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DESIGN DEVELOPMENT AND FABRICATION OF PHARMACEUTICAL CO-CRYSTAL: ENHANCE AQUEOUS SOLUBILITY AND IN-VITRO DISSOLUTION RATE OF BCS CLASS 2 OR 4 ACTIVE PHARMACEUTICAL INGREDIENT

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ABSTRAC

In last couple of years many API discoveries found to be poorly soluble in aqueous medium. These poorly soluble APIs have low bioavailability & low absorption. So, to deal with this challenge co-crystal technique found to be boon to pharmaceutical industry. Co-crystals optimize the In-vitro powder dissolution rate of Biopharmaceutical classification system (BCS) class 2 or 4 drugs. Crystalline structure of co-crystals comprises of API and one or more Co-former must be either amino acid or carboxylic acid such as (oxalic acid, succinic acid, serine, proline, glycine, etc.) In stoichiometric ratio hydrogen bonded interactions done between drug and Co-former which improves the aqueous solubility of co-crystal. Co-crystals are prepared by following methods such as Liquid assisted grinding, Hot melt extrusion method, Solvent evaporation method, Anti solvent method, Spray drying method, etc. And further characterized by High performance liquid chromatography, Fourier transform infrared spectroscopy, Differential scanning calorimetry, Powder x-ray diffraction and In-vitro dissolution studies of the formulation.

KEYWORDS: - Co-crystal, Co-former, Solubility Enhancement, Co-crystal screening, Synthon approach, Theoretical screening.

1. INTRODUCTION

In present era, to enhance aqueous solubility of BCS class 2 drugs is the most challenging issue came into existence for the R&D department in pharmaceutical industries.[1] The US food and drug administration (FDA) issued a guidance regarding co-crystals in 2013 and a document was issued by the European medicines agency (EMA) in 2014. Thus, an environment for development of co-crystals as an API (Active pharmaceutical ingredient) is being prepared. In accordance with the FDA guidance and EMA document, it is essential to determine that an API and Co-formers was suitable for co-crystal. In particular, the FDA guidance co-crystals should be discerned from salts. Co-crystal is a supramolecular compact structure formed by mixing of APIs and Co-formers in between API and supramolecular syntonic hydrogen bonds or other non-covalent bonds forms in a stoichiometric ratio.[2] It is very complex process to develop a new formulation with low aqueous soluble BCS class 2 (low aqueous solubility and high permeability) and class IV (low aqueous solubility and low permeability) drugs such as amphotericin B,[3,4] furosemide, acetazolamide, ritonavir[5]. To deal with these challenges the key role of co-crystals came into prevalence. Co-crystallization technique is a novel discovery for enhancement of physicochemical and mechanical properties of APIs. Co-crystals are broadly defined as an alternative approach for the crystal engineering which recognizing the molecules between different material species of molecules. Co-crystals are structurally homogeneous they are composed of APIs and Co-formers. Co-formers help to increase the solubility of poorly soluble drugs includes (BCS class 2 or 4) without affecting the pharmacological effect of the APIs. Polymorphism is important parameter for the pharmaceutical industry because the chemical and physical properties of API changes with change in different packing in the crystals including bioavailability and aqueous solubility of API. Co-crystals are formed by syntonic bonds, and a differ in these bond design can lead to syntonic polymorphism.[6] Co-crystals enhances the solubility of the APIs as well as dissolution rate, bioavailability, flow property, hygroscopicity and stability. It is an attractive approach to improve and modify the physicochemical properties without obtaining any change in covalent bonds of the API molecule itself.[7] The goal of this article is to convey broad overview of pharmaceutical co-crystals. Mainly focusing on all the challenges including physicochemical properties of APIs, solubility, techniques of formulation, development in screening, mechanism of co-crystals and at the end characterization of co-crystals.[8,9] Physical stability of APIs is an another lead component of its regulatory approval,

manufacturing, improving formulation and storage protocols.[10,11]

2. Synthon Approach / Hydrogen bonding

Co-former selection is the key role to synthesize the co-crystals based on the "Synthon approach". Which constructs within the co-crystal a super molecule by utilizing specific molecular fragments to establish "supramolecular synthons". The basic requirement for a suitable selection of Co-former is to be pharmaceutically allowable, i.e. Generally recognized as safe (GRAS) components.[12,13] According to synthonic bonding a stable functional group present in the API and Co-former play a main role in the fabrication of crystal forms[14]. Furthermore, Co-formers should be relatively cheap, with low molecular weight, and occupy multiple binding sites which can be associated in the formation of intermolecular strong interaction.[15] Carboxylic acid represents one of the most generally studied functional groups in synthon engineering and they live in around 30 of the 100 top-selling traditional medicines. 60 carboxylic acids thus represent an excellent outset for synthon engineering of pharmaceutical co-crystals. Their reciprocal H^+ bond donor and acceptor spots makes supramolecular homo-synthon favourable.[16,17] Still, co-formation is doubtful in competitive situations. Hydrogen bonding interaction can be intramolecular or intermolecular interaction. Co-formers should have proton acceptor and donor group which can be interact with hydrogen bonding with API. It should contain functional groups like amines, amides, carboxylic acid, alcohols which can produce strong hydrogen bonds. Co-crystals were constructed in a 1:1 stoichiometric ratio of API and Co-former N-H•••O=C and C=O•••H-O hydrogen bonds, respectively.[18] Common hydrogen bond formed from carboxylic acids, pyridines, amides and other aromatic nitroge.[19] Hydrogen bonding or synthon approach can be screened by using cambridge structural database software which is very sophisticated and accurate software,[20]

3. Co-crystals

The first novel delivery of pharmaceutical co-crystals was invented by the German chemist Friedrich Wohler in 1844. He discovered co-crystals quinhydrone by grinding of quinine with hydroquinone. A pharmaceutical co-crystal is a multicomponent crystal system in which at least two components are solid (API & Co-former) and one component might be solvent which is additional component depend on the formulation technique and always have established stoichiometric ratio, such as 1:1 (1 mole of API:1 mole of Co-former), 1:2 (1 mole of API:2 mole of Co-former) and 2:1 (2 mole of API:1 mole of Co-former).[21] Co-former which is invented by crystal engineering which were assembled from Hydrogen bonding, π-π stacking, Vander walls interaction, these all are the intermolecular interactions. Co-crystal engineering modifies the internal structure of solid material by changing intermolecular structure that adjust the forming and breaking of non-covalent bonds like Hydrogen bonds, π-π stacking, Vander walls forces, Halogen bonds, etc.[22] Design of co-crystals resides in the form of Solvates, Polymorphs, Hydrates.[23,24]

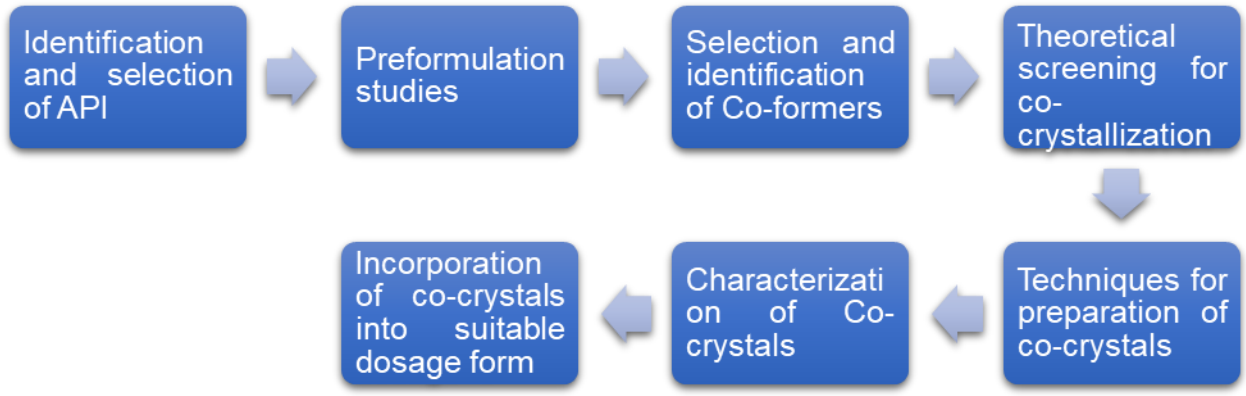

Figure 1: Design of co-crystal formation.[25,26]

4. Theoretical screening for co-crystallization

4.1. pKa approach

Simple and prominent approach to identification of co-crystal formation. A salt is obtain if the difference between the pKa base and pKa acid (δ pKa) is >3, where as a δ pKa <0 will generally result in the fabrication of a co-crystal.[27–29] ΔpKa (δ pKa = pKabase-pKaacid) must be less than 0.

4.2. Theoretical prediction of co-crystal formation by Hoy's molar attraction method.[30]

For calculation constant functional groups values found from the various literatures.[31]

Formula to calculate Hoy's molar solubility parameters (δ) = Molar attraction constant / Molar volume constant.[32]

5. Techniques for fabrication of co-crystals

Traditionally improvement of dissolution profiles can be obtained by reduction in particle size, modification in polymorphic form or multicomponent crystals synthesis.

The latter approach includes bi-component crystallization system deserves particular attentiveness due to the variety of co-crystals fabrication methods.[33] Classical approaches for the production of co-crystals includes solution-based methods (e.g. Reaction re-crystallization via slow evaporation, cooling or anti-solvent addition) and mechanical methods (e.g. Neat and liquid-assisted grinding).[34] Comparison between various methods are mentioned in Table 1. Recently, co-crystallization commercialized as an innovative approach, to improve the solubility of insoluble drugs. It offers a simple, cost-effective, time saving method, sometimes organic as well.[35] Discussed methods of preparation of co-crystals in current review have been reported by the researchers in various literatures.

5.1. Anti-solvent method

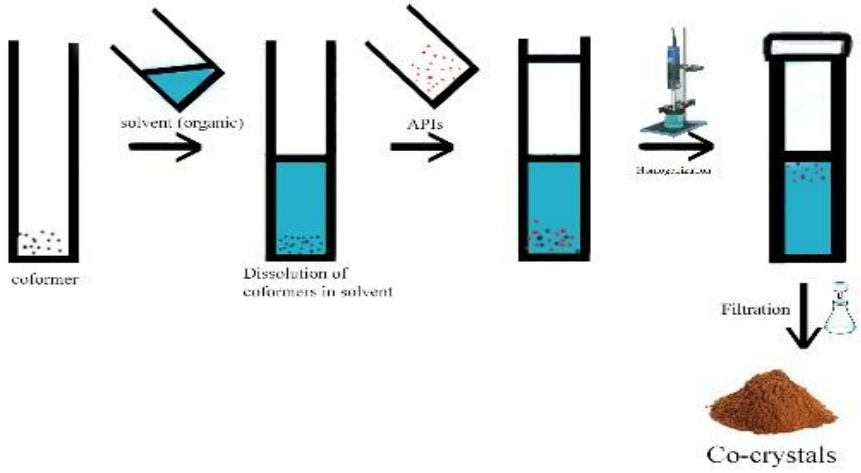

Figure 2: Schematic procedure of anti-solvent method.

In the first step of these method co-former dissolved in different or suitable organic solvents. After dissolving co-former in the solvent, API dispersed in co-former containing solution with the help of dispersion homogenizer. Anti-solvent co-crystallization was performed at 25°C instead of 45°C resulted solution added to suitable solvent to precipitate co-formered API. The final resultant solution was filtered using whatman filter paper and co-crystals was collected. Formulated co-crystals was characterized by PXRD.[36,37]

5.2. Solvent evaporation method

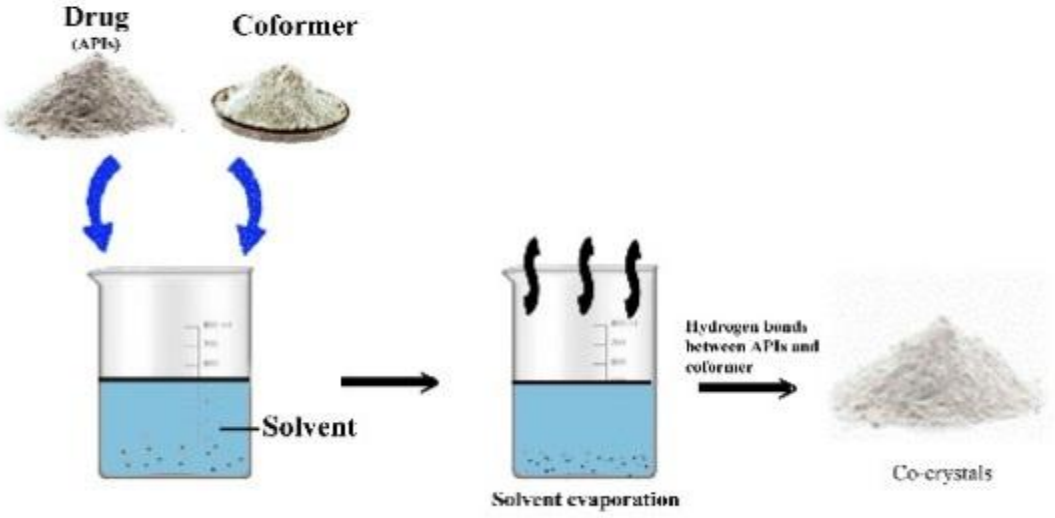

Figure 3: Schematic procedure of solvent evaporation method.

API and co-former dissolved in [1:1] stoichiometric ratio in suitable solvent. After preparing solution of API and co-former, solvent was evaporated which leads to formation of Hydrogen bonds between functional groups of API and co-former. At the end of the process heat stable co-crystals was obtained. This method is based on the dissolution of API and co-former in a mixture of solvents.[38,39]

5.3. Slow solvent evaporation technique

The general procedure involved dissolving stoichiometric amounts of API and co-former in the

selected suitable solvent and continuously stirring at room temperature. After all components had been soluble in solvent, the resulted solutions were filtered into glass vials and left for several days and each glass vial had been covered with parafilm™. Co-crystals were filtered for further screening.[40]

5.4. Slurry technique

In these technique API and co-former was dissolved in the suitable solvents and prepared a slurry of APIs and co-former. Solvent is drained out from the slurry and remaining solid product was dried, after drying co-crystals was obtained. This technique is very easy and required small number of solvents, advantage of this process is being less hazardous than other industrial techniques.[29,41]

5.5. Sonic slurry technique

Researchers had dissolved API and co-former in [1:1] stoichiometric ratio in suitable solvent and transfered it into the jacketed vessel containing side port for an ultrasound probe. Maintained the reaction temperature at 15°C using refrigerated and heating circulator. Using magnetic stirrer the slurry was stirred at 60rpm. At the beginning of the formulation a mixture of plate and needle like crystals was observed that crystals were converted into uniform block within 60mins. Remaining slurry was filtered through whatman filter paper. The solid mass obtained was dried under the vacuum at 35°C for 24 hours, it gave around 60 - 70% yield.[42]

5.6. Grinding method have been widely used for co-crystal formation over the year. It was found to be more efficient technique than other techniques. This method reduces time, and the quantity of API that is to be ground with multiple co-formers simultaneously; further, it enables to identify the synthon approach between the API and co-former.[43]

It's of two types,
Neat or dry grinding [small scale method]
Wet grinding or liquid assisted grinding [small scale method]

5.6.1. Neat/ dry/ solid state grinding technique

Figure 4: Schematic procedure of neat grinding method.

Neat grinding technique is easiest method for formation of co-crystals. In these technique API and co-former mixed together in 1:1 equimolar ratio and crushed or grind with the help of ball mill or mortar and pestle. At the interval of 15, 30, 45 mins samples were taken out for the characterization of co-crystals and stable co-crystal was determined by the melting point and FTIR.[15]

5.6.2. Co-crystallization using ball milling [bm]

A stoichiometric quantity of API was weighted and stoichiometric amount of each co-former was added in the ratio of 1:1 or 1:2 or 2:1. Then, the powders were transferred to a stainless-steel grind vessel containing two 15mm stainless-steel balls. The mixtures were grounded in two cycles of 10min at 25Hz using a ball mill.[44]

5.7. Liquid assisted grinding technique

Figure 5: Schematic procedure of LAG.

Despite advantages of grinding method in co-crystal synthesis, the efficiency of the process is frequent limitations of its application for large-scale production. It is because of poor energy input provided within the method, that prevents complete interaction between the reacting compounds. Therefore, grinding the elements mixture was administrated within the presence of a little quantity of solvent that act as catalysts. The modification of the tactic is referred because of the liquid motor-assisted grinding technique.[15] A particularly successful method of screening is liquid-assisted grinding method, in which a mixture of [API and co-former] co-crystal components was mechanistically treated in the presence of a catalytic quantity of a solvent.[45] At the interval of 15,30,45 mins samples were taken out for the characterization of co-crystals and these step act as catalysts for the reaction that increases rate of reaction. These method is useful for preparation of high purity crystal in less amount of time.[36,46]

5.8. Hot melt extrusion method

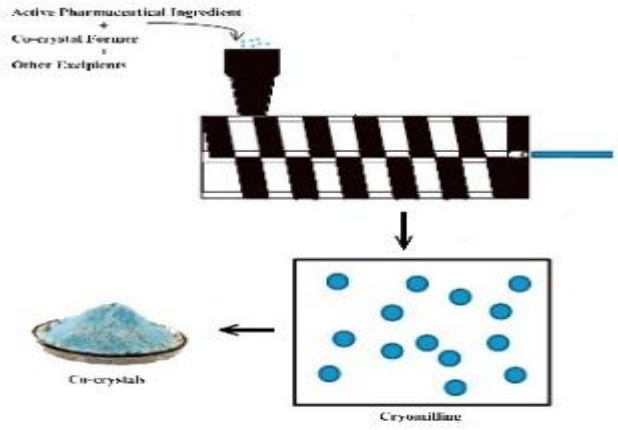

Figure 6: Schematic procedure of hot melt extrusion method.

API and co-former was mixed in 1:1 stoichiometric ratio without using solvent and applied heat on it. The procedure of application of heat improves surface contact between API and co-former. At the end of the process co-crystals were obtained. There is one disadvantage of this method that these method are not acceptable for heat sensitive APIs.[10]

Table 1: Co-crystal manufacturing process.[47]

Name of techniques	Purity of physical or chemical mixture	Scalability	Applicable APIs
Spray drying	○	●	□
Liquid assisted grinding	□	□	●
Freeze drying	○	○	□
Hot melt plate	○	○	●
Crystallization from solution	●	●	□
Melt mixture cooling	□	□	○
Microwave heating	○	○	○

● = Very good
○ = Good
□ = Fair
Ratings may vary depending on the co-crystals and required amount.

6. Characterization of formulated co-crystals

6.1. IR/FTIR

Infrared spectroscopy was used to provide additional evidence of co-crystal formation, since this technique is a fast, simple, very efficient, and widely used technique for the purpose of functional groups identification. In general, the spectrum of a supramolecular adduct shows the bands of each starting component, and the occurrence of an intermolecular interaction may be revealed by small changes, both in intensity and in position, that the absorptions of interacting functional groups, or close to interacting groups, disclose with respect to the pure starting components.[48] Fourier transform infrared spectrum analysis (FTIR) is a technique that is employed to get spectrum of absorption, emission and photoconduction of solid co-crystals. The FTIR spectra of the co-crystals was detected using an IR spectrophotometer and a KBr pellet as a beam splitter.[49] FTIR can be used to collects high spectral resolution knowledge over a large range, sometimes between 4000 and 400 cm^{-1} for mid-IR region wavelength, and between 10,000 and 4000 cm−1 for near-IR region wavelength. For the quintessential FTIR, the resolution is 4 cm^{-1}[41].

6.2. X-ray diffraction (PXRD)

Single X-ray optical phenomenon is a preliminary characterisation technique was used for identification of the solid-state structure and purity of co-crystals at an atomic level. SXRD and PXRD contain the indistinguishable structural data, that is distributed in 3-dimensional structure within the single crystal optical phenomenon pattern, whereas single diffraction composed into one dimension within the powder diffraction pattern. However, the difficulty is that one pharmaceutical co-crystal that is hired for single x-ray optical phenomenon testing cannot continuously be made. Therefore, PXRD was used to verify the formation of co-crystals. Polymorphic solvates can have totally different X-ray powder optical phenomenon patterns dissimilar in crystal structure.[50] PXRD pattern is a plot of the optical phenomenon intensity as operate of 2θ values were integrated and obtained test area were compared with the reference area or equal surface inside the structure of crystals studied that the relation between position of atomic planes in structure of crystals and therefore the angles of incidence at that these planes turn out the foremost intense reflections of magnetism radiations. Since distinct PXRD patterns correspond to totally different crystal structures, they will be thought of as "fingerprints" of specific crystalline phases. Powder XRD is a non-destructive technique and it produces a unique powder pattern for different solid materials. PXRD has achieved an important role in the pharmaceutical formulations to identifying various solid dosage forms of APIs and also in identifying the whether the material has crystallinity or not.[51,52]

6.3. Differential scanning calorimetry (DSC)

DSC was used to determine the preferred pairing ratio between API and Co-former.[48] It is a thermo-analytical technique within which the distinction within the quantity of warmth needed to extend the temperature of a sample and reference is measured as a perform of temperature. Each of the sample and reference area unit maintained at nearly identical temperature throughout the experiment. Normally, the temperature program for a DSC analysis is designed specified the sample holder's temperature will increase straightway as a perform on time. The reference sample ought to have a well-defined heat capability over the vary of temperatures to be scanned.[7,53] To formulate a co-crystal, the physical mixture of drug and Co-former can be used to identify whether stable co-crystals are forming or not for that the physical mixture of API and Co-former is heated using DSC in the ratio of 1:1 or in stoichiometric ratio, two exothermic peaks must be analysing. Formation of stable co-crystals shows two exothermic peaks and three endothermic peaks.[54] DSC was performed using DSC instrument under nitrogen purge. Sample was kept in the metalic pans aluminium is used as a metal, sealed, put into provided three vent holes and apply heat. Calibration of the instrument was carried out using standard solution. The DSC graph was detected by software.[51,55–58]

7. *In-vitro* powder dissolution study

Dissolution is the method by which a solidified substances enters into a solvent to form a solution. It is a test used all over the procedure of a pharmaceutical product to determine the rate of release of a drug substances from the dosage form. Dissolution study of co-crystal determines the solubility of poorly soluble APIs. *In-vitro* dissolution test is carried out using paddle type USP apparatus II or as per the dosage form. Before starting the dissolution study, co-crystals were sieved using suitable mesh. Suitable medium was used to perform dissolution test.[59] Powder dissolution studies was performed in triplicate in suitable buffer. The rotation speed of paddles was set at 100rpm with dissolution bath temp of 37.0 ± 0.5°C. The samples were withdrawn at a particular time intervals and absorbance was determined using uv spectrophotometer or HPLC.

8. Commercially available co-crystals

Some examples of Commercially available co-crystals presented in Table 2.

Table 2: Commercially available co-crystals.

Sr no.	Name of API	Solubility	Co-former	Techniques of preparation and screening	Reference
1	Itraconazole	Itraconazole is an anti-fungal BCS class 2 API with very low water solubility with high permeability.	Tartaric acid, fumaric acids, succinic acid, maleic acid, malonic, glutaric acid, Adipic acid.	Solvent assisted grinding method. And Synthon approach, pKa approach, fedor's substitution, hoy's molar method.	[60]
2	Meloxicam	Meloxicam is a BCS class 2 API which is NSAIDS (Non-Steroidal Anti-Inflammatory Drug).	Aspirin was considered as a suitable Co-former.	Solvent drop grinding method. And Synthon approach.	[17]
3	Curcumin	Curcumin is a nutraceutical compound. It has various pharmacological effects including anti-inflammatory, antiviral, antifungal, antibacterial and antioxidant properties. It has poor aqueous solubility.	Ascorbic acid.	Solid state grinding method. And Synthon approach.	[53]

CONCLUSION

Pharmaceutical co-crystals as a solid powdered dosage form becoming extensively important and alternate way to improve or enhance the solubility and biological-availability of poorly aqueous soluble BCS class 2 or IV drugs, especially for the neutral compounds or with having weakly ionisable groups. Synthon approach, pKa approach and Hoy's molar attratction these parameters are more important for the selection of Co-formers. Stable co-crystal identified with the help of flash point and characterized by HPLC, DSC, FTIR and PXRD showed the successful preparation of co-crystals. Co-crystals produced by Solid-state grinding, Liquid assisted grinding, Anti solvent method, Solvent evaporation method, Freeze drying method, Hot melt plate method, Spray drying method and the Slurry method. For the development of co-crystals commercially or for marketing purpose preclinical trials and clinical trials are necessary. Pharmaceutical co-crystals will gain a larger application in low aqueous soluble API development.

List of abbrevations

BCS=Biopharmaceutical classification system
API=Active pharmaceutical ingredient
EMA=European medicines agency
USFDA=United state food and drug administration
LAG=Liquid assisted grinding
HPLC=High performance liquid chromatography
FTIR= Fourier transform infrared spectroscopy
IR spectroscopy=Infra red spectroscopy
DSC= Differential scanning calorimetry
PXRD= Powder x-ray diffraction
CGMP=Current good manufacturing process
GMP=Good manufacturing process
ICH=International council of harmonization
DPI= Drug product intermediate
ASMF= Active substance master file
DMF= Drug master file

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