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A REVIEW: SOLUBILITY ENHANCEMENT TECHNIQUES BY CO-CRYSTALLIZATION

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Abstract- Design and synthesis of pharmaceutical Co-crystals have received great interest in the recent years. Co-crystallization of drug substances offer a tremendous opportunity for the development of new drug products with superior physical and pharmacological properties such as solubility, stability, hydroscopicity, dissolution rates and bioavailability. This short review summarizes this highly topical field, covering why the topic is of interest in pharmaceutical formulation, the definitions and practical scope of co-crystals, co-crystal preparation and characterization, comparison of different (traditional and novel) methods for co-crystal formation and implications for regulatory control and intellectual property protection. Traditionally, co-crystal can be prepared by solvent evaporation method, grinding, and slurry method, but, every method has limitation for certain condition. The current trend for Co-crystal formation uses the sophisticated method such as hot-melt extrusion method, spray drying method, supercritical fluid technology and the newest, and laser irradiation method. Development of new method is not only to overcome the limitation of traditional Co-crystallization methods but also to generate a simpler step and continuous process for the production of Co-crystal product. This article gives a brief explanation of each method that can be used to generate pharmaceutical Co-crystals.

Key word:- Bioavailability, Crystallisation, Pharmaceutical Co-crystals, Solubility

I. 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[2,25].Solubility is a property of substance in a particular solvent. In quantitative terms it is concentration of dissolved solute in asaturated solution at a specific temperature[1,24]. Drugs that have low solubility are biopharmaceutics classification system (BCS) class II drugs, e.g., phenytoin, danazol, nifedipine, and BCS class IV drugs, e.g., hydrochlorothiazide, furosemide, and taxol[4].

Table 1:- BCS classification according to solubility of drugs[3,4,26]

Class 1	High solubility/high permeability	B-blockers Propranol, Metoprolol
Class 2	Low solubility/high permeability	NSAID's Ketoprofen, Antiepileptic Carbazepine, Phenytoin, danazole, nifedipine
Class 3	High solubility/low permeability	B blockers Atenolol,H2antagonist Ranitidine
Class 4	Low solubility/low permeability	Diuretics Hydroclorthiazide, frusemide, taxol

Table 2:- Solubility Expression[1,33]

Defination	Parts Of Solvent Required For 1 Part Of Solute
Very Soluble	Less Than 1
Freely Soluble	From1-10
Soluble	From 10-30
Sparingly Soluble	From30-100
Slightly Soluble	From 100-1000
Very Slightly Soluble	From 1000-10000
Insoluble	Greater Than 10000

II. CO-CRYSTALS

Co-crystals was discovered in late 1800s and early 1900s , the first reported co-crystals, quinhydrone was studied by Friendrich wohler in 1844. Due to various stability issues, API cannot be properly formulated and hence they are converted into solid forms such as polymorphs, salts, solvates, hydrates, amorphous, and co-crystals. Each of them imparts a different physiochemical property and affects other performance. Currently the most challenging situation is to enhance solubility of certain drugs. It's easy to solve solubility problem of amorphous form, but difficult for crystalline drug so the concept of co-crystals came into existence. The term ―co-crystall‖ and design rules of hydrogen bonding of an organic co-crystal were first reported by Etter[7]. Pharmaceutical cocrystallization is a reliable method for changing the physical and technical properties of the drug without altering their pharmacological activities. Co-crystal is a novel product to improve drug solubility and is also referred to as molecular complexes. It has witnessed increasing usage as an essential choice to polymorph during the selection of solid-phase APIs[17].Co-crystals are multicomponent molecular crystals where all components are at a stoichiometric ratio and comprise of two or more chemically different molecules includes modification of drugs to alter physical properties of a drug, especially a drug's solubility without altering its pharmacology effect[13].

III. CHARACTERIZATION OF CO-CRYSTALS

Characterization of co-crystals includes study of physicochemical properties of co-crystals (melting point, Differential Scanning Calorimetry, Thermo Gravimetric Analysis) and structural elucidation of co-crystals (infrared spectroscopy, single crystal X-ray crystallography and powder x-ray diffraction)[6].

Solubility

Co-crystallization is used mainly for the enhancement of solubility of BCS class II drugs(Tab.1)[6]. With development of co-crystal one can increase the solubility of poorly soluble drug , many researchers have improved solubility of drug with this technique . Co-crystals of efavirenz was synthesized by using oxalic acid dihydrate and citric acid monohydrateas conformers to improve its solubility and dissolution rate. As both conformers have high water solubility that is 14.3g/100 ml and 64.7g/100 ml respectively and contain hydrogen bond donor and acceptor groups, which can be used for designing co-crystals of efavirenz leading to improvement in solubility[7].

Stability

Stability is an important parameter to be considered for any formulation. It is important to ensure the chemical stability, solution stability, thermal stability and relative humidity stability of co-crystals. The relative humidity stability of the co-crystals can be analyzed by water absorption/desorption experiments[6].

Melting Point

Melting point is the temperature at which solid and liquid phases of co-crystal are in equilibrium. When the cocrystal is formed, the melting point of API changes and is intermediate between themelting point of the API and the conformer[6].

Tabletability

Various prerequisites for tabletting such as good mechanical strength and flowability is proposed to be increased by co-crystallization. For example, the co-crystal of carbamazepine and saccharine was found to be denser to pure carbamazepine. The compression properties of paracetamol improved in the presence of theophylline, oxalic acid, naphthalene and, phenazine[22].

Permeability

Recent investigation states that co-crystals not only can improve dissolution properties of drugs but also may modify the permeability of drugs. These results may expand the applications of co-crystals from class II drugs to class III and more importantly to class IV of BCS. Drug absorption and distribution of drugs mainly depends upon the permeability of drugs across the biological membrane.

Permeability of drugs mainly depends upon the n-octanol/water partition coefficient by using log P and (C log P) for unchanged form of drug. The co-crystal of BCS class III drug (5- fluorouracil) was synthesized using 3hyroxybenzoic acid, 4- aminobenzoic acid and cinnamic acid and it was reported that co-crystal has better permeability to that of pure drug. Permeability of drugs, however, has been improved through the use of coformers/excipients such as lactic acid, tartaric acid, fumaric acid and glutaric acid (higher lipophilicity of the acids). These coformers are applicable not only to molecules of a specific physical and chemical nature, but to a wide range of crystalline materials and is often required to determine the appropriate approach towards improving solubility and permeability during drug development. Permeability study of hydrochlorothiazide and co-crystals with different coformers was studied by using Franz diffusion cells. The amount of drug flux in all co-crystals was higher as compared to pure drug except for succinamide co-crystals. And it was concluded that Co-crystals permeability was improved due to formation of heterosynthon between drug and conformer[7].

Bioavailability

Bioavailability is defined as the rate and extent of pure drug that reaches into systemic circulation. Low oral bioavailability of APIs is one of the major challenges in development of formulations, with help of cocrystallization one can enhance or improve the bioavailability of API . Many researchers have enhanced the bioavailability of different drugs with conversion in co-crystal form. Co-crystal of Fexofenadine was synthesized by Mounika et al using Tartaric acid as coformer by solvent evaporation technique and it was concluded that cocrystals Fexofenadine shows maximum release as compare to the formulation[6].

IV. IMPORTANCE OF SOLUBILITY ENHANCEMENT

Oral drug delivery is the most convenient and preferred route of administration due to its ease of administration, high patient compliance, cost effectiveness, least sterility contains and flexibility in the design of dosage form. Solubility is a vital parameter to attain desired drug concentration in systemic circulation for achieving necessary pharmacological response. Poorly water-soluble drugs generally require high dose to achieve therapeutic plasma concentrations after oral administration. For a drug molecule to be absorbed, should be in the form of aqueous solution at the site of absorption. Therapeutic effectiveness of drug depends on its solubility and bioavailability. Currently only 8% of new drug candidates have both high solubility and permeability. The basic aim of formulation and development section is to make that drug available at proper site of action within optimum dose. The two parameters Solubility and permeability are the deciding factors for in-vivo drug absorption, thus needs to be modified by various enhancement techniques[19].

V.FACTORS AFFECTING TO SOLUBILITY

Particle Size

As the particle becomes smaller, the surface area to volume ratio increases and the larger surface area allow a greater interaction with the solvent. Hence smaller the particle size greater the dissolution and thus higher the solubility. The effect of particle size on solubility can be described by the following equation.

$$\text{Log} \quad s/s0 = 2\,\gamma\, V/2.303\, R\, T\, r$$

Where,

S0 - Solubility of infinitely large particles S- Solubility of fine particles V- Molar volume γ- Surface tension of the solid r- Radius of the fine particle[19] .

Temperature

As the temperature is increased than the solution process absorbs energy and the solubility will be increased but if the solution process releases energy then the solubility will decrease with increasing temperature. A few solid solutes are less soluble in warm solutions. For examples all gases, solubility decreases as the temperature of the solution increases[11]. A few solid solutes are less soluble in warm solutions. For all gases, solubility decreases as the temperature of the solution increases[27].

Pressure

For solids and liquid solutes, changes in pressure have practically no effect on solubilitybut for gaseous solutes, an increase in pressure, increases solubility and a decrease inpressure, decrease the solubility. Nature of the solute and solvent only 1 gram of lead (II) chloride can be dissolved in 100 grams of water at roomtemperature while 200 grams of zinc chloride can be dissolved. The great difference inthe solubility's of these two substances is the result of differences in their natures[10].

Molecular Size

The solubility of the substance is decreased when molecules have higher molecular weight and higher molecular size because larger molecules are more difficult to surround with solvent molecules in order to solvate the substance[10].

Nature of Solute And Solvent

The nature of solute and solvent depends on concentration of solute in specific quantity of solvent at specific temperature. Example: at room temperature in 100gm of water only 1gm of lead (II) chloride can be dissolved while 200 grams of zinc chloride can be dissolved[11].

Polymorphs

Polymorphs can vary in melting point. Since the melting point of the solid is related to solubility, so polymorphs will have different solubility's. Generally the range of solubility differences between different polymorphs is only 2-3 folds due to relatively small differences in free energy[10].

Polarity

Polarity of the solute and solvent molecules will affect the solubility. Generally likedissolves like means nonpolar solute molecules will dissolve in non-polar solvents andpolar solute molecules will dissolve in polar solvents. The polar solute molecules have apositive and a negative end to the molecule. If the solvent molecule is also polar thenpositive ends of solvent molecules will attract negative ends of solute molecules. This isa type of intermolecular force known as dipole-dipole interaction. The other forces calledLondon dispersion forces where the positive nuclei of the atoms of the solute moleculewill attract the negative electrons of the atoms of a solvent molecule. This gives the nonpolarsolvent a chance to solvate the solute molecule[10].

VI.METHOD OF CO-CRYSTAL PREPARATION

Solution Methods

In these methods, there are ternary phases (API, co-former and solvent) in the solution, and the perfect state is that the co-crystal is supersaturated while the reactants (API and co-former) are saturated or under saturated under the experimental conditions. Hence, the degree of super saturation with respect to co-crystal in solution is the key parameter for co-crystallization and can be adjusted by the concentrations of API and co-former. To guide the path of co-crystal formation, a phase diagram that describes the conditions for thermodynamic stability must be established, which can guarantee that the co-crystal stays in the thermodynamically stable region and exclude the crystallization of pure reactants. The location of the modynamically stable co-crystal phase regions is mainly determined by the solubility of the reactants. Fig. 1 demonstrates the ternary phase diagrams, which illustrate how to reach the super saturation of co-crystals when the reactants are in a saturated or unsaturated state, according to the solubilities of reactants. As shown in Fig. 1a, reactants A and B have similar solubilities and can be congruently saturated in the given solvent; thus, co-crystals can be formed in an equivalent reactant concentration. In Fig. 1b, the reactants exhibit different solubilities in non-congruently saturating solvents, in which the co-crystal can be generated by using nonequivalent reactant concentrations to reach the co-crystal stable region[14,28].

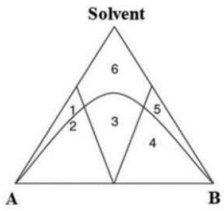

Fig.1(a)

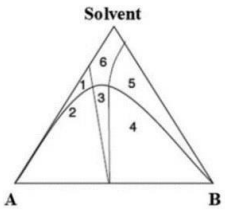

fig.1(b)

Solvent Evaporation

Solvent evaporation is a simple technique in the manufacture of co-crystal using a coformer with a suitable solvent. Molecular interactions on the solubility process of the two compounds form hydrogen bonds in the cocrystallization process. The solvent evaporation process aims to remove the solvent, resulting in the formation of crystalline solids which have different physicochemical properties from the pure substance. This method has the advantage of being thermodynamically produced co-crystal. Several studies reported that the BCS class II multicomponent crystal formulation using this method can improve bioavailability such as simvastatin and ketoprofen[9].

Cooling Crystallization

The drug gets recrystallized by changing the solution temperature via super saturation. A sufficient amount of drug is dissolved at 40.0 ± 0.5°C in a certain quantity of solvent. By continuous stirring, (0.25°C /min) the solution is then cooled in the water bath to 10.0 ± 0.5°C. After vacuum filtration, the crystals are washed with distilled water and dehydrated for 24 hr at room temperature and then placed in desiccators[8].

Grinding Method

Grinding methods have been widely used for the co-crystal formation over the past few years and found to be superior than other methods (solutions or melt). Grinding techniques are of two types neat or dry grinding and wet drying. In dry grinding, drug and conformer are mixed together in a stoichiometric ratio and ground them by using either mortar and pestle or ball mill. Wet grinding was performed in a similar manner that of neat grinding by addition of some drops of solvent in the mixture [18].

Antisolvent Addition

In this method coformer and active pharmaceutical ingredient (API) was precipitated or recrystalization using buffers (pH) and organic solvents as an antisolvent. The Adefovir dipivoxil co-crystal was synthesized by sea et al using Antisolvent precipitation technique. Co-crystals of aceclofenac using chitosan, in which chitosan solution was prepared by soaking chitosan in glacial acetic acid. A weighed amount of the drug was dispersed in chitosan solution by using high dispersion homogenizer. This dispersion was added to distilled water or sodium citrate solution to precipitate chitosan on drug[7].

Liquid-Assisted Grinding

Liquid-assisted grinding involves the grinding of the API and the coformer together, along with the addition of a minute quantity of solvent (typically a few tenths of one equivalent of solvent per mole of starting materials). The solvent acts as a catalyst but is not involved in the end product. The advantages are higher rate of formation of cocrystal, higher yield, and precise control over the transformation of API into its polymorphs, better product crystalinity, and applicability to a variety of co-crystal formers. The method enhances the selectivity of the cocrystallization. This method avoids excessive use of solvent and is regarded as a "green" process[6].

Super Critical Fluid Method(SCF)

Super critical fluid is fluid which exists as single fluid above its critical temperature and pressure.SCF shows the properties of both a liquid and a gas above its critical condition. It is safe, environmentally friendly, and economical. The low operating conditions (temperature and pressure) make SCFs attractive for pharmaceutical research. At near-critical temperatures, SCFs are high compressible, allowing moderate changes in pressure to greatly alter the density and mass transport characteristics of a fluid that largely determine its solvent power [19] Once the drug particles are solubilised within SCF, they may be re-crystallized at greatly reduced particle sizes. Carbon dioxide is the most commonly used SCF because it is chemically inert, non toxic and non flammable. Other supercritical solvents include nitrous oxide, ethylene, propylene, propane, npentane, ethanol, ammonia, and water[11].

Sonocrystallization Method

The development of sonochemical method for preparation of organic co-crystals of very finite size has been done. This method was primarily developed for preparation of nanocrystals. Caffeine-maleic acid co-crystal preparation commenced with use of ultrasound method. The comparative study of method of preparation of caffeine and theophylline as API and L-tartaric acid as coformer by Solvent drop grinding method and sonochemical method has been commenced. The results of methods were consistent hence sonocrystallization proves to be a significant approach[16].

Hot Melt Extrusion

Extrusion is useful method for synthesis of co-crystals, it involves highly efficient mixing and improved surface contacts, Co-crystals are prepared without use of solvent. The selection of this method primarily depends on thermodynamic stability of compound. This method was studied with the use of four models for co-crystal formation. Solvent drop extrusion technique used to optimize and make the process more flexible. Solvent drop extrusion technique gives an advantage to carry out process at lower temperature. Hot melt extrusion method was used in synthesis of Carbamazepine-nicotinamide co-crystals with polymer as former. Continuous cocrystallization, API and coformer poured in the twin extruder. As a result of continuous addition of mixture the barrel temperature also increases[16].

Slurry Conversion

Drug + Coformer (In a stoichiometric ratio)

Addition of solvent to form slurry

Slurry conversion experiments were conducted in different organic solvents and water. Solvent (100 or 200 ml) was added to the co-crystal (20 mg) and the resulting suspension was stirred at room temperature for some days. After some days, the solvent was decanted and the solid material was dried under a flow of nitrogen for 5 min. The remaining solids were then characterized using PXRD. For eg DWI et al reported synthesis of nicotinamide co-crystal by slurry method. Author mixed both powders of Artesunate and nicotinamide homogeneously in mortar and added water to the mixture to form slurry. Noriyuki et al studied synthesis of corystals of stanolone and mestanolone using slurry crystallization41. Prafulla et al synthesized caffeine/maleic acid co-crystal by ultrasoundassisted slurry co-crystallization techniques. Erizal et al prepared co-crystals of trimethoprim and sulfamethoxazole by slurry technique. Co-crystallization was formed by simply adding water as solvent to mixture of trimethoprim and sulfamethoxazole and developed co-crystals was characterized by thermomicroscopy, scanning electron microscope, powder X-ray diffraction, differential scanning calorimetry. Author also studied effect of temperature on formation of co-crystal and observed that transformation to co-crystalline phase was accelerated by increasing the temperature of storage [13].

Dry or Neat Grinding Method

In the DG method, the solid form of the API and conformer get ground together manually using a mortar and pestle or mechanically by using a ball mill. Brexpiprazole is a drug that lies in BCS Class II. To improve its solubility, the ball milling technique is used and has been found to be one of the convenient methods to prepare co-crystals with conformers, for example, succinic acid and catechol. The main problem lies with the dry grinding method, that is, one cannot ensure the formation of a stoichiometry mixing of co-crystals, which requires further an additional step to get a pure co-crystal product[5,30].

VII.MISCELLANEOUS CO-CRYSTAL PREPARATION

Laser Irradiation

This method consists of using a high-power CO2 laser to irradiate powder blends of co-crystal formers and induce their recrystallization to a co-crystal structure. Titapiwatanakun et al. have used this method to produce caffeine co-crystals with oxalic acid and malonic acid. Interestingly, these authors have found that the co-crystal formers need to sublime to a considerable extent for the co-crystallization to take place, which indicated that the mechanism of the molecular rearrangement between API and coformer molecules and the nucleation of the cocrystal is likely to take place in the vapor phase[15].

Resonant Acoustic Mixing

Resonant acoustic mixing has been used to mix the target molecule and coformer in the presence of a liquid to form a co-crystal in the absence of any grinding media. In this method, mechanical energy is transferred acoustically into a wetted powder mixture, encouraging intimate mixing of the components. A range of carbamazepine co-crystals were successfully produced using a labRAM resonant acoustic mixer operating at 80−100G and 60 Hz. The co-crystal products were isolated at a range of laboratory scales, 100 mg and 1.5 and 22 g, and the technology appeared amenable to scale-up[15].

Freeze-Drying

Freeze-drying, technically known as lyophilization, has been mostly used as a processing technique to preserve a wide variety of products, which include food and pharmaceuticals. This process works by freezing the material and then reducing the surrounding pressure to allow the frozen water in the material to sublime directly from the solid phase to the gas phase. It has also has been demonstrated recently to be a feasible method for the preparation of new solid forms of co-crystal systems[15].

Electrospray Technology

Electrospraying is a process of simultaneous droplet generation and charging by means of an electric field. In this process, a solution containing the dissolved substances flows out from a capillary nozzle, which is maintained at high potential, through an electric field, which causes elongation of the solution droplets to form a jet. The solution jet is dried and the generated particles are collected on a charged powder collector[15].

Microfluidic And Jet Dispensing Approaches

Micro fluidics is a versatile technology that allows assays to be conducted at very high throughput by running thousands of samples per second and controlling fluids in networks of micrometre – sized channels. According to this platform saturated solutions of parent compounds and coformers were dissolved in various solvents at very small quantities for a single chip through combinatorial mixing. By applying a two-phase screening process caffeine was processed with a wide range of co formers and various solvents to identify combinations with the highest propensity for Co-crystals. The parent compound (caffeine) was introduced in the chips vertically while the co formers horizontally. The results proved that Co-crystals screening using microfluidic chips is reliable and reproducible[15].

Spray Drying

Spray drying is a continuous single-step method of transformation of liquids (solutions, suspensions, slurries) to solid powders. It is advantageous due to its continuous, highly controllable, and fast process. Although spray drying has been widely used in formulating amorphous solid dispersions because of the fast solidification process, it has also been employed in synthesis of co-crystals. Alhalaweh and Velaga spray dried several combinations of API-coformer with the aim of co-crystallization. They claim that co-crystallization has been observed in highly supersaturated regions of the drug due to the rapid solvent evaporation, presence of the coformer, or interaction between the drug and coformer in liquid form. Another application of spray drying to generate pharmaceutical cocrystals was done to prepare the carbamazepine−nicotinamide co-crystal (CNC; 1:1). Also, it was proved that TPD can be used for the formation of co-crystals by industrially feasible spray drying methods[15].

VIII.APPLICATION OF CO-CRYSTALLIZATION TECHNIQUES IN THE PHARMACEUTICAL INDUSTRY

To harness the ability of co-crystals for the production of improved drug forms, we need to optimize/develop cocrystallization techniques for industrial purposes. Industrial production of co-crystals requires scalable, robust, and environmentally friendly co-crystallization techniques. The quality of the product should not be compromised by largescale production. API-conformer lability, solubility and stability of components, vulnerability to form polymorphs, amorphous states or solvates of components are the criteria for the selection of the co-crystallization technique. The purity, morphology, and particle size distribution of co-crystals are greatly influenced by the choice of the co-crystallization technique. Despite a large number of reported co-crystallization techniques, very few methods are scalable. Spray drying, spray congealing, and HME are some of the scalable co-crystallization techniques. Fruitful application of these co-crystallization techniques in industrial setup requires an indepth understanding of the theory of the technique, process parameters that need to be controlled to get a high yield and good quality product, and the effect of other excipients on the co-crystal composition during manufacturing[5]. Recently multi-drug co-crystal(MDC) is also gaining attraction among pharmaceutical scientists[19]. Co-crystals also used for the in process separation and purification of the API. Rajput et al investigated on various new solid forms of etravirine (anti-HIV drug) and found improved solubility and stability of etravirine co-crystals when compared to salts.

It was concluded that the co-crystals approach is a better option for improving the solubility of API compared to salt formation. Nutraceuticals, which are having good health benefits can also be used as coformers for bettercombined health benefits along with the API. By using the coformers such as saccharin sodium, the bitter taste of the API can be modified thereby co-crystallization technique can be utilized in case of fast dissolving tablets. Though there are plenty of co-crystals available in the literature, some of the reported co-crystals are presented, based on the method of preparation[29,19,31].

IX.CONCLUSION

Co-crystals are an excellent alternative for drug development to enhance solubility, bioavailability, stability and processability. However, there are several challenges including co former selection, physicochemical characterization and formulation. Careful drug conformer screening and formulation design can lead to successful Cocrystals development. In this review,we discussed in detail a wide range of technologies applied for experimental screening, synthesis and manufacturing of pharmaceutical co-crystals in order to overcome poor physical properties of APIs. This review insight is given on the proposed mechanisms of co-crystallization in different techniques. On early development, co-crystallization processes mainly focus on traditional methods, such as solvent evaporation, grinding, and slurry method. But, as time goes by, the scientist who concern on this field then develop simpler and newer method for co-crystallization processes to overcome previous methods limitation. Novel methods that can be used for co-crystallization are hot-melt extrusion, spray drying, supercritical fluid technology, laser irradiation, freeze drying, microfluidic and jet dispensing etc. Those methods successfully form various kind of pharmaceutical co-crystal. But, every method still needs to investigate thoroughly to understand the clear co-crystallization mechanism for each method.

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