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Review Article
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A CRITICAL REVIEW ON DIFFERENT PHARMACEUTICAL ASPECTS OF SOLID DISPERSION TECHNIQUE FOR SOLUBILITY ENHANCEMENT

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ABSTRACT

Solid dispersion is the prerequisite technique for increasing the dissolution and bioavailability of the hydrophobic drugs. The technique generally provides more significant enhancement in solubility or dissolution rate as compared to other techniques which mainly relies only on the reduction of particle size. The factor of re-crystallization associated with reduction of particle size has great negative impact of further reduction of solubility but in more generalized view along with reduction of particle size the factor which increases the wettability by reducing the contact angle between particle and water is mainly important and solid dispersed particles are formulated with this approach only as they composed of matrix dispersion of hydrophobic drug and hydrophilic polymer which increases the wettability of drug molecules and also reduces the size to form molecular dispersion. The recent research in the field of polymerization has also made it possible to make available those polymers which allows intermolecular hydrogen bonding with drug molecules in the solid dispersed particles, these bondings have significant effect over the prevention of precipitation during solubilization of particles. Thorough knowledge regarding the physicochemical properties of the solid dispersed particles are very essential for understanding the relation or mechanism of wetting of particle and the release mechanism of drug. However, in this review the current researches are highlighted with their modifications over the conventional methods.

KEY WORDS

Bioavailability, Contact angle, Particle size, Re-crystallization, Wetting.

INTRODUCTION

The emergence of high throughput screening and combinatorial chemistry has resulted in a significance increase in the volume of new candidate compounds which are having acceptable therapeutic activity but interestingly, most of them are poorly aqueous soluble, formulating with poor bioavailability.[1] The scientific framework especially Bio-pharmaceutics Classification System (BCS) classifies drug substances on its aqueous solubility and intestinal permeability,[2], aids in depicting their bioavailability. Among the four classes class II and class III drugs are generally of poorly aqueous soluble in nature but differ in their intestinal permeability as one shows high permeability while other shows low permeability respectively. The low lipid permeability drugs needs to be administer with lipids and their derivatives as excipients for increasing their bioavailability but drugs with high permeability shows low bioavailability because of their rate limited dissolution profile and for such drugs reduction of the particle size,[3], salt formation [4] and preparation of solid dispersions [5] increases the rate of dissolution.

Undoubtedly, Solid dispersions as per Chiou and Riegelman defined the system as an attractive means of enhancing drug solubility by 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.[6] The inert carrier commonly used are water soluble polyvinyl pyrrolidone (PVP), a vinyl derivative, a cellulose ether, hydroxypropyl methylcellulose (HPMC) or water miscible polymer such as polyethylene glycol (PEG) or low molecular weight materials such as sugars. The drug used can be in the state of small crystalline or amorphous particles but the final dispersions results should not have sharp X-ray diffraction (XRD) peaks and a distinct melting point as indicated by differential scanning calorimetry (DSC) instead the particles should be in molecularly dispersion or is in fully amorphous state and if crystalline they must be in nanometer size crystals. The physico-chemical phenomena affecting the dissolution of solid dispersed particles involves a series of steps such as wetting, solvent penetration, disintegration, swelling and transport of components and all of these steps are affected by the interaction between the penetrating solvent, the polymer and the drug. The same had been demonstrated by Matsumoto and Zografi, [7], that the interaction of polyvinyl pyrrolidone with indomethacine impact the distribution of surface active groups at the outermost atom layer of the grains in the dosage form, thus affecting wetting as there are chances of change in the polymer chain mobility and chain-chain cohesion by bridging thus influencing solvent penetration and dissolution rate. In one more study by D.A. Alderman, [8], it was demonstrated that the transport of components was affected by the swelling of the polymer matrix to transforms into a gel which in turn acts as a transport barrier and other factors which influences the barrier performance are molecular size of the drug, local concentrations, molecular and particle size of the polymer and even air entrapped. The most important step for faster dissolution is the wetting of particles as even fine particles may not produce the expected faster dissolution and absorption due to possible aggregation and agglomeration caused by the increased surface energy and subsequent stronger van der Waal's force of attraction and the same mechanism was noted by Lin *et al* [9] in their paper which demonstrates that in vitro dissolution rates of micronized griseofulvin and glutethimide were slower than those of the coarser particles. Similar is the case for drugs with plastic properties as these particles have more tendencies to stick together even if the particles can be produced by the controlled precipitation mechanism. In this review we had tried to explain about solid dispersion with the factors and relations affecting its manufacturing, physicochemical properties of solid dispersed particles, wetting properties of solid dispersion and the possible mechanism of drug release from solid dispersion.

METHODS OF PREPARATION

Melting method:

The melting or fusion method was first proposed by Sekiguchi and obi [10] to prepare solid dispersion of sulfathiazole as drug and urea as inert carrier. Here the physical mixture of a drug and its carrier was melted simultaneously and the molten mixture was then cooled and solidified under rigorous stirring. The rapid/quench cooling is the most commonly method used to prepare eutectic mixture. The final solid mass was then crushed, pulverized and sieved to prepare a solid dispersion in which hydrophobic drug was present as a fine crystals suspended in the hydrophilic carrier. With more modifications in case of solidification the homogeneous melt was dried over ferrite plate or a stainless steel plate using air flow or flow of water on the opposite side of the plate as reported by Goldberg *et al* [11] and Chou and Riegelman. [12]. In certain cases the solidified masses were often found to require storage of one or more days in a desiccator at room temperature for the ease of hardening and powdering. The dissolution behavior

of drug through such solid dispersion technique was noted to improve by the reduction of particle size and through incorporation within a hydrophilic carrier which increases the wettability of drug. The above technique was further modified to obtain the control drug release as reported by Tran *et al*.[13]. In another study by Hong and Oh [14] the use of carbopol as coating material on the outer side of the core material containing solid dispersed particles was reported to allow the controlled release of the drug from the dosage form. The use of binary system is very essential as it reduces the melting point of the system on comparison with the individual melting point of the components of the system, under such conditions the binary system can be easily used for the drugs which can be decomposed at or near its melting point. The problem of drug decomposition and loss of volatile compounds by heating can also be avoided if the physical mixture is heated in a sealed container or by melting under vacuum or under the covering of an inert gas for the prevention of the oxidation of the drug or carrier.[15]

Solvent Method:

The molecular dispersions as solid solutions were reported by Goldberg [11,16] as advantageous over eutectic mixtures. The solid solutions are generally used to prepare by dissolving the carrier and drug as physical mixture into the common solvent, followed by the evaporation of the common solvent. In one study by Dahlberg *et al* [17] the preparation technique employed the dispersion of polymer in the solution for swelling followed by dissolution for at least one hour with solvent/polymer ratio of 10:1 and a drug concentration of 15% (w/w), relative to the polymer weight. The common solvent used was mixture of different organic solvents in different proportions referred to as “solution, su” and “solution, so” if such mixture contains some part of water as solvent for the effect of cosolvancy. The solvents were then subsequently evaporated from the obtained solutions/suspensions by two methods which differ in the rate of solvent removal, one was rotatory evaporation which is a slow drying process and other was spray drying which is a fast drying process. The spray drying is the process where a solution of carrier and drug is evaporated by spraying the solution as fine droplets into a chamber under controlled conditions of heat, humidity and air flow. In another study, it was found that drying process is important for altering the structure of a powder to manipulate wettability, when one or more surface active components were present as surface active substances and generally tend to absorb to the air/liquid interface of the spray droplet before it turns into a dry particle. So the substance with the strongest affinity for liquid/air interface will tend to dominate the surface of the powder, thus migration of hydrophobic drug towards the surface increases the contact angle between powder surface and penetrating surface and in such case rate limiting dissolution can be obtained so for decreasing the contact angle in such cases surfactant might be used.[18,19]

In another study by Purvis *et al* [20] the ultra-rapid freezing process was used to produce solid dispersed particles of Repaglinide, here the drug was dissolved into 1,3-dioxane and the polymer into the water/t-butanol cosolvent system, the final dispersion of both medium followed by lyophilization yields particles with enhance dissolution.

The supercritical fluid can also be used to prepare solvent free solid dispersions. The gas anti-solvent crystallization technique using supercritical carbon dioxide as processing medium, had considered to prepare an enhance release dosage form for the poorly soluble carbamezapine employing PEG 4000 as a hydrophilic carrier as demonstrated by Moneghini *et al*.[21]

Eutectic mixtures and solid solutions published during 90s were later regarded as first-generation

solid dispersions.[22] The carriers used in the first generation solid dispersions were mostly crystalline compounds such as sugars and urea. Theses carriers were beneficial kinetically in retaining the dispersed drug throughout the matrix but limited in the dissolution rate of drug as significant energy was required to dissolve the carrier itself as reported by Chiou and Riegelman.[12]. Instead the amorphous carriers are more advantageous as compare to crystalline carriers and constitute the second generation solid dispersions. Depending upon the miscibility of drug with the amorphous carriers the two types of formulations can be produced are Glass solution and amorphous solid suspension. Glass solution is produced when polymeric carrier is miscible with drug that is capable of dispersing drug molecules on a molecular level. The glassy solution has the molecular conformation of a frozen high temperature solution possessing high viscosity due to presence of an amorphous polymer having high glass transition temperature (Tg). The formation of glassy solution is advantageous in terms of solubility and dissolution as high viscosity hinders molecular motion and homogeneity thus offering maximum size reduction with maximum surface area.[23] An amorphous solid suspension usually produced when the drug and polymer have limited miscibility or when the drug is oversaturated within the matrix, such immiscibility is the result of limited molecular interaction between drug and polymer which in turn results in phase separation.[24] In both the glass solution and amorphous solid suspensions, oversaturation results in the high probability to re-crystallization upon cooling or during storage, to overcome such problem a polymeric carrier with high miscibility with drug molecule should be selected.[25] The third generation solid dispersion incorporating surfactants are the most recent development in this case which are designed to produce the highest degree of solubility enhancement and prevention of morphological changes during administration and aging. The different generations of development of solid dispersions were mentioned in Figure 1.[26]

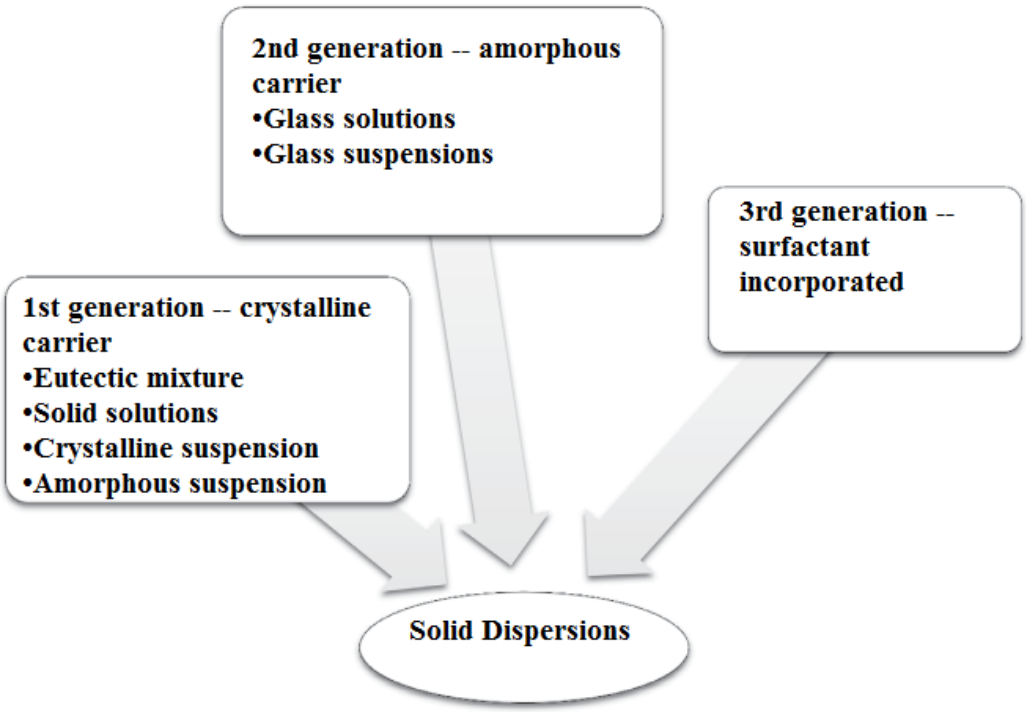

Fig.1. Categorization of solid dispersions developed over the past 50 years. [26]

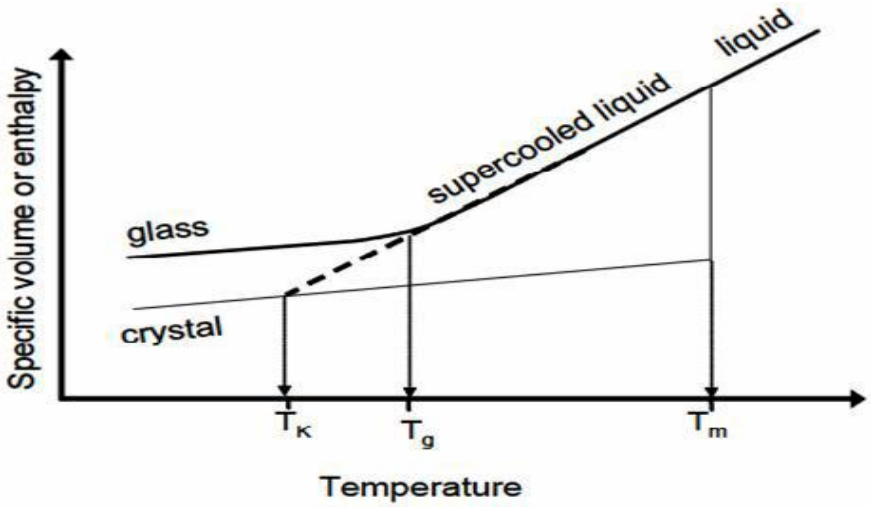

Fig.2. Diagram depicting the volume or enthalpy changes from crystalline to the glassy state. [34]

Hot Melt Extrusion:

The process involves the blending of active compounds and pharmaceutical class matrix carriers at elevated temperatures, with intense mixing thus allowing the transformation into fluid like state permitting homogeneous mixing by the high shear of extruder screws. The die at other side then shapes the melt in the required form such as granules, pellets, tablets or powder. A standard extruder generally divided into six main function zones: solid conveying zone, melting/plastification zone, melt conveying zone, devolatilization, mixing zone and discharge die forming. [27] The thermal stability is the prerequisite for any material that is to be melt extruded. The meltable materials are normally low melting point waxes or thermoplastic polymers. The drug release kinetics is greatly dependent upon the use of formulation excipients as for drug components embedded in waxy materials, such as microcrystalline wax, corn and polyethylene glycol/oxide and is typically erosion-based, or diffusion based. [28] The saturation limit of a drug in polymer is to a great extent dependent upon drug-polymer interactions.

PHYSICOCHEMICAL PROPERTIES OF SOLID DISPERSED PARTICLES

The two component system of solid dispersed particles composing drug and the polymer generally forms multiple structures depending on their composition.[29] The reason for this multiple structure formation is the partial miscibility of the drug and polymer due to which drug may only be in solution at low concentration.[30] The success of solid dispersed particles as depicted in two step of initial dissolution of drug along with polymer matrix to form a supersaturated solution and maintenance of supersaturation for long period for drug absorption depends upon thermodynamic stability and kinetic stability.[31] The homogeneous solution with respective thermodynamic stability and kinetic stability inhibit the instability, on concerning drug precipitation as point of instability.

Thermodynamic stability refers to the solid solubility of one solid into the other and kinetic stabilization refers to immobilization of supersaturated drug concentrations into a highly viscous matrix, preventing phase separation and crystallization referred to as the anti-plasticizing effect [32]. The effect of thermodynamic stability on drug precipitation was depicted by Huang and Dai [33] in their paper where it was cleared that the molecular dispersion of drug within the polymer matrix at lower equilibrium concentration generally forms the thermodynamically stable homogeneous solution. However such conditions is

appropriate only when drug is dispersed at lower concentration and at high temperature as on decrease in temperature creates the supersaturation of solution and the precipitation of the drug. The limit of the processing temperature can be stipulated by the curve of drug solubility in possible temperature-composition phase diagram for the drug polymer solid dispersion. Along with thermodynamic stability the role of glass transition temperature (Tg) is also important to predict the storage stability of a solid dispersion as can be determined from Figure 2 [34] which shows relationship between temperature (T) and volume (V) for liquid, glassy and crystalline state of a material. In case of glass solution the kinetic stabilization is generally referred to determine the anti-plasticizing effect and it can be achieved at 'Tg – 50°c' which means that the molecular mobility of drug molecules becomes negligible at 50°c below the glass transition temperature (Tg)of the solid dispersed particles [35],[36] and this inhibition of mobility is prerequisite for preventing phase separation and crystallization but on concerning the feasibility of mechanism, it is generally very much impossible to maintain the temperature at Tg – 50°c and especially at the time of its dissolution within the body. But if some ways, the transition temperature of solid dispersion may be elevated the problem can be rectified as in the study of Mooter *et al* [37] where it was determined that the increase in concentration of polymer results in the increase in glass transition temperature of the solid dispersed particles. Thus finally it has been cleared that the thermodynamic stability requires dispersion at higher temperature but less than transition temperature for kinetic stability.

In another study by Six K *et al* [38] it was depicted that there was a relation between the glass transition temperature and the composition of the mixture of solid dispersion and the relation can be expressed by the Gordon-Taylor/Kelly-Bueche equation in combination with the Simha-Boyer rule.

$$Tg_{mix} = (w_1 Tg_1 + K w_2 Tg_2) / (w_1 + K w_2) \quad (1)$$

Equation 1 is the Gordon Taylor equation in which *w* stands for the weight fraction and *Tg* for the glass transition temperature (in K) subscripts 1 and 2 represent the amorphous compounds with the lowest and the highest glass transition temperature, respectively and K is a constant that can be estimated with the Simha–Boyer rule-

$$K \cong \rho_1 Tg_1 / \rho_2 Tg_2 \quad (2)$$

Where ρ is the density of the amorphous components.

Drug precipitation or crystallization generally takes place in two steps as nucleation and crystal growth. The detailed study on nucleation and crystal growth along with the rate of their formation and its effect over stability was reviewed by Janssens and Mooter.[39] In another study by Xu and Dai [40] it was depicted that there are variety of polymer excipients, especially cellulose derivative absorbs over the surface of crystals and forms intermolecular hydrogen bonding with drug molecules. Such interaction in turn results in suppression of the nucleation or crystal growth, thus prolonging the supersaturation and inhibiting the drug precipitation.

RELATION BETWEEN SOLID DISPERSION AND WETTING

In general, wetting is a measure of the ability of a bulk powder to imbibe a liquid under the influence of capillary forces which in turn depends upon particle size, density and porosity of the powder bed that is final surface composition of the powder surface.[41] The surface composition for complete dissolution requires the presence of hydrophilic groups at the outer surface of particles but in concern of solid dispersed particles especially containing hydrophobic drug molecules matrixed in it influences the overall hydrophobicity of the powder as high surface coverage of hydrophobic drug generally gives poor wetting properties thus it

can be stipulated that the amount of drug at the powder surface significantly influences the dissolution and physical drug stability and for good wetting properties the outer surface requires to composed of hydrophilic groups.

In one study by Buckton and Beezer [42] it was claimed that the wetting was a reflection of the functional groups that were present at the surface of the particles and alteration in the surface of the particles manipulate the wettability. The possibility to alter the surface of the particles may depend greatly on the preparation technique as there was a kind of competition for the absorption of surface active groups or the less soluble material at the air/liquid interface before it turns into a dry particle. The different preparation techniques involving such competition are mainly of two types, in which one is water based solution and other is non aqueous solution. The water based formulations, the only one which allows absorption of surface active groups at the surface but the feasibility of the process is possible if drying process is instantaneous involving spray drying or lyophilization of the formulation to obtain the dried particles. In case of non aqueous based formulations the substance with greater affinity for the liquid/air interface will tend to dominate the surface of the powder and mostly hydrophobic drugs take the chance, retarding or inhibiting the drug dissolution so for such cases surfactants needed to be incorporate to promote better powder wetting.[43]

The importance of wetting and wettability of the powder is generally determined by the contact angle measurement and can be correlate to improved intrinsic dissolution data for a poorly water soluble drug as reported by chokshi *et al*.[44]. Similarly, in another study by Dahlberg,[17], the relation between polymer-drug interactions and wetting was also determined by the contact angle measurement as the high surface coverage of hydrophobic drug generally gives poor wetting properties with large contact angle. In this study, five model drugs with different solubility and hydrophobicity were allowed to incorporate in hydrophilic polymer matrices consisting of either hydroxypropyl methylcellulose (HPMC) or polyvinyl pyrrolidone (PVP). A series of water contact angle measurements were performed on all solid dispersed tablets and on tablets compacted from pure polymers or pure drugs and it was found out that incorporation of a model drug substance exhibited a higher contact angle than pure PVP and the contact angle measured for PVP was lesser as compared to that obtained by HPMC, showed the increased wettability of the powder by the PVP as compare to HPMC.

DRUG RELEASE MECHANISM

Numerous theories have been proposed regarding the release of drug from solid dispersions but probably the formation of the drug-rich layer suggested by the Higuchi *et al* [45] and applied to solid dispersions by Corrigan [46] provides a satisfactory explanation. In case of solid dispersed particles prepared from glass solution the use of hydrophilic polymers especially cellulose derivative generally forms intermolecular hydrogen bonding with drug molecules and such interaction results in diffusional release of drug molecules. At low drug loading with high polymer and surfactant concentration the release of drug generally follows the carrier controlled and drug controlled dissolution model as depicted by Craig.[47] According to carrier controlled dissolution model, the contact of water imparts excessive wetting with minimum contact angle to drug molecules matrixed in the solid dispersed particles, this results into dissolution of drug molecules within the concentrated carrier layer prior to release through diffusion at a sufficiently rapid rate, that there is an insufficient time for drug molecule to release as intact into the medium. The above condition mainly relies on the viscosity of the concentrated carrier layer as greater the viscosity

lesser the release of drug but greater is the time for drug molecule to form molecular dispersion within the concentrated viscous layer.

According to drug controlled dissolution model, the drug molecules diffuses out from solid dispersed particles as intact, means there is no prior dissolution of drug molecules within the concentrated carrier layer instead drug releases as solid particles. In this case the dissolution is generally favored by the properties of drug like size, physical form, *et al*. instead of concentration of polymer.

CONCLUSION

The increasing research over solid dispersion technique has made it possible to approve the various poorly soluble drug molecules in the market, suggesting it as an efficient technique for drug solubilization. The current thinking regarding the manufacturing of solid dispersed particles and drug release depending upon physical and chemical properties has been outlined in this article. The final relation of particles with wetting is the most important aspect of determining the efficiency of solid dispersion and this is the relation which needs further clarifications.

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