



A REVIEW OF PHARMACEUTICAL NANO-COCRYSTAL: A NOVEL STRATEGY TO IMPROVE THE CHEMICAL AND PHYSICAL PROPERTIES FOR POORLY WATER SOLUBLE DRUGS

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ABSTRACT

Drugs are a crucial commercial good in our lifestyle because they help us stay healthy and treat illnesses. Poor solubility, permeability, bioavailability, dissolving rate, hygroscopicity, tablet ability, compressibility, and stability of medicines are major causes of medication failure during clinical development. To overcome the shortcomings of pharmaceuticals, several methods can be created including salt formation, Nano-formulations, co-solvency, complexation with cyclodextrins and surfactants, micronization, solid dispersions, coamorphous formulations, cocrystallization, nanococrystallization, etc.

Nanococrystallization is the approach that has the best chance of enhancing the physical and chemical characteristics of APIs without altering their chemical composition. With the extra advantage of a carrier-free delivery route, nanococrystallization offers a flexible technique for saving poorly soluble medicines. In this review, we provide a comprehensive analysis of nanococrystals. In these we also compare the cocrystal with nano cocrystal along with the formulation methods, advantages and characterization techniques for nanococrystals.

Keywords: Cocrystal, Nanocrystal, Nanococrystal, Nanoparticles, Solubility.

1. INTRODUCTION

Pharmaceutical companies are constantly working to develop an appropriate dosage form, which is primarily in the solid state. However, some dosage forms are deficient in solubility, dissolving, physical, and chemical characteristics. Approximately 40% of commercial medications have solubility problems, which is a fact [1].

Pharmaceutical crystal: A solid whose elements are arranged in a highly ordered microscopic structure to form a crystal lattice that extends in all directions is said to be crystallised.

Pharmaceutical Cocrystal: Cocrystals are crystalline single phase solids made up of two or more molecules in a stoichiometric ratio that are neither solvents nor simple salts, according to the ideal definition [2].

Pharmaceutical Nanococrystal: Nano-cocrystal formulations, which combine the advantages of cocrystal and nanocrystal technologies, have been suggested as a potential strategy to improve oral bioavailability and dissolving rate. To our knowledge,

however, there have only been a few studies on nanococrystals, specifically those involving the nano-cocrystal formulations of itraconazole-adipic acid, indomethacin-saccharin, furosemide-caffeine, and myricetin-nicotinamide.

Nano-cocrystals means crystals in the nanometer range, which can further improve the solubility of drugs compared to cocrystals. In addition, some authors also reported that nano-drugs are in fact typically dispersed to improve their stability [3].

The basic components of these pharmaceutical cocrystals are cocrystal former (CCF) and API. Covalent bonds or hydrogen bonds are used to bind these compounds together. The API and the co crystal former are both said to have existed in a solid state by many accounts, but by exception, some accounts include liquid components that are present at ambient temperature [4].

Cocrystals, solid molecular-scale combinations of several compounds, are intended to be custom-made

materials with more employability than their pristine individual constituents in industries like explosives and medicine. Cocrystals are created in the medical field by crystallizing pharmaceutical active components with carefully selected cofomers to provide drugs with improved stability, high solubility, and thus high bioavailability and optimum drug uptake. Because nanoparticles have a higher surface to volume ratio than their micron sized equivalents, scaling up may improve these characteristics even more [5].

Pure solid drug nanoparticles encased in a stabilizer layer make up drug Nano crystals. Rarely a stabilizer is necessary. However, stabilizing nanoparticles against particle aggregation primarily requires a layer of polymer and surfactant. One ingredient can serve as the basis for the stabilizer layer, but it's also common to utilize a combination of materials, such as a polymer and a surfactant. Drug Nano crystal functionality can be achieved by including some functional/linking groups on the stabilizer layer. Often Nano crystals are referred to solid micelles [6].

2. APPROACH FOR NANO CRYSTAL

There are many methods to increase solubility, including salt production, complexation, solubilization, pH adjustment, chemical modification, and liposomal administration. However, some restrictions, such as the limited solubilizing agents' capacity, the altered pharmacological activity of pharmaceuticals after chemical modification, and the poor physical & chemical stability of liposomes, prevent the widespread implementation of these conventional techniques. Additionally, medications should have particular qualities like adequate ionizing ability, solubility in particular organic solvents, and appropriate molecular size or shape [7].

An urgent need exists to investigate novel solutions to these issues, and Nano crystallization for particle size reduction has emerged as a useful method. The process of micronizing poorly soluble medications effectively reduces particle size to the micrometer range, increasing the surface to volume ratio and, ultimately, the rate of bioavailability. However, due to air entrapment and poor wettability, micronization is less effective for highly lipophilic medications in achieving the desired bioavailability. Therefore, "nanonization," or the process of changing micronized particles into nanoparticles, is a practical advancement [8, 9].

3. METHODS OF PREPARATION of NANO-COCRYSTAL

The development of reliable Nano-co-crystal formulation preparation methods is currently in the exploratory phase. When preparing medication Nano suspensions, such as those that are already on the market, bead milling is the more reliable process when compared to crystallization procedures for creating Nano-co-crystals. Utilizing medium with low solubility for milled compounds and providing adequate cooling during milling will reduce instability both during and after preparation [10]. Both a bottom-up method, such as precipitation, and a top-down method, such as ball milling, can be used to create nano-cocrystals [11].

3.1. Top-down synthesis

3.1.1. Milling

3.1.1.1. Solid state grinding

Most of the cocrystals are produced by this method. This is a process in which a ball mill is used for the mixing of solid cocrystal material with the help of mortar and pestle in a stoichiometric ratio. Time required for this process is 30-50 min. As this is solid state grinding there is no need of solvent. As a result of this process increase in surface area of particle occurs due to the reduced fine particle size [12].

3.1.1.2. Liquid state grinding

As the name implies, the process involved liquid for grinding to produce fine particles [13]. For the creation of cocrystals with a high degree of purity, this approach is a good option. The creation of polymorphic cocrystals is selective. The crystalline polymorph form can be changed into another organic substance by including solvents with various polarities [4].

3.1.2. High Pressure Homogenization

When creating pharmaceutical Nano sized crystals, high pressure homogenization (HPH), which is frequently used to create Nano sized crystals, has the potential to speed up the dissolution process and enhance drug bioavailability. The HPH method has been used to create nano-cocrystals of BE (Baicalein) Nano crystals and BE-NCT (Baicalein nicotinamide) utilizing poloxamer 188 as a stabilizer [3].

3.2. Bottom up technique

According to the EMAMI the Anti-solvent precipitation method is suitable type of method of the bottom up

technique to produce Nano sized cocrystal [14]. The use of this approach in the medical profession has been constrained by a lack of systematic research in the selection of anti-solvents.

3.3. Precipitation technique

Nanocrystals are pure solid particles, crystalline in nature, with a mean diameter $<1 \mu\text{m}$. The goal of Pradip Thakor's research was to create a process for precipitating nano-cocrystals of a water-insoluble medication and a water-soluble coformer. This study used the model cocrystal of carbamazepine nicotinamide [15].

4. FORMULATION OF NANO COCRYSTALS AND THEIR APPLICATIONS

4.1. TRICOR®

Patients with primary hypercholesteremia should take Tricor®. It has been marketed by Abbott laboratories in the USA since December 2004 and contains the API fenofibrate. Elan's unique wet-milling method was used to create nanocrystalline particles, which significantly improves the drug's solubility characteristics.

4.2. Paliperidone palmitate

Nano crystals were first made available by Janssen Pharmaceuticals in Belgium under the brand name Invega® Sustenna™, which received FDA approval in July 2009. The long-acting, once-monthly injectable solution is the first of its kind for the treatment of schizophrenia. The monthly injection provides several benefits over oral drug therapy, such as preventing the possibility of relapse caused by patients failing to take their prescription [16].

5. CHARACTERIZATION TECHNIQUE FOR THE NANOCOCRYSTAL

5.1. Molecular Vibration Spectroscopy

The IR (Infra-Red) spectroscopy has greater advantage that we can study any sample by virtually and any virtually state. The vibrational and rotational energies, as well as the bond length and bond angle, vary depending on the type of crystal. As a result, various crystals can be identified using vibration spectroscopy [4].

5.2. Thermal Analysis

According to the paper titled theoretical fundamentals of differential scanning calorimeters, the DSC has advantages other than is its very simple method, rapid, simple for operating [15].

5.3. Microscopy Technique

Various analytical techniques are used for the determination of molecular level chemistry of cocrystals. For the characterization of nanococrystals we mainly use either of the two techniques *i.e.* Atomic force microscope (AFM) and Transmission electron microscope (TEM) [17].

5.4. Solid state NMR spectroscopy

Atoms in crystals' dynamics, behaviors, and chemical environments can be studied using solid-state NMR spectroscopy. As a result, solid-state NMR spectroscopy is a crucial technique for investigating and identifying crystal structures according to the Pinon [18].

6. NANOCOCRYSTAL IN CHEMOTHERAPY

Cancer can be efficiently treated with chemotherapy. Drug resistance is a limitation in this therapy, which restricts its widespread use. Numerous particular cytotoxic medications for cancer cells are continually being developed as a solution to this problem. However, many of them have low *in vivo* bioavailability and solubility. Chemotherapy medicines made of Nano crystals with superior solubility and bioavailability have been utilized to treat specific cancers. Meghna created Nano suspension PIK75 using pressure homogenization methods, namely the high pressure homogenization method. The outcomes demonstrated that Nano suspension PIK75 has improved plasma stability and an 11-fold increase in saturation solubility [13]. Nevirapine suspensions with Nano crystal modifications showed superior targeting, increased bioavailability, and extended drug residence times at the target location. [19]. The overall result of the nanococrystal is that the better approach for chemotherapy other than using cytotoxic drugs. Neoplasms have been successfully treated using nanocrystal and NCC technology [20].

7. NANOCRYSTALS HAVE ADVANTAGES OVER MICROCRYSTALS

- Greater bioavailability due to microcrystals' slower rate of dissolution and higher saturation solubility.
- High adhesiveness in comparison to microcrystals, which is a key element in the improvement of poorly soluble medication absorption.
- Greater stability when compared to micro-suspensions due to the lack of aggregation and Ostwald ripening (crystal development).
- Improved biological performance of medications in all dosage forms and administration methods [21].

8. CONCLUSION

The purpose of review was to study the improvement in the solubility and dissolution rate of water insoluble drug by Nanococrystalization technique. Pharmaceutical nano-cocrystals have been used as a novel approach to improve the solubility, stability and bioavailability of drugs. Both *in vitro* and *in vivo* evaluations suggesting that the nano-cocrystals could be proposed as an advanced strategy for dissolution rate and bioavailability enhancement of poor soluble natural products. This review thoroughly described the procedures utilized to manufacture nanococrystals, and it also covered the characterization techniques that were used to thoroughly examine the nano-cocrystals. In the future, we are convinced that pharmaceutical nano-cocrystals will have greater commercial acceptance in the pharmaceutical business.

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Conflict of interests

There is no conflict of interest.

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