Advance Journal of Pharmaceutical Research & Review
Volume 1, Issue 3, September 2024, PP: 64-69, ISSN No: 3048-491X

Solid Dispersion Technique-A Prominent Technology for Solubility Enhancement-A Review

Dr.Christopher Vimalson.D*, Dr.Alagarraja.M, Mr.Naveen Yadhav.J.K, Abrar Ahamed. M, Devippriya.M, Krishnakanth.R, Mohamed Kani.Y, Nivetha.A
United College of Pharmacy, Periyanaickenpalayam, Coimbatore - 641020.
Affiliated to the Tamilnadu Dr MGR Medical University, Chennai

ABSTRACT:
Due to its simplicity and ease of consumption, the oral route of drug administration is the most popular and favoured way of delivery; yet, it might provide challenges if the medication has poor membrane penetrability or is poorly soluble. The majority of medications are taken orally—nearly 90%. The solubility of a drug molecule in an aqueous media plays a major role in the pharmacokinetic profile and sufficient and consistent bioavailability of pharmacological compounds taken orally. The therapeutic efficacy of a medication is determined by its bioavailability and, eventually, its solubility. Non-optimal biopharmaceutical properties account for almost 40% of novel candidates that enter the drug development pipeline and ultimately fail. A number of factors can limit the amount of drug absorbed from the gastrointestinal system, but the two most important ones are inadequate membrane permeability and poor water solubility.

Keywords: Bioavailability, Solubility, Solid Dispersion, and Rate of Dissolution

I. Introduction:

Due to its simplicity and ease of consumption, the oral route of drug administration is the most popular and favoured way of delivery; yet, it might provide challenges if the medication has poor membrane penetrability or is poorly soluble. The majority of medications are taken orally—nearly 90%.Drug absorption sufficient and reproducible bioavailability, pharmacokinetic profile of orally administered drug substances is highly dependent on solubility of that compound in aqueous medium.[1]

One crucial factor in achieving the appropriate drug concentration in the systemic circulation and demonstrating a pharmacological response is solubility.More than 40% of new candidates entering drug development pipeline fail because of non-optimal biopharmaceutical properties. Biopharmaceutical characteristics have undergone a noticeable change as a result of the application of drug discovery techniques over time.Poorly water-soluble drugs involve many difficulties in the development of pharmaceutical dosage forms for oral delivery systems due to their low bio-availability.[2]

A number of characteristics, the most important of which are the drug's poor water solubility and poor membrane permeability, can impede the absorption of the drug from the gastrointestinal tract. An oral active drug cannot cross the GI tract membranes and enter the systemic circulation until it has dissolved in the stomach and/or intestinal fluids. Therefore, increasing solubility and increasing oral bioavailability of active drugs are the two main goals of pharmaceutical researchand dissolution rate of poorly water-soluble drugs and enhancing permeability of poorly water soluble drugs.[3]

A class of dosage forms known as "solid dispersions" are those in which the medication is dissolved in a matrix that is biologically inert, typically with the intention of enhancing oral bioavailability. More specifically, Chiou and Riegelman defined these systems as „the dispersion of one or more active ingredients in an inert carrier matrix at solid-state prepared by the melting (fusion), solvent or melting- solvent method", while Corrigan suggested the definition as being a „product formed by converting a fluid drugcarrier combination to the solid stateThese dosage forms have historically been thought of as being interchangeable with methods that improve the drug's in vitro release over regular dosage forms.[4]

Solid Dispersion:

Solid dispersions are collections of solid products consisting of two or more different components, often a hydrophilic matrix and a hydrophobic medication.There are two types of matrix: crystalline and amorphous. The medication may be distributed as crystalline, amorphous, or molecular particles (clusters).[5]

Advantages of Solid Dispersion:

In order to increase the solubility of pharmacologically active components in a carrier or matrix in the solid state, solid dispersions are produced using distinct technical proceduresand increase the rate of dissolution, which, in turn, modulates the therapeutic action due to increased bioavailability.They have also been used to increase

the chemical stability of drugs in solution or suspension.Crystalline carriers were used to prepare SD's first generation. These carriers include sugars and urea, which do not release the medication at the desired rate because to their disadvantage of crystal formation in SD while being thermodynamically more stable. Solid dispersions are a useful formulation tool for novel chemical entities with very poor aqueous solubility, as they can help with preclinical safety and early clinical trials. It provides a means to rapidly assess the safety and efficacy profile of the drug substance that may be otherwise difficult to obtain.[6]

Disadvantages of Solid Dispersion:

Furthermore, the majority of polymers employed in solid dispersions have the ability to absorb moisture, which can cause phase separation, crystal development, or other changes during storage, such as amorphous to crystalline state conversion or metastable crystalline form conversion to a more stable structure. This may result in decreased solubility and dissolution rate.demerits of solid dispersions is their poor scale-up for the purposes of manufacturing.[7]

Biopharmaceutical Classification System (BCS):

Screening investigations of novel chemical entities and formulation design and development often face the difficulty of solubilising poorly soluble medicines. It is possible to modify several approaches in order to enhance the solubilisation of poorly soluble drugs and thereby increase their bioavailability. medications taken orally only fully absorb when they have reasonable solubility in the stomach medium and such medications demonstrate goodbioavailability.Bioavailability depends on several factors, drug solubility in an aqueous environment and drug permeability through lipophillic membranes being the important ones.[8]
There are four classes into which all medications have been placed:
class I is highly soluble and highly permeable,
class II isvery porous and poorly soluble,

class III: very permeable and low solubility,

class IV :Low soluble and low permeable class.

Insufficient bioavailability is frequently caused by poorly water soluble medicines' weak solubility and slow rate of dissolution in aqueous gastrointestinal fluids.In particular, class II (high permeability and low solubility)substances according to the BCS, the bioavailabilitymay be enhanced by increasing the solubility and dissolution rate of the drug in the gastrointestinal fluids. This could be accomplished, according the Noyes and Whitney equation, by increasing the drug's surface area that is accessible to the dissolving liquid and improving its solubility. In addition to increasing wettability or micronising medicinal ingredients to improve surface area and substituting amorphous material for crystalline medicines to promote solubility, using solid dispersion is a way to influence both surface area and solubility.The dispersivity of the drug in the carrier ranges beginning from a suspension of course drug particles to a suspension of fine drug particles and finally to a drug when a single medication molecule is distributed throughout the carrier substance. The drug surface area that is exposed to the dissolving solvent rises in the same order as the particle size decreases, as previously noted.Additionally, the soluble nature of thedrug in the dissolution medium is influenced by the interaction of one drug molecule with the surrounding molecules.[9]

Carriers for solid dispersion:
a) Three types of acids: citric, tartaric, and succinic.
b) Sugars – Dextrose, sucrose, sorbitol, Maltose, Galactose, Xylitol.
c) Polymeric materials – Polyvinylpyrollidone, PEG 4000, PEG 6000, HPMC, CMC, Guar gum, Xanthum gum, Sodium alginate, Cyclodextrin.
d) Surfactants – Poloxamer, Tween, Span, Gelucire 44/14, Deoxycholic acid, Polyoxyethelene stearate, Vitamin E
e) Miscellaneous - Urea, Urethane, Hydroxyalkyl xanthenes, Pentaerythritol.[10]

Ideal properties of carrier:
The aspects of the drug's dissolution that are disseminated are largely determined by the carrier's qualities. For a carrier to be appropriate for raising the dissolution rate, it must satisfy the following requirements.
a)It should have inherent fast dissolving qualities and be freely soluble in water.
b) It should be non-toxic and pharmacologically inert.
C)For the melt process, it must have a low melting point and be heat stable.
d) It should be soluble in variety of solvents and pass through a vitreous state upon solvent evaporation for the solvent method.
e) It should be able to preferably, increase the aqueous solubility of the drug.
f) It should be chemically compatible with the drug and should not form a strongly bonded complex with the drug.[11]

Methods of preparation of solid dispersions:
There are several methods used to prepare solid dispersions which have been developed from simple manual procedures to advanced techniques requiring

special equipment to fulfill the needs of modern pharmaceutical industry.
A quick discussion of a few of these diverse approaches is provided below.

1.Co-melting method:

Using this procedure, a physical mixture of a medication and a water-soluble carrier is prepared, and it is then heated until it melts. After that, the molten mixture quickly solidifies in an ice bath while being vigorously stirredThe resulting solid mass was crushed, pulverised, and sieved.The modification in the method can be done by pouring the homogenous melt in the form of a thin layer onto a ferrite plate or a stainless steel plateand cooled by water or air moving across the plate's other side. It is also frequently possible to achieve a super-saturation of a medication or solute in a system by quickly cooling the melt from a high temperature.Under these conditions, the solute molecule in the solvent matrix is stopped in its tracks by the instantaneous solidification process. For basic eutectic mixtures, the quenching method produces a much finer dispersion of crystallites.. Advantage of co-melting method is that it is economic and solvent less process, however thisThe medicine or carrier that is unstable at fusion temperature or evaporates at higher temperatures is not suited for this approach. Some of the means to overcome these problems could be by heating the physical mixture in a sealed container or melting it under vacuum or in presence of inertgassuch as nitrogen to stop the medicine or carrier from oxidatively degrading.[12]

2. Fusion method:

It is a modification of co-melting method. The carrier is placed in a porcelain dish and heated till melting over steam bath.With a glass rod, the precisely weighed quantity of medication is progressively distributed into the molten vehicle.. After complete dispersion of drug within carrier, the dish is removed from steam bath and left aside to cool at room temperature till solidification of its contents.. The resulting solid dispersion is next sieved and ground. This method is useful in reducing thermal decomposition of drugs.[13]

3. Solvent evaporation method:

A common volatile solvent is used to dissolve the medication and carrier, and it is subsequently extracted under vacuum.When a solid dispersion forms, it is crushed and sieved.[14]

4. Kneading technique:

Using this technique, the carrier becomes paste after being soaked in water.The medication is combined and kneaded for a predetermined period of time. After that, the kneaded mixture is dried and, if needed, put through a sieve. Drugs that are thermolabile can be treated with this technique; however, medications that are moisture-sensitive cannot.[15]

5. Co-precipitation method:

The drug is added to the carrier solution in the required amount. The system is shielded from light and maintained under magnetic agitation. After forming a precipitate, it is vacuum-filtered and allowed to dry at room temperature.[16]

6. Co-grinding method:

A blender is used to mix the medicine and carrier physically for a set amount of time at a specific speed. Next, the slurry is poured into a vibrating ball mill's chamber. The mixture of powders is ground up. After that, the product is gathered and stored in a glass vial with a screw top at room temperature until needed.[17]

7. Gel entrapment method:

An organic solvent is used to dissolve hydroxyl propyl methyl cellulose, which is used as a carrier, to create a transparent and clear gel.After a few minutes of sonication, the medication is dissolved in the gel.Under vacuum, organic solvent evaporates.A mortar and pestle are used to grind and filter solid dispersions.[18]

8. Spray drying method:

The drug is dissolved in an appropriate solvent, and water is used to dissolve the necessary quantity of carrier. After combining the solutions using sonication or another appropriate technique, a clear solution is created. This is then spray-dried with a spray dryer to create a solid dispersionin form of fine, free-flowing particles.[19]

9. Electrospinning method:

Solid fibres are created by the electrospinning technique, which involves delivering a melt or polymeric fluid stream via a millimeter-scale nozzle. In this procedure, a conducting capillary connected to a reservoir holding a polymer melt or solution and a conductive collection screen are subjected to a strong electrostatic field. Charge species accumulating on the surface of a pendant drop destabilise the hemispherical shape into a conical shape as the electrostatic field strength increase to a certain value (commonly known as Taylor cone). Beyond the critical value, a charged polymer jet is ejected from the apex of the cone and carried to the collection screen via the electrostatic force.[20]

This method may be used to control the release of biomedicines and prepare nanofibres. This

method is inexpensive and easy to use, thus it can be used in the future to prepare solid dispersions.[21]

10. Freeze-drying method:

This process consists of dissolving the drug and carrier in a common solvent, which is immersed in liquid nitrogen until it is fully frozen. Then, the frozen solution is further lyophilized. Although research concludes that this is a viable and appropriate method for adding medicinal compounds to stabilising matrices, the method is not well utilised for the creation of solid dispersions due to economical reasons. Advantages of freeze drying include that the drug is subjected to minimal thermal stress during the formation of the solid dispersion and the risk of phase separation is minimized.[22-24]

11. Supercritical fluid (SCF) method:

Supercritical fluid methods are mostly applied with carbon dioxide (CO2), which is used as either a solvent for drug and matrix or as an anti-solvent. This technique consists of dissolving the drug and the carrier in a common solvent that is introduced into a particle formation vessel through a nozzle, simultaneously with supercritical CO2 (the gas is heated beyond its critical temperature and pressure). Solid dispersion particles precipitate on the vessel's walls and bottom as a result of the SCF quickly extracting the solvent when the solution is sprayed. Advantages of this technique include reduction of particle size and residual solvent content as well as the high yield.[25-27]

12. Direct capsule filling:

The technique includes direct filling of hard gelatin capsules with the liquid melt of drug and carrier.When it cools to room temperature, the molten dispersion inside the capsule solidifies to create a plug.Benefits include avoiding grinding-induced alterations in the drug's crystallinity, lowering of cross contamination and operator exposure in a dust-free environment, better fill weight and content uniformity.[28]

Analysis of solid dispersions:[29]

Various methods, which can contribute information regarding the physical nature of the solid dispersions includes

1) Thermal analysis (DSC): for the behaviour of mixing and phases
2) IR/Raman/ss- NMR – for interactions study
3) XRD – Identify amorphous arrangement (disordered nanocrystalline or true amorphous)
4) Microscopy

CHARACTERIZATION OF SOLID DISPERSIONS:

In solid dispersions, several drug molecular structures inside the matrix may be encountered. There are numerous methods available for examining the molecular arrangement in solid dispersions. Nonetheless, the majority of work has gone into distinguishing between crystalline and amorphous materials.

Many techniques are available which detect the amount of crystalline material in the dispersion.[30]

Drug -carrier miscibility:

It is carried out by DSC, X-ray diffraction[31] and NMR 1H Spin lattice relaxation time

Drug carrier interactions: It is carried out by FT-IR spectroscopy, Solid state NMR and Raman spectroscopy

Physical Structure:

It characterized by following techniques; Surface area analysis Surface properties Scanning electron microscopy Dynamic vapor sorption Raman microscopy Inverse gas chromatography

Amorphous content:

The DSC, powder X-ray diffraction, polarised light optical microscopy, and hot stage microscopy were used in this investigation.

Dissolution enhancement:[32]

The following parameters were used to assess the solid dispersion's ability to promote solubility:

- Breakdown
- Dissolution from within
- Solubility in motion

Dissolution in mediums that are biorelevant Differential Scanning Calorimetry Modulated by Temperature (TMDSC)

Temperature Modulated Differential Scanning Calorimetry (TMDSC): can be used to assess the degree of mixing of an incorporated drug.[33]

Stability:

Isothermal calorimetry, DSC (Tg, Temperature recrystallization), and saturated solubility tests were used to investigate the stability of the solid dispersion.

Water vapour sorption:

When the hygroscopicity varies, amorphous and crystalline materials can be distinguished using water vapour sorption. Precise information regarding the hygroscopicity of totally crystalline and entirely amorphous samples is needed for this technique.[34]

Isothermal Microcalorimetry:

The crystallization energy of an amorphous material heated above its glass transition temperature (Tg) is measured via isothermal microcalorimetry. There

are certain restrictions with this method. First off, this method can only be used if the physical stability is such that crystallization occurs only during the measurement. Secondly, it is imperative to allow all amorphous material to crystallise.[35]

APPLICATIONS OF SOLID DISPERSION:

There are many more advantages that solid dispersion systems can offer, some of which are listed below::

1) To improve the solubility of medications that are poorly soluble in order to boost the rate of dissolution, absorption, and bioavailability.
2) To prevent hydrolysis, oxidation, recrimination, isomerization, photo-oxidation, and other breakdown processes from occurring to unstable pharmaceuticals.
3) To lessen a drug's adverse effect
4) Disguising a bad drug scent and flavor.
5) Enhancement of medication dissolution from gels and ointments.
6) To keep things from becoming incompatible.
7) To achieve a uniform dispersion of a minimal quantity of medication in a solid condition.
8) To administer gaseous or liquid substances in a dosage that is solid, up to 10%.
9)) To combine a fast-release main dose with a sustained-release dosage form.
10) To provide a sustained release schedule for soluble medications employing insoluble or weakly soluble carriers.
11) To lessen the pre-systemic inactivation of medications such as progesterone and morphine.

II. CONCLUSION:

Enhancing the solubility of medications that are poorly soluble in water is still one of the most difficult areas of drug research. The rate-determining stage in oral medication absorption is solubilization, which might have an impact on the drug's absorption in vivo. Many medications have solubility issues, which affect their absorption and necessitate solubility improvement. One of the most appealing methods for enhancing a drug's poor water solubility is the use of solid dispersions. Solubility augmentation is aided by a variety of solubility enhancers, including water-soluble carriers, co-solvents, surfactants, and superdisintegrants via the solid dispersion approach (fusion method and solvent evaporation method). These greatly contribute to increasing the bioequivalency and bioavailability.

REFERENCE:

[1]. Prasad K , Narayanan N, Rajalaxmi G. Preparation and evaluation of solid dispersion of Terbinafine hydrochloride. International Journal of p‟ceutical sciences Review & Research 2010, 3(1), 130-134
[2]. Bajaj H, Bisht S, Yadav M, Singh V. International Journal of pharma and Biosciences 2011, 2(1), 202-216
[3]. Pawar A R, Choudhary P D. Novel techniques for solubility , dissolution rate and bioavailability enhancement of class II and IV drugs. Asian Journal of Biomedical & P‟ceutical sciences 2012, 2(13), 9-14
[4]. Duncan Q M, Craig. The mechanism of drug release from solid dispersion in water soluble polymers. International Journal of Pharmaceutics 2002, 231, 131-144
[5]. Dhirendra k, solid dispersions: a review, pak. j. pharm. sci., vol.22, no.2, April 2009, pp.234-246
[6]. Vasconcelos T, Sarmento B, Costa P, Solid dispersions as strategy to improve oral bioavailability of poor water soluble drugs, Drug discovery today, 2007, 12(23), 1068-75
[7]. Babu PS, Chowdary KPR. Enhancement of dissolution rate of celecoxib by solid dispersion in superdisintegrants. Ind Drugs. 2008; 45(7):547-552.
[8]. Chaudhary A, Nagaich U, Gulati N, Sharma V, Khosa R. Enhancement of solubilization and bioavailability of poorly soluble drugs by physical and chemical modifications. Journal of Advanced Pharmacy Education & Research 2012, 2(10), 32-67
[9]. Savjani K T, Gajjar A K, Savjani J K. Drug solubility: Importance and Enhancement techniques. ISRN Pharmaceutics 2012, 1- 10
[10]. Howlader S I, Chakrabarty J K, Khandokar S F, Kumar U, Sarkar R. Enhancing dissolution profile of Diazepam using hydrophilic polymers by solid dispersion technique. International current pharmaceutical Journal 2012, 1(12), 423-430
[11]. Kapoor B, Kour R, Kour S, Behl H. Solid dispersion- An Evolutionary approach for solubility enhancement of poorly water soluble drugs. International Journal of Research advances in pharmaceutical research 2012, 2(2), 1-16
[12]. Kalaiselvan R, Mohanta GP, Manna PK, Manavalan R. Studies on mechanism of enhanced dissolution of albendazole solid dispersions with crystalline carriers. Indian J Pharm Sci 2006; 68(5): 599-607
[13]. Akiladevi D, Shanmugapandiyan P, Jebasingh D, Basak S. Preparation and evaluation of paracetamol by solid dispersion technique. Int J Pharm Pharm Sci 2011; 3(1): 188-191.
[14]. Abd Alaziz DM, Sammour OA, Elshamy AA, Neseem DI. Formulation and evaluation

of binary and ternary solid dispersions of domperidone by solvent evaporation method. Afr J Pharm Pharmacol 2014; 8(3): 66-80

[15]. Ghareeb MM, Abdulrasool AA, Hussein AA, Noordin MI. Kneading technique for preparation of binary solid dispersion of meloxicam with poloxamer 188. AAPS Pharm Sci Tech 2009; 10(4): 1206-1215.

[16]. Shah N, Iyer RM, Mair HJ, et al. Improved human bioavailability of vemurafenib, a practically insoluble drug, using an amorphous polymer-stabilized solid dispersion prepared by a solvent-controlled coprecipitation process. J Pharm Sci 2013; 102(3): 967-981.

[17]. Nokhodchi A, Talari R, Valizadeh H, Jalali MB. An investigation on the solid dispersions of chlordiazepoxide, Int J Biomed Sci 2007; 3(3): 211-216.

[18]. Bhise SB, Rajkumar M. Effect of HPMC on solubility and dissolution of carbamazepine III in simulated gastrointestinal fluids. Asian J Pharm 2008; 2(1): 38-42.

[19]. Bakatselo V, Oppenheim RC, Dressman JB. Solubilization and wetting effects of bile salts on the dissolution of steroids. Pharm Res 1991; 8(12): 1461- 1469.

[20]. Hohman MM, Shin M, Rutledge G, Michael PB. Electrospinning and electrically forced jets. II. Applications, Physics Fluids 2001; 13(8): 2221-2236.

[21]. Neamnark A, Rujiravanit R, Supaphol P. Electrospinning of hexanoyl chitosan, Carbohydrate Polymers 2006; 66: 298-305.

[22]. Van DJ, Drooge WL, Hinrichs MR, Visser HW Frijlink. Characterization of the molecular distribution of drugs in glassy solid dispersions at the nano-meter scale, using differential scanning calorimetry and gravimetric water vapour sorption techniques. Int J Pharm 2006; 310(1): 2+ 20-229

[23]. Majerik V, Charbit G, Badens E, Horváth G, Szokonya L, Bosc N, N Teillaud N. Bioavailability enhancement of an active substance by supercritical antisolvent precipitation. J Supercrit Fluids 2007; 40(1), 101-110.

[24]. Serajuddin ATM, Sheen PC, Mufson D, Bernstein DF, Augustine MA. Effect of vehicle amphiphilicity on the dissolution and bioavailability of a poorly water soluble drug from solid dispersions. J Pharm Sci 1988; 77(5), 414- 417

[25]. Ahmed E. Aboutaleb, Sayed I. Abdel-Rahman, Mahrous O. Ahmed, Mahmoud A. Younis. Improvement of domperidone solubility and dissolution rate by dispersion in various hydrophilic carriers. J App Pharm Sci 2016; 6(7): 133-139

[26]. Ahmed E. Aboutaleb, Sayed I. Abdel-Rahman, Mahrous O. Ahmed and Mahmoud A. Younis. Design and evaluation of domperidone sublingual tablets. Int J Pharm Pharm Sci 2016; 8(6): 195-201.

[27]. Vyas V, Sancheti P, Karekar P, Shah M, Pore Y. Physicochemical characterization of solid dispersion systems of tadalafil with poloxamer 407. Acta Pharm 2009; 59: 453–461.

[28]. Zaini E, Umar S, Firdaus N. Improvement of dissolution rate of valsartan by solid dispersion system using D (−) mannitol. Asian J Pharm Clin Res 2017; 10(3): 288-290.

[29]. Sharma A, Jain C. Solid dispersion: A promising technique to enhance solubility of poorly water soluble drugs. Inernational Journal of Drug delivery 2011, 3, 149-170.

[30]. Kaushal A.M, Guptam P., Bansal AK., Amorphous drug delivery systems: molecular aspects, design, and performance. Crit. Rev. There. Drug Carrier Syst., 2004; 21(3):133-193.

[31]. Taylor L.S., Zografi G., Spectroscopic characterization of interactions between PVP and indomethacin in amorphous molecular dispersions. Pharmaceut. Res., 1997; 14:1691-1698

[32]. Cilurzo F., Minghetti P., Casiraghi A., Montanari L., Characterization of nifedipine solid dispersions. Int. J. Pharmaceut., 2002; 242(1-2):313-317.

[33]. Pikal M.J., Lukes A.L., Lang J.E., Gaines K. Quantitative crystallinity determinations for beta-lactam antibiotics by solution calorimetry: correlations with stability. J. Pharmaceut. Sci., 1978; 67(6):767-73.

[34]. Buckton G., Darcy P., The use of gravimetric studies to assess the degree of crystallinity of predominantly crystalline powders. Int. J. Pharmaceut., 1995; 123:265-271.

[35]. Sebhatu T., Angberg M., Ahlneck C., Assessment of the degree of disorder in crystalline solids by isothermal microcalorimetry. Int, J. Pharmaceut., 1995; 104:135-144.