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RESEARCH ARTICLE

Polymorphism study of some organic compounds

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ABSTRACT

Polymorphs of a compound are different crystal forms in which the lattice arrangement of molecules are dissimilar. These distinct solids usually have different melting points, solubilities, densities and optical properties. Many polymorphic compounds have flexible molecules that may assume different shapes of these solids shows that their crystal lattices impose certain conformational constraints. When melted or in solution, different polymorphic crystals of this kind produce the same rapidly equilibrating mixture or molecular species. Polymorphism is similar to, but distinct form, hydrated or solvated crystalline forms. It has been estimated that over many known organic compounds may be capable of polymorphism. Many pharmaceutical compounds exist in different crystalline forms and thus exhibit polymorphism. Polymorphism may affect chemical and Physical Stability, apparent solubility, dissolution, bioavailability and bioequivalence and manufacturability of drug product, which require special attention during product development as it affects the quality, safety and efficacy of drug product. In this article we had performed polymorphism study of some synthesized compounds and identified their shapes by using motic microscope.

INTRODUCTION

When the crystalline structure of the same chemical compound exhibits two or more patterns of the repeated unit cells, these crystalline structures are called polymorphs and the phenomena is referred as polymorphism [1]. Polymorphs are different crystalline forms of the drug substances that may be having different physicochemical properties such as solubility, dissolution rate, stability, and bio availability [2]. Polymorphism word found from Greek word poly means many and morphs mean shape. Thus it is defined as ability of a molecule exhibits in two or more than two crystalline phases [3]. These crystalline phases have different arrangements or conformations of the molecules in the crystal lattice [4]. Polymorphism play an important role in all of chemical research where full characterization of a material; has pivotal role in their uses such as Pharmaceutical, polymer, agrochemical, pigments and fine chemicals [5]. Each drugs exhibits in different forms and each forms having their distinct chemical and physical properties like melting point, solubility, stability, dissolution rate, optical, electrical, and mechanical properties, vapour pressure and density [6]. These proportion are reflect with manufacturing of drug substances then drug product and then stability, dissolution rate, bio availability of drug product. Polymorphism is very common among pharmaceutical substances and thermodynamic stability of polymorphs has influence on drug product pharmaceutical properties like bio availability, process ability [7]. Most of the polymorphic forms are highly prone to temperature. Major challenges arrive in differentiating, isolation, and characterization of polymorphs in pharmaceutical. It is an effective element in drug development [8].

Crystalline solids that involve the inclusion or incorporation of solvent molecules in the crystal lattice are known as solvates, pseudopolymorphs, or solvate morphs, although the latter two terms are by no means widely

accepted. Solvates in which the solvent molecule is water are known as hydrates [9]. Nature of water in the environment as well as the inclusion of water in solvent mixtures during crystallization, the formation of hydrated crystal structures is common. Moreover, water's small size and ability to serve as both a hydrogen bond donor and acceptor make it likely to be incorporated in many locations within the lattice it her as a space filler or a sastabilizing force whose departure would eventually lead to the collapse of the crystal structure.

A survey of the1999 European Pharmacopeia, which contained 808 organic compounds, revealed that approximately a third of the molecules listed can form hydrates. Monotrophy occur when one form is stable and the other metastable [10]. The metastable changes to the stable form at all temperature and the change is not reversible. Thus there is no transition temperature as the vapour pressures are never equal. This type of polymorphism is exhibited by phosphorus. For.eg. Nicergoline, a potent blocking agent for α-1-adrenoreceptors exhibits two forms triclinic form and orthorhombic form. This triclinic form is stable at melting point 134°C, while orthorhombic form is melt at 120-122°C and transfer in to stable form [11]. Although the existence of three different crystal forms of calciumcarbonate (calcite, vaterite and aragonite) was identified by Klaprothin 1788, formal recognition of the phenomenon of crystal polymorphism is attributed to the work of Mitscherlich in 1823 [12]. In more general terms, the solid phase of a material, whether formed of organic molecules, inorganic ions or extended covalent networks, can exhibit different structures which, although possessing the same chemical composition, may manifest different properties [13].

In addition to these polymorphic modifications the material may also lack long-range order and appear as an amorphous solid, which can be considered as another polymorph. The strong interest in crystal polymorphism within the pharmaceutical and scape can be attributed to its frequent occurrence and the fact that significant differences in chemical and physical characteristics may arise with changes in the solid-state form, thus affecting the manufacturability, performance, and/ or quality of the drug product. Some have suggested that virtually all chemical compounds have more than one crystalline form [14]. The prevalence of polymorphism is often linked with McCrone's statement "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 money spent in research on that compound". Others have made similar suggestions, including Buerger & Bloom, who commented in 1937 that "polymorphism is an inherent property of the solid-state and it fails to appear only under special conditions", and Kuhnert-Brandstatter, who more recently noted in 1975 that "probably every substance is potentially polymorphous [15]. The only question is, whether it is possible to adjust the external conditions in such a way that polymorphism can be realized or not [16]." These comments likely are a bit exaggerated, as isolation of new polymorphs is most often a result of chance or serendipity. Moreover, for some small molecules such as naphthalene, only one crystalline form exists even though the molecule has been crystallized many times, and for others such as dibenzylidenesorbitol, a nucleating agent, or clarifier used in polymer manufacturing, a crystalline phase is unattainable [17].

In dyanamic allotrophy has several forms which can coexist in equilibrium over a range by the temperature. The separate forms usually have different molecular formulae but the known as dynamic allotropy, resembles enantiotropy transition point. In some cases one polymorphic form can change into another at a definite temperature when the two forms have a common vapour pressure. This temperature is known as the transition temperature [18]. One form is stable above this temperature and the other form below it. When the change of one form to the other at the transition temperature is reversible, the phenomenon is called Enantiotropy and the polymorphic forms enantiotropes. Polymorphism studies are generally done to isolate impurities by recrystallization [19].

Crystallization has impact on micromerities of drugs like compressibility and wet ability. Crystalline forms play an important role in product properties such as suspension stability and hardness of tablets. This can be done by using dehydrating agent like dried absolute alcohol and glycerol, due to this stability of substances is enhance. Crystallization enhanced stability of product example like amorphous penicillin G is less stable than its crystalline salts. Similarly amitryptyline is more stable in

crystalline form. Some drugs show their drug properties in crystalline form like penicillin G. Its unwanted degradation in gastrointestinal fluid can prevent by using crystalline form.

The relevance of crystal polymorphism also extends to the intellectual property domain, as different crystal forms are considered patentable inventions. Generally, brand-name pharmaceutical manufacturers (or innovators) will patent every viable polymorph of a drug molecule in addition to filing patents related to methods of use and process of manufacture to ensure that the innovators have exclusive rights to the invention. Consequently, solid form screening has been regarded as anessential activity in the drug development process [20-29]. Nonetheless, in hope of gaining early access to the marketplace, generic pharmaceutical manufacturers continually search for novel polymorphic forms of a drug and increasingly challenge the originator's patents in order to circumvent the drug's intellectual property protection [30-32].

A recent example highlighting the patent battle over polymorphs between brand-name and generic manufacturers is the antibiotic. Brand name pharmaceutical companies have used composition of matter patents to extend the life of a drug and impede competition from generic manufacturers. The exploration of the "crystal form space" of a substance is the search of polymorphs and solvates in order to identify the most stable form and the existence of unstable forms that interconvert (enantiotropism) or do not (monotropism) as a function of the temperature. This also applies to amorphous and solvate forms [33-38].

Polymorphism is not limited to drug substances; it also can strike antioxidants (or polymer additives) used in polymer-based medical devices as well as excipients, thereby having profound implications for the drug products. In the former case, antioxidants are a source of extractable and leachable compounds form medical devices, and the solid-state properties of the stabilizer may impact the diffusion co-efficient, dissolution rate, solubility, and transport properties of the additive in the polymer. Moreover, the study highlighted the importance of understanding polymorphic behaviour in connection with investigating leachable compounds [39-42].

MATERIALS AND METHODS

All chemicals and solvents were purchased from commercial sources like Research laboratory Mumbai and Lobachemie purified by distillation if necessary and residual water was removed and by using standard procedures and the reagents were purchased from S.D fine. All compounds were synthesized with help of reported literature by using conventional methods of synthesis using reflux condenser. Experiment was performed by using hot plate. Compounds were re-crystallized with mixture of different solvents and single solvents by slow evaporation method and shapes are identified by using motic microscope.

Compounds used for Polymorphism Study

1. 2,3-diphenyl quinoxaline
2. 2,4,5-triphenyl-1-*H* imidazole
3. 5,5-diphenyl hydantoin
4. 2-acetoxy benzoic acid
5. Benzophenoneoxime
6. P-amino benzoic acid
7. Sulphanilamide
8. 2-methyl benzimidazole

Selection of Solvent System

The solvent was selected on a trial and error basis.

Solubility was checked in following solvents:

1. Methanol
2. Ethanol
3. Ethyl acetate
4. Hexane
5. Acetonitrile
6. n-butanol
7. Acetone
8. Isopropyl alcohol

General Procedure for Recrystallization

The polymorphs were prepared by the method of crystallization from a single and multiple solvent. The compounds were weighed (10 mg) and taken in a petri plate and solvent (10 mL) was added. The mixture was gradually heated up to its boiling point then filtrate was allowed to cool at room temperature and crystallization was observed.

RESULT AND DISCUSSION

Compounds were re-crystallized with mixture of different solvents and single solvents like methanol, chloroform, butanol, acetone, ethyl acetate, n-hexane and ethanol etc by slow evaporation method for purification of drugs,

better chemical stability, handling of drug and to enhanced physical stability.

Table 1: Microscopical observation of crystals under motic microscope

Sr. no	Name of compound	Solvent	Crystal shape
1	2,3-diphenyl quinoxaline	Methanol	Needle clusters
2	2,4,5-triphenyl-1-H imidazole	Ethanol	Simple needle
3	5,5-diphenyl hydantoin	Ethyl acetate	stellar dendrites crystals
4	2-acetoxy benzoic acid	Hexane	Radiating dendrites crystals
5	Benzophenoneoxime	Acetonitrile	Needle crystal
6	P-amino benzoic acid	n-butanol	Irregular shaped crystals
7	Sulphanilamide	Acetone	Needle bunch
8	2-methyl benzimidazole	Isopropyl alcohol + ethanol	Crossed needle

CONCLUSION

As Polymorphism may affect chemical and Physical Stability, apparent solubility, dissolution, bioavailability and bioequivalence and manufacturability of drug product, which require special attention during product development as it affects the quality, safety and efficacy of drug product. In this article we had performed polymorphism study of some synthesized compounds and identified their shapes by using motic microscope. By observing compounds under motic microscope shows different shape of cystals like simple needle, neddle clusters and crossed needle etc.

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