SOLID DISPERSION INCORPORATED GEL SYSTEM: A NOVEL APPROACH IN TRANSDERMAL DRUG DELIVERY.

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ABSTRACT

Solid dispersion incorporated gel is the unique approach in topical drug delivery system to enhance the in vitro transdermal penetration of poorly soluble drugs. This article reviews preparation technique for solid dispersion incorporated gel as a recent and newer technology for transdermal drug delivery system. Drug penetration through the skin in gel form depends upon the aqueous solubility of drug. Drug insolubility is one of the formulation barrier and solid dispersion is favorable approach to improve solubility and bioavailability of poorly soluble drugs. It refers as dispersion of active ingredient in different carriers like β-cyclodextrin, PEG, PVP, Sodium lauryl sulphate (SLS) and Urea at determined concentration. Gels are semisolid polymeric matrix system in which drug is dispersed in different polymers like carbomer, HPMC, polaxomer and natural gums. Solid dispersion of drug is incorporated in gel, of suitable polymer with trituration to get homogenous dispersion of drug in gel. The resulting solid dispersion incorporated gel is characterized for various physicochemical parameters like, pH, drug content, spreadability, viscosity, extrudability, and in vitro drug release. Solid dispersion incorporated gel is the safe and effective way of treatment for poorly soluble drugs used in management of different diseases.

Key words: Solid dispersion incorporated gel, Insolubility, topical delivery.
INTRODUCTION

Formulation and development of most effective product from poorly soluble drugs is the most challenging task in pharmaceutical industries and success of product is depends on how readily product make the drug available at the site of action.\textsuperscript{[3]} Drug release, drug dissolution rate, bioavailability these properties are mainly affecting by poor solubility of drug. There are some methods are used to improve the solubility like co-solvancy, salt formation, addition of solubilizing agent, complexation, micronisation and solid dispersion.\textsuperscript{[4]}

Solid dispersion has attracted considerable interest as an efficient mean of improving solubility of many of hydrophobic drugs. Solid dispersion of poorly soluble drugs with water soluble carriers reduces the formulation problems. Solid dispersion is dispersion of an active ingredient in a carrier at solid state. As per BCS class II drugs with low solubility and high permeability, are the ideal candidates for improving solubility by solid dispersion.\textsuperscript{[5]} Solid dispersion of drug to formulate topical gel has considerable interest to improve drug permeation through skin and drug bioavailability. Solid dispersion incorporated gel is the better approach to enhance the in vitro topical permeation.\textsuperscript{[1]}

In recent years, Transdermal drug delivery is an attractive and has increasing attention as a new and effective administration route due to the several advantages such as systemic effect, an absence of hepatic first pass metabolism, better control of blood level, low risk of systemic toxicity, etc. Transdermal formulation like Gel, ointment, cream, patches and lotion are available but out of these gel is preferred due to its better application property and better percutaneous absorption. Gels are the semisolid system consisting of dispersion of particles and having great approach in topical drug delivery.\textsuperscript{[6]}

Drugs which are not suitable by oral rout and the drugs which are lose their bioavailability due to the first pass metabolism, topical delivery is the most suitable mean for drug delivery.\textsuperscript{[7]} Some drugs used for local action on the skin like antibiotics, should be given through skin, are formulated in transdermal system. Drug showing poor drug solubility are first processed through solid dispersion as resulting in improved solubility, this solid dispersion is incorporated in suitable polymer system to form a gel. This prepared gel is characterized to determine the efficacy of product and skin irritation test. Optimized result will show solid dispersion incorporated gel will show better transdermal delivery.
Examples of reported solid dispersion incorporated gel.\textsuperscript{[25,26,27]}

<table>
<thead>
<tr>
<th>DRUG</th>
<th>CATEGORY</th>
<th>POLYMER</th>
<th>APPLICATION</th>
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<tbody>
<tr>
<td>Aceclofenac</td>
<td>NSAID</td>
<td>HPMC</td>
<td>Solubility enhancement.</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>NSAID</td>
<td>Carbopol 941, Phospholipon 80H.</td>
<td>Solubility and permeation enhancement.</td>
</tr>
<tr>
<td>Ketokonazole</td>
<td>Antifungal</td>
<td>HPMC, SLS and Dimethyl sulfoxide.</td>
<td>Solubility and permeation enhancement.</td>
</tr>
<tr>
<td>Meloxicam</td>
<td>NSAID</td>
<td>Carbopol 940, PVP, Urea.</td>
<td>Solubility enhancement</td>
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**SOLID DISPERSION**

Solid dispersion was introduced in early of 1970’s, it refers a solid product consisting drug carrier system.\textsuperscript{[8,9]} Solid dispersion is the efficient mean of solubility enhancement to overcome the problem of Insolubility, Bioavailability, Drug dissolution and Drug permeation through skin. Term solid dispersion is defined as “A dispersion involving the formation of eutectic mixtures of drugs with water soluble carriers by melting of their physical mixture” \textsuperscript{[8]}

Much of research has been reported on solid dispersion. Many of solid dispersion systems have been introduced in pharmaceutical literatures to study various dissolution properties of poorly soluble drugs. Formulation of drug processed with solid dispersion offers variety of processes and excipient option which shows flexibility in formulating drug delivery for poorly soluble drugs. With introducing recent advances it is estimated that 40% of currently introduced new chemical entities shows poor water solubility.\textsuperscript{[10]}

Solid dispersion is group of solid product consisting of two different products hydrophilic matrix and hydrophobic drug. Drug is molecularly dispersed in matrix system either in amorphous form or in crystalline form. Based on this molecular arrangement in matrix system, types of solid dispersion have been introduced, as follows.\textsuperscript{[10]}

1) **Eutectic mixture**: Eutectic mixture consists of two compounds which are miscible with each other in liquid state but only in limited extent in the solid state. It process of rapid cooling of a co melt of the two compounds with physical mixture of very fine crystals of two compounds. Mixture consisting of slightly soluble drug and water soluble carrier, dissolved in aqueous medium, the carrier will dissolve rapidly, releases fine crystals of drug.\textsuperscript{[10]}
2) **Solid solution:** Solid solution is solid solute dissolved in solid solvent in which two components crystallize together in a homogeneous phase. In solid solution particle size of drug has been reduced to its molecular dimension, so in solid solution poorly soluble drug in rapidly soluble carrier achieves a faster dissolution.

**Classification of solid solution**

- According to extent of miscibility:
  1. Continuous solid solution.
  2. Discontinuous solid solution.
- According to crystalline structure of solid solution:
  2. Interstitial solid solution.

3) **Glass solution and suspension:** A glass solution is a homogeneous, glassy system in which a solute is usually obtained by abrupt quenching of the melt. Glass suspension are mixture precipitated particles suspended in glass solvent.

4) **Amorphous precipitation in crystalline matrix:** Instead of forming a simple eutectic mixture in which both drug and carrier crystallize simultaneously from a solvent method of preparation, the drug may also precipitate out in an amorphous form in crystalline carrier.\(^{[10]}\)

**BASIC COMPONENTS OF SOLID DISPERSION:** Solid dispersion is most effective method of solubility enhancement, process of solid dispersion is carried out with its suitable basic components,
Drug: According to biopharmaceutical classification system, drugs are divided in to four classes. Class II includes the list of drugs with low aqueous solubility and high membrane permeability. These are most suitable and preferable candidates for solid dispersion as to improve solubility and to formulate dosage form.

Carrier: Dissolution characteristic of dispersed drug is depends upon suitable carrier. A water soluble carrier shows faster release of the drug. Ideal carrier should pusses following properties,
1. It should b readily soluble in water.
2. Non toxic and physiologically inert.
3. High molecular weight.
4. Melting point should be nearer to drug.

Carrier system and its examples

<table>
<thead>
<tr>
<th>FIRST GENERATION (crystalline carrier)</th>
<th>SECOND GENERATION (polymeric carrier)</th>
<th>THIRD GENERATION (surfactants)</th>
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<tbody>
<tr>
<td>E.g. Urea, Sugars, Organic acids.</td>
<td>E.g. PVP, PEG, HPMC, Cyclodextrin.</td>
<td>E.g. Polaxomer, Tween 80, Gelucier44/141.</td>
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Solvent: To mix the drug and carrier in order to improve solubility solvent plays an important role. solvent should pusses following properties,
1. drug and carrier should be soluble in solvent.
2. should be non toxic.

E.g. Water, Methanol, Ethanol, Acetic acid, Chloroform, DMSO.\(^8\)

Advantages of solid dispersion: 1. **Particle size reduction:** in solid dispersion after carrier dissolution the drug is molecularly dispersed in solvent, and this principal is depends upon drug dissolution of drug. mixture of poorly soluble drug and highly soluble carrier shows high drug dissolution. Due to availability of higher surface area results increased drug bioavailability.

2. **Improved wettability:** carriers like cholic acid and bile salt which pusses surface activity, when used they significantly improves the wettability property of drug. Recently, third generation carriers are mainly used as they includes surfactants. As improve wettability drug shows hogher dissolution property.
3. **Drug particle with higher porosity**: Drug which processed through solid dispersion, found that they shows higher degree of porosity. Increase in porosity is depends on properties of carrier, linear polymer produces larger and more porous particles than reticular polymers which results higher dissolution rate and also improve drug release profile from system.

4. **Amorphous state**: Drug with poor solubility shows higher solubility in amorphous state than crystalline state. Drug in its amorphous state requires no energy to break up the crystal lattice during the process of dissolution. Amorphous composition is detected by the difference between melting temperature of drug and carrier.

**Disadvantages of solid dispersion**

1. **Instability**: Several system shows decrease in dissolution rate with aging because of change in crystallinity. Solid dispersion is readily affected by moisture and temperature than physical mixture.

2. **Risk of precipitation**: If drug is dissolved in aqueous media having pH at which compound is less soluble, there may the risk of precipitation.

3. **T tolerability and toxicity**: these are related to the pH, non physiological and extreme pHs results in tolerability and toxicity (local and systemic).

4. **Risk of degradation**: A dissolved drug in aqueous media is less stable than crystalline form, selected pH may accelerate the different degradation mechanism.\(^{[10]}\)

**METHODS OF SOLID DISPERSION**

**Melting/Fusion method**

This method is introduced by Sekiguchi and Obi (1961), in which physical mixture is prepared by melting the mixture of poorly soluble drug and water soluble carrier with heating and resulting product is rapidly solidify in ice bath with vigorous stirring. The final product is crushed, and passed through the sieve. Use of heating, there may be the chances of degradation of drug during melting. To avoid such a limitation several modifications are introduced in melting process, such as, hot stage extrusion, melt agglomeration, injection molding, hot spin melting.

**Solvent evaporation**: In solvent evaporation, drug and carrier is dissolved in same solvent. Solvent is evaporated until a thin solvent free film is left. film is further dried to the constant weight. In this method there is no chances of thermal degradation, as heating is not a part of process.
**Melt evaporation:** This method involves the dissolving the drug in a suitable solvent, and incorporation of this solution directly into the melt of polyethylene glycol 6000, without loss of its solid property. This melt with drug solution is the evaporated until a clear and solvent-free film is formed. The film is further dried to its constant weight, it is possible that selected solvent or drug may not be miscible with melt. Solvent may affect the polymorphic form of drug, and precipitate as solid dispersion. This is the single unique technique with advantage of both melt and evaporation methods.

**Melt Agglomeration:** In this process, binders act as a carrier. Solid dispersion is prepared by heating of binder with drug and excipients to a temperature above the melting point of binder or by spraying a dispersion of drug in molten binder on heated excipient, using high shear mixer. A rotary processor is alternative equipment for melt agglomeration. Rotary processor preferable for high melt agglomeration due to the easy control on temperature and high binder contents can be incorporated in the agglomerates.

**Lyophilisation:** Lyophilisation is the process of preparing the molecular mixture of drug and carrier by dissolving in common solvent, then frozen and sublimed to obtain a lyophilized molecular dispersion. This technique is alternative technique to the solvent evaporation and useful method for low melting point substances.

**Electrospinning:** In this, liquid stream of drug or polymer is subjected to the specific potential. When electric forces overcome the surface tension at the air interface, fibers of submicron diameters are formed. This diameter of fibers are depends on surface tension, dielectric constant, electric field strength and feeding rate. Dissolution of electrospun sample is depends on drug: polymer ratio.\[^{9,10,11}\]

**Applications of solid dispersion**

1. To improve the absorption, bioavailability and dissolution rate of poorly soluble drug by improving the solubility.
2. To reduce the decomposition and side effects of drug.
3. To mask the unpleasant taste and odour of drug.
4. To improve drug release from ointment, creams and gel.
5. To avoid various incompatibilities related to polymer and excipients.
6. To obtain homogeneous mixture.\[^{11,12}\]
Characterization of solid dispersion

1. **Microscopic method**: This technique measures the mechanical properties like degree of crystallinity. Different amorphous and crystalline form can determined by this method. Scanning electron microscopy is used to study microscopic surface morphology of drug, carrier, polymorphs of drug.\[^{11,12,13}\]

2. **Powder X-ray diffraction**: Detection of crystallinity in mixed system is determined by Powder X-ray diffraction. More crystallinity causes brittleness. Crystallinity parts give sharp narrow diffraction peaks and amorphous form gives very broad peak, by using ratio between these intensities can be used to calculate the amount of crystallinity in material.\[^{14,15}\]

3. **Differential scanning Calorimetry (DSC)**: this method is used to determine the amount of crystalline material by detecting the thermal events occurs during the heating. These thermal events can be glass transition, recrystallization, melting or degradation. Melting energy is used to determine the crystallinity.\[^{16}\]

4. **Fourier transforms infrared spectroscopy (FT-IR)**: Fourier transform infrared spectroscopy studies were performed to help and to assist in evaluation of possible chemical interaction between drug and polymer so it helps to determine possible functional group. Interaction between drug and polymer in solid dispersion would result in band shifts compared to the spectra for drug and polymer.\[^{17}\]

5. **In vitro dissolution studies**: Dissolution apparatus is used for evaluation of in vitro drug release profile of solid dispersion with suitable dissolution medium. Dissolution rate is determined by sampling, 5 ml of sample withdraw at specific time interval and analyze sample spectrophotometrically at specified wavelength to calculate mean value.\[^{18}\]

**GEL**: Gels are transparent and translucent semisolid formulation containing high ratio of solvent/gelling agent. Gel is defined as semirigid system in which the movement of dispersing medium is restricted by interlacing three-dimensional networks of particles are solvated macromolecules of the dispersed phase. The USP defines gel as a semisolid system consisting of dispersion made up of either small inorganic particle or large organic molecule enclosing and interpenetrated by liquid. Gels have visco-elastic property. Thinning under pressure allows it easily applicable on skin and it’s solid like matrix makes it adhere onto the skin when application is over. Most topical gels are prepared with organic polymers, such as
carbomers, that impart an aesthetically pleasing, clear, sparkling appearance to the products and are easily washed off from the skin with water. Use of type of bases in formulating a topical dermatological product greatly influences its effectiveness. Bases containing large amounts of oleaginous substances which provide an emollient effect to dry irritated skin.[22]

Advantages of topical gel
- They can avoid gastrointestinal drug absorption difficulties caused by gastrointestinal pH and enzymatic activity and drug interaction with food and drinks
- To avoid the first pass effect that is the initial pass of the drug substance through the systemic and partial circulation following gastrointestinal absorption, avoiding the deactivation by digestive and liver enzymes
- They are less greasy in nature and can be easily removed from the skin.
- Cost effective
- Reduction of dose as compare to the oral dosage form
- Localized effect with the minimum side effects

Disadvantages
- Poor permeability of some drugs through the skin
- Possibility of allergenic reactions
- Can be used only for drugs which require very small plasma concentration for action
- Enzyme in epidermis may denature the drugs
- Larger particle size drugs not easy to absorb through the skin [7,21,22]

Classification of gel
1. Based on colloidal system
   a) Single phase system: These consist of large organic molecule existing on the twisted stand dissolved in continuous phase.
   b) Two phase system: If particle size of dispersed phase is relatively large and forms three dimensional structure throughout gel.
      E.g. Aluminium hydroxide gel USP.

2. Based on nature of solvent:
   a) Hydrogel: In this gel contains water as their continuous liquid phase.
      e.g. Gelatin and polaxomer gel.
b) **Organic gel:** These contain non aqueous solvent as a continuous phase.

c) **Xerogel:** It is solid gel with low solvent concentration and produced by evaporation of solvent of freeze drying

E.g. Dry cellulose and polystyrene.

3. **Based on rheological properties**
   a) Plastic gel.
   b) Pseudo plastic gel.
   c) Thixotropic gel.

4. **Based on physical nature**
   a) Rigid gel.
   b) Elastic gel.[6,7,22]

**Ideal properties of topical gel**
- Should be inert, compatible with other additives.
- Should be non-toxic.
- Should be stable at storage condition.
- Should be free from microbial contamination.
- Should be maintain all rheological properties of gel.
- Should be economical.
- Should be washable with water and free from staining nature.
- Should be convenient in handling and its application.
- Should be passes properties such as thixotropic, greaseless and emollient.[22]

**Method of preparation**

1. **Cold method:** In this method the entire ingredient mixed together to form a homogeneous mass, under low temperature at about 5°C. In this polymer and penetration enhancer are mixed together to form a solution A, then drug and solvent mixed to form solution B. After that mix solution ‘B’ in solution ‘A’ with constant stirring.

2. **Dispersion method:** In this polymer disperse over water for 2 hrs, till all the polymer socked in water then add remaining ingredient with constant stirring to form homogeneous mixture.
3. **Chemical reaction**: In this process gel is formed due to precipitation.

E.g. Aluminum hydroxide gel and Silica gel, silica gel is prepared by interaction of sodium silicate with acid in water.

4. **Temperature effect**: With decreased in temperature, solubility of most lipophilic colloid like, gelatin, agar is reduced. So that when cool concentrated hot sol gel are produced.

5. **Flocculation**: In this method gelatin is produced by addition of sufficient quantity of salt to precipitate to produce age state but insufficient to bring about complete precipitation.[6,7]

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**SOLID DISPERSION INCORPORATED GEL**

Solid dispersion is the strategy to improve dissolution and bioavailability by particle reduction. Class II drugs should focused on enhancement of aqueous solubility.

Solid dispersion incorporated gel is prepared by dispersion method by soaking the polymer in water for 24hr and then add solid dispersion of drug with simultaneous addition of solvent and continuous trituration.[1]

**Evaluation of gel**

1. **Physical appearance and homogeneity**: After preparing a gel, it should be examined for its clarity, Colour, homogeneity, and presence of fibers or particles in preparation.

2. **Measurement of pH**: pH of gel is determined by digital pH meter. 1gm of gel is dissolved in 100 ml of distilled water to measure pH, after measurement of pH of each formulation is done in triplicate and average value is calculated.
3. **Drug content:** In this 1 gm of gel is mixed in 100 ml of solvent. Prepare aliquots of different concentration by dilution, filter the stock solution and measure the absorbance. Drug content is calculated by using equation which is obtained by linear regression analysis of calibration curve.

4. **Viscosity determination:** Brookfield viscometer is used for the measurement of viscosity. Viscosity of gel is obtained by multiplication of the dial reading with factor given in the Brookfield viscometer catalogues.

5. **Spreadability:** Spreadability is the term expressed to denote the extent of area to which gel readily spread on application to skin or affected part. Therapeutic efficacy of a formulation is depends upon spreading value.

   Spreadability is the time in seconds taken by two slides to slip off from gel and placed in between the slides under the certain load. If time taken to separate the two slides is less than, better the spreadability of gel.

   Formula for spreadability:
   \[
   S = \frac{M \cdot L}{T}
   \]
   Where,
   - \(M\) - weight tied to upper slide.
   - \(L\) – Length of glass slide.
   - \(T\) – Time taken to separate the slide.

6. **Extrudability:** After filling the gel in collapsible tubes, the extrudability of gel is determined in terms of weight in grams required to extrude a 0.5 cm ribbon of gel in 10 sec.

7. **Skin irritation study:** Skin irritation study is carried out on animals like guinea pig. Skin irritation is determined by, applying the gel on specified area, for specific period of time and observed for any sensitivity reaction.

8. **In vitro diffusion study:** Diffusion study is carried out by Franz diffusion cell, to study dissolution release of gel through cellophane membrane. In this 0.5gm of sample is taken in cellophane membrane and diffusion studies are carried out at room temperature using 250 ml of phosphate buffer (pH 7.4) as dissolution medium.
9. Stability: Stability study for gel is carried out by freeze – thaw cycling. In this syneresis is observed by subjecting the product temperature at 4°C for 1 month, at 25°C for 1 month, and then at 40°C for 1 month. Then gel is exposed to ambient room temperature and liquid exudates separating is noted.

10. Consistency: Consistency is measured by dropping a cone attached to a holding rod from a fix distance which should fall on the center of the glass cup filled with gel. Penetration by cone is measured from the surface of the gel to the tip of the cone inside the gel.

CONCLUSION
From above study, we can concluded that by formulating solid dispersion incorporated gel there will be better improvement of dissolution and diffusion poorly soluble drug and we can also overcome the gastric side effect of the drug.

REFERENCES


