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Co-Crystals of Anti-Diabetic Drugs for Enhancement of Physiochemical and Biopharmaceutical Properties: A Comprehensive Review

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Abstract

Co-crystal of anti-diabetic drugs promotes enhanced drug solubility, which significantly improves the bioavailability, results in better management of disease. Conventional forms of drugs available for managing diabetes exhibits low solubility and stability, therefore frequent dosing required to maintain the blood levels. Due to sustained and progressive course of diabetes, co-crystallization approach is promising in terms of improving aqueous solubility with higher bioavailability and reduced dosage schedule. This review article will provide comprehensive information about anti-diabetic drug co-crystals, drug-drug co-crystals along with some herbal active components which when combined with anti-diabetic drugs show remarkable synergistic effects. In addition, Specific drug co-crystals cases are discussed to illustrate the enhancement in performance due to formation of hydrogen bonding in co-crystal structure. Apart from this, latest developments in clinical trials and patent landscapes are also mentioned in this article. This review provides a compiled data on anti-diabetic co-crystals till date, their preparation techniques along with the valuable outcomes. Further, critical insight to facilitate the industrial production, advanced technological methods such as microfluidic crystallization process can execute high-throughput analysis of drug and co-former combination with minimum consumption of sample. Continuous-flow microfluidic system could hold up scalable manufacturing of co-crystals while their uniformity remains intact.

Keywords

anti-diabetic co-crystals, bioavailability enhancement, improved solubility, patents, herbal bioactive

1 Introduction

Diabetes is a long-term metabolic disorder, which is characterized by high blood sugar levels. In the body, blood glucose levels are regulated by a hormone called insulin, which is produced by the pancreas. When the glucose level increases in the blood, the pancreas secretes insulin, which commands cells to uptake glucose from the bloodstream. However, in this condition, either the body does not produce enough insulin or there is a lack in the utilization of the insulin it produces [1]. According to the report published by World Health Organization (WHO) in 2022, about 14% of the adult population has diabetes, which is double the figures of the year 1990. Apart from this, the survey also stated that approximately 60% of adults suffering from diabetes were not taking any medicines for their disease [2]. Considering the mortality rate, diabetes caused 1.5 million deaths in 2019, with 48% of these occurring before the age of 70. Additionally, diabetes-related kidney failure caused around 460,000 deaths. Overall, death rates increased by 3% between 2000 and 2019. This metabolic disease generally impacts the living conditions and life expectancy of patients. In fact, due to hyperglycemia, the risk for other comorbid conditions rises eventually, affecting multiple

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organs of patients [3]. Diabetes can be categorized into two categories: Type 1 and Type 2. Type 1 diabetes is basically an autoimmune disorder in which the insulin-producing cells are attacked by immune system of the body, though the exact reason for the attack is not fully understood, it is widely accepted that this can be a result of complex interaction between genetics vulnerability with environmental triggers. In Type 2 diabetes, the body either does not produce enough insulin or the cells do not respond to the insulin that is produced, a condition known as insulin resistance. Gestational diabetes is another type of diabetes that is more prevalent nowadays and develops in some women during the pregnancy period and may or may not end after pregnancy [4]. The treatment regime generally depends upon the severity of the disease. The primary course of treatment for Type 1 is insulin alone, and it is available in various forms, such as fast-acting lispro, aspart, and glulisine. The next type includes long-acting, which consists of detemir, glargine and degludec. The last category is intermediate-acting, also known by the name of neutral protamine hagedorn (NPH) insulin; it consists of Humulin N and Novolin N. The guidelines for Type 2 diabetes comprise four well-defined stages, which should be used on the same patient only. At the Initial stage, the first choice of drug for treatment is metformin. However, recent guidelines emphasize on patient-centric approach in which sodium-glucose cotransporter 2 (SGLT2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonist can be given as first line of treatment drugs in patients who have comorbid conditions such as cardiovascular disease, heart failure or chronic kidney disease, irrespective of the hemoglobin A1c (HbA1c) levels. If HbA1c levels do not reach desirable levels after 3 months, medical specialist will add a second line treatment drug that include dipeptidyl peptidase-4 (DPP-4) inhibitors, Thiazolidinediones, Sulfonylurea, SGLT2 inhibitors, GLP-1 receptor agonist and basal insulin (This is stage 2). At the stage 3, when the recommended level of HbA1c levels not reached, the third category of drug will be added in order to control the level of blood sugar in optimum range. Finally, the Fourth stage, when the desired level of HbA1c (after 3 months of passing stage 3) not reached, the treatment plan will consist of combined therapy which contains metformin, basal insulin and mealtime insulin or GLP-1 receptor agonist [5].

However, the main concern for diabetes treatment is the bioavailability of these drugs, as most of them face issues that limit their absorption and therapeutic efficacy. Drugs that are used in the treatment of Type 2 diabetes have been reported to have low solubility and permeability, thus classified as either class 2 or class 4 under the biopharmaceutics classification system (BCS). To rectify this, new strategies have been designed in order to counter this problem and enhance their solubility without any alterations in their molecular structure and mechanism of action [6]. A significant approach known as co-crystallization is popularly used to ameliorate their physicochemical characteristics. These crystalline solids are made up of two or more different molecules or compounds. The molecules are arranged in a specific ratio within the crystal lattice. Co-crystals are generally formed by non-ionic and non-covalent bonds such as hydrogen bonds, π–π stacking, and van der Waals forces. These interactions result in co-crystal lattice energy that is in general more stable than the crystal lattice of individual components [7]. The process of co-crystallization is shown in underlying Fig. 1.

Co-crystallization is a distinctive method, as it does not alter the therapeutical features of a drug; instead, it enhances the drug properties, such as dissolution profile, physical and chemical stability, and bioavailability, by establishing suitable bonds between pure drug and coformer [8]. Moreover, co-crystals can exhibit synergistic effects; the combined effect of constituents as co-crystals is more than the individual effects. To elaborate, alpha-glucosidase inhibitors medicines are given orally to slow down the carbohydrate digestion and absorption. Blocking of this enzyme leads to a slower and smaller rise in blood glucose levels after eating meals. Xue et al. have reported the alpha-glucosidase inhibition activity of gallic acid-glutaric acid co-crystals. The enzyme activity results have shown that both gallic acid and glutaric acid represent alpha-glucosidase inhibition activity, but gallic acid-glutaric acid co-crystals have shown stronger inhibition properties even at moderate concentrations as compared to gallic acid and glutaric acid alone. Thus, showing a synergistic effect in co-crystals form [9]. Additionally, they can play a pivotal role in modifying the mechanical properties of active pharmaceutical ingredient (API), making them more acceptable for compression, thus improving tabletability [10]. APIs, which have sensitive functional groups, make them vulnerable in harsh conditions of strong acids and bases but can be made stable easily by co-crystals formation. This novel advantage

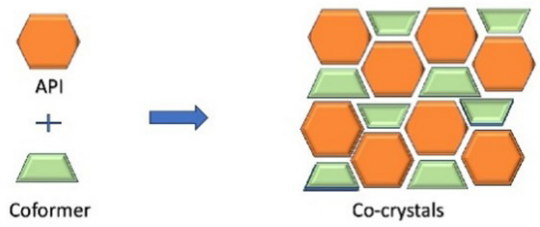

Fig. 1 Illustration of a pharmaceutical co-crystal

readily enhances the stability of APIs, protecting them from degradation during storage and processing. Humid conditions generally affect the stability of drugs, as they have a tendency to absorb moisture, but co-crystals can effectively block water molecules from interacting with API by making hydrogen bonds between API and coformer, and as a result, decrease hygroscopicity [11]. Co-crystals have attained success in improving physicochemical characteristics of drugs significantly, however, from a regulatory perspective, the US Food and Drug Administration do not consider co-crystal as new product rather they are labelled as drug intermediate or solid-state modifications similar to solvates. Many researchers have put their efforts into the preparation of pharmaceutical co-crystals that can alter the solubility of class 2 and class 4 anti-diabetic drugs [12].

2 Co-crystals preparation techniques

The preparation of co-crystals involves selecting a suitable co-crystallization technique based on the solubility, nature, and thermal stability of the drug, coformer, and solvent used. In general, there are two classes of co-crystallization techniques, namely solution-based and solid-based methods. Solution-based methods consume more solvent, which may alter the intermolecular interactions between the drug and coformer. In contrast, solid-based methods consume little to no solvent and utilize mechanical forces for co-crystals. Solid-based crystallization methods can be classified as a green chemistry approach, as they do not involve the use of any organic solvents. The most commonly used solvent-based techniques are solvent evaporation, anti-solvent, and cooling crystallization. Solvent evaporation uses mixing of a stoichiometric ratio of drug and coformer in a suitable solvent and allows for evaporation to obtain co-crystals [13]. On the other hand, anti-solvent crystallization involves preparing an API and coformer solution in a solvent, followed by the addition of anti-solvent to decrease coformer solubility, resulting in precipitation of co-crystals. Cooling crystallization involves reducing the temperature of an API and coformer solution, resulting in reduced solubility and leading to the formation of co-crystals. In contrast, solid-state methods allow for co-crystal preparation without the need for solvents, requiring almost no solvent at all. Neat grinding involves the dry grinding of solids together in a mortar and pestle, a ball mill, or a vibrator mill. Whereas, liquid-assisted grinding involves the usage of a little amount of solvent during the grinding of solids. Hot melt extrusion consists of co-crystals formation by heating the drug and coformer at a higher temperature, followed by extrusion to form co-crystals [14]. Various crystallization techniques have been utilized by the researchers for preparing anti-diabetic drug co-crystals, represents in Table 1 [14–23]. In order to conform the formation, structure and physical properties, various characterization techniques (mentioned in Fig. 2) are employed such as powder

Table 1 Different techniques for the preparation of pharmaceutical co-crystals

Preparation techniques	Methods	Description	Ref
Solid based	Neat grinding	Solid material subjected to crushing manually or mechanically	[14]
	Liquid assisted grinding	Mixing of two components with addition of small amount of solvent.	[14]
	Hot melt extrusion technique	Drug and coformer are processed together under heat and mechanical shear to form co-crystals	[15]
Solvent based methods	Solvent evaporation	Drug and coformer dissolved in a suitable solvent followed by complete evaporation of the solvent	[16]
	Anti-solvent method	Addition of drug-coformer solution to an anti-solvent leading to co-crystallization	[17]
	Cooling crystallization	Solubilization of drug and coformer in a suitable solvent followed by sudden lowering of its temperature causing co-crystallization	[18]
	Reaction crystallization	Crystallization process is activated by reaction process which involved acid-based interactions	[19]
Miscellaneous methods	Ultrasound assisted crystallization	High frequency sound waves applied to the solution containing both drug and coformer	[20]
	Slurry crystallization	Drug and coformer suspended in solvent in which they have limited solubility, during agitation process crystallization occurs at solid-liquid interface, after completion the solvent is removed and co-crystals dried under nitrogen flow	[21]
	Microwave assisted crystallization	Solution of drug and coformer placed in microwave radiation reactor at suitable temperatures and pressure	[22]
	Electrospray method	Solution of drug and coformer in a suitable solvent pumped through capillary nozzle followed by a high voltage charge, this converted charged liquid in to microdroplets, after evaporation of solvent co-crystals formed	[23]

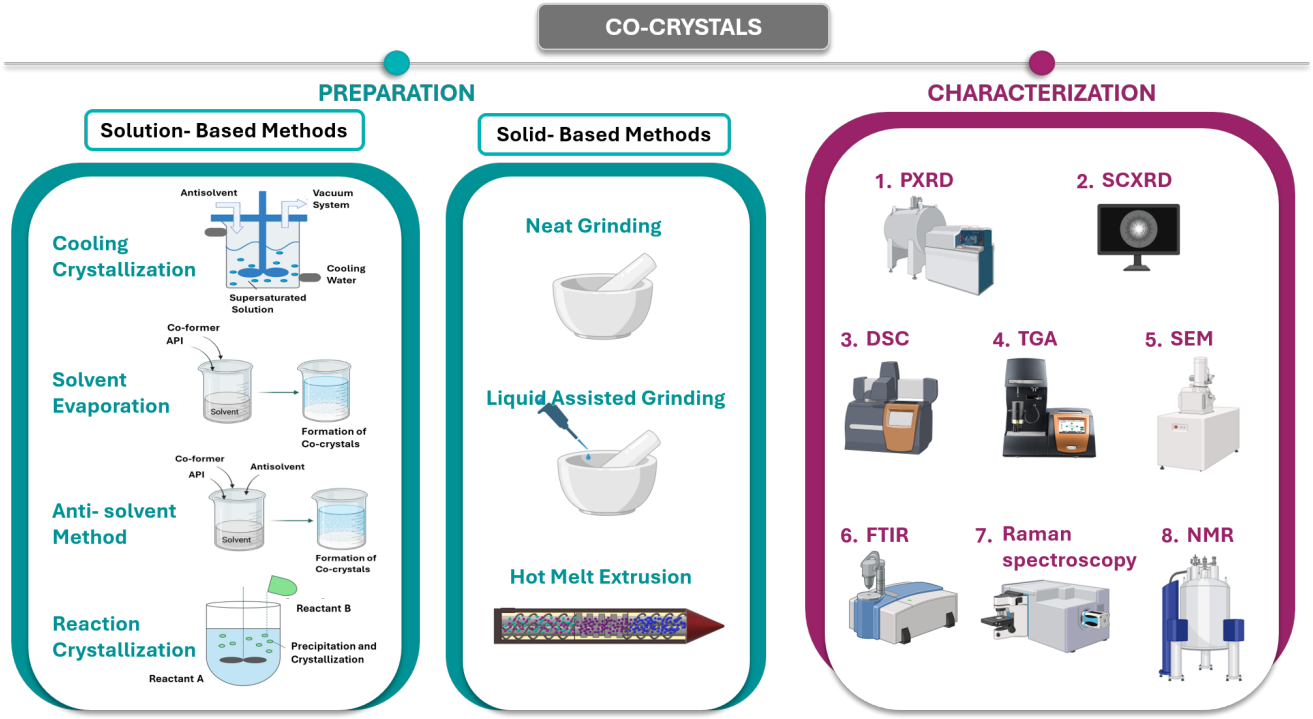

Fig. 2 Various preparation and charaterization techniques of pharmaceutical co-crystals

X-ray diffraction (PXRD), single crystal X-ray diffraction (SXRD), Fourier transform infrared spectroscopy (FTIR), Raman spectroscopy, and Nuclear magnetic resonance spectroscopy (NMR). Further, the thermal analysis done by differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA) [11, 20]. Various methods of preparation are mentioned in Table 1.

3 Co-crystals of anti-diabetic drugs

Solubility of anti-diabetic drugs is the rate-limiting step for their absorption and effectiveness, as only dissolved drugs can be absorbed and transported throughout the body. This stage became more critical, as most of the anti-diabetic drugs have poor aqueous solubility, which further affects their absorption [24]. Glibenclamide is one such anti-diabetic drug whose therapeutic action is compromised due to its poor aqueous solubility. However, co-crystallization is a suitable approach for enhancing the solubility, bioavailability, and therapeutic efficacy of anti-diabetic drugs. In this context, Malik et al. reported co-crystals of glibenclamide with caffeic acid demonstrated enhancement in the dissolution profile of the drug. This significant improvement was attributed to hydrogen bond formation betweenthe sulfonyl group of glibenclamide and the hydroxyl group of caffeic acid. Further, the *in-vivo* studies conducted showed a fast reduction in blood glucose level as compared to the drug alone [25]. Further, co-crystals of glibenclamide with nicotinamide in the ratio of 1:2 is prepared by Budiman et al. where they noticed rise in solubility as compared to the pure drug and its physical mixture. The hydrogen bond formation between drug and coformer readily affects the hydrophilicity of API, thus increasing its dissolution [26]. Additionally, various researchers have used different coformers such as vanillic acid, malonic acid, aspartame, ascorbic acid, saccharin, and oxalic acid to make successful co-crystals of glibenclamide [27–30]. Another co-crystallization experiment on glimepiride, a sulfonylurea-class drug classified by its low water solubility, was carried out by Zidan et al. Co-crystals of glimepiride with oxalic acid have shown significant improvement in solubility and systemic bioavailability. The dissolution of Glimepiride-oxalic acid co-crystals reached 71.93% within 5 min as compared to plain Glimepiride, which was only 7.83% in the same period. Moreover, studies have shown around 97.3% of drug release takes place after 120 min from the Glimepiride-oxalic acid co-crystals form, whereas only 22.06% of pure glimepiride was dissolved in this time period. Further, *in-vivo* data have demonstrated that the C_{max} (which means maximum concentration of a drug measured in the bloodstream) of glimepiride-oxalic acid co-crystals was 2.62-fold higher than that of the glimepiride suspension. The area under curve ($AUC_{0-\infty}$: representing the total amount of drug actively present in the blood stream overtime) and mean residence time (MRT) have shown a 2.66-fold and 1.17-fold rise, respectively, as

compared to glimepiride suspension [31]. Further co-crystals of the glimepiride drug with tartaric acid were successfully prepared by Jaafar and Radhi [27]. The FTIR studies have revealed the formation of a hydrogen bond between the hydroxyl group of coformer with the S=O group of glimepiride. *In-vitro* studies have demonstrated that glimepiride-tartaric acid co-crystals (1:2 molar ratio) have shown 99.92% of drug release within 5 min. Different coformers, which were used by various researchers to prepare co-crystals of anti-diabetic drugs, are listed in Table 2 [25–48].

Table 2 Co-crystals of anti-diabetic drugs reported by various researchers

Drug	Coformer	Preparation technique	Results	Ref
Glibenclamide	Caffeic acid	Solvent evaporation	The sulfonyl group of glibenclamide forms a hydrogen bond with caffeic acid. *In-vivo* results showed fast reduction in blood glucose level.	[25]
Glibenclamide	Nicotinamide	Solvent evaporation	Hydrogen bonding enhances the hydrophilicity of the drug. Solubility enhanced to 73.03%* from 25.11%.	[26]
Glimepiride	Oxalic acid	Ultrasound-assisted	Enhancement in solubility and dissolution rate. *In-vivo* studies in rats represents increase in C_{max}, longer t1/2, $MRT_{0-\infty}$**, and a 2.66-fold rise in AUC.	[31]
Glimepiride	Citric acid Tartaric acid Oxalic acid dehydrate	Solvent evaporation	Hydrogen bond formed between sulphonamide group of glimepiride and the hydroxyl group of carboxylic acids (coformers), showed significant enhancement in dissolution rate.	[27]
Gliclazide (GL), tolbutamide (TOL)	Piperazine (PPZ)	Liquid-assisted grinding	GL-PPZ showed solubility enhancement by 6.6 times, while TOL-PPZ showed 80-fold increase in its solubility.	[32]
Glibenclamide	Malonic acid	Solution crystallization	Two-fold improvement in solubility of glibenclamide: *In-vivo* data showed 1.45-fold increase in AUC_{0-24} and 1.36-times enhancement in C_{max}.	[28]
Glibenclamide	Aspartame	Solvent evaporation	Hydrogen bonding between the amine group of the drug and the hydroxyl group of aspartame results in an increase of solubility. The pure drug showed 2 μg/ml solubility and co-crystals showed 31.71 μg/ml solubility in same time period.	[29]
Glibenclamide	Ascorbic acid	Solvent evaporation	Solubility of (1:2) co-crystals increased 26 times as compared to pure drug. The dissolution rate increased to 63.23% from 46.83%.	[30]
Glibenclamide	Saccharin	Solvent drop grinding	Hydrogen bonding formed between the amide group of glibenclamide and the sulfonyl group of saccharin. *In-vitro* results showed 97.68% drug release from (1:2) co-crystals form as compared to only 65.32% percent release from pure glibenclamide tablet.	[33]
Glibenclamide	Oxalic acid	Solvent drop grinding	Intermolecular hydrogen bonds between glibenclamide and oxalic acid, two-times improvement in dissolution profile.	[34]
Glimepiride	Caffeine	Solvent drop grindin	*In-vivo* studies showed a 1.25-fold increase in drug release in the first 6 h as compared to the parent drug, significant increase in bioavailability.	[35]
Glimepiride	Salicylic acid	Slow solvent evaporation	Hydrogen bonding between sulphonyl group of glimepiride and amide group of salicylic acid, solubility enhanced.	[36]
Gliclazide (GL)	Malic acid (MA) Succinic acid (SA)	Liquid-assisted grinding	GL-MA showed 1.47 times increase in C_{max}, and a 1.65-fold increase was noted in GL-SA co-crystals, approximately a 2-times rise in solubility.	[37]
Gliclazide	Benzoic acid (BA) Itaconic acid (IA)	Solvent evaporation	A 3.3-times improvement in the dissolution rate of GL-IA and a 5.2-times improvement in GL-BA co-crystals were reported. 53.26% cumulative release from benzoic acid co-crystals and 37.86% in IA co-crystals as compared to the pure drug, which was 27.64%.	[38]
Gliclazide	3,5-dinitrosalicylic acid 2,6-pyridine dicarboxylic acid L-proline	Liquid-assisted grinding	Gliclazide-3,5-dinitrosalicylic acid co-crystals showed 6.3 times increase in solubility, dissolution enhanced by 1.5 times, and relative bioavailability increased by 1.8 times.	[39]

* The increase in solubility is measured in percentage.
** MRT: mean residence time average amount of time drug molecule spend in the body from the moment they are adminsitered until they are eliminated.

Table 2 Co-crystals of anti-diabetic drugs reported by various researchers (continued)

Drug	Coformer	Preparation technique	Results	Ref
Gliclazide	Sebacic acid Hydroxy acetic acid	Liquid-assisted grinding	A three-times rise in equilibrium solubility and 1.5-fold enhancement in intrinsic dissolution rate.	[40]
Gliclazide	Tartaric acid Succinic acid	Solvent evaporation	Gliclazide-tartaric acid (1:2) showed a 78% rise in the dissolution profile, while gliclazide-succinic acid (1:3) showed a 75% increase.	[41]
Gliclazide	Tromethamine	Solvent evaporation	Hydrogen bonding results in improvement of dissolution rates as fast and full release of the drug.	[42]
Gliclazide	Nicotinamide	Solvent evaporation	Hydrogen bonding showed enhancement in dissolution rates	[43]
Glipizide (GPZ)	Picolinic acid (PA) Adipic acid (AA) Isonicotinic acid (IA) Fumaric Acid (FA) Sorbic acid (SA)	Liquid-assisted grinding	An increase in dissolution rates noted as GPZ-PA 6-fold, GPZ-AA 4.5-fold, GPZ-INA 3.7-fold GPZ-FA 2.3-fold, GPZ-SRA 1.7-fold. *In-vivo* studies indicated high C_{max} and reduction in blood glucose level.	[44]
Glipizide	Glutaric acid	Liquid-assisted grinding, slurry crystallization, solvent evaporation	Solubility was enhanced by 53 times in water, 22 times in acidic buffer and 26.8 folds in basic media.	[45]
Pioglitazone (POI)	2-naphthalene sulfonic acid (NSA) Maleic acid	Solvent drop grinding	*In-vitro* results showed dissolution profile enhanced by 7 times in POI-NSA co-crystals.	[46]
Metformin	Citric acid	Liquid-assisted grinding	N–H–O intermolecular hydrogen bonding, solubility enhanced 1–4 folds, improved bioavailability.	[47]
Canagliflozin	Thiourea	Sonocrystallization	Increased solubility and dissolution rates.	[48]

4 Drug-drug co-crystals of anti-diabetic agents

The potent effect of anti-diabetic drugs can be enhanced by combining them into co-crystals forms. To elaborate, the interaction between the molecules leads to a greater therapeutic effect than the drugs alone in their individual forms. This can be due to improvement in the bioavailability profile, which further increases the concentration of drug in the bloodstream and enhances the therapeutic efficacy. Li et al. who have prepared glimepiride and Metformin co-crystals, have shown remarkable improvement in hypoglycaemic effect in Diabetic/obese (db/db) mice as compared to these drugs when used alone [49]. Additionally, *in-vivo* studies showed glimepiride activated AMP and STAT3 signalling, downregulated the TXNIP expression, and upregulated the MaFa expression. Glimepiride also promoted the secretion of insulin in the pancreas of db/db mice, which further enhanced the anti-diabetic effect. Further, the mechanical properties of the drug metformin (a class III BCS drug) can be ameliorated by incorporating it with other drugs in co-crystal form. When metformin is combined with Dobesilate (reported by Jiang et al. [50] the hygroscopicity of the drug is reduced sharply due to the formation of a hydrogen bond between them. Thus, increasing the plastic flow further leads to improved tabletability. Moreover, a synergistic effect against diabetic retinopathy was also observed. Further, co-crystallization of metformin with ibuprofen and naproxen (non-steroidal anti inflammatroy drugs (NSAIDs)) done by Qin et al. reported increase in solubility of these NSAIDS as compared to parent drug alone [51]. Further the *in-vivo* studies done on λ-carrageenan induced inflammatory mice revealed that metformin-ibuprofen and metformin-naproxen co-crystals have also shown potent synergistic antinociceptive effects. Various co-crystals of anti-diabetic drugs in combination form are listed below in Table 3 [49–53].

5 Herbal co-crystals with anti-diabetic potential

Herbal bioactive with anti-diabetic activities are preferred due to their non-toxic behaviour, but their usage is limited due to poor aqueous solubility, stomach instability, and membrane permeability. However, incorporating them into appropriate dosage forms can provide greater stability, increase solubility, enhance bioavailability, and improve therapeutic efficacy. Herbal co-crystals can overcome these limitations without altering their properties. Many researchers have successfully presented herbal bioactive in the form of co-crystals. Rutin, one of the most effective natural bioflavonoids, is known for its antihyperglycemic effect. However, due to its poor solubility and oral bioavailability, its application becomes limited. To improve its bioavailability, Zhang et al. prepared rutin co-crystals with L-proline by the slurry conversion method [54]. The co-crystals revealed improved solubility and dissolution rate compared

Table 3 Summary of literature reported on drug-drug co-crystals of anti-diabetic agents

Drug	Coformer	Preparation technique	Results	Ref
Glimepiride	Metformin (MET)	Liquid-assisted grinding	*In-vivo* studies showed an amplified anti-diabetic effect as compared to GLI or MET alone by activation of the AMPK/TXNIP/Mafa pathway, which protects β-cell dysfunction.	[49]
Metformin	Dobesilate	Solvent cooling and evaporating co-crystallization	The hygroscopicity of metformin is reduced due to hydrogen bonding and the synergistic effect against diabetic retinopathy.	[50]
Metformin	Ibuprofen Naproxen	Solvent evaporation	Enhanced solubility and intrinsic dissolution rate, synergistic antinociceptive effects.	[51]
Metformin·HCl	Sodium salicylate	Solvent evaporation	Results showed enhancement in plastic flow and improved tabletability.	[52]
Metformin	Dichloroacetate (DCA)	Slurry crystallization, solvent evaporation method	Results showed a synergistic effect on apoptotic cell death, thus enhanced anti-leukemic activity.	[53]

to pure rutin. The *in-vivo* pharmacokinetic studies of co-crystals in Wistar rats showed 3.8 times higher C_{max} and a 5.6-fold enhancement in AUC_{0-10h} than the parent drug. In addition, a significant drop in fasting blood glucose level was observed after treating with co-crystals, showed only 0.9% rise in fasting blood glucose as compared to 7.3% rise in fasting blood glucose levelwith pure drug. Thus, rutin co-crystal have shown better effect on reducing fasting blood glucose. This study clearly indicated the potential of herbal co-crystals in the management of diabetes. Gallic acid, a potent polyphenolic component, exhibits good anti-diabetic effects but has low aqueous solubility and bio-availability. The co-crystals were prepared by Xue et al. by using glutaric acid as a coformer by using EtOH-assisted grinding method [9]. The inhibition efficiency of gallic acid, glutaric acid, and their co-crystals form are studied on the alpha-glucosidase enzyme. Both gallic acid and glutaric acid showed a dose-dependent glucosidase inhibitory activity, while the co-crystals of gallic acid and glutaric acid showed a higher inhibitory activity than those of the two parent components ($p < 0.01$). This represents that crystallization with glutaric acid makes the binding of gallic acid with the alpha-glucosidase enzyme stronger, which results in a positive synergistic effect [55]. Reported co-crystals of herbal bioactive are listed below in Table 4 [9, 54, 55].

6 Patents of co-crystals of anti-diabetic drugs

Patents are granted to provide protection by giving exclusive legal rights to their inventor, such as to use, to make, to sell, and to license their invention for a specific period of time (generally 20 years). Patent protection rights for co-crystals of anti-diabetic drugs provide significant benefits to the pharmaceutical industry, as new solid dosage forms can be obtained, offering unique compositions along with improved physiochemical properties. For instance, patent no. W002012090225A2 describes co-crystals of metformin and oleoylethanolamide in 1:1 aims to enhance bioavailability index of metformin along with an extra anti-obesity effect. These co-crystals improves the drug's residence time in bloodstream, which further reduce the dosage of Metformin and also improved patient compliance [56]. Various patents related to anti-diabetic co-crystals are mentioned in Table 5 [56–60]. Furthermore, the work related to patent process is illustrated in Fig. 3.

7 Pre-clinical and clinical studies of co-crystals of anti-diabetic drugs

Preclinical studies are performed on animal groups such as Wistar rats, mice, and dogs, as their anatomy and physiology have more resemblance to human beings. The pharmacokinetics and pharmacodynamics profile

Table 4 Reported work on herbal co-crystals with anti-diabetic potential

Drug	Coformer	Preparation technique	Results	Ref
Rutin	l-proline and d-proline	Slurry conversion	Enhanced solubility and bioavailability: AUC_{0-10h} of Rut-l-Pro was 5.6-fold that of rutin, and C_{max} was 3.8 times.	[54]
Gallic acid	GA-p-aminobenzoic acid (co-crystal A) and GA-amino acetic acid (co-crystal B)	Solvent-assisted grinding	Co-crystals A showed 2.24-fold increase, while co-crystal B indicated a 1.70-fold increase in $AUC_{0-\infty}$. Alpha glucosidase inhibition activity is .4-fold high in co-crystal A.	[55]
Gallic acid	Glutaric acid	EtOH-assisted grinding method	Results showed α-glucosidase inhibition activity and synergistic effect.	[9]

Table 5 Published patents on co-crystals of anti-diabetic drugs

Patent no.	Drug	Title	Remarks	Ref
W02012090225A2	Metformin and Oleoylethanolamide	Novel synergistic co-crystals to improve bioavailability and efficacy as anti-diabetic agents and ant-obesity agents	Improved bioavailability of metformin, thus improved anti-diabetic action along with anti-obesity features.	[56]
W02015198227A1	Dapagliflozin Citric acid	Dapagliflozin-citric acid co-crystal, preparation, and use to treat type-2 Diabetes mellitus	Dapagliflozin have advanced solubility, stability and processability.	[57]
US20120258170A1	Quercetin Metformin	Pharmaceutical co-crystal of quercetin	Improved stability and dissolution rate of metformin, solubility of quercetin enhanced.	[58]
US9006188B2	Dapagliflozin Asparagine	Co-crystal of dapagliflozin	Improvement in physiochemical properties such as high stability, lower hygroscopicity.	[59]
EP3349762B1	Empagliflozin	Co-crystal of sglt2 process for their preparation and pharmaceutical composition	Higher solubility and dissolution rate, improved flow properties.	[60]

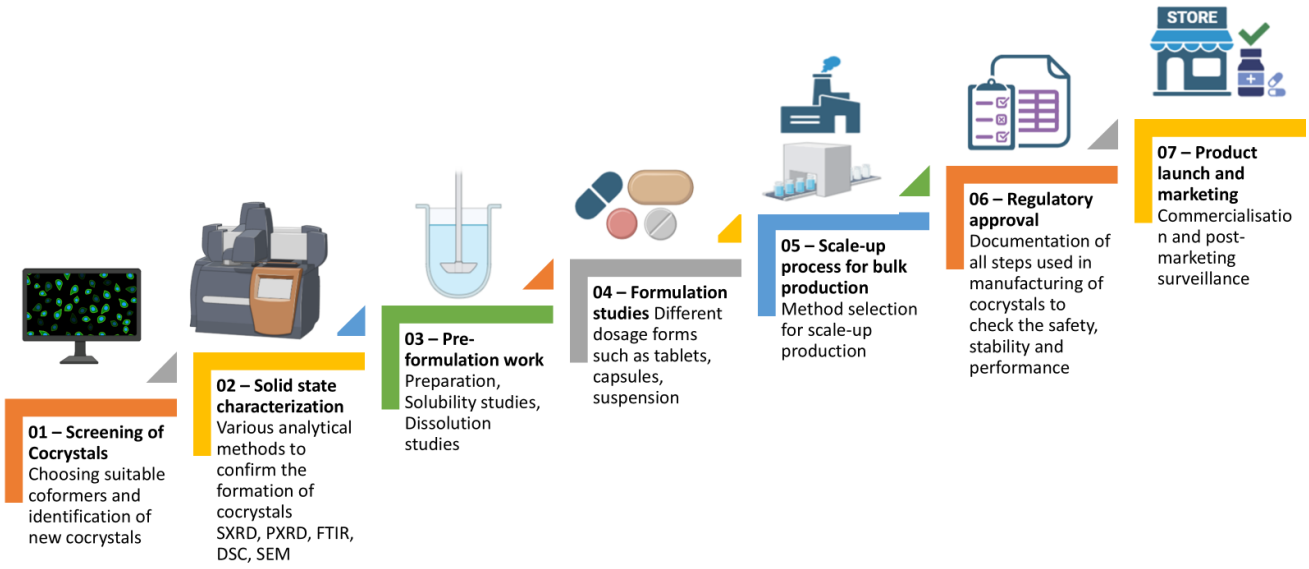

Fig. 3 An overview of the pharmaceutical manufacturing process, covering seven sequential steps from initial cocrystal screening to final product launch and marketing, including major milestones in formulation, analytical characterization, and regulatory approval

can provide the drug's mechanism of action along with its absorption, distribution, metabolism, and excretion profile (ADME). For instance, co-crystals of glimepiride with oxalic acid have shown significant improvement in solubility, which leads to enhanced systemic bioavailability. *In-vivo* data have also shown promising results, with 2.62 times higher C_{max}, 2.66-fold higher $AUC_{0-\infty}$, and 1.17 times higher MRT as compared to glimepiride suspension [27]. Another study on beagle dogs and mini pigs was done by Hyuk et al. [61] to find out the comparison of physiochemical properties and bioequivalence of novel dapagliflozin-di-L-proline co-crystals loaded tablets with the commercially available dapagliflozin propanediol hydrate co-crystals tablets. Less hygroscopicity and less water content were observed in the new formulation than in the previous one; however, bioequivalence parameters (C_{max}, AUC) were the same as those of commercially available tablets [59]. Based on pre-clinical findings, human safety assessment is carried out to rule out whether the drug is safe or not. Furthermore, dose determination and identifying whether the drug works accurately according to its intended profile in humans. In addition to this, to obtain approval from apex regulatory bodies such as Central Drug Standard Organisation (CDSCO), Food and Drug Administration (FDA), and European Medicines Agency (EMA), the clinical data is required; only then can marketing of the drug could take place.

8 Outlook and future perspectives

The co-crystallization process is one of the significant techniques used to improve the physiochemical properties of drugs, mostly belonging to BCS class II and IV. Various anti-diabetic drug's properties such as their aqueous solubility, bioavailability can be enhanced effectively by the

process of co-crystallization. Many researchers have prepared and performed characteristics evaluation along with *in-vitro* studies. Results have shown remarkable improvement in physiochemical properties and therapeutic performances. Another novel and promising approach is combination of herbal entity with anti-diabetic drugs to develop a phytopharmaceutical product. These synergistic interactions can potentially manage the glycaemic control. Reported work of rosiglitazone and berberine co-crystals have indicate enhancement in solubility of rosiglitazone, yet *in-vivo* therapeutic effects are not fully explored. Adverse effects such as gastrointestinal discomfort or metabolic interactions may occur, highlighting the importance of systematic safety evaluation of herbal bioactives. Pharmacokinetic profiles are required to understand the drug absorption and optimal dosing strategies. These herbal entities can act as a potent substituent at the place of modern medicines because they are generally considered as safe. Nevertheless, like all other pharmacologically active compounds, their effects may depend upon dose, formulation and individual patient conditions. Moreover, enhancement of solubility and bioavailability by co-crystallization process may increase the systemic exposure of active constituents. Though this can definitely improve therapeutic efficacy, but critical step related to careful dose optimization in order to maintain safety and avoid excessive exposure is required. Therefore, evaluation of pharmacokinetic parameters and dose–response relationships remain essential during the development of such systems. Originating from natural resources, they provide sustainable and environmentally friendly alternative over various pharmaceutical products. The half lethal test of quercetin and puerarin co-crystals conducted by Jie et al. revealed that the LD_{50} (which means lethal dose 50%, it is standard metric used in toxicology to measure the acute toxicity of a substance) value of puerarin -4,4'bipyridine (PUE-4,4'BIP) co-crystals is 2.290gm/kg and quercetin-4,4'bipyridine (QUE-4,4'BIP) is 3.3633gm/kg [62]. This result indicates that both herbal components are having relatively low toxic profiles, still research data on these herbal bioactive is very scarce to carry manufacturing process at industrial level. Scientist have done various experimentation to accelerate their physiochemical properties but clinical studies to understand the body response to treatment and how might it effect the health outcomes is still undiscovered. The clinical investigations on these potent herbal constituents can provide real time monitored data about the effectiveness and new advancement in the field of medicines. Another important aspect in field of co-crystals is microfluidic continuous flow systems. This advanced system offers a hopeful substitute to traditional batch system as it can manage crystallization parameters effectively, which are required for continuous production of high-quality co-crystals at industrial level. The technical aspects such as nucleation, mixing and supersaturation can be attained precisely with this microfluidic system. Further, 3D printing facilitate customized design for microfluidic chip, which enables microfluidic flow reactors to control fluid dynamics (mixing, diffusion, laminar flow). Moreover, channel length can be modified rapidly by 3D-printed reactor. For instance, better control over size and polymorphism has been noticed in carbamazepine + saccharin co-crystals when prepared with 3D printed spiral microfluidic reactor [63]. However, batch crystallization does not show such type of control and precised work. Despite its accuracy, the handling of solids in continuous flow remains a challenging task. Persistent hurdles in the form of crystal deposition, clogging and scale up level from laboratory to industrial manufacturing are the primary obstacles. To reap the full capacity of microfluidic continuous flow crystallization, multidimensional strategy should be adopted that can integrate the technology innovations, understanding of process, regulatory requirements and industry viability. Other than microfluidic approaches, continuous crystallization technologies also have great potentials for manufacturing pharmaceutical co-crystals on a large scale. Some of these systems are mixed suspension mixed product removal (MSMPR), continuous oscillatory baffled reactors (COBR), and plug flow reactors (PFR), which allow for controlled crystal growth, reproducibility, and consistent product quality. Besides, industrially relevant techniques, spray drying, and hot-melt extrusion (HME) offer high-throughput manufacturing options with improved process efficiency. The overall continuous approaches benefit co-crystal production in particular since structural uniformity, scalabilities, and industrial relevance can be supported by sophisticated controlling of the critical process parameters (CPPs). To conclude, though many plant-origin flavonoids and alkaloids have shown promising preclinical studies, but transforming these results in to effective formulations, it requires rigorous clinical trials and safety studies. Likewise, microfluidic continuous flow system still faces lack of established GMP protocols, which leads to difficulties in validating non-standard reactors. Therefore, limitation of this system can be addressed effectively via smart engineering in

which material choices and process integration should be considered wisely, which can make them more viable for pharmaceutical co-crystals manufacturing.

9 Conclusion

Over recent years, co-crystal engineering has evolved as a promising technique to enhance the performance of anti-diabetic drugs. A significant number of pharmaceutical patents have been registered, and few of them have also been approved for clinical trials. Poor solubility of anti-diabetic drugs limits their absorption and effectiveness. The co-crystallization process has the potential to enhance a drug's aqueous solubility without any alterations to its molecular structure. Hydrogen bonding, which forms during the crystallization process, creates more hydrophilic surface faces that increase the solubility. Furthermore, the structure of the drug became more stabilized due to the formation of intermolecular forces. Drug-drug co-crystals can deliver two APIs (active pharmaceutical ingredients) in a single dosage form, thus attaining synergistic activity, which further increases the clinical efficacy of drugs. Many organizations have already filed patents related to this, and some have launched the co-crystal-marketed formulation as well. In herbal-drug co-crystals, the overall anti-diabetic effect is enhanced as the herbal entities contribute their own bioactivity with the conventional drugs. As a consequence, synergistic effects along with improved physiochemical properties can be witnessed. However, certain challenges persist in incorporating herbal products in formulation, especially their stability and toxic profiles. Clinical trials should be carried out effectively in order to obtain the safety profile. Additionally, for making them viable for industrial production, the continuous flow crystallization experiences scientific and technical limitations such as flow rate, temperature and mixing intensity. As a result, hinder their worldwide applications.

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