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SOLID DISPERSIONS: A TECHNIQUE OF SOLUBILITY ENHANCEMENT METHOD COMPREHENSIVE REVIEW

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ABSTRACT

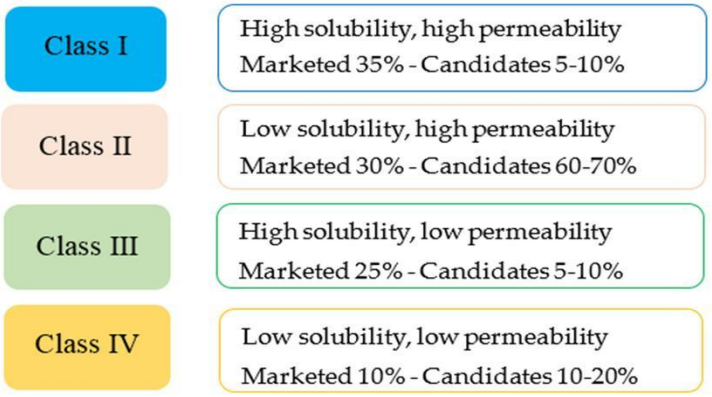
During preparation of every pharmaceutical formulation the main goal is to deliver the product with good bioavailability, because it is the main parameter that contributes to the therapeutic activity of the drug molecule. The major drawback in most of the formulations existing today is solubility which directly effects dissolution, poor dissolution effects bioavailability at end. To address the solubility problem of a drug molecule, we have many solubility enhancement methods for poorly water-soluble drugs such as Micronization, nanoparticles, use of salt forms and use of surfactant spray freezing etc. Every method has its own limitations, like in micronization of the drugs often leads to agglomeration and decreases the wettability.so, solid dispersions methods like hot melt extrusion, solvent evaporation, spray drying, supercritical fluid methods etc. are the promising methods to address all the problems of solubility and bioavailability. This article gives an overall view of solid dispersions and its role in improving solubility and bioavailability of poorly water-soluble drugs.

KEYWORDS: Solid dispersion, Bioavailability, supercritical fluid extraction, solvent evaporation, cellulose polymers, stability, solubility.

INTRODUCTION

Solid dispersions are dispersions of hydrophilic carrier and hydrophobic drug molecules dissolved in volatile-solvents such as methanol in which liquid solvent is removed by evaporation by applying reduced pressure which results in formation of amorphous precipitate of the drug [1]. Basically, they are two component systems, generally they are two component systems. First time solid dispersions are prepared by Sekiguchi and obi on drug sulfathiazole by using water soluble inert carrier. [2] As we know that amorphous form of drug is more soluble than its crystalline form so solid dispersions are the best approach for solubility enhancement. [3] In case of particle size reduction the agglomeration occurs, but in solid dispersions particles no need to exist in a micronized state. [4] The relation between solubility and permeability is clearly understood by

Biopharmaceutical system of classification



SOLUBILITY

Solid dispersions will enhance the solubility and permeability of class – 4 drugs.

Methods include:

1) Physical methods

Used for compounds which are non-molecular

- Micronization
- Nano crystal method
- Crystal polymorph
- Spray freezing into liquids
- Supercritical fluid recrystallization

2) Chemical methods

- Prodrug
- Salts from the drug Prodrug concept can increase the solubility and bioavailability of drugs.[5]

Example: The salt form of Diclofenac (Na diclofenac) shows great stability, solubility and bioavailability.
For weakly acidic drugs, the microenvironment required to introduce Alkalizers can improve the maximum therapeutic effect and bioavailability of the drug. [6]

As we know solubility of drug governs dissolution this is explained by
Noyes - whitney equation:

$$dc/dt = D\,S_w\,(C_s - C_b)\,/\,h\,V$$

$(C_s - C_b)$: Concentration of gradient of the solution
D: The diffusion coefficient of the substance
S_w: The surface area of exposed solid
V: The volume of solution
h: Thickness of stagnant layer

Table 1.

Parameters	Impact on solubility of drug
D	Directly proportional to solubility
$(C_s - C_b)$	Directly proportional to solubility
S_w	Directly proportional to solubility
V	Inversely proportional to solubility
h	Inversely proportional to solubility

TYPES OF SOLID DISPERSIONS

1. Based on carrier-first generation-we use crystalline carriers. Example: urea & sugars.
2. Second generation-we use amorphous carriers Example: povidone, P&G, HPMC, ethyl cellulose. Here supersaturation of drugs is due to forced solubilization.
3. Third generation-new approach where we use carriers with self-emulsifying properties & adding surfactants like inulin, poloxamer407. Based on their molecular arrangement- 1) Eutectic mixtures 2) Crystalline & substitution solid solutions.[7]

METHODS OF PRODUCTION OF SOLID DISPERSION

1) Lyophilization technique
2) Solvent evaporation
3) Hot- stage extrusion
4) Surface active agents / Surfactants
5) Melt agglomeration method
6) Kneading technique
7) Freeze drying method
8) Drug size reduction
9) Supercritical fluid method
10) Fusion method
11) Electrospinning
12) Dropping solution method
13) Co - precipitation

1. Lyophilization

Drug + carrier is dissolved concurrently in cyclohexanol solvent & then frozen & sublimation done under vacuum to obtain a lyophilized molecular dispersion.[8]

2. Hot stage extrusion

In this method drug & excipients like polymers, are added together & heated at fixed temperature & then cooled & pulverised & moulded into tablets, pellets, microspheres etc.
It is a non-stop solvent free process & it is an economical approach but this also has its own drawbacks like, stability of polymer & API if they are heat sensitive.[9]

3. Melt agglomeration

In this method drug & carrier are added to a volatile solvent where the carrier acts like a binder, gradually we need to add drug the molten carriers. At temperature where the carriers present in melting range above the temperature the carrier bind completely with drug then remove solvent from the mixture by various methods such as rotary evaporator, freeze drying, spray drying. [10]

4. Fusion method

In this method the hydrophilic carrier matrix used is sulfathiazole and urea. This matrix polymers along with drug melted together above their eutectic point temperature then, the melted molecule composition is cooled for solidification then after drying the final mass is crushed and sieved to obtain uniform particle size. [11]
We need to take care about the temperature and compatibility of drug and polymer during this method optimum temperature should be applied, if above the required temperature is applied this leads to degradation of product during process itself.

Cooling and heating temperatures need to be controlled throughout the processes to avoid the phase separation and degradation of drug molecules. [12]

Example: Itraconazole drug carrier PEG3350,8000 at melting point 120.

5. Solvent evaporation method

First step here is drug and polymer matrix dissolved in suitable solvent and techniques and drug is collected.
Issues to be addressed here are:

Compatibility of solvent with drug and matrix material

Both drug and solvent should be compatible with each other, and compatible with each other too. Particle size of drug and polymer should be less for proper dissolving of them in solvent even though we can adjust this by adding surfactant or solubilizer [13]. Solvent residues after

drying should be in detectable limits and that should not be toxic.

Phase separation

This occurs during evaporation of solvent here crystallization of drug or matrix material may occur due to the melting and glass transition temperature. Different types of preparation of solid dispersion by solvent evaporation method are: vacuum drying, freeze drying, spray freeze drying, spray freeze drying. Of all methods risk of phase separation is less with freeze drying and suitable for thermolabile substances. In spray drying we can change particle size but switching droplet size and as surface area is more risk of phase separation can also be minimized. Spray drying is preferred if we want to prepare solid dispersion of pulmonary /nasal preparation.

DRUG	Carrier	Solvent	Solvent removal
Carbamazepine	PVK K30, Gelucire 44/14	Methanol	Under vacuum in a rotavapor at 40^0C and 45 rpm for 24 hours.
Furosemide	PVP	Methanol	Using a rotary evaporator under reduced pressure at 70^0C.
Piroxicam	DMPC, PEG 4600	Chloroform	Under current of N_2 gas for a period of 6 hrs.
Itraconazole	Lactose, MCC	Dichloromethane	Evaporated at 60^0C for 4 hrs.
Phenytoin	PEG 6000, PVP K30	Ethanol	Under reduced pressure at 40^0C.

6. Super critical fluid extraction

A fluid which exhibits properties of both gas and liquid above the critical point is called supercritical fluid. In this process the solubility of solvent in solution is determined by solvating efficacy of supercritical fluid at optimum temperature and pressure. The best supercritical fluid is CO_2 because of its unique characteristics like non-corrosive, non-flammable, Non-toxic nature.

As CO_2 is a polar compound it is difficult to extract polar compounds so, we need to add co-solvents to enhance solubility of molecules. After solubilisation the next step is removal of solvent. This can be done by changing temperature or pressure so that supercritical fluid no longer retains its character, so we can easily remove solvent.

METHODS USED IN LARGE SCALE

1) Hot-melt extrusion
2) Spray drying
3) Vacuum drum drying
4) Melt extrusion method

USAGE OF SOLID DISPERSIONS TECHNIQUE FOR POORLY WATER-SOLUBLE DRUG'S

Solubility plays a vital role in drug working models. Solubility of a drug will have direct or indirect effect on pharmacokinetic and pharmacodynamic properties. So, this problem needs to be addressed. Novel approaches for increasing solubility are, using inert carriers by preparing amorphous solid dispersions, increasing surface area by decreasing size of particles, and prodrug approaches. We are aiming towards amorphous forms for increasing solubility because they are highly soluble but, due to high energy state they are less stable. Though the crystalline forms are stable we use least stable crystalline forms because the most stable crystalline forms are less soluble. [14]

Low solubility of drug leads to decreased absorption because, poor water solubility causes less dissolution of drug in body fluids as this in sequence decreases bioavailability

Example: Ritonavir a poorly water-soluble drug prepared by using Gelucire as a carrier by solvent evaporation method was found to increase its bioavailability in solid dispersion form.

STABILITY OF SOLID DISPERSIONS

Solubility & dissolution of solid dispersion must remain unaltered. Their efficiency is determined by maintaining physical stability.

For amorphous solid dispersion to exist in stable state it should have less molecular mobility during storage as mostly amorphous solid dispersions are in thermodynamically unstable they transform to crystalline form gradually leads to poor dissolution. [15]

By adjusting the proper ratio of carrier drug & glass temperature physical stability can be maintained. Drug load has effects on the physical so, for the drug to be stable loading dose should be optimum.

To prepare a stable form molecular mobility & T/g, T_g of polymer matrix should be considered. Randomized mobility should be decreased & matrix with high T_g & high molecular height is used. [16][17]

Excipient & polymer used should be thermostable, because thermal stability effects shelf-life of the product so, drug polymer complex should not effect the stability. The main reason for enlargement of solid dispersions in final dosage forms is that they are physically stable.

For freeze drying solid dispersion the stability studies were done to investigate the storage stability of short term while they are in nitrogen filled freeze drying vials stored at suitable temperature in laboratory.[18]

If the samples are crystallized the stability studies are further stopped.

For the improvement of stability, the API is kinetically trapped in between the polymer chains in a high energy non-crystalline state.

CELLULOSE BASED POLYMERS USED FOR PREPRATION OF SOLID DISPERSIONS

Polymers play a vital role in achieving a steady state, with amorphous solid dispersion by restoring the drug in amorphous form in the carrier matrix system.
That prevents the drug from crystallisation in a polymer matrix.

On contact with the aqueous medium, the medicine is released from the amorphous soil dispersion, which leads to supersaturation. Continuous release of drug further causes it to exterminate energy and destroy the crystal lattice.[19]

Polymer category	Examples	Properties	Advantages	Limitations
Conventional cellulose esters and ethers	CHC, HPMC, HPC, EC, MC, CA, CAB, HPC-Pen106-AA-H	Hydrolytically stable, water-insoluble, pH non-responsive	Safe, low moisture absorption ability	Lacks very strong H-bond donor or acceptor groups
pH-responsive cellulose esters and ethers				
Cellulose succinate	CABSu, HPMCAS	Water insolubility at low pH, amphiphilic, stability of HPMCAS at high temperature and shear, Highly soluble in organic solvent, dissolve at pH 5–7	Moderate moisture absorption ability, Strong drug-polymer interactions	CABSu hydrolytically unstable, HPMCAS is complex to synthesize and analyze. Synthesis of HPMCAS may be difficult to control due to the potential for variable chain extension of the hydroxypropyl group.
Carboxymethylcellulose derivatives	CMC, CMCAB	Good organic solvent solubility, Broad miscibility with hydrophobic drugs, pH-sensitive, Swells at neutral pH	Aqueous based coatings applications	Polymer with low DS, insufficient to provide bulk solubility, polymers vulnerable to cross-linking, polymer synthesis
Cellulose phthalate derivatives	HPMCP CAPhth	Dissolves at 5 pH Dissolves at higher pH (more than 6)	More rigid cellulosic polymer backbone sterically hinder recrystallization of drug and improve the stability	Limited miscibility with drugs
Cellulose ω-carboxy esters	CA AdP, CA Sub, MCAd, CAB Seb, CAP Sub, CAP Seb, CAB Sub, CA Seb,	High T_g, More hydrophobic, Amphiphilic nature	Good solubility in medium polar solvent, Broader miscibility with	Cross-linking potential during synthesis

Keywords: CAAdP- Cellulose acetate adipate propionate; CAPhth- Cellulose acetate phthalate; CA Sub- Cellulose acetate suberate; CA Adp- Cellulose acetate adipate; CA Seb- Cellulose acetate sebacate; CHC- 5-carboxypentyl hydroxypropyl cellulose; CMC- Carboxymethyl cellulose; CMCAB- Carboxymethyl cellulose acetate butyrate;; EC- Ethylcellulose; HEC-Hydroxyethyl cellulose; HPC- Hydroxypropyl cellulose; HPC-Pen106-AA-H- Hydroxypropyl pent-4-enyl cellulose; HPMC- Hydroxypropylmethyl cellulose; HPMCAS- Hydroxypropylmethylcellulose acetyl succinate; HPMCP- Hydroxypropylmethyl cellulose phthalate

Finally, supersaturation attains and forms the stable crystalline form.

Cellulose has β.D-anhydro glucopyranose units, which are 1-4 linked These are polar polymers. The HLB value is 12.45.
Cellulose reacts with hydroxyl groups by etherification and esterification.

Role of cellulose

- Helps to stabilize the compound
- Drug possess a strong interaction with polymer
- Possess a high transition temperature (T_g)
- It maintains the stability of amorphous solid dispersion.

ADVANTAGES

- Solid dispersion will increase the surface area while decreasing the particle size & get a larger dissolution rate accomplished. [20]
- Increasing the permeability of particles is done by solid dispersion. so that bioavailability is increased. [21][22]
- Super saturated solutions are present in solid dispersion drugs. These are in the form of metastable polymorphic. [22][23]
- Changing the liquid form of the drug into solid form is done with these solid dispersions. [24]

- Expand in adsorption extent & rate of dissolution & reduction in pre-systemic metabolism. [25]
- By solid dispersion it is easy to bring out quick disintegration oral tablets. By solid dispersion the bitter taste of the drug is masked. [26]
- It also improves the drug porosity. Even without water the patient can self-medicate due to fast dispersion. [27]
- Particle size reduction is in high degree which is advantageous over conventional grinding which produces no dust & there is no risk of eruption for suitable waxy substances. [28]
- The advantage of solid dispersion is the use of amorphous solids. It is the amorphousness of a given drug that is frequently used & studied. [29]
- The oral bioavailability of drug substance is controlled by main forces like permeability & solubility. [30]
- High degree of porosity is found in the particles of solid dispersion & it depends on carrier properties for occurrence, complicated polymer & larger polymers these are produced by linear polymers which are present in rate of dissolution. [31]
- Suitable for thermolabile substances.
- Usage of large quantities of solvent is difficult to remove complete solvent. [32]

DISADVANTAGES

- Usage of large quantities of solvent is difficult to remove complete solvent.
- The major disadvantage of solid dispersion is recrystallization. They are thermodynamically unsteady & have the propensity to modify into a more stable state as an amorphous system under recrystallization.[33][34]
- Despite huge proficiency with solid dispersions, they are not mainly used in trading products, due to there is a chance of crystallization in storage conditions & during the process of manufacturing. [35]
- It shows modification in crystallinity & reduction in rate of dissolution with ageing.
- The most crucial disadvantage is instability. Decaying effect on solid dispersion is mostly based on temperature & moisture content. [36]
- It is sticky in nature, so handling is perplexing.
- Disadvantage of solid dispersion is their poor bolster for the grounds of manufacturing.[37]
- In solid dispersion the used polymer can soak up moisture & cause phase-separation, crystal growth & inter change amorphous form to crystalline form so, that these will give low dissolution rate & solubility. [38]
- It is a tough method of preparation. In physicochemical characteristics it begins duplicate. [39]

Evaluation of solid dispersions done by different methods

- Scanning Electron Microscopy
- Electron Microscope
- X-ray diffraction studies
- Thermo-microscopic studies
- Differential scanning calorimetry
- FT – IR spectroscopy
- Hot stage and electron microscopy
- Infrared Spectroscopy
- Dissolution testing
- Raman Spectroscopy

APPLICATIONS

- It enhances the dissolution rate, solubility, stability and bioavailability and absorption of medicament. [40]
- Side effects of drugs are lowered.
- Altered the taste, odour and colour of the medicament. [41]
- Incompatibility is neglected.
- Homogeneity is maintained in the drug, which is in solid state.
- Bring down pre-systemic pacifying of drugs such as Morphine, Progesterone.increase solubility or can be used in combination with Poloxamer P85 which increase solubility and permeability.

- **Marketed products**

Zelboraf [R] Roche	Vemurafenib
Stivarga[R] Bayer	Regorafenib
Afinitor[R] Votubia[R]	Everolimus

PRODUCT NAME	DRUG NAME
Spororanox	Itraconazole
Grispeg	Griseofulvin
Keretra	Lopinavir
Rezulin	Troglitazone
Hepcure	Hepatitis B

CONCLUSION

In this article we gave you a detailed study about all aspects of solid dispersions. The study of solid dispersions briefs us that large amounts of drugs that go through evolution are ineptly water-soluble, solubilization technologies become crucial attributes to show them profitable in the market. Individual things such as high molecular weight, hydrolytic stability & hydrophilicity make better dissolution & bioavailability of active pharmaceutical ingredients with substandard water solubility in the pharmaceutical industry. The trading application is restricted but in modern days considerable deal of knowledge has been collected about solid dispersion technology. In spite of the fact that there are some obstacles like expanding or extending & manufacturing price to reduce, there will be considerable assurance that solid dispersion technology will advance the drug release profile of poorly water-soluble drugs. Solid dispersion is an easy and well technique for developing the aqueous solubility of drugs.

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