a broad array of coformers is impractical due to the considerable time and resources involved economic constraints, and resource-intensive nature of these methods. The current state of affairs necessitates a more efficient and cost-effective approach to coformer selection in cocrystallization studies[15].
Advancements in robust and sophisticated computing systems have paved the way for in-silicocoformer screening, allowing for the rapid identification of optimal coformers from extensive compound libraries. Insights into molecular crystal structures, predictions of intermolecular interactions, and knowledge-driven cocrystal creation are all made possible by the extensive chemical information included in the Cambridge Structural Database (CSD). It is possible to do effective in-silico pre-screening of coformers using tools. These computational approaches enable a more streamlined and cost-effective process for identifying potential coformers[16]. In addition to computational methods, several strategies for coformer selection have been proposed. These diverse approaches contribute to a comprehensive toolkit for efficiently and systematically selecting coformers in cocrystallization studies[17,18].
The hydrogen bonding capabilities of FEX include carbonyl (C=O) in carboxylic acid and cyclic tertiary nitrogen as acceptors, and -OH in carboxylic acid, secondary & tertiary -OH groups as donors. Three aromatic rings, which may play a role in π-π interactions with conformers, are also present. Because of its reuptake mechanism by p-gp, the medication fexofenadine has a low bioavailability. Thus, as conformers, we chose nutraceuticals that inhibit p-gp, such as curcumin, quercetin, proanthocyanidin, and piperine. Methods grounded in knowledge, such as ΔpKa values and the drug's and conformer's tendency to create hydrogen bonds, were used to choose the conformers. The pH value for FEX is 9.01 on the base scale while for CUR it is 9.08 on the acid scale. Consistent with the pKa rule published in the literature, the observed ΔpKa was -0.07, which is less than zero. The tendency to establish hydrogen bonds was assessed using the molecular docking method. Each docked complex had its binding affinity measured in kcal/mol and its intermolecular interactions recorded. With FEX, CUR established the strongest conventional hydrogen connection among all the conformers. The oxygen atoms of the FEX secondary hydroxyl group and the hydrogen atoms of the CUR aromatic ring form an O-H-O hydrogen bond in the FEX-CUR complex. Crystallization by supramolecular synthons may be enhanced by the medication FEX's acceptor site, which interacts with the donor site of its CUR coformer counterpart. The permeability and bioavailability of a medication may be enhanced by this hydrogen bond in the FEX-CUR cocrystal. The contact between the aromatic rings of CUR and FEX, which is not covalent, and the aromatic ring next to the secondary -OH group of FEX are also noteworthy. The almost flat shape of the CUR molecule provides more surface area for π-π stacking due to the van der Waals forces. These are significant factors that promote enhanced bioavailability and cell membrane permeability. Table 1 displays molecular docking outcomes, indicating that only Curcumin and Quercetin among the coformers exhibited non-covalent interactions with FEX. Curcumin demonstrated a binding energy of -4.5 kcal/mol, while Quercetin exhibited a stronger interaction with a binding energy of -5.0 kcal/mol, accompanied by formation of two hydrogen bonds[19].
However, Curcumin was selected over Quercetin because the main oxidation product of Quercetin displays high reactivity towards thiol which can lead to loss of protein function. Quercetin is contraindicated to the patients with kidney disease[20].
The pharmaceutical sector has the opportunity to employ naturally occurring nutraceuticals, a novel class of chemicals with an established safety record, as promising candidates for cocrystallization. An item that has physiological advantages as well as items that aid in disease prevention and treatment, are known as nutraceuticals[21]. Polyphenols (including coumarins, stilbenes, flavonoids, and phenolic acids) and vitamins (including nicotinic acid, retinoic acid, pyridoxine, L-ascorbic acid, folic acid, menadione, etc.) are the major components of nutraceuticals. Furthermore, nutraceuticals are now the drug industry's go-to coformers due to their patentability and widespread availability over-the-counter. By combining nutraceuticals with APIs, bad physicochemical properties including stability, solubility, and bioavailability can be improved, leading to safer materials with better characteristics. So, the idea behind this work was to create pharmaceutical cocrystals of FEX using nutraceuticals as conformers; this might improve its pharmacokinetic profile. Popular method of cocrystal formation is solid-state grinding which includes LAG and NG. However, highly crystalline cocrystals can be obtained by using small amount of liquid as catalyst which enhances molecular diffusion and thus, accelerates cocrystal formation[22,23].

Scanning Electron Microscopy (SEM)

Presence of both drug and nutraceutical conformer as in crystalline form is reflected from the SEM photomicrograph of FEX: Curcumin (2:1) cocrystal which shows granular, cuboidal irregular shaped crystals same as for pure components.

FTIR

FTIR spectrum of FEX (Fig 2a) depicted all the characteristic peaks of it confirming pure form of the drug and absence of any impurity. In Fig 2b, prominent absorption band at 3506 cm^{-1} signifies the presence of

phenolic O-H stretching vibrations in Curcumin. No broadening of any of the characteristic peaks as well as no new peaks was observed in FTIR spectrum of physical mixture as shown in Fig 2c. This confirmed the absence of any hydrogen bond formation as well as any other type of chemical interaction between drug and conformer in physical mixture suggesting mere mixing does not result in formation of cocrystal[24,25]. The FTIR spectrum in Fig 2d of the developed cocrystal reveals a subtle peak shift in the O–H carboxylic acid stretch of FEX, shifting from 3293 to 3297 cm-1. This shift suggests the occurrence of hydrogen bonding between FEX and Curcumin, indicating the formation of the cocrystal[26].

Differential Scanning Calorimetry (DSC)

Sharp endothermic peaks in Fig. 3a and 3b confirms crystalline nature of both FEX and Curcumin in their pure form. Complicated change in the DSC thermogram was observed for physical mixture (Fig. 3c) wherein endothermic peak at 171°C with a small and broad endothermic peak at 185°C were observed[27]. This shift in the melting peaks might result from the physicochemical interaction between drug & co-former when temperature of their physical mixture was raised in the DSC pan[28]. Fig 3d displays the DSC thermogram for FEX: CUR (2:1) using the LAG method, where a noticeable sharp endothermic peak at 208°C stands out. This particular peak, different from the individual peaks of both components, strongly suggests the formation of a cocrystal[29].

PXRD

The PXRD study as demonstrated in Fig 4 affirms the crystalline nature of both the drug and conformer samples procured[30]. The PXRD pattern of the prepared cocrystal exhibits distinct sharp peaks and some new peaks characteristic crystalline peaks were observed[31,32].

From the FTIR, DSC and XRD data, it is established that the formed FEX-CUR cocrystal is a crystalline compound which demonstrates improved pharmaceutical and physicochemical properties compared to the original components. In the FEX-CUR cocrystal, an O-H-O hydrogen bond is present, involving the oxygen atom of the secondary hydroxyl group of FEX & hydrogen atom of the para-hydroxy group on aromatic ring of CUR.

Everted Intestinal Sac Permeability Study

It governs how rapidly a dissolved form of drug will enter into the bloodstream by crossing the intestinal wall[33]. Permeability is a complicated kinetic process that depends on the drug's physiochemical nature as well as the biophysiochemical characteristics of the gastrointestinal barrier membrane permeability studies for BCS Class III drugs are essential for gaining insights into their absorption behavior, predicting bioavailability, guiding formulation design, meeting regulatory requirements, and optimizing drug development processes[34,35].

Despite good solubility, Fexofenadine struggles to passively diffuse. This limits its absorption into the bloodstream and systemic circulation. Therefore, it's important to evaluate permeability of developed cocrystals and method used everted gut sac. An everted intestinal sac study is a laboratory technique applied for evaluation of drug absorption & transport across intestine. It is clearly evident from fig 5a-b that all the cocrystals formed exhibited higher permeation compared to pure Fexofenadine using both methods, however, 2:1 ratio found to be the most promising with highest permeation for both coformers selected. Furthermore, with Piperineas a conformer 2.25-fold higher permeation was observed whereas 2.68-fold improvement in permeability was reported using Curcumin, compared with pure drug permeation at the end of 120min. This outperformance of curcumin as permeability enhancer can be explained with the help of docking outcomes. Fexofenadine did not form hydrogen bond with Piperine whereas Curcumin formed one hydrogen bond with the binding energy of -4.5Kcal/mol. However, inherent higher permeability of Piperine might have resulted in increased permeability of Fexofenadine[22,23].

It is also observed that permeability of drug was more in case of cocrystals developed using LAG method. This could be due to use of solvent which acts as lubricant, reduces friction and promotes particle movement leading to faster and more efficient grinding. Also, solvent used can dissolve and activate the starting material facilitating interactions between drug and conformer. Better crystallinity and minimization of amorphization is reported with LAG method[36].

By comparing the results of permeability study of pure drug, cocrystals developed using piperine and curcumin as coformers, signifies role of excipients as p-gp efflux transporter inhibitors in improving permeability of drugs, which are substrate of such transporter proteins. Thus, current study suggests developing cocrystals using p-gp efflux transporter inhibitor coformers can be a strategic approach in pharmaceutical formulation design to improve bioavailability, increase drug delivery efficiency, potential dose reduction and for addressing multidrug resistance issues etc.

In-vitro Dissolution Study

In-vitro dissolution studies are instrumental in evaluating the permeability and bioavailability of cocrystals. Objective of this study was to show that formation of cocrystals to improve permeability using coformers as permeability enhancers are not affecting dissolution of drug adversely.

The *in-vitro* dissolving investigation showed that drug release from tablet containing FEX-CUR cocrystal was complete after 60min, however pure drug release was partial. FEX is BCS Class III (high solubility, poor bioavailability). Coforming FEX with Curcumin cocrystal tablets enhanced medication release.

Dissolution parameters are used in pharmaceutical and pharmacokinetic studies to assess rate & extent of drug dissolution from a product, such as a tablet or capsule. They provide valuable information about the drug's release characteristics, which can have implications for its bioavailability and therapeutic efficacy. As briefed in Table 2, MDT for cocrystal tablet was less as compared to pure drug tablet and marketed tablet, which can be correlated with highest MDR for cocrystal tablet. MDR is almost five times greater than that for pure drug tablet and DE was approximately 60% for cocrystal tablet.

Thus, *in-vitro* release study demonstrated attempts to improve permeability of BCS Class III drug using nutraceuticals as coformers hampered neither solubility nor dissolution negatively from the developed dosage form.

CONCLUSION

FEX, a BCS Class III drug & is a substrate of p-gp efflux transporter causing low oral bioavailability. Drug–Nutraceuticalcocrystals of FEX with Curcumin were effectively formulated by neat grinding & liquid assisted grinding approaches to make use of inhibitory effect of Curcumin on p-gp. FEX-CUR (2:1) exhibited 2.68-fold higher permeability and 2.62-fold growth in drug release equated to pure FEX. FTIR study confirmed the formation of cocrystal whereas DSC and PXRD study established crystalline nature of cocrystals. FEX–CUR cocrystals displayed superior tableting performance. Co-crystallization with Curcumin deals an appreciated mode to expand physicochemical characteristics of Fexofenadine HCl.

Acknowledgements

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Conflict of interest: Nil

List of Abbreviations

FEX: Fexofenadine HCl; BCS: Biopharmaceutical Classification System; p-gp: p-glycoprotein; PIP: Piperine; CUR: Curcumin; NG: Neat grinding; FTIR: Fourier Transform Infrared Spectroscopy; DSC: Differential Scanning Calorimetry

LAG: Liquid assisted grinding; SEM: Scanning Electron Microscopy; CSD: Cambridge Structural Database; HSP: Lattice energy calculations and Hansen solubility parameter; MDR: Mean Dissolution Rate; MEPS: molecular electrostatic potential surfaces; MDT: Mead Dissolution Time; DE: Dissolution Efficiency

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