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Review Paper

Spherical Cocrystal Technology - Role of Polymers in Enhancing Physicochemical and Mechanical Properties of Drugs

Gaytri Mapari*, Neha Bombilwar, Reshama Patil, Vandana Patil, Sachidanand Angadi

Pharmaceutics, Yash Institute of Pharmacy, ChhatrapatiSambhajinagar, Maharashtra, India, 431136.

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ABSTRACT

Spherical cocrystal technology is an advanced approach used to improve the performance of pharmaceutical drugs, especially those with poor solubility and flow properties. In this technique, an active pharmaceutical ingredient (API) is combined with a suitable coformer to form cocrystals, which are then shaped into spherical particles. The addition of polymers plays a crucial role in this process by improving the stability, uniformity, and surface characteristics of the particles. Polymers help in controlling crystal growth, preventing aggregation, and enhancing wettability, which leads to better solubility and dissolution rate of the drug.Moreover, spherical cocrystals exhibit improved flowability and compressibility, making them highly suitable for tablet formulation without the need for additional excipients. This reduces manufacturing complexity and cost. Polymers such as HPMC, PVP, and PEG are commonly used due to their biocompatibility and effectiveness in modifying drug properties. Overall, polymer-assisted spherical cocrystal technology offers a promising strategy to overcome limitations of poorly soluble drugs and enhance their bioavailability and processing characteristics in pharmaceutical development

INTRODUCTION

Spherical cocrystal technology is an emerging and innovative approach in pharmaceutical formulation aimed at improving the physicochemical and mechanical properties of drug substances. Many active pharmaceutical ingredients (APIs) suffer from poor solubility, low flowability, and inadequate compressibility, which can limit their effectiveness and complicate manufacturing processes.[1-2] To overcome these challenges, cocrystallization is used, where an API is combined with a suitable coformer to form a stable crystalline structure without altering its

***Corresponding Author:** Gaytri Mapari
Address: *Pharmaceutics, Yash Institute of Pharmacy, ChhatrapatiSambhajinagar, Maharashtra, India 431136*
Email ✉: gaytrimapari240@gmail.com
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pharmacological activity. In spherical cocrystal technology, these cocrystals are further modified into spherical agglomerates using techniques such as spherical crystallization. This transformation improves particle size distribution, surface morphology, and micromeritic properties. The spherical shape enhances powder flow and packing ability, making the material more suitable for direct compression into tablets.[3]

Polymers play a vital role in this technology by acting as crystallization modifiers and stabilizers. They help control nucleation and crystal growth, prevent aggregation, and improve wettability and dissolution behavior. As a result, spherical cocrystals not only enhance drug solubility and bioavailability but also simplify downstream processing.[4-5]

Direct tableting of active pharmaceutical ingredients (APIs) is possible when powders have a good flow property and compression characteristics, which is a problem for major of the active ingredients that have poor compressibility and flow. However, on addition of excess amount of diluents or by wet or dry granulation satisfactory results can be obtained.[6-8] The addition of excess amount of directly compressible diluents is not favored, as they may increase the compressibility but may not increase the flow property of powder blend while wet granulation is a process that consumes time, energy, and required maintenance of lot of documentation.[9] The spherical crystallization (SC) is a technique, which has shown promising results in the improvement of particle size, flowability and compression characteristics of active pharmaceutical agents. The SC by the spherical agglomeration (SA) method is defined as an agglomeration process that transforms crystals directly into a compacted spherical form during the crystallization stage and this process also ensures the tablet size reduction by omitting the use of large amounts of fillers.[10] The direct compression method for tablet manufacturing is cost efficient and easy to validate. Various other techniques such as hydrotropy, sono crystallization, hot melt extrusion technique, steam aided granulation, floating granulation, dried nano suspensions, liquisolid technology, and cryo techniques are available for improvement of solubility, but SA technique not only increases the dissolution it also improves the powder characteristics of the active ingredient.

2 Spherical Crystallization Techniques

2.1 Spherical agglomeration method

In this process, drug is dissolved in a system of water, ethanol and chloroform behaving as poor solvent, good solvent, and bridging liquid, respectively.[11] As the drug solution is poured in the poor solvent simultaneous crystallization of the API takes place, a third liquid known as bridging liquid that has low miscibility with the poor solvent but having a good affinity with the drug is added in a controlled manner to the crystallization vessel.[12] Therefore, it forms a bridge between the particles and cause binding of the particles.[13] In this process, it should be taken care of that the good solvent and poor solvent should have greater affinity than drug affinity of drug and the good solvent.[14-15] The process is shown in Figure 1.

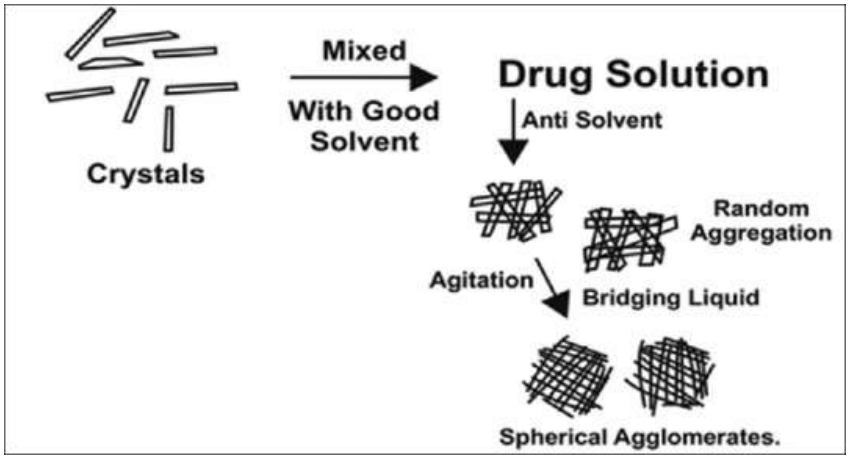

Fig 1. Process of spherical agglomeration[2]

2.2 Crystallo-co-agglomeration

As the crystallo-co-agglomeration (CCA) fig 2 name suggests, the crystallization takes place in the presence of an external inert material or diluents.[16] SC technique[17] limited its applicability only to the high dose pharmaceuticals whereas CCA was effective in case of low dose active ingredients utilizing another active ingredient or a diluent such as talc, sodium starch glycolate, and starch. Some researchers have utilized another pharmaceutical entity as a substrate for developing mixed dose spherical crystals.[18]

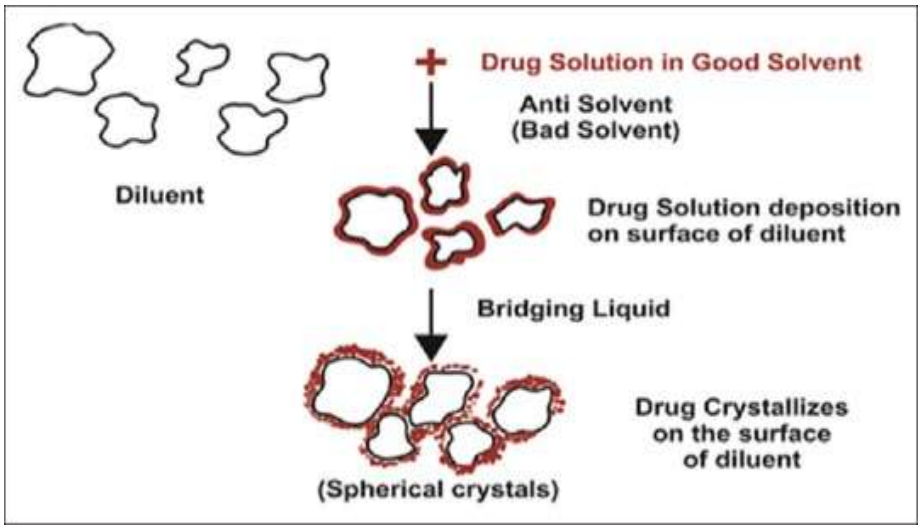

Fig 2. Crytsallo-co-agglomeration process for preparation of spherical crystals[2]

2.3 Ammonia diffusion system

In this technique, ammonia water acts both, as a good solvent and a bridging liquid in one single step.[19] API's which are zwitterionic in nature, are soluble in acidic and alkaline solution but insoluble in neutral and organic solvents, by virtue of which, makes it difficult to use the general SA techniques.[20] Ammonia water (predominantly alkaline) solution of drug when added to the mixture of a water miscible and immiscible organic solvent, the ammonia water diffuses out to the outer layer of organic solvents, the residual ammonia water acts as bridging liquid thereby binding the crystals simultaneously and producing larger uniform shaped particles.[21]

3. Role of Polymers in Enhancing Physicochemical and Mechanical Properties of Drugs

Polymers play a very important role in modern pharmaceutical formulation. Many drugs, especially new chemical entities, have problems like poor solubility, low stability, poor flowability, and weak compressibility. These issues can reduce drug effectiveness and create difficulties during manufacturing. To overcome these challenges, polymers are widely used as excipients because they can modify and improve both physicochemical and mechanical properties of drugs.[22]

What are Polymers?

Polymers are large molecules made up of repeating units called monomers. In pharmaceuticals, polymers can be natural (like starch, cellulose), semi-synthetic (like HPMC), or synthetic (like PVP, PEG). They are safe, biocompatible, and widely used in drug delivery systems.

4. Role of Polymers in Enhancing Physicochemical Properties

4.1 Solubility Enhancement[23-24]

Many drugs are poorly soluble in water, which reduces their bioavailability. Polymers help improve solubility by:

a. Forming solid dispersions
b. Improving wettability
c. Reducing crystallinity of drugs

For example, PVP and PEG increase the dissolution rate of poorly soluble drugs.

4.2 Stability Improvement

Drugs can degrade due to heat, light, and moisture. Polymers protect drugs by:

a. Forming a protective matrix
b. Preventing oxidation and hydrolysis
c. Stabilizing amorphous forms

4.3 Control of Drug Release

Polymers help in controlled and sustained drug release by:

a. Forming gel layers (e.g., HPMC)
b. Controlling diffusion of drug molecules
c. Extending drug action

4.5 Improvement in Bioavailability[25-26]

By enhancing solubility and dissolution, polymers increase the amount of drug absorbed in the body.

Table 1: Role of Polymers in Physicochemical Properties

Property	Role of Polymer	Example Polymer
Solubility	Improves wettability and dissolution	PVP, PEG
Stability	Protects from degradation	HPMC, Eudragit
Drug Release	Controls release rate	HPMC, Carbopol
Bioavailability	Enhances absorption	PEG, PVP

5. Role of Polymers in Enhancing Mechanical Properties[27-28]

Mechanical properties are important for manufacturing processes like tablet compression and capsule filling.

5.1 Flowability Improvement

Poor flow of powders leads to uneven filling during tablet production. Polymers:

a. Improve particle size and shape
b. Reduce interparticle friction
c. Enhance flow properties

5.2Compressibility Enhancement

Compressibility is the ability of powder to form tablets. Polymers:

a. Act as binders
b. Improve cohesion between particles

c. Produce strong tablets

5.3Particle Size Modification

Polymers help in forming spherical particles or granules, improving:

a. Uniformity
b. Packing ability
c. Handling propertie

5.4Reduction of Dust Formation

Polymers reduce fine particle formation, making handling safer and easier.

Table 2: Role of Polymers in Mechanical Properties[29]

Property	Role of Polymer	Example Polymer
Flowability	Reduces friction, improves flow	PEG, MCC
Compressibility	Acts as binder, forms strong tablets	PVP, HPMC
Particle Size	Helps in granulation and agglomeration	Carbopol, PEG
Dust Reduction	Reduces fine particles	HPMC

Table 3: Commonly Used Polymers in Pharmaceuticals

Polymer Name	Type	Application
PVP	Synthetic	Solubility enhancer, binder
PEG	Synthetic	Plasticizer, solubility enhancer
HPMC	Semi-synthetic	Controlled release, binder
Carbopol	Synthetic	Gel formation, controlled release
MCC	Natural	Filler, compressibility enhancer
Eudragit	Synthetic	Controlled and targeted drug release

Table 4: Methods for Preparation and Enhancement Using Polymers[30]

Method	Principle	Role of Polymer	Advantages	Limitations
Spherical Crystallization	Formation of spherical agglomerates using solvent change	Controls crystal growth, improves sphericity	Enhances flowability and compressibility	Requires careful solvent selection
Solvent Evaporation Method	Evaporation of solvent to form solid particles	Stabilizes drug, improves uniformity	Simple and cost-effective	Residual solvent issue
Antisolvent Crystallization	Drug precipitates when mixed with antisolvent	Prevents aggregation, controls particle size	Produces fine and uniform particles	Difficult to control nucleation
Spray Drying	Rapid drying of drug-polymer solution	Forms amorphous solid dispersion	Improves solubility and dissolution	Expensive equipment required
Hot Melt Extrusion	Drug and polymer melted and mixed	Enhances solubility and stability	No solvent required, continuous process	High temperature may degrade drug
Co-crystallization	API + coformer forms stable crystal	Polymer acts as stabilizer	Improves solubility and bioavailability	Selection of coformer is critical
Wet Granulation	Formation of granules using liquid binder	Acts as binder to improve compressibility	Improves flow and tablet strength	Additional drying step needed
Direct Compression with Polymer	Mixing drug with polymer and compressing	Improves binding and flow	Simple and fast process	Not suitable for all drugs

6. **Applications in Advanced Drug Delivery Systems[31]**

Polymers are used in many advanced formulations such as:

a. **Spherical cocrystals** – Improve solubility and flow
b. **Hydrogels** – Used for topical and wound healing
c. **Nanoparticles** – Enhance drug targeting
d. **Transdermal patches** – Controlled drug delivery

7. **Advantages of Using Polymers**

a. Improve drug solubility and stability
b. Enhance bioavailability
c. Provide controlled drug release
d. Improve manufacturing properties
e. Reduce production cost

8. **Limitations of Polymers**

a. Some polymers may interact with drugs
b. High concentration may affect drug release
c. Cost of some synthetic polymers is high
d. Moisture sensitivity in some cases

CONCLUSION

Polymers are essential components in pharmaceutical formulations. They play a key role in improving both physicochemical and mechanical properties of drugs. By enhancing solubility, stability, flowability, and compressibility, polymers help in developing effective and stable dosage forms. Their use in advanced technologies like spherical cocrystals further improves drug performance. Therefore, polymers are highly valuable in modern drug delivery systems and continue to be an important area of research in pharmaceutical science.

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