

Drug - Drug Solid Dispersion: A Unique Approach in Solubility Enhancement

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ABSTRACT

Over 40% of active pharmaceutical ingredients in development are poorly water soluble drugs which limit formulation approaches, clinical application and marketability because of their low dissolution and bioavailability. Solid dispersion has been considered one of the major advancements in overcoming these issues with several successfully marketed products. Extensive review of the literature indicates that physiological inert carriers have so far been used in solid dispersions for improving dissolution of poorly soluble drugs but in, novel approach will obviate the need for use of physiological inert carrier to improve dissolution of poorly soluble drugs and cost effective in developing formulations for clinical use.

Drug-drug Solid dispersion is a unique approach to present a poorly soluble drug in an extremely fine state of subdivision to the gastro intestinal fluids. It can be prepared by fusion, co-precipitation and kneading methods. Solid dispersion can form either a eutectic mixture or solid solution or glass solution or amorphous precipitation in a crystalline carrier or compound or complex formation.

Benefits of novel drug-drug solid dispersion not only for improving the dissolution of the poorly soluble drug without the use of soluble physiological inert carriers but also for the soluble drugs available in the fixed dose combination can be used to solid disperse the poorly soluble drugs.

Keywords: Drug-drug solid dispersion, physiological carriers, solvent effect, solvent evaporation

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INTRODUCTION

The poor aqueous solubility and dissolution rate of is one of the biggest challenges in pharmaceutical development and is becoming more common among new drug candidates over the past two decades due to the use of high through put and combinatorial screening tools during the drug discovery and selection phase. According to the Biopharmaceutics Classification System, a drug compound is poorly soluble if highest dose strength is not soluble in 250 ml aqueous media over the pH ranges at 3-7. These compounds mostly belong to Class-II, which are poorly soluble and highly permeable according to the pH of the gastrointestinal fluid and tend to present solubility or dissolution rate-limited. Despite their high permeability, these drugs often have low oral bioavailability because of low solubility. [1,2]

Table 1: Drug on the Basis of BCS Classification

Sr no.	Class	Solubility	Permeability
1	Class 1	High solubility	High permeability
2	Class 2	Low solubility	High permeability
3	Class 3	High solubility	Low permeability
4	Class 4	Low solubility	Low permeability

Solid dispersion is one of the approaches employed to improve dissolution of poorly soluble drugs whose absorption is dissolution rate limited. Sekiguchi and obi1 were the first to report an improved dissolution of the drug from sulfamethazole-urea solid dispersion. Following their findings, more works in this direction were carried out. Generally combination therapy required treating the

disease condition like anti-inflammatory, antihypertensive, anticancer therapy; antiparkinsonism etc. and the combination of two drugs will enhanced the activity. [2] Some poorly soluble drug not absorbed from the stomach and dissolution rate limited absorption problem and hence an improved dissolution through solid dispersion approach will improve absorption and bioavailability. Preparation of drug-drug solid dispersions results in particles with reduced particle size and thus the surface area is improved and increased dissolution rate is, the ultimate result is improved bioavailability. [3]

RATIONAL OF DRUG-DRUG SOLID DISPERSION:

Drug-drug solid dispersion improve wettability in during production, and improved wettability results in increased solubility, and increase the solubility without using physiological inert carrier. By using drug-drug solid dispersion we can supply fixed dose combination soluble and the insoluble drug. Particles in solid dispersions have been found to have a higher degree of porosity; the increased porosity of solid dispersion particles accelerates the drug release profile. Solid dispersions drugs are presented as super saturated solutions which are considered to be metastable polymorphic form. Thus presenting drugs in amorphous form increase the solubility of the particles. Rapid dissolution rates that result in an increase in the rate and extent of the absorption of the drug, and a reduction in presystemic both can lead to the need for lower doses of the drug. [4]

Formulator prepared solid dispersion by using the salt and the physiological inert carrier so far been used in solid dispersion for improving the dissolution of poorly soluble drug the physiological inert carrier like given below.

Physiological Inert Carrier for Solid Dispersion: [5]

- 1. First generation carriers:** Example: Crystalline carriers: Urea, Sugars, Organic acids⁹.
- 2. Second generation carriers:** Example: Fully synthetic polymers include povidone, polyethylene glycols and polymethacrylates. Natural product

based polymers are mainly composed by cellulose derivatives, such as hydroxypropylmethylcellulose, ethylcellulose or hydroxypropylcellulose or starch derivates, like cyclodextrins¹⁰.

- 3. Third generation carriers:** Example: Surface active self-emulsifying carriers Poloxamer 408, Tween 80, and Geluincire 44/1411.

Some problem with the carrier in the formulation like solubility within the solvent, incompatibility with the drug, toxicity, inertness, heat stability, compatibility with the chemical, and the strongly bond formation.

The drug-drug solid dispersion are the novel approach to enhanced the solubility to avoiding the physiological inert carrier with obviating the problem with this carrier in this study we are enhanced the solubility without carrier by taking the fixed dose combination of drug. It is found that the salt form of drug will increase the solubility of insoluble drug by forming the complex. So in this study the highly soluble drug act as salt for the insoluble drug, the study of novel drug- drug solid dispersion approach where in a poorly soluble drug is dispersed in a soluble drug and hence the present study was directed towards developing solid dispersion of soluble and insoluble drug.

Definition of Solubility:

The amount of substance which passes into the solution in order to establish at the constant pressure and temperature to produce the saturated solution is "solubility".

Definition of Solid Dispersion:

Solid dispersion technology is the science of dispersing one or more active ingredients in an inert matrix in the solid stage to achieve an increased dissolution rate or sustained release of drug, altered solid state properties and improved stability.[5,6]

Definition Drug-Drug Solid Dispersion:

The drug-drug solid dispersion is defined as the it is the solubility enhancement method in the category of solid dispersion with use of two drug in which insoluble drug are dispersed in soluble drug without physiological inert carrier and soluble drug itself act as carrier for solubility.[7]

SIGNIFICANCE OF DRUG-DRUG SOLID DISPERSION: [8]

- 1) Preparation of drug-drug solid dispersions results in particles with reduced particle size and thus the surface area is improved and increased dissolution rate is, the ultimate result is improved bioavailability.
- 2) Wettability is improved during solid dispersion production. Improved wettability results in increased solubility.
- 3) Cost effective.
- 4) Increase the solubility without using physiological inert carrier.
- 5) By using drug-drug we can supply fixed dose combination soluble and the insoluble drug.
- 6) Particles in solid dispersions have been found to have a higher degree of porosity; the increased porosity of solid dispersion particles accelerates the drug release profile.
- 7) In solid dispersions drugs are presented as super saturated solutions which are considered to be metastable polymorphic form. Thus presenting drugs in amorphous form increase the solubility of the particles.
- 8) Rapid dissolution rates that result in an increase in the rate and extent of the absorption of the drug, and a reduction in presystemic both can lead to the need for lower doses of the drug.
- 9) Easy process.
- 10) No special technique required.
- 11) Less time required during production

DISADVANTAGES: [8, 9]

- 1) The key disadvantages of solid dispersion are related to their instability. Several systems have shown changes in crystallinity and a decrease in dissolution rate with aging.
- 2) Moisture and temperature have more of a deteriorating effect on solid dispersions than physical mixtures. Some solid dispersion may note them to easy handling because of tackiness.
- 3) Two fixed dose combination is required.
- 4) Drug-drug solid dispersion it is compulsory to one of the drug is highly soluble.

DISSOLUTION RATE:

According to Noyesh-Whitney equation provides some hints as to how the

dissolution rate of even very poorly soluble compounds might be improved to minimize the limitations to oral availability.

$$dC / dt = AD (C_s - C) / h$$

Where,

dC/dt - the rate of dissolution,

A-The surface area available for dissolution,

D-The diffusion coefficient of the compound,

C_s- the solubility of the compound in the dissolution medium,

C - The concentration of drug in the medium at time t,

h- Thickness of the diffusion boundary layer adjacent to the surface of the dissolving compound.

➤ **To increase the dissolution rate from equation the following approaches are available**

- 1) To increase the surface area available for dissolution by decreasing the particle size of drug.
- 2) Optimizing the wetting characteristics of compound surface.
- 3) To decrease the boundary layer thickness.
- 4) Ensure sink condition for dissolution.
- 5) Improve apparent solubility of drug under physiologically relevant conditions.
- 6) Drug administered in fed state is a way to improve the dissolution rate. [10]

MATERIALS FOR THE PREPARATION OF DRUG-DRUG SOLID DISPERSION:

✓ **DRUG**

✓ **SOLVENT**

DRUG: [2]

Drug for the drug-drug solid dispersion in two form in that one drug are the insoluble and the another drug is highly soluble drug so we increase solubility of insoluble drug by using the highly soluble drug which act as salt or carrier.

DRUG CANDIDATE SUITABLE FOR THE DRUG-DRUG SOLID DISPERSION:

- 1) It should be the two drug combination in a same therapy. E.g. anti-inflammatory with anti-acidic drug.
- 2) It should be the compatible with each other.
- 3) It should compatible with the solvent.
- 4) Soluble drug increase the solubility of insoluble drug. [1]

Table 2: List of few Insoluble Drugs

Insoluble Drugs	Category
Fenofibrate	Antihyperlipidemic
Glipizide	Antidiabetic
Acyclovir	Antiviral
Valdecoxib	Anti-inflammatory
Flurbiprofen	Anti-inflammatory
Efavirenz	Antiviral
Chlordizepoxide	Antipsychotic
Itrconazole	Antifungal
Furesamide	Diuretic
Tolubutamide	Antidiabetic
Hydrochlorthiazide	Antihypertensive
Lornoxicam	Anti-inflammatory
Ibuprofen	Anti-inflammatory
Aceclofenac	Anti-inflammatory
Ketoprofen	Anti-inflammatory
Indomethacin	Anti-inflammatory
Diclofenac	Anti-inflammatory
Morphine	Anti-inflammatory
Ioperamide	Antidiarrheal
Naproxen	Anti-inflammatory
Nimodipine	Antihypertensive
Ciprofloxacin	Antimicrobial

Table 3: List of few Soluble Drugs

Soluble Drug	Category
Losartan	Antihypertensive
Paracetamol	Antipyretic
Ranitidine	Antihistaminic
Carbamazepine	Antipsychotic
Dapsone	Antileprotic
Phenytoin	Antiepileptic
Valproic acid	Antipsychotic
Trimethoprim	Antimicrobial
Sufamethoxazole	Antimicrobial
Metoprolol succinate	Antihypertensive

Table 4: Overview on Common Solvent of Drug-Drug Solid Dispersion

Solvent	Melting Point (°C)	Boiling (°C)	Vapour Pressure at 25°C kPa
Water	0	100	3.16
Ethanol	-93.9	65	16.9
Methanol	-117	78.5	5.79
Chloroform	-63	62	26.1
DMSO	19	189	0.08
Acetic acid	17	189	1.64

Methods of Preparation of Drug-Drug Solid Dispersion:

Solvent Evaporation Method:

Organic solvent having insoluble and soluble drug in dissolved form & it is evaporated after complete dissolution. The solid mass is ground, sieved & dried. Steps involved in the method are,

1. Preparation of a solution containing both insoluble & soluble drug.

Solvent:

Solvent for drug-drug solid dispersion is essential for the making proper dispersion of insoluble drug. The solvent act on the polymorphic form of drug which precipitate as solid dispersion generally the organic solvent used this are the agent extremely mix the drug with each other. The choice of solvent and its removal rate are critical parameters affecting the quality of the solid dispersion and the selection of the solvent and the removal of solvent are difficult some time solvent are toxic. [12]

Ideal Properties of Solvent for Drug-Drug Solid Dispersion:

- 1) It should be physiological inert.
- 2) It should be the non-toxic.
- 3) It should easily available.
- 4) It is costly effective.
- 5) It should easy to remove.
- 6) It should be compatible with drug.
- 7) It should dissolve drug easily.
- 8) It should nonirritant.
- 9) It should be non-reactive.
- 10) Do not impart any undesired color, odour and taste of the drug.
- 11) It should stable over the wide range of temperature.
- 12) It should effective in the low concentration.
- 13) Must be free from the microorganism.
- 14) Must not interfere with bioavailability of drug.
- 15) Must be accepted by the regulatory authorities. [13]

2. The removal of the solvent resulting in the formation of solid mass.

Formed mass depends on the nature of solvent & rate & temperature of evaporation of the solvent. Decomposition of drug can be avoided because low temperature is required for the evaporation of the solvents. Major drawbacks include time consuming process, expensive & crystal forms are difficult to reproduce.

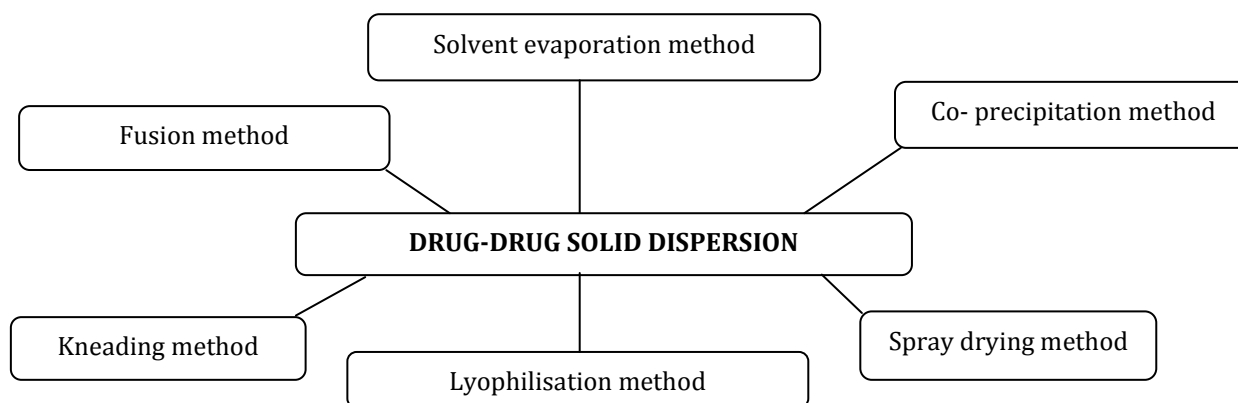


Figure 1: Methods of Preparation of Drug-Drug Solid Dispersion

1) Fusion Method:

The melting or fusion method, first proposed by Sekiguchi and Obi involves the preparation of physical mixture of a drug and a water-soluble carrier and heating it directly until it melted. So we will taking the insoluble and soluble drug heat until melt. The melted mixture is then solidified rapidly in an icebath under vigorous stirring. The final solid mass is crushed, pulverized and sieved. However many substances, either drugs or carriers, may decompose or evaporates during the fusion process which employs high temperature. Some of the means to overcome these problems could be heating the physical mixture in a sealed container or melting it under vacuum or in presence of inert gas like nitrogen to prevent oxidative-degradation of drug or carrier.

2) Kneading Method:

A mixture of accurately weighed soluble and insoluble drug and is wetted with solvent and kneaded thoroughly for some time in a glass mortar. The paste formed is dried and sieved&Packed in the container.

3) Co Precipitation Method:

Accurately weighed freely soluble drug and dissolved in water and insoluble drug is dissolved in organic solvent. After complete dissolution, the aqueous solution of soluble drug is then poured into the organic solution of the drug. The solvents are then evaporated. The dispersion is pulverized with pestle and mortar, sieved and dried.

4) Spray Drying Method:

Spray drying method consists of dissolving or suspending the drug and freely soluble drug 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.

5) Lyophilisation method:

Lyophilization has been thought of a molecular mixing technique where the insoluble drug and soluble drug are co-dissolve in a common solvent, frozen and sublim to obtain a lyophilize molecular dispersion. This technique was propose as an alternative technique to solvent evaporation.[15]

How Drug Release from Drug Drug Solid Dispersion:

a) Reduction of particle size:

In case of glass, solid solution and amorphous dispersions, particle size is reduce to a minimum level. This can result in an enhance dissolution rate due to an increase in both the surface area solubilization.

b) Solubilization effect:

The soluble drug material, as it dissolves may have a solubilization effect on the drug. This was shown to be the case for soluble drug and on insoluble drug as well as for numerous other drugs.

c) Wettability and dispersibility:

The soluble drug material may also have an enhancing effect on the wettability and dispersibility of the drug in the dissolution media. This should retard any

agglomeration or aggregation of the particles, which can slow the dissolution process.

d) Metastable Forms:

Formation of metastable dispersion with reduce lattice energy would result in faster dissolution rate.

e) Other Mechanism

➤ Partial transformation of crystalline drug to the amorphous state or altering the crystalline morphology . The suggested mechanism behind this tremendous increase in dissolution rate may include:

- ✓ Formation of solid solution
- ✓ Formation of complexes
- ✓ Intimate mixing of the drug with hydrophilic excipients
- ✓ Reduction of aggregation and agglomeration
- ✓ Improved wetting of the drug and solubilization of drug by the carrier at the diffusion layer.

f) Solvent effect of drug-drug solid dispersion:

The solvent effect of soluble drug on a insoluble drug is found by study which increase the solubility of insoluble drug the solvent effect increase the wettability and dispersibility criteria of insoluble drug, insoluble drug was disperse in soluble drug matrix in amorphous or solid solution in solid dispersion, and on exposure to dissolution medium, the matrix dissolves and releases the dispersed drug in a pure state of subdivision which facilitates dissolution of insoluble drug without interfering the solubility and dissolution of the freely soluble pure drug and its drug release criteria from the dispersion follows the first order kinetic.

Advantages of drug-drug solid dispersion:

It is possible that such a technique be use:

- ✓ To fabricate fixed dose combination
- ✓ To obtain a homogeneous distribution of a small amount of drug in solid state.
- ✓ To stabilize the unstable drug.
- ✓ To dispense two drug compounds in a combination by increasing solubility.
- ✓ To formulate a fast release primary dose in a sustained release dosage form.
- ✓ To formulate sustained release regimen of soluble drugs by using poorly soluble of insoluble carriers.

- ✓ Polymorphs in a given system can be converted into isomorphous, solid solution, eutectic or molecular addition compounds.

- ✓ To increase solubility without carrier .

Disadvantages of drug-drug solid dispersion:

- It is not used commercially due to its stability problems.
- During processing & storage due to mechanical stress, temperature & humidity more chances of amorphous state undergo crystallization.
- Phase separation may occur because some time it absorb moisture.
- Chances of conversion of metastable crystalline form to more stable structure.
- Poor scale up for manufacture.
- Too expensive.
- It is not applicable to thermolabile substances.
- Also cooling & solidifying methods are difficult to carry out.
- In case of hydrophobic drugs solvent used will be more & the drug concentration will be less to get desired therapeutic effect.
- Fixed dose combination required in which one of the drug are in the soluble form .
- Alone drug therapy cant prepare the drug drug solid dispersion.

In-vitro Evaluation of Drug-Drug Solid Dispersion:[1]

Several different molecular structures of the drug in the matrix can be encountered in solid dispersions. Several techniques have been available to investigate the molecular arrangement in solid dispersions.

Drug content :

Make the standard solution of the soluble and insoluble drug is use in the mixed standard scan in the range of both drug wavelength by uv spectroscopy, prepare the standard curve of absorbance vs concentration.

Phase solubility study :

Excessive amount of pure insoluble drug added to the 100ml of deaerated water containing varying concentration of soluble drug in a stoppered glass flask kept suspension on intermittent shaking at 72 hrs $37 \pm 2^\circ$ C, filtered through whatman filter and analyze by spectrophotometer .

Powder x ray diffraction:

The powder samples were pack in the x-ray holder from the top before analysis. X-ray powder diffraction patterns will record on Rigaku diffractometer using nilfilter, Cu α K radiation, voltage of kV and a 300mA current. These samples will continuously spun and scane at a rate of 0.02°s⁻¹ over a 2 θ range of 3-50°.

Thermal analysis :**a. Differential Scanning Calorimetry (DSC):**

The data obtain from the DSC is melting point depressions, enthalpy of fusion and degree of crystallinity.

b. Differential Thermal Analysis (DTA):

In DTA, the temperature difference that develops between a sample and an inert reference material is measure, at identical heat treatments. Changes in the sample which lead to the absorption or evolution of heat can be detect relative to the inert reference. Phase transitions or chemical reactions can be follow by absorption or evolution of heat.

c. Cooling curve Methods:

Physical mixtures were heat. Then homogeneous melt Temperature of each mixture are note. Plot Temperature time curve Phase diagram of the samples. Major disadvantages include Time consuming. Requires relatively large amount of sample. Heat sensitive material.

d. Thaw Melting Methods:

Samples are frozen Heat & it suddenly converted from solid state –liquid state. Disadvantage: Depends upon subjective observation, therefore not highly reproducible Thaw point and melting point can be noted.

Scanning electron microscopy:

Morphology of insoluble and soluble drug system was characterize by scanning electron microscope (Jeol model) operating at 20.0kV accelerating voltage. Samples is coat by gold before examination (cathode dispersion).

Equalibrium solubility study:

The equilibrium solubility study show that the solubility of insoluble drug increased with increase in concentration soluble drug, thus indicating the solvent effect of soluble drug on insoluble drug.

Physical appearance:

Includes visual inspection of solid dispersions.

Percent Practical Yield:

Percentage practical yield is calculated to know about percent yield or efficiency of any method,thus its help in selection of appropriate method of production. SDs were collect and weigh to determine practical yield (PY) from the following equation.

$$PY (\%) = \frac{[\text{Practical Mass (Solid dispersion)}]}{[\text{Theoretical Mass (Drug+ Carrier)}]} \times 100$$

Dissolution Studies:

The dissolution studies of solid dispersion was perform in 500ml at 37°C by the USP- II paddle apparatus at suitable rpm. Drug was disperse in medium. Aliquots of suitable ml from the dissolution medium were withdrawn at different time interval and replenish by an equal volume of fresh dissolution medium. The samples were filter through whatman filter paper and analyze for drug contents by measuring the absorbance at suitable wavelength using UV/visible Spectrophotometer.[16]

Drug carrier compatibility:

This study is done to determine the interactions if any between the drug and carrier and to determine the formation of inclusion complexes.

Methods used for this purpose are spectroscopic method :

(a) Fourier Transform Infra Red (FTIR) Spectroscopy:

Infra red studies was carried out to rule out interaction between drug and carrier used in Fourier Transform Infra Red spectrophotometer.

(b) Differential Scanning Calorimetry:

Differential scanning calorimetry was perform by Differential scanning calorimeter to obtain suitable thermograms. The accurately weigh sample is place in an aluminium pan and an empty aluminium pan will use as reference. The experiment is perform under nitrogen flow, at a scanning rate 30°C/min, range of 50-350°C.

(c) UV visible Spectroscopy:

Spectra of pure drug and disperse drug are scane. Calculation of molar extinction

provides evidence of any decomposition.[17]

Research aspects on drug-drug solid dispersion:

Investigate the effect of a drug-drug solid dispersion approach on the dissolution on hydrochlorothiazide in a fixed dose combination with Losartan potassium. Solid dispersion on hydrochlorothiazide and losartan potassium was prepared by coprecipitation method increase the solubility of the hydrochlorothiazide drug. Other than this hydrochlorothiazide with captopril drug-drug solid dispersion increase solubility of the hydrochlorothiazide by solvent effect of captopril as carrier reported by rajendran.

CONCLUSION

The novel drug drug solid dispersion approach is promising to improve dissolution and bioavailability of poorly soluble drugs that are presented in fixed dose combinations with soluble drugs. This novel approach will obviate the need for use of physiological inert carrier to improve dissolution of poorly soluble drugs and cost effective in developing formulations for clinical use. In the clinical practice several fixed dose combinations of poorly soluble and soluble drugs are used for the treatment of diseases. The findings of present study demonstrated the benefits of drug-drug solid dispersion for improving the dissolution and absorption of poorly soluble drugs.

The review suggest benefits of novel drug-drug solid dispersion not only for improving the dissolution of the poorly soluble drug without the use of soluble physiological inert carriers but also for the soluble drugs available in the fixed dose combination can be used to solid disperse the poorly soluble drugs.

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