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Review Article

NOVEL APPROACHES IN THE PREPARATION OF SOLID DISPERSION ON SOLUBILITY: A REVIEW

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ABSTARCT

Over the years, a multiplicity of solubilization techniques have been studied and extensively used by many scientists. Estimates up to 40% of novel chemical entities revealed by the pharmaceutical industry today are poorly soluble or lipophilic compounds. The solubility issues complicating the delivery of these new drugs also affect the delivery of many accessible drugs. A variety of techniques are available for enhancement of solubility. Solid dispersion is one of the most hopeful approaches for solubility enhancement. The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous.There are many types of solid dispersions which includes solid solutions, Glass solutions,Simple eutectic mixtures, amorphous precipitation in a crystalline carrier and according to the way in which the solvate molecules are distributed in the solvendum.Different methods are also been used for preparation of solid dispersions such as Solvent method, Melting solvent method (melt evaporation),Melting method, Melt extrusion method, Lyophilisation Technique, Melt Agglomeration Process, the use of surfactant, electrospinning and super critical fluid (SCF) Technology. This review also focused some of the novel techniques used in solid dispersion techniques.

Keywords: Solubility enhancement, Solid dispersions, Poorly soluble drugs.

INTRODUCTION

A solid dispersion can be defined as "the dispersion of one or more active ingredients in an inert carrier matrix in solid-state prepared by a melting (fusion), solvent, or melting-solvent method. Aqueous solubility of any therapeutically active pharmaceutical ingredient is a vital property, which plays major role in dissolution, absorption, and bioavailability. To improve the dissolution and bioavailability of poorly water-soluble drugs, researchers have employed various techniques such as micronization, solubilisation, salt formation, complexation with polymers, changing in physical forms (amorphous), use of prodrugs and drug derivatization, pH alteration and addition of surfactants. Some studies used the solid-dispersion technique for dissolution enhancement of poorly water-soluble drugs. Among the various approaches, the solid-dispersion technique has often proved to be the most successful in improving the dissolution and bioavailability of poorly soluble, active pharmaceutical ingredients because it is simple, economical, and advantageous. The first drug whose rate and extent of absorption was significantly enhanced using the solid dispersion technique was sulfathiazole [1].

Solid dispersions are new approaches and technologies in oral drug delivery controlled release and immediate release society. The common terminology of solid dispersions is solid solutions, eutectic mixtures, amorphous formulations, physical mixtures of microcrystalline drug dispersed in carriers. The solid dispersion isphysically stabilized and high energy state products. There are number of products were marketed which are formulated using solid dispersion technology.

Approximately 40-70% of new drug candidates display poor oral absorption characteristics, due to poor solubility which tends to delay in development / failure of drug approval for the oral dosage form. Such drug candidates are therefore unlikely to be successfully formulated as an oral dosage forms using conventional drug delivery technology. This creates need of developing novel and innovative oral drug delivery technologies that can successful delivery the new drugs of the future. This review summarized mainly the different approaches used in the solid dispersion techniques. Summarizes the marketed product available which are made by using solid dispersion techniques. Moreover, this review article mainly emphasis on novel polymers / carriers used to enhance the dissolution of poorly soluble drugs which leads to bioavailability enhancements.

Solid Dispersion Based Marketed Products

A variety of solid dispersion based products [2] are marketed are listed below.

Product	Company	Year Approved	Technology
GrisPEG	Pedinal Pharm 1975 Inc.	1975	Melt process; exact process unknown
Cesamet	Eli Lilly	1985	Process Unknown
Sporanox	J&J	1996	Spray dry onto substrate
Rezulin	Pfizer	1997	Extrusion
Kaletra	Abbott	2005 (sNDA)	Extrusion
Torcetrapib	Pfizer	Ph III	Spray Drying
Ibuprofen	Soliqs	--	Melt-extrusion
Isoptin SRE-240 (Verapamil)	Soliqs	--	Melt-extrusion
LCP-Tacro(Tracrolimus)	LifeCycle Pharma	--	Melt-granulation
Intelence (Etravirine)	Tibotec	--	Spray drying
Certican (Everolimus)	Novartis	--	Melt or Spray drying
Afeditab(Nifedipine)	Élan Corp.	--	Melt/absorb on carrier

Advantages of Solid Dispersions

There are various reasons for the improvement of solubility of poorly water-soluble drug using solid dispersion technology. The reasons for solid dispersion or advantages [3-4] of solid dispersions are as follows

- Particles with reduced particle size
- Particles with improved wettability
- Particles with higher porosity
- Drugs in amorphous state

Different Methods Used for the Preparation of Solid Dispersions

1. Hot melt Extrusion
2. Spray Drying
3. Surface Solid Dispersion Technology
4. Solvent Evaporation Method
5. Lyophilisation (freeze drying)
6. Electrostatic Spinning Method
7. Supercritical Fluid Technology

Hot Melt Extrusion

In this process either drug solubilised in polymer, drug particles dispersed in polymers or drug-excipients mixture granules or paste prepared then extruded into a polymeric film, injection moulding, cylinders/strands are prepared. The polymeric films are used to prepare fast dissolving strips and transdermal patches. The injection moulded, cylinders/strands are used to prepare tablets dosage forms, capsules and performance capsules and other dosage forms like ocular, sub-cutaneous inserts, biomedical devices and implants.

Spray Drying

Spray drying method consists of dissolving or suspending the drug and polymer in a common solvent or solvent mixture and then drying it into a stream of heated air flow to remove the solvent. Due to the large surface area of the droplets, the solvent rapidly evaporates and solid dispersion is formed within seconds, which may be fast enough to phase separation. Spray drying usually yields drugs in the amorphous state, but sometimes the drug may be partially crystallized during processing

Surface Solid Dispersion Technology

The technique involves deposition of the drug on the surface of certain materials that can alter the dissolution characteristics of the drug. Deposition of drug on the surface of an inert carrier leads to a reduction in the particle size of the drug, thereby providing a faster dissolution rate. Various hydrophilic materials with high surface area can be utilized for deposition of the drug on their surfaces. Surface modification and solid-dispersion formulations using hydrophilic excipients can significantly alter the dissolution behaviour of hydrophobic drug materials. Two techniques are used to prepare surface solid dispersion such as co-evaporation and co-grinding. In co-evaporation method drug is dissolved in a minimum amount of ethanol in which hydrophilic carrier was suspended. The suspension was continuously stirred at 100 rpm using an electronic stirrer at room temperature until all the solvent evaporated. Physical mixtures were formulated by mixing drug and carrier in geometric proportions using a mixer without applying pressure.

Solvent Evaporation Method

Drug and carrier were dissolved in a common solvent (chloroform) and solvent wasevaporated to form the solid mass. Basically, this solvent evaporation method involves two steps and these are: (i) preparation of a solution containing both matrix material or carrier and drug and (ii) the removal of the solvent resulting in the formation of the solid mass.

Electrostatic Spinning Method

Electrostatic spinning method involves the introduction of a liquid into an electric field whereby the liquid is caused to produce fibres. After being drawn from the liquid the fibres harden, which may involve mere cooling, chemical hardening or evaporation of solvent, and then hardened fibres may be collected upon a suitably charged surface.

Supercritical Fluid Technology

Supercritical fluid (SCF) technology offers tremendous potential and the low operating conditions (temperature and pressure) make the method more attractive for pharmaceutical research.This technique consists of dissolving the drug and the inert carrier in a common solvent that is introduced into a particle formation vessel through a nozzle, simultaneously with CO_2. When the solution is sprayed, the solvent is rapidly extracted by the SCF, resulting in the precipitation of solid dispersion particles on the walls and bottom of the vessel.

Merit and Demerits of Different Solid Dispersion Techniques

Methods	Advantages	Disadvantages
Fusion	Short time process Solvent free	Not suitable for thermally labile drugs
Hot melt extrusion	Solvent free Good controlled temperature system Large scale production available	Not suitable for thermally labile drugs Carriers without proper thermoplastic properties cannot be used
Spray drying	Short time process Micro- to nano-particulates obtained Robust process Large scale production available	Possible solvent residue in the product
Freeze drying	Robust process Large scale production available Mild production condition	Possible solvent residue in the product Time consuming High cost
Supercritical fluid drying (as anitsolvent)	Mild production condition	Possible solvent residue in the product Solubilizing power of supercritical fluid (CO_2) limited

Classification of Excipients used in Preparation of Solid Dispersions

First generation carriers

Urea, sugars, organic acidspolyurethane fibre, acetamide, nicotinamide, nicotinic acid ascorbic acid, succinimide [5-6].

Second generation carriers

Povidone (PVP),Polyvinylpyrolidone (PVP)/polyvinyl acetate, polyethyleneglycols (PEG) and polymethacrylates (Eudragits). HPMC, acetate, succinate, hydroxypropylmethylcellulose (HPMC),ethylcellulose or hydroxypropylcellulose, cyclodextrins and dextran.

Third generation carriers

Poloxamer 408, Tween 80, and Gelucire 44/1411 Labrasol, Inutec SP1, Myrj 52

Characterization of Solid Dispersion

Drug-carrier miscibility

- Hot stage microscopy
- Differential scanning calorimetry (DSC)
- Powder X-ray diffraction(XRD)
- NMR 1H Spin lattice relaxation time

Drug carrier interactions

- FT-IR spectroscopy
- Raman spectroscopy
- Solid state NMR

Amorphous content

- Polarised light optical microscopy
- Hot stage microscopy
- Humidity stage microscopy
- DSC (MTDSC)
- ITC
- Powder X-ray diffraction

Stability

- Humidity studies
- Isothermal calorimetry
- DSC (Tg, temperature recrystallization)
- Dynamic vapour sorption
- Saturated solubility studies

Dissolution enhancement

- Dissolution
- Intrinsic dissolution
- Dynamic solubility
- Dissolution in bio-relevant media

Novel techniques / carriers in solid dispersion

Use of inutec SP1 as a new carrier in the formulation ofsolid dispersions for poorly soluble drugs [7].The dissolution properties of the solid dispersions were significantly improved in comparison to pure itraconazole (glassy or crystalline) or physical mixtures with Inutec SP1. This study proves the potential of the new polymeric surfactant as a carrier in the formulation of solid dispersions for poorly soluble drugs.

Daemd et al [8] investigated the performance of three new solid dispersion formulations of itraconazole in human volunteers in comparison with Sporanox, the marketed form. Solid dispersions made up of itraconazole (40%, w/w) and HPMC 2910, Eudragit E100 or a mixture of Eudragit E100-PVPVA64 were manufactured by hot-stage extrusion and filled in gelatin capsules. The mean bioavailability of itraconazole was comparable after administration of the HPMC solid dispersion, compared to Sporanox, while it was lower after administration of the Eudragit E100 or Eudragit E100-PVPVA64 dispersions.

Law et al [9] evaluated the use of phosphatidylcholine as carrier for solid dispersion. The in vitro dissolution and in vivo absorption of solid dispersions of nifedipine-polyethylene glycol (nifedipine-PEG) and nifedipine-phosphatidylcholine-polyethylene glycol (nifedipine-PC-PEG) were investigated. The incorporation of 5% PC into the nifedipine-PEG solid dispersion demonstrated no change in the solid-state characteristics of nifedipine as in the nifedipine-PEG solid dispersion. The dissolution of nifedipine from the solid dispersions was markedly enhanced as compared with the pure drug. The incorporation of PC into the nifedipine-PEG solid dispersion resulted in a 2.6 and 2.2 fold increase in nifedipine initial dissolution rate and dissolution after 60 minutes respectively. This was attributed to the formation of lipid vesicles which entrapped a certain concentration of nifedipine during dissolution. The area under the curve after oral administration of the nifedipine-PC-PEG solid dispersion was 3.4 fold greater than that of the nifedipine-PEG solid dispersion.

Johan unga et al [10] studied the crystallisation of polymer when incorporating the lipid along Polyethylene glycol. The lipids were melted with PEG 4000 and the crystallisation of the polymer studied with differential scanning calorimetry (DSC) and small angle X-ray diffraction (SAXD). PEG 4000 can crystallise into lamellar structures with either folded or fully extended polymer chains. All lipids increased the fraction of the folded form and lowered the crystallisation temperatures. Some lipids were incorporated to a high extent into the amorphous domains of the PEG lamellae and thereby swelling the structure, which also resulted in a high degree of chain folding. Partial least squares (PLS) modelling indicated that small hydrophilic lipids increased the folding of PEG and that large non-polar lipids retarded the unfolding during secondary crystallisation. This work shows that there is a large difference in the behaviour of PEG depending on lipid added. Differences are explained in terms of molecular properties for the lipids, demonstrated by the use of PLS modelling to describe the behaviour of PEG solid dispersions.

Chul soon yong et al[11]developed sibutramine base-loaded solid dispersion with enhanced solubility and bioavailability, various solid dispersions were prepared using a spray drying technique with hydrophilic polymers such as gelatin, HPMC and citric acid. Their solubility, thermal characteristics and crystallinity were investigated. The dissolution and pharmacokinetics of the sibutramine base-loaded solid dispersion were then compared with a sibutramine hydrochloride monohydrate-loaded commercial product (Reductil®). The solid dispersions prepared with gelatin gave higher drug solubility than those prepared without gelatin, irrespective of the amount of polymer. The sibutramine base-loaded solid dispersions containing hydrophilic polymer and citric acid showed higher drug solubility compared to sibutramine base and sibutramine hydrochloride monohydrate. Among the formulations tested, the solid dispersion composed of sibutramine base/gelatin/HPMC/citric acid at the weight ratio of 1/0.8/0.2/0.5 gave the highest solubility of 5.03 ± 0.24 mg/ml. Our DSC and powder X-ray diffraction results showed that the drug was present in an altered amorphous form in this solid dispersion. Thus, the sibutramine base-loaded solid dispersion prepared with gelatin, HPMC and citric acid is a promising candidate for improving the solubility and bioavailability of the poorly water-soluble sibutramine base.

Vasavada et al[12]the aqueous solubility and dissolution of famotidine from solid glass dispersions of xylitol, prepared by the fusion method, were investigated. Both famotidine and xylitol exhibited minimal degradation during the fusion process. Famotidine alone and in the presence of xylitol was found to be relatively stable in water at 37 ± 0.5°C for at least 3 days, less than 4% degradation was observed at the end of 72 h. Solubility of famotidine from solid glass dispersions and physical mixtures containing varying proportions of famotidine and xylitol at 37 ± 0.5°C was found to be higher than that of famotidine alone in water. However, the solid glass dispersions were more effective in enhancing the solubility of famotidine. A 1:40 famotidine:xylitol dispersion produced greatest solubility enhancement (31%). The solubility of famotidine from physical mixtures increased linearly with the increase in xylitol concentration, but the relationship was not linear for glass dispersions. Dissolution studies on glass dispersions with famotidine: xylitol ratios of 1:1, 1:10 and 1:20 in water at 37 ± 0.5°C revealed a marked increase in the dissolution rate of famotidine from solid glass dispersions when compared to

the dissolution rate of famotidine powder alone. The increase in the dissolution rate was greatest at the lowest drug level (1:20) with 100% of the drug dissolving within one minute. Thermograms of the solid glass dispersions obtained by differential scanning calorimetry showed no evidence of chemical interaction between famotidine and xylitol. The phase diagram of the dispersion system by the capillary tube method suggested the formation of a eutectic mixture of famotidine and xylitol at a drug: carrier ratio approaching 1:40.

Piroska Szabo-Revesza et al[13]investigated the applicability of sucrose laurate as surfactant in solid dispersions. Although this surfactant has a US Drug Master File, it has not been used so far in internal pharmaceutical products. High drug-loaded solid dispersion systems consisting of gemfibrozil as a model drug and PEG 6000 as a carrier, with or without sucrose laurate (D1216), were prepared by the melting method. Cytotoxicity studies on Caco-2 monolayer cells were also performed, in order to gain information on the applicability of D1216 in oral formulations. The results showed that the presence of the surface-active agent did not affect the solid-state characteristics of the model drug significantly. A markedly improved dissolution of gemfibrozil from the ternary soliddispersion systems was observed as compared with the binary soliddispersion systems. The optimum concentration range of the D1216 in the formulations was determined to be 5–10%. The effective final concentrations of D1216 in the dissolution experiments proved to be non-toxic towards CaCo-2 cells. The results suggest the potential use of D1216 in innovative internal pharmaceutical formulations.

Mariarosa Moneghinia et al[14]used the microwaves irradiation for the preparation of solvent-free soliddispersions. In particular, the microwave technology has been considered in order to prepare an enhanced release dosage form for the poorly soluble drug Ibuprofen (IBU), employing PVP/VA 60/40 (PVP/VA 64) and hydroxypropyl-β-cyclodextrin (HP-β-CD) as hydrophilic carriers. Their physico-chemical characteristics and dissolution properties were compared to the corresponding physical mixtures and the drug alone. The results of physico-chemical characterization attested a correspondence of the solid state of the drug before and after irradiation treatment and that an amorphous form of the drug was obtained. This result, together with the presence of the hydrophilic polymers determined a remarkable enhancement of the in vitro dissolution rate of the drug suggesting that the microwave technique could be considered as a new and interesting method to prepare drug–polymer systems.

Guyn van den Mooter et al [15] characterized the solid state properties of ternary solid dispersions made up of PVP VA64, Myrj 52 and itraconazole. The solid dispersions were prepared by dissolving the materials in methylene chloride, followed by evaporation under reduced pressure of the solvent at 55 °C in a rotovapor. Binary and ternary solid dispersions were characterized by standard and modulated temperature differential scanning calorimetry and X-ray powder diffraction. Although PVP VA64 and itraconazole were found to be completely miscible in the solid state, addition of a small amount of Myrj 52 to the drug–polymer system leads to separation of itraconazole thus demonstrating that Myrj 52 expels the drug from the polymer phase.

Odon planinsek et al [16] prepared solid dispersion using porous SiO2 (Sylysia) with carvedilol from acetone solution was used to improve dissolution of this poorly water-soluble drug. Solvent evaporation in a vacuum evaporator and adsorption from acetone solution were the methods used to load various amounts of carvedilol into the Sylysia pores. The impregnated carriers were characterized using nitrogen-adsorption experiments, X-ray diffraction, wettability measurements, attenuated total reflectance FTIR spectroscopy and thermal analysis. The impregnation procedures resulted in a significant improvement of drug release compared to dissolution of pure carvedilol or its physical mixtures with Sylysia. The results showed that when the drug precipitated in a thin layer within the carrier the dispersion retained a high specific surface area, micropore volume, and drug-release rate from the solid dispersion. Increasing the amount of drug in the solid dispersion caused particle precipitation within the pores that decreased the carrier's specific surface area and pore volume and decreased the release rate of the drug.

Marasini et al [17] prepared solid dispersions of poorly water-soluble ionizable drug Telmesartan were prepared at different drug-to-carrier ratios by the spray-drying technique, and were characterized by dissolution and aqueous solubility studies. The optimum formulation was investigated by dissolution studies at different pH and water media The optimum formulation of pH(M)-SD consisted of TMS/PVP (Polyvinylpyrolidone) K30/Na(2)CO(3) at a weight ratio of 2/0.5/3 and showed significant improvement in the aqueous solubility and dissolution rate by approximately 40,000- and 3-fold, respectively, compared to TMS powder. Furthermore, area under the drug concentration time-curve (AUC) of TMS from the pH(M)-SD increased by 13.4- and 2.1-fold, compared with TMS powder and commercial product, respectively. According to these observations, taken together with dissolution and pharmacokinetic behaviours, pH-modulated SD in the presence of an alkalizer for a poorly water-soluble ionizable drug, TMS, appeared to be efficacious for enhancing its bioavailability.

Wolska et al [18] prepared solid lipid microspheres (SLM) with incorporated Cyclosporine A (Cs), suitable for ocular application. For this purpose, SLM were formulated by using different lipids and three different nonionic surfactants. The SLM were produced using a hot emulsification method. The SLM dispersions contained 10, 20 or 30% of lipid (w/w) and up to 2% (w/w) of Cs. The size of the microspheres with Cs ranged from 1 to 15μm. Physically stable SLM with Cs were prepared using Compritol, as a lipid matrix, and Tween 80, as a surfactant. In contrast, dispersion with Precirol alone, formed semi-solid gels during storage, while in formulations with Precirol and Miglyol, crystals of Cs were observed. In vitro release profile of Compritol formulations showed that 40% of Cs is released within 1h, while the release of the following 40% takes more time, depending on lipid content in the formulations. The large part of Cs, added to SLM formulations (from 45 to 80%), was found on the surface of microparticles, but no drug crystallization occurred during a long-term storage.

Hegge et al [19] curcumin is under investigation as a potential photosensitizer (PS) in antimicrobial photodynamic therapy (aPDT). The therapeutic potential of curcumin as a PS is limited by its low aqueous solubility, susceptibility to hydrolytic and photolytic degradation, and limited phototoxicity toward Gram negative (G-) bacteria. Supersaturated solutions of curcumin have demonstrated high phototoxicity toward several species of Gram positive (G+) bacteria as well as the G-Escherichia (E) coli. Thus, solid dispersions that can form supersaturated solutions of curcumin upon hydration may be beneficial in aPDT. In the present study, solid dispersions of curcumin have been prepared through lyophilization of concentrated solutions obtained from dissolution of hydroxypropyl-β-cyclodextrin (HPβCD)-curcumin co-precipitates. Hydroxypropyl methylcellulose (HPMC) was added to curcumin solutions prior to lyophilization. The resulting lyophilizates were porous, amorphous and hydrated and dissolved rapidly in contact with a model physiological salt solution. The detected drug load of the lyophilizates was in the range 0.5-1.0% (w/w) and was dependent on the selected ratio between HPβCD and curcumin in the co-precipitate. The lyophilizate with the highest drug load could easily be dissolved in aqueous medium to form curcumin solutions of relevant concentrations for aPDT (i.e., 10μM). Selected solutions of the curcumin solid dispersions showed a pronounced decrease in curcumin concentration up to 90% after storage for 168h, which indicated that supersaturated curcumin solutions were initially formed upon dissolution of the lyophilizates. Both freshly prepared and 2days old solutions of one selected curcumin lyophilizate induced significant inactivation of E. coli (~1% bacterial survival) after exposure to a light dose of only 5J/cm(2).

Aejaz et al[20] prepared ternary solid dispersion using PVP-SLS-Meloxicam and the solid dispersion is evaluated for in-vitro and in-vivo. The study showed that increase in dissolution rate of meloxicam and increased anti-inflammatory efficacy. This increased dissolution is due to the increase in wettability and hydrophilic nature of carrier.

Amir et al[21]prepared the solid dispersion of Meloxicam by Dropping Method to Improve the Rate of Dissolution. Meloxicam/polyethylene glycol, formulated by dropping method. The dissolution was performed and compared with physical mixtures and tablets of ME–PEG 4000 (1:3 ratio). The results indicated that the round particles (solid drops) exhibited a higher dissolution rate than physical mixture and pure drug. X-ray powder diffractometry (XRPD) data was interpreted by using Self-modeling curve resolution (SMCR) as a chemometric method. The results indicated the presence of a new crystalline phase in the solid dispersion, which can help the fast and quantitative dissolution from the solid drops. The round particles can be adapted to individual therapy by using a distributor.

In Hwan Beaka et al [22] compared the ability of dutasteride amorphous solid dispersions to form supersaturated solution. Solid dispersion was manufactured by spray-drying processes, and identified the effects of supersaturation on increasing the bioavailability of dutasteride.

The excipients used for solid dispersion is Eudragit E, hydroxypropyl-β-cyclodextrin (HP-β-CD), hydroxypropyl cellulose, (HPC), hydroxypropylmethyl cellulose (HPMC), and Polyvinylpyrolidone (PVP K30). A solid dispersionwith Eudragit E displayed a high maximum supersaturation with extended supersaturation, compared with a water-soluble polymer.

Teresa et al [23] prepared the solid dispersions of Flunarizine using povidone. The solubility study shows that the solid dispersion showed higher solubility than the physical mixture.

CONCLUSION

Since the concept of solid dispersion technology was introduced in 1960s, great progresses have been made in solid dispersion technology as solid dispersion offers a variety of opportunities. A single solid dispersion method cannot be universally accepted for a variety of drug materials. In developing a new solid dispersion system for a given drug, it is important to understand the physicochemical properties of the drug and carrier that best match the properties and find a solid dispersion method. The preparation method and the amount of the carrier also play a vital role in the enhancement of drug dissolution rate. Most of the solid dispersion work is in lab-scale setups; therefore the manufacturing process requires enough knowledge to scale up to the commercial scale and sufficient study requires on stability of solid dispersions.

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