International Journal of Research in Pharmacy and Pharmaceutical Sciences
www.pharmacyjournal.in
ISSN: 2455-698X
Received: 08-04-2024, Accepted: 01-05-2024, Published: 24-05-2024
Volume 9, Issue 2, 2024, Page No. 13-18

Co-crystallization: Technique for solubility enhancement - A review

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Abstract
In recent years, there has been a lot of interest in the design and synthesis of pharmacological co-crystals. A great chance exists for the production of novel pharmaceutical products with enhanced pharmacological and physical characteristics, such as bioavailability, stability, hydroscopicity, solubility, and dissolution rates, through co-crystallization of medicinal components. When developing a therapeutic formulation, the physicochemical qualities of active medicinal ingredients, such as their solubility and flow characteristics, are vital. The compound's physical form and formulation may have an impact on the drug's biopharmaceutical characteristics. While keeping the drug molecule's inherent action, the physical characteristics of the active pharmaceutical ingredients can be changed by the use of crystal engineering. The benefits of co-crystals over salts, solvates (hydrates), solid dispersions, and polymorphs are discussed in this article along with their formation mechanism, preparation techniques, and use in altering the physicochemical properties of active pharmaceutical ingredients. An attempt is made to incorporate documented works on co-crystals, which contribute to a deeper understanding of the idea.

Keywords: Cocrystallization, solubility, bioavailability, co-crystals, dissolution.

Introduction

A number of methodologies can be adapted to improve solubilization of poor water-soluble drug and further to improve its bioavailability. The techniques generally employed for solubilization of drug includes micronization, chemical modification, pH adjustment, solid dispersion, complexation, co-solvency, micellar solubilization, hydrotropy etc. Solubilization of poorly soluble drugs is a frequently encountered challenge in screening studies of new chemical entities as well as in formulation design and development. Solubility is a property of substance in a particular solvent. It is the amount of dissolved solute in a saturated solution at a particular temperature, expressed quantitatively. Biopharmaceutics classification system (BCS) class II medications, such as phenytoin, danazol, and nifedipine, and BCS class IV pharmaceuticals, such as furosemide, hydrochlorothiazide, and Taxol, are examples of drugs with low solubility [1]. The Biopharmaceutical Classification System (BCS) classes II and IV comprise 75% of the therapeutic candidates that were still in development but had low solubility, according to recent research [2, 3].

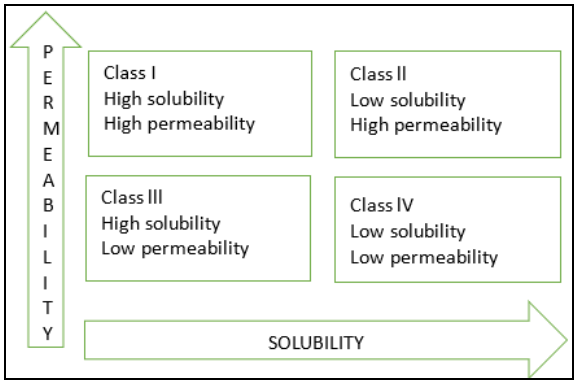


Fig 1: BCS Classification system

A modern and developing method for creating pharmaceutical products with enhanced physicochemical and mechanical properties is cocrystallization. To improve an API's properties, crystal engineering techniques can generate cocrystals, metastable polymorphs, high energy amorphous forms, and ultrafine particles [4]. Cocrystals approach is unique it does not alter the drug's pharmacological properties while potentially enhancing a number of its physicochemical properties, including melting point, tabletability, solubility, stability, dissolution, permeability, and bioavailability [5]. Numerous methods, such as the solid-state method, the solution-based method, and the supercritical fluid method, can be used to manufacture cocrystals. The supercritical fluid approach employs carbon dioxide as a supercritical atomization enhancer, while the solid-state method utilizes less solvent than the solution-based method. Freeze drying, laser irradiation, and electrospraying technology are more methods for producing cocrystals [6]. In cocrystal research characterization of cocrystals is important, the various physiochemical properties of cocrystals can be characterized by differential scanning calorimetry (DSC), powder X-ray diffraction (PXRD), Fourier transform infrared spectroscopy (IR), Raman spectroscopy, solid state nuclear magnetic resonance spectroscopy (SSNMR), scanning electron microscopy (SEM), terahertz spectroscopy, and single crystal X-ray diffraction (SXRD).

According to the definition by the US Food and Drug Administration (FDA), cocrystals are crystalline materials composed of two or more different molecules, typically drug and cocrystal formers (coformer), in the same crystal lattice. Pharmaceutical cocrystals have made it possible to engineer solid state forms of active pharmaceutical ingredients (APIs) other than the typical solid-state forms, like salts and polymorph. Cocrystals are multicomponent systems in which one component is API and another is coformer.

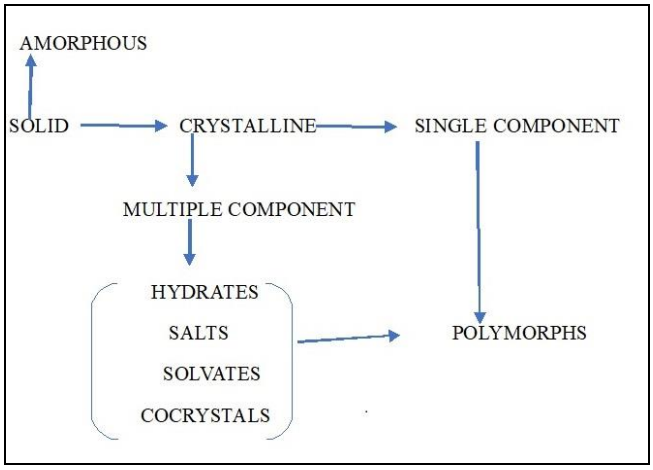


Fig 2: API solid form classification based on structure and composition

Co-crystals incorporate pharmaceutically acceptable guest molecules into a crystal lattice along with the API. Co-crystals have regained attention as attractive alternate solid forms for drug development. Fig. 2

Scientists working in the chemical sciences, pharmaceutical industry, and regulatory bodies are becoming more interested in the cocrystal notion of supramolecular chemistry. Cocrystal engineering for pharmaceuticals has surfaced represents a new chapter in the history of medicine, bringing forth a novel moiety with enhanced pharmacokinetic and pharmacodynamic qualities, as well as better solubility, dissolution, and bioavailability. Cocrystals are solids that are crystalline and unagitated, consisting of two or more molecules that are bound together by the same crystal lattice. Pharmaceutical cocrystals, on the other hand, are defined as crystalline single-state solids made up of two or more distinct molecular amalgams bound together by a predetermined stoichiometric ratio. Often the following is an acknowledged definition of pharmaceutical cocrystals that was published in Crystal Growth and Design after it became widely agreed upon during the 2011 Indo-US meeting: "Cocrystals are solid, crystalline, single-phase materials that are neither solvates nor simple salts. They are often made up of two or more distinct molecular and/or ionic compounds in a stoichiometric ratio. As a result, it is a multi-component crystal that has been altered by intermolecular interactions between a conformer and an active medicinal ingredient (drug), such as hydrogen bonding, van der Waals force, and π-π interactions [7]. cocrystal has more exotic qualities than the original drug molecule, including stability, dissolving rate, micrometric properties, physiochemical properties, and melting point variation. Permeability, in addition to other diverse drug moiety characteristics. Because of their originality and nonobvious invention, they may therefore be easily patented. Cocrystals are multicomponent crystals made up of hydrates, inclusion crystals, clathrates, solvates, and salts. One component of solvates is liquid at room temperature, but both components of cocrystals are solid at room temperature [8]. Melting point: This physical characteristic of a solid is used to assess its purity. Unadulterated materials or solid melt at acute meeting point with limited dispersion. Any API's thermodynamic stability may be determined by its melting point, so choosing a coformer with a high melting point is crucial for cocrystal synthesis because it improves stability and is also advantageous for thermolabile drugs [9]. non-ionizable medications, which are incapable of forming salt crystals, can be used to make cocrystals. Moreover, concerning ionizable medications, the quantity of more appropriate cocrystal formers than salt formers are possible [10].

Chemistry of co-crystal formation

Through co-crystal engineering, an API's solid-state characteristics can be enhanced without compromising its underlying structure. The theory that crystalline solids are real examples of self-assembly is the focus of the application of supramolecular chemistry principles to the solid state known as "crystal engineering" [11, 12]. Intermolecular forces including hydrogen bonding, π-π stacking interactions, and van der Waals contact forces combine to form cocrystals. By altering the intermolecular interactions that control the breaking and formation of non-covalent bonds, such as hydrogen bonding, van der Waals force, stacking, electrostatic interactions, and halogen bonding, crystal engineering allows a solid material's crystal packing to be modified [13]. The field of cocrystal study often uses the term supramolecular synthon. It is described as structural components of supramolecules that are assembleable and/or formable by recognized synthetic processes involving intermolecular interactions. APIs can co-crystallize with cocrystal formers containing carboxylic acids, amides, carbohydrates, alcohols, and amino acids [14].

Methods of co crystals formation

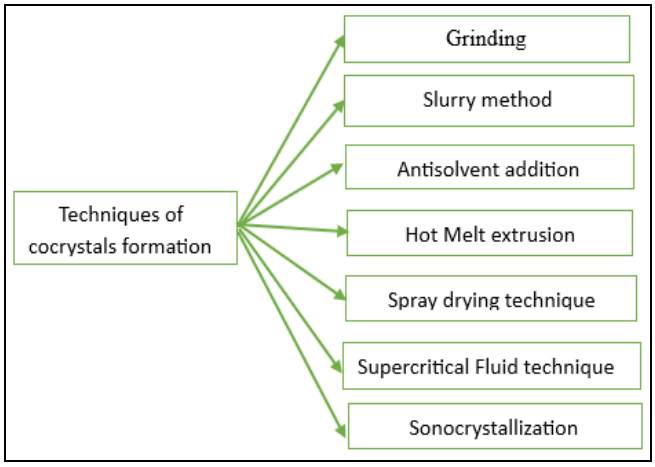
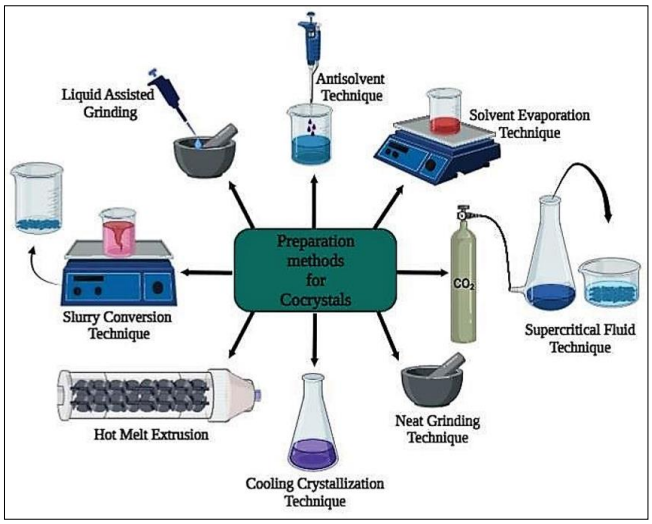


Fig 3: Various techniques of cocrystals formation.



A. Grinding method

It is one of the mostly used techniques for the cocrystal formation from the last few years. There are two types of grinding method are used: (a) dry grinding method and (b) wet grinding method.

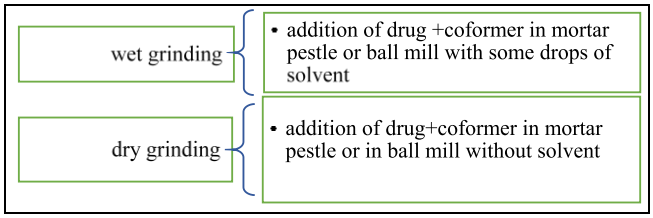


Fig 4: Types of Grinding method

Method of dry grinding the most popular and regularly used method for creating cocrystals involves mixing coformers and API with a mortar and pestle at a stoichiometric ratio. This process is mechanical and time-consuming, yet it is straight forward, easy to use, environmentally friendly, and very prolific [15]. Grinding helped by liquid in order to create co-crystals, liquid-assisted grinding, or LAG, modifies the solid-state grinding process by adding a tiny amount of solvent. Here, the cocrystals' production is accelerated by the additional solvent. This method has an advantage over the solvent evaporation technique since it requires less solvent and takes less time.

B. Slurry method

It is also among the simplest methods for the cocrystal formation phase of the crystallization process. After dissolving the chosen medication and coformer in an appropriate solvent to create a suspension, the mixture is agitated, filtered, and dried. Using a slurry method of crystallization, the medication celecoxib-venlafaxine cocrystal (NSAIDs + antidepressant) was created and patented. High solubility BCS class I drugs overcome the solubility issue with venlafaxine (BCS class I) and celecoxib (BCS class II). This method involves creating a slurry of API and coformer in an appropriate solvent, stirring it well with a glass rod or magnetic stirrer, and letting the solvent cool gradually at room temperature until cocrystal formation occurs [16].

C. Antisolvent addition

Another technique for producing co-crystals of superior quality is antisolvent crystallization. In this to attain supersaturation during procedure, a second liquid such as an organic solvent or buffer is added to the drug coformer medium which cause the co-crystal to precipitate, the additional liquid needs to be miscible with the solvent. This method's disadvantage is that it requires a lot of solvent for preparation [17, 18].

D. Hot melt extrusion technique

This approach involves heating the drug and conformer to a certain temperature, which enhances surface interactions regardless of the solvent. A catalysing agent is required to increase the production of cocrystals because the temperature is designed specifically to melt the matrix alone. Twin screw and single screw cocrystals of carbamazepine with cinnamic acid have the best dissolution rates when compared to single screw cocrystals. The advantage of this method is that it doesn't require the use of organic solvent and has a rapid operating period for increased conversion. Co-crystals can be made using hot melt extrusion as a single step, continuous manufacturing method. Using this procedure, the drug and coformer are heated to a high intensity and mixed to become miscible in the molten stage, resulting in the formation of co-crystals [19, 20]. The medication and coformer must meet certain requirements in order for this approach to work, including becoming miscible when melted.

E. Spray drying

The co-crystals can be prepared using spray dryers. To produce high-quality co-crystals, the partners are dissolved in a common evaporating solvent and sprayed into a heated air stream to allow the solvent to evaporate [21, 22]. Following cocrystal preparation, a thorough examination was conducted to verify the cocrystal's purity and authenticity.

F. Supercritical fluid techniques

The most popular supercritical fluid for creating co-crystals is CO_2, since it can permeate through solids. The drug and coformer are dissolved in CO_2 and added to a stainless-steel vessel. The CO_2 expands quickly as the pressure is gradually reduced, resulting in the creation of co-crystals. The primary drawbacks of this approach are the drug's and coformer's restricted solubility in the supercritical fluid and the co-crystal's lower purity [23, 18].

G. Sonocrystallization

Co-crystals can be created using a sonoreactor. This method involves dissolving medicines and coformer in a common solvent and maintaining a consistent temperature for sonication. To keep the sonicator's temperature steady, cold water is supplied. The tremendous energy that causes size reduction and supersaturation, which leads to crystallization, is what creates the air bubbles or voids. Co-crystal formation is accelerated by further solvent evaporation [22, 23].

Characterization of co crystals

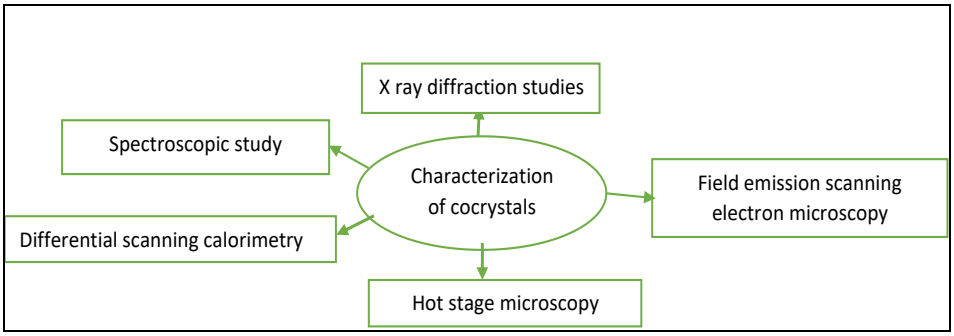


Fig 5: Characterization of cocrystals

A. Field Emission scanning electron microscopy

FESEM or topography is used to study the surface morphology of co-crystals. Micrographs of components and co-crystals obtained in the FESEM studies are utilized for the comparison. In the field emission electron microscope, heat energy is not used so-called "cold" source is employed. A strong electric field is utilized to emit the electrons from the surface of the conductor. A tungsten filament with a thin and sharp needle is employed as a cathode. The field emission source is attached with a scanning electron microscope for the capture of micrographs of co-crystals [24, 25].

B. Hot stage microscopy

The hot stage microscopy investigation includes both heat analysis and microscopy. A solid form's physicochemical properties are examined in relation to temperature and time. The co-crystal sample, which was placed on a glass slide, underwent modifications during the heating process that were plainly visible under a microscope. These changes included crystalline transformation and variations in melting and melting range [26].

C. X ray diffraction studies

X-ray diffraction of powder the method most frequently employed to characterize co-crystals is PXRD. Using this method, it was possible to see that the diffractogram of the co-crystal and the API were different from one another based on the X-ray diffraction pattern [26].

D. Differential scanning calorimetry

The appearance of an exothermic crest followed by an endothermic crest in the DSC spectra is utilized to determine cocrystal formation. The presence of crests, or peaks, in the compound determines the cocrystal formation. Additionally, it can be used to ascertain a compound's or molecule's melting point, polymorphic nature, glass temperature, heat of fusion, and exothermic or endothermic behaviour [27].

E. Spectroscopic study

Nuclear Magnetic Resonance in vibrational spectroscopy (infrared and Raman) can be used to identify the structural behaviour of co-crystals since the energy absorbed or dispersed by the chemical bonds in the co-crystals will differ from that of the pure components. Because of the hydrogen bonding that occurs between them, cocrystals have a distinct spectrum of bands in infrared spectroscopy than the pure drug and coformer. The bands of functional groups that have experienced hydrogen bonding clearly differ from one another [27, 28].

Application of cocrystals

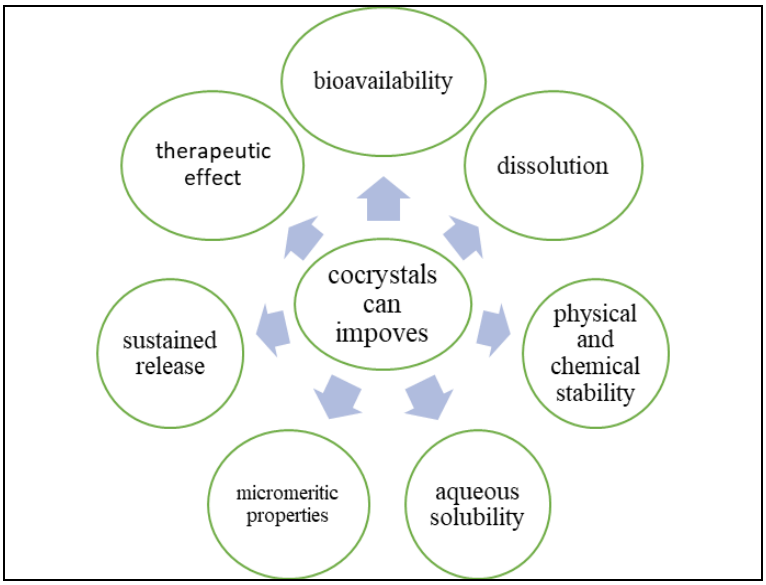


Fig 6: Application of cocrystals

Bioavailability

Cocrystals have the potential to improve drug delivery and, as a result, clinical outcomes by increasing solubility. Moreover, cocrystals can alter the pharmacodynamic and pharmacokinetic characteristics of pharmaceuticals. The increased solubility enhances the rate of dissolving, which eventually raises the drug's bioavailability [29].

Dissolution

The concept of intrinsic dissolution involves measuring the speed at which a pure drug substance dissolves from a consistent surface area. This assessment remains uninfluenced by formulation variables and delves into the inherent qualities of the drug concerning dissolution media attributes such as pH, ionic strength, and counter-ions. This intrinsic dissolution rate serves as a valuable indicator for predicting the *in vivo* functionality of APIs falling within the realm of BCS class 2. Despite the importance of investigating intrinsic dissolution rate, its complexity can amplify when dealing with cocrystals [30].

Aqueous solubility

The "spring and parachute" action of cocrystals is most commonly used to relieve solubility concerns in weakly soluble pharmaceuticals, specifically those classified as BCS class 2 and 4 compounds. The increase in medication solubility can be attributed to changes in the molecule's underlying crystal structure. This change in medication solubility can occur in two ways: it can increase the drug's bioavailability or it can cause problems if the rise is significant, possibly resulting in drug precipitation within the solution due to supersaturation [31].

Stability

A change in a substance's state that does not coincide with a change in its chemical makeup is referred to as a physical change. Solid-state materials' physical attributes include elasticity, hardness, plasticity, hygroscopicity, melting temperature, and solubility. Cocrystallization is an effective method for enhancing the physical characteristics and preserving the physical stability of medicinal compounds, which are susceptible to unfavourable physical changes during production and storage. Cocrystallization is a powerful approach for improving the physical properties and maintaining the physical stability of drug substances. The physical properties of solid-state materials include melting point, hygroscopicity, solubility, hardness, plasticity, elasticity. Chemical degradation of drug substances tends to occur during the manufacturing and storage stages, which challenges the development of a stable pharmaceutical formulation. It is critical to develop an effective strategy to eliminate or minimize drug degradants. pharmaceutical cocrystals have emerged as a prospective approach to overcome the chemical instability of APIs in the solid state [32].

Mechanical properties

In the production of solid dosage forms, the mechanical characteristics of crystalline materials play a crucial role in the operations of blending, milling, granulating, tableting, and coating. The mechanisms of mechanical deformation for solid materials comprise fragmentation, plastic, viscoelastic, and elastic materials. Better plasticity qualities typically translate into greater compressibility, which is permanent and irreversible once tension is removed. The development of tablet formulations is hampered by the weak mechanical characteristics of many organic substances. It has been shown that cocrystallization, which modifies crystal packing, significantly enhances the mechanical qualities of pharmaceuticals [33].

Sustained release

Because the sustained release dosage form produces a steady-state blood level with less plasma variations, it offers significant advantages in terms of decreased dosing frequency, greater patient compliance, and mitigated side effects [34]. Different approaches to formulation have been utilized to provide sustained release patterns, including osmotic pump drug delivery systems, membrane-controlled, and polymeric matrices. Cocrystallization has been shown to be an alternate strategy for sustaining medication release in recent years [35].

Therapeutic effect

The therapeutic effect of a drug substance is often influenced by its physicochemical properties. The limitation of low solubility or permeability of BSC II and BCS IV class drugs would immensely restrict the therapeutic effect of the medicines. The cocrystal strategy has been considered an effective technique to improve bioavailability and thus enhance the therapeutic effect [36].

Advantages of co-crystals

- When compared to amorphous materials, cocrystals have the benefit of stable crystalline structures since covalent bonds do not need to be broken. Theoretically, any kind of API (strongly ionizable or nonionizable) can form cocrystals.
- Multi-drug co-crystals, or MDCs, have the potential to provide synergistic effects in addition to the improved solubility, dissolution, and bioavailability provided by regular co-crystals.
- MDCs improves or modifies the properties of the drug substances in the preparation of new strategies for the development of combination therapy.
- Because of their intermolecular interactions, multidrug co-crystals can stabilize unstable molecules.
- For successful production of multi drug co-crystals use not only crystallography but also some other processes are also considered.
- In pharmaceutical co-crystals production, the compatibility of two drugs, differentially solubility and variations in dose must be considered.

Conclusion

Our goal in writing these review articles is to provide an overview of the structure of cocrystallization while highlighting the most notable advancements in our understanding of its physicochemical features. The main reason to the increase interest in cocrystals is the necessity to improve drugs properties. The improvement of solubility, dissolution rate and, consequently, bioavailability has been frequently reported, as well as the increase of stability and other properties which have developed interest in formulation and development of co-crystals. We hope that our attempt to provide a co-crystal overview of physicochemical qualities, advantages and disadvantages, applications, and information regarding co-crystallization would be useful to the audience as they deepen their understanding of co-crystallization techniques and related case studies. Further scientific research and communication lead to the management and evolution of an ecologically organized system of co-crystallization processes, as well as the potential physiochemical properties, benefits, and uses of co-crystallization.

Acknowledgement

The authors are thankful to AICTE New Delhi for providing the financial support during M. Pharm study tenure. Also, thankful to the principle of GOVERNMENT COLLEGE OF PHARMACY, KARAD for allowing to publish this article and gave us other facilities.

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