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Insights of Dosage form Design: Polymorphs and Co-crystals

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Abstract

Formulators are charged with the responsibility to formulate a bioequivalent product (in case of ANDA) product which is physically and chemically stable, manufacturable at commercial scale. Different crystal structures in polymorphs arise when the drug substance crystallizes in different crystal packing arrangements and/or different conformations. Besides, Polymorphs cocrystallization is now important method to achieve crystalline forms of molecules where alternative polymorphs or salts or solvates are desired. Regulatory road map for polymorphs approval is quite clear and for cocrystals draft guidance is on scientific advisory form public. From Intellectual property perspectives polymorphs and cocrystal patents are approved in different countries within the meaning specified in the act. Overall the patentability of polymorphs and cocrystals directly affects the business driven strategy for research based Pharmaceuticals as well as collaborative research universities for science updation for better health care.

Keywords: cocrystal, polymorph, dosage form, regulatory performs, intellectual property.

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Prologue: Insights of Dosage form Design

Over the past number of years, the fraction of new chemical entities (NCE) approaching the marketplace are very infrequent and steadily decreasing.

For the successful development and commercialization of NCEs (also called as API) it required that API should possess adequate processability, stability, and bioavailability. Once the complete understanding of the physicochemical and biopharmaceutical properties of the drug substance are known then the formulator can design dosage of clinical relevance. Based on powder morphology; drugs are classified as amorphous and crystalline form; wherein each has its own set of merits and demerits for design of dosage form. Crystal engineering is an emerging area which relates to molecular solids possess crystalline state. The field of Crystal modification is gaining an increased interest within the pharmaceutical industry because it enables preparation of materials with modified and desirable physical properties. There are few challenges associated with the nature of API in the development and manufacturing of solid dosage forms such as tablet is poor tabletting performance. In particular, usually the industry demands for crystals with stable and better processing characteristics such as flow properties and compressibility.[1] Nowadays pharmaceutical co-crystals have become an important part of a landscape that was previously occupied only by polymorphs, salts, and solvates/hydrates as it offers opportunity to diversify the number of crystal forms known for an API and to improve their physical properties of clinical relevance with patent protection as a business driven strategy.

Polymorphism and Dosage Design

Polymorphism is the ability of substances to crystallize in more than one distinct crystal habit. Polymorphism has a great deal of impact on pharmaceuticals and is considered as an important factor during product development. The differences in dissolution rate and solubility that polymorphs can produce may have a dramatic impact on bioavailability when dissolution is the rate-limiting step in the absorption process. Polymorphism is a dominating factor related to the physicochemical and biological properties of API and dosage form design. There are several examples from the pharmaceutical industry where a new crystal form significantly affected the performance of a dosage form, sometimes with serious clinical effects. However, any subsequent alteration in the crystal form drastically affects the stability of the apparently stable polymorphic form and ultimately finished dosage form.[2] Recent, intellectual property protection reflects number of granted patents and application filed by innovator and generic developers related to polymorphs, solvates, hydrates and salts for NCEs. Abbreviated new drug application (ANDA) a bioequivalent version of innovator product, take account of polymorphism as an important insight of dosage design and regulatory approval.

Polymorphs and Physicochemical properties

Different polymorphic forms of a drug have influence on absorption of drug from its finished dosage form and ultimately affecting the efficacy of dosage form. Typically, polymorphs, hydrates, solvates, and physical size of drug particles may have considerable impact on the rate and extent of drug absorption.

Substances that have no crystal structure are the amorphous forms, which have different physical properties to that of crystalline forms. Amorphous forms usually dissolve faster than crystalline forms because of high free energy, as no energy is needed to break up the crystal lattice. Amorphous form may however have stability problems and may have to evaluate crucially. During preparation of drug, organic solvents are used in preparation or purification which may get incorporated (one or more solvent molecules) within the crystal lattice and forms solvates. The most common solvate utilized often is water. If water molecules get entrapped in a crystal structure, hydrates are formed. In hydrates, the tendency of the crystal to attract additional water to initiate the dissolution process is reduced, and therefore solvated (hydrated) crystals tend to dissolve more slowly than anhydrous forms (e.g. Esomeprazole magnesium, a proton pump inhibitor exists in dihydrate form A, B and trihydrate form)[3].

Thermodynamics of polymorphs

Most drugs exhibit structural polymorphism and it is always preferable to develop the most thermodynamically stable polymorph of the drug to assure reproducible bioavailability of the product over its shelf life under a variety of real-world storage conditions. Thermodynamically stable polymorph is more chemically stable than a metastable polymorph. The lowest energy polymorph is always the most chemically stable form, and will not convert to another polymorph during storage and processing. Unexpected appearance or disappearance of a polymorphic form may lead to serious pharmaceutical consequences.

In the case of a most thermodynamically stable polymorph of the drug whose absorption is solubility-limited and thus cannot achieve the systemic exposure required for therapy. In this case, a more soluble form of the drug is desired to deliver the therapeutic dose. A metastable polymorph or amorphous form of such drug is developed to get such benefits. Though the metastable crystalline polymorphs are least chemically stable than the most physically stable crystalline form but having a good solubility than stable form.

Utilization of a metastable form of a drug for processing would becomes advantageous only when undertaken drugs for which a very complete understanding exists with respect to polymorphic form dependent chemical stability, physical stability, and most importantly, solubility and bioavailability of the drug.

Enalapril maleate is known to exist in two polymorphic modifications (I and II) with Form II being the more thermodynamically stable. Both forms exhibit similar properties, as exemplified by their similar solubilities, dissolution characteristics, heats of solution, IR and Raman spectra, XRD data and DSC thermograms.

Interestingly, although tablets manufactured *via* wet granulation using Form I of enalapril maleate and one molar equivalent of sodium bicarbonate are quite stable, tablets manufactured from Form II give rise to unacceptably high levels of the diketopiperazine degradation impurity. Hence, with the given drug product formulation, an inadvertent change in polymorphic form would negatively impact drug product stability, and it would be important to incorporate controls on the drug substance polymorphic forms.

Conversely, tablets manufactured via wet granulation from either Form I or II and two molar equivalents of sodium bicarbonate are equally stable.[4]

Polymorph Screening

Screening for polymorphs of APIs has become a common practice. The extent and type of polymorph screening performed depends on the stage of development and the business strategy of the innovator or generic company. Since exhaustive polymorph screening is resource intensive and attrition of early drug candidates is very high, exhaustive screening would not be practical from a business perspective for early drug candidates.

Polymorph screening approaches may be categorized as rational design for resource saving and comprehensive design to discover all possible solid forms of a drug candidate.

The goal of a rationally designed polymorph screen is to discover all relevant forms of a drug candidate that may be encountered during development, particularly the thermodynamically most stable form, as early as possible while expending minimal resources. In a comprehensive polymorph screen, the objective is to gain further confidence that all relevant forms have been identified and to secure freedom to operate with, or exclusive rights to, all possible solid forms of a drug candidate. The solvents are those that are commonly used for scale-up and processing. These solvents are used in rational screening approaches because those screens are often used early in the drug-development process, and thus the methods for crystallizing any solid forms that are identified may be readily transferred to the development chemist. Furthermore combinations or hybrids of these approaches are often used for effective polymorph screening.[5]

Process induced Phase Transformation and its knock

The physical form (polymorphic form) of the active pharmaceutical ingredient (API) can significantly influence the stability and performance of the dosage form, therefore a thorough understanding of the physicochemical properties of polymorphs is of primary importance to the selection of a suitable crystalline form and development of a successful pharmaceutical product.

Even though an appropriate physical form of the API may be selected, it may not be retained in the final pharmaceutical product.

Physical characterization of the final product is necessary to detect the overall effect happened due to of processing. However, multiple phase transformations may be able to also occur during the sequence of pharmaceutical processing steps. Monitoring the each phase of processing is the best approach to detect phase transformation during processing such as:[6,7].

(a) Phase transformations during various pharmaceutical unit operations,

(b) The detection of such phase transformations, and

(c) Assessment of Potential impact of phase transformations on the final product quality.

The potential advantages and disadvantages of such transitions are to be understood sometimes, a transition can be beneficial in some respects and disadvantageous in other aspects. While phase transformations of the API have a direct effect on the stability and performance of the final product, any such phase change affects product quality. Changes can be divided as per

(a) Solid-state manipulation intentionally brought about by pharmaceutical processing

(b) Unintended transformations that may have a major impact on product quality and stability[8].

Processing-related Stress

During pharmaceutical processing, various formulation-specific processes are carried out using a wide variety of techniques and equipment. The major processing-related stresses include mechanical, thermal and those due to interaction with other components. The thermal and mechanical stress, occurs during processing such as during the freezing of aqueous solutions and during wet granulation respectively, can lead to phase transformations, the presence of water in both cases can cause hydrate crystallization Multiple operations can be carried out using specialized equipment, as in a fluid-bed

granulator, wherein granulation and drying are simultaneously accomplished.

The material may therefore be exposed to several stress–relaxation Processes in a single step.

The final physical form of the material is expected to be influenced by the type, intensity and duration of each stress[9].

Mechanical Stress	Thermal Stress	Interaction with Other Components
Milling Compression	Freezing Drying	Hydrate Formation Complexation
	Melting	Salt–Free-acid/Base Conversion Metastable Phase Formation Multiple Interactions

Co-crystals and dosage form design:

Formulators are charged with the responsibility to formulate a bioequivalent product (in case of ANDA) product which is physically and chemically stable, manufacturable at commercial scale.

Hence, the prior assessments of all physical & physicochemical characteristics of API are of great importance for effective and bioequivalent (in the case of ANDA) dosage form.

Hence selection of the crystal form in formulation development process is crucial for the performance of dosage form because the crystal form acts as a barrier to drugs product performance by showing low aqueous solubility, slow dissolution rate, flow related troubles, performance and stability related issues. Hence the nature of physical form of API tends to exhibit greatest effect on formulation development strategy. Approaches are developed for such API which includes salt preparation, solvates, hydrates, solid dispersion, polymorphs, cyclodextrin complexation, etc.

In recent years co-crystal approach has been emerged as a promising valuable crystal engineering approach for improving the solubility and dissolution rate and also improving other properties of API with low aqueous solubility and stability. Pharmaceutical co-crystals are the crystalline materials comprised of an API, one or more unique co-crystal formers both of which are solids at room temperature. Pharmaceutical co-crystals comprises of an API (Host, neutral or in ionic form) and pharmaceutically accepted compounds (Guest)[10]. The co-crystals are formed because of several types of interactions including hydrogen bonding, π-staking, Vander walls forces, etc. Co-crystals may include one or more solvent / water molecule in crystal lattice. The main difference between co-crystals and salts is that in salts, a proton is transformed from acidic to the basic functionality of the constituent free base molecule or vice versa is applicable, whereas in co-crystals no such transfer occurs[11].

Formulation development of nonionisable or poor salt forming APIs, there are few options for developing faster dissolving more soluble crystalline forms. In the pharmaceutical co-crystals, the co-crystal formation is potentially employed with all APIs including acidic, basic, and nonionic molecules. This has been an advantage of co-crystals over salt form. Also in the salt formation there is generally a single acidic or basic functional group is involved but the co-crystals can simultaneously address multiple functional groups in a single drug molecule[12]. The cocrystallization is now recognized as an important method to achieve crystalline forms of molecules where alternative polymorphs or salts or solvates are desired[13].

Benefits of Co-crystals:

Co-crystals are more thermodynamically stable than amorphous form of API. Cocrystalization technique is suitable for all ionic, weakly ionic and nonionic APIs. Co-crystals of API overcomes various undesirable properties of API such as low aqueous solubility, poor oral bioavailability, less stability, poor compressibility, flowability and hygroscopicity. Recent year's number of patent grants and applications has been seen for API physicochemical modification along with increased efficacy.

Cocrystallization techniques

Solid Based Methods	Solvent based methods	Electrically Assisted method
Neat grinding/cogrinding	Solvent drop grinding	Sonocrystallization
Hot melt extrusion	Antisolvent addition	Microwave assistance
	Solvent evaporation	
	Slurry conversion	
	Sonocrystallization	
	Solvent mediated phase transformations(SMP)	

Regulatory performs: Polymorphs and cocrystals

Polymorphic forms of a drug substance differ in internal solid-state structure, but not in chemical structure. Section 505(j) (2) of the act specifies that an ANDA must contain, among other things, information to show that the active ingredient in the generic drug product is the "same as" that of the reference listed drug (RLD). When a United States Pharmacopeia (USP) monograph exists for a particular drug substance, standards for identity generally refer to the definition (e.g. chemical name, empirical formula, molecular structure, description) at the beginning of the monograph. However, FDA may prescribe additional

standards that are material to the sameness of a drug substance.

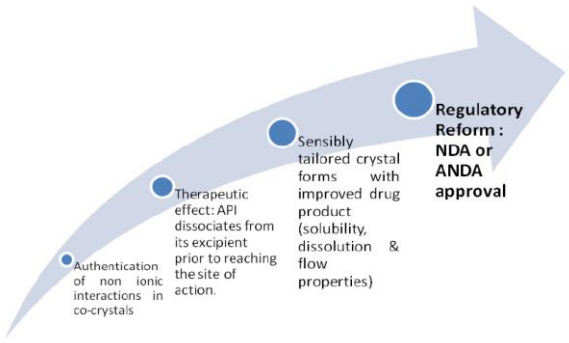
Therefore, differences in drug substance polymorphic forms do not render drug substances different active ingredients for the purposes of ANDA approvals within the meaning of the Act and FDA regulations. FDA demonstrates that, among other things, the drug product exhibits sufficient stability and is bioequivalent to the RLD. While the polymorphic form can affect drug product stability and bioequivalence, these performance characteristics are also dependent on the formulation, the manufacturing process, and other physicochemical properties (e.g. particle size, moisture) of both the drug substance and formulation excipients. Using a drug substance polymorphic form that is different from that of the RLD may not preclude an ANDA applicant from formulating a generic drug product that exhibits bioequivalence and stability, and the drug substance in the generic drug product need not have the same polymorphic form as the drug substance in the RLD.

Over the years, FDA has approved a number of ANDAs in which the drug substance in the generic drug product had a different polymorphic form from the drug substance in the respective RLD (e.g. warfarin sodium, famotidine, and ranitidine). FDA also has approved some ANDAs in which the drug substance in the generic drug product differed in solvate or hydrate forms from the drug substance in the corresponding RLD (e.g. terazosin hydrochloride, ampicillin, and cefadroxil).[14]

For Co-crystals at present no regulatory prototype exists for governing co-crystals. The issue of whether a new co-crystal of a marketed API may be eligible for regulatory approval *via* the NDA or ANDA system is not clear till date but it will impact the overall utility of co-crystal technology towards the generic pharmaceutical industry, and may possibly in the future marketplace.

In draft guidance for industry published by US FDA[15], co-crystals should be classified as dissociable "API-excipient" molecular complexes (with the neutral guest compound being the excipient) because of the fact that the molecular association of API and its excipient(s) occurs within the crystal lattice of co-crystals. Co-crystal is treated as a drug product intermediate in which API that has been processed with a co-crystallizing excipient to generate an "API-excipient".

Therefore when going for NDA or ANDAs containing or claiming to contain co-crystal, the one has to consider the following things (represented pictorially) carefully and to submit appropriate data.



Steps of regulatory performs of Co-crystallized NDA or ANDA

Steps of regulatory performs of Co-crystallized NDA or ANDA

Polymorphism in Co-crystals – Unique characteristics

Pharmaceutical co-crystals may be polymorphic. Aitipamula et al analyzed for the co-crystals deposited in the Cambridge Structural Database (CSD). There were a total of 3624 co-crystals present in the CSD, of which 44 co-crystals are polymorphic. A total of 46 polymorphic co-crystals were reported to date. Of these 46 co-crystals, 33 co-crystals were sustained by strong hydrogen bonding and the remaining 13 co-crystals are sustained only by weak interactions. Interestingly analysis of the co-crystals deposited into the CSD suggests that the number of co-crystal polymorphs being added to the database is increasing in recent year[16]. Recent research findings address toward occurrence of polymorphism in co-crystals[17].

The different crystal structures in polymorphs arise when the drug substance crystallizes in different crystal packing arrangements and/or different conformations. In co-crystals, polymorphism is either true polymorphism in which the different polymorphs of same compound have precisely the same stoichiometry. In distinction, pseudo-polymorphism, there are different polymorphs with different stoichiometries and different crystal structures. The polymorphism in co-crystals comes too often under the later class.

In co-crystals the polymorphism is governed by variations in the hydrogen bonding schemes of the coformers in the crystal lattice. In order to control the extent of polymorphism in co-crystals, designing the co-crystals by crystal engineering strategies which relies on developing an understanding and rationalization of intermolecular interactions in the context of crystal packing to design predictable structural motifs, followed by the subsequent utilization and exploitation of this understanding in the design of new solids with specific desired structural properties which offers at least a partial solution to the problem[18]. The concepts of supramolecular synthesis and crystal engineering have gained prime importance in recent years when there is a clear need for better

understanding and control of crystalline forms in the context of pharmaceutical development.

Sr. No.	Example	Details	Reference
1	Carbamazepine-Saccharin; carbamazepine-nicotinamide	CBZ-SAC form I CBZ-SAC form II CBZ-NCT form I CBZ-NCT form II	19
2	Carbamazepine-Isonicotinamide	CBZ-INA form I CBZ-INA form II	20
3	carbamazepine-nicotinamide (CBZ-NCT)	CBZ-NCT form I CBZ-NCT form II	21
4	Carbamazepine-Malonic acid	CBZ-MA form A CBZ-MA form B CBZ-MA form C	22
5	Caffeine-GA	Caffeine-GA form I Caffeine-GA form II	23
6	Caffeine-Trifluoroacetic Acid	Co-crystal E Form I Co-crystal E Form II	24
7	4-hydroxybenzoic acid -2,3,5,6-tetramethyl pyrazine	(4HBA)- (TMP) (2:1) form I (4HBA)- (TMP) (2:1) form II	25
8	Chlorzoxazone:2,4-dihydroxybenzoic acid	Form I	26
9	Ethenzamide-Saccharin	EA-SAC form I EA-SAC form II	27
10	Ethenzamide- 3,5-Dinitrobenzoic Acid	EA-DNBA form I EA-DNBA form II	28

Pharmaceutical co-crystals show a strong tendency to form polymorphs furthermore their interconversion from one form to another or into other undesirable forms during the manufacturing processes can also be seen. Therefore investigating the general occurrence of polymorphism in existing co-crystals is subject of growing interest.

It has been also proposed that formulation as a co-crystal would reduce the impact of polymorphism for highly polymorphic compounds[29] although this conclusion is based on assumption that fewer polymorphic arrangements are available when two compounds are present in the unit cell. Furthermore another assumption is that co-crystals are less prone to polymorphism[30]. Still no strong evidences were available to prove such hypotheses therefore needs more attention and research in this area.[31]

McCrone stated that: "every compound has different polymorphic forms" and that, .in general, the number of forms known for a given compound is proportional to the time and energy spent in research on that compound"

In co-crystals arena, studies concerning polymorphism are in ongoing phase and needs more time and research to upend any strong conclusion.

Intellectual Property rights for Polymorphs, Co-crystals and Business driven strategy

Polymorphs and Patentability:

Polymorphic forms are the new forms of existing APIs and such new forms can be patented by simply proving its novelty over existing one. Since every substances represent different properties associated with every different crystal structures achieved by crystal modifications, which creates an opportunity to claim an invention over the new properties of new form. Therefore, in current scenario polymorphism is one of the exigent issues in patent hierarchy. Development of novel crystal forms i.e. new polymorphs becomes a strategy tool for seeking additional patent protection over a new chemical entity, however only in few cases polymorph patent proved beneficial to sustain the market exclusivity of the product where the polymorphic form is genuinely the key factor for products presence in market as the other polymorphs are not having specified activity or efficacy, hence even a new polymorph patent of such API will have a distinct commercial advantage with respect to market exclusivity. There are numerous instances where innovator and non-innovator companies have acquired patents on particular polymorphic forms of API, in few cases patent protections of particular polymorph extends beyond the expiry of basic molecules patent thereby helping to extent product life[32].

Among one the routes of filing of ANDA with paragraph IV certification that USFDA allows, which involves ANDA filing provided the solid form discovered by the generic manufacturer bypasses innovators patent. On successful paragraph IV filling and approval, generic manufacturer gets market exclusivity rights for 180 days to market his generic product accompanied by innovator product.[33]

Polymorphs are patented in US and Europe after proving its novelty, non-obviousness and utility and exemplified in various review articles, also can be searched at patent web site of respective country.

In US, "New" refers to anything under the sun that is made by man, such as a new composition of matter or any new and useful improvement (35 USC & 101).

Patent protection is normally granted only on individual polymorphic forms that have been identified, characterized, and differentiated, so there is a powerful incentive to identify and protect alternative forms that may otherwise be identified and developed by a competitor or a generics manufacturer.

In the United Kingdom, a new crystal modification is not prima facia patentable; the inventor must demonstrate that it is an unobvious. New crystal forms can be patented without showing unexpected properties, since one of ordinary skill cannot predict the structure, properties, or method of preparation of that crystal form prior to its discovery variant of the previously known material.

Co-crystals and Patentability:

In recent time an article by Andrew Trask, provided an open eyed landscape on how the developing field of cocrystallization may impact the pharmaceutical intellectual property domain[34]. According to the article co-crystals are eligible for patent protection when screened through the eyes of novelty, non-obviousness and utility (Industrial applicability). In any case where the solid form offers a commercial advantage over the original form, whether it is a polymorph or solvate or hydrate of co-crystal, the solid form patent would provide significant patent protection even after the expiration of the new chemical entity patent.

As the new polymorphs are novel and non-obvious and can be patented. Unlike polymorphs and salts, co-crystals are new compositions of matter and equally patentable as well. Co-crystals also show polymorphism and so can opt for patent. There will not be any surprise when we will see number of co-crystals getting patent protection in upcoming future[35].

However, a solid form that was not found by the innovator, but was found and patented by a competitor, could significantly alter this strategy. Similarly co-crystal screens for potential drugs could generate new solid forms which can be protected, not only the co-crystals found, but also any polymorphs, hydrates, solvates, or other solid forms of the individual co-crystals.

Novelty and non-obviousness:

In new polymorph patent application the first question arises that is the crystalline form novel? In such case anticipation with respect to novelty is the deciding factor for patentability, similarly in co-crystals the same question surges to decide the novelty of invention. For a new solid form of existing compound to be novel irrespective of that it is either polymorph or co-crystal, it should not appear in the prior art expressly or inherently. If such happens in the prior art then invention is expected to be obvious. In co-crystals, prior art references are limited since prior art reference for the specific compound with the specific the coformer would likely not be published in connection with the crystallization of the API. Such lack of prior art is an advantage from the IP perspective in connection with novelty.

The inventive step in co-crystals can be summarized by these two statements;

i) If the co-crystal composition carries patentability, it claim as new composition;

ii) If the crystalline form carries patentability, same considerations as with polymorphs.

However another criterion of patentability is non-obviousness. The subject matter should not be obvious to a person having ordinary skill in the art. It is not possible to predict- how many different co-crystal forms can be prepared, as yet unknown, crystal forms, or to predict the properties of any, as yet unknown, crystal forms.

Utility /Industrial applicability: When generic pharmaceutical companies use polymorphs and hydrates they file Abbreviated New Drug Applications (ANDAs), which requires the submission of minimal bioavailability and clinical data and does not require proving safety or efficacy. New salts of an API, however, use a slightly different regulatory pathway, a so-called 505(b) (2) application, and require more testing and clinical data than an ANDA submission. The classification of co-crystals as a generic has not yet been addressed and still a clear path for co-crystals from the viewpoint of regulatory is not clear[36].

Currently in the area of co-crystals several patents in US, Europe and other countries has been granted such as US6570036 (Co-crystallization Processes), US7452555 (Cocrystallization), US7803786 (Pharmaceutical co-crystal compositions and related methods of use), US7935817 (Salt form and co-crystals of adefovir dipivoxil and processes for preparation thereof), EP1608339B1 (Pharmaceutical co-crystal of celecoxib-nicotinamide), EP1962600B1 (Metronidazole cocrystals), EP2488169B1 (Co-crystals of Tramadol and Coxibs) etc.[37,38] and can be cited at Patent web site of respective country. At present number of patent applications claiming co-crystals are in prosecution phase. Besides of this many more applications are also being filed day-after-day.

Section 3 (d) of India Patent act and patentability of polymorphs:

As per section 3 (d) salts, esters, ethers, polymorphs, metabolites, pure form, particle size, isomers, mixtures of isomers, complexes, combinations and other derivatives of known substance shall be considered to be the same substance, unless they differ significantly in properties with regard to efficacy"[39]. Hence, polymorphs patentability should pass this significantly differed efficacy. Recently a research disclosure for anti-cancer molecule imatinib mesylate (Glivec) for crystalline form has not been successful to obtain patent in India[40].

Till date in India there is no clear methodology to patentability of co-crystals, however few patents were filed in Indian patent office, some of them are granted and some still are under prosecution. For example- IN864MUM2005 (Novel cocrystallization), IN3073KOL2006 (Gossypolco-crystals and the use thereof), IN818CHE2008 (O-desmethyl venlafxine cocrystals), IN2303CHE2009 (Stable cocrystals of temozolomide), IN3190CHE2010 (Novel polymorphs and cocrystals of curcumin), IN8827DEL2010 (New co-crystal compounds of rivaroxaban and malonic acid), IN2454DEL2011 (Novel choline cocrystal of epalrestat), etc. Furthermore IN4367KOL2008

(Cocrystal of c-glycoside derivative and l-proline) received grant of patent which is IN256260 on May 2013[41]. However co-crystals will also likely to face hurdle of section 3(d) of Indian patent act, which describes the things which are not inventions within the meaning of this act. In US and Europe the numbers of granted patents of co-crystals are more which reflects the successful intellectual property protection for co-crystals. Overall the patentability of polymorphs and cocrystals directly affects the business driven strategy for research based Pharmaceuticals as well as collaborative research universities for science updation for better health care.

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