EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 6
Issue: 3
308-312
Year: 2019

SOLID DISPERSION

Aietesam Mohiuddin*[1] and Atika Tahreem[2]

[1]Assistant Professor, Deccan School of Pharmacy, Department of Pharmaceutics, Deccan School of pharmacy, Dar-us-Salam, Aghapura, Hyderabad – 500001, Telangana, India.
[2]Student, Deccan School of Pharmacy (affiliated to OU), Department of Pharmaceutics, Deccan School of Pharmacy, Dar-us-salam, Aghapura, Hyderabad – 500001, Telangana, India.

***Corresponding Author: Aietesam Mohiuddin**
Assistant Professor, Deccan school of pharmacy, Department of Pharmaceutics, Deccan school of pharmacy, Dar-us-salam, Aghapura, Hyderabad – 500001, Telangana, India.

Article Received on 23/12/2018 **Article Revised on 14/01/2019** **Article Accepted on 05/02/2019**

ABSTRACT

Introduction: The enhancement of oral bioavailability of poorly water-soluble drugs remains. One of the most challenging aspects of drug development. Although salt formation, Co-solubilization and particle size reduction have commonly been used to increase . Dissolution rate and thereby oral absorption and bioavailability of such drugs there are practical limitations of these techniques. The increase in drug dissolution rate from solid dispersion system can be attributed to a number of factors like particle size, crystalline or polymorphic forms and wettability of drug etc. **Objectives:** The objectives of solid dispersion are. 1. Formulation of solid dispersion for the improvement of solubility and dissolution characteristics of gliclazide. 2. Characterization and confirmation of amorphous dispersion. 3. Characterization of solubility, dissolution rate and stability. 4. In vivo evaluation of bioavailability. **Conclusion:** The aim of current investigation was to prepare and evaluate third generation solid dispersions of Ibuprofen using modified Guargum as carrier. The prepared solid dispersions were characterized for preformulation parameters, percentage yield, drug content, solubility study,Invitro dissolution and stability study. The solid dispersions were prepared by solvent evaporation method and Melt dispersions method. The flow properties of formulations F1-F6 were found to be satisfactory. Percentage yield was in the range 85-99%.The In-vitro release of formulation was in the range 27.33- 82.31. F2 was found to be having a better release among all the formulations. Stability study was performed for one month and was found to be stable.

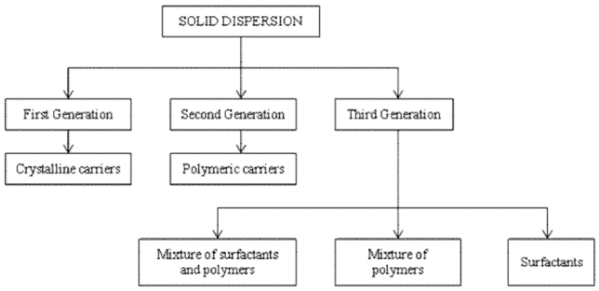
KEYWORDS: Bioavailibility, Co-solubilization, Guargum, Evaporation, Preformulation.

INTRODUCTION

The enhancement of oral bioavailability of poorly water-soluble drugs remains One of the most challenging aspects of drug development. Although salt formation, Co-solubilization and particle size reduction have commonly been used to increase Dissolution rate and thereby oral absorption and bioavailability of such drugs there are practical limitations of these techniques The salt formation technique is not feasible for neutral compounds and also the synthesis of appropriate salt forms of drugs that are weakly acidic or weakly basic may often not be practical.

Definition 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.

Classification



Types of Solid Dispersions

A) Simple Eutectic Mixture

Eutectic mixture of a sparingly water-soluble drug and a highly water-soluble Carrier may be regarded thermodynamically as an intimately blended physical mixture of its two crystalline components. These systems are usually prepared by Melt fusion method.

B) Solid Solutions
Solid solutions consist of a solid solute dissolved in a solid solvent. These systems are generally prepared by solvent evaporation or co-precipitation method, whereby guest solute and carrier are dissolved in a common volatile solvent such as alcohol. The solvent is allowed to evaporate, preferably by flash evaporation. As a result, a mixed crystal containing amorphous drug in crystalline carrier is formed because the two components crystallize together in a homogenous single phase system. Such dispersions are also known as Co-precipitates.

C) Glass Solution
A glass solution is a homogenous system in which a glassy or a vitreous carrier solubilizes drug molecules in its matrix. PVP dissolved in organic solvents undergoes a transition to a glassy state upon evaporation of the solvent. The glassy or vitreous state is usually obtained by an abrupt quenching of the melt.

D) Compound or Complex Formation:
This system is characterized by complexation of two components in a binary System during solid dispersion preparation. The availability of drug from complex or Compound depends on the solubility, association constant and intrinsic absorption rate of complex.

E) Amorphous Precipitation
Amorphous precipitation occurs when drug precipitates as an amorphous form in the inert carrier. The higher energy state of the drug in this system generally produces much greater dissolution rates than the corresponding crystalline forms of the drug. It is postulated that a drug with high super cooling property has more tendency to solidify as an amorphous form in the presence of a carrier.

Mechanism of Dissolution Rate Enhancement
a) Reduction of Particle Size
In case of glass solution, solid solution and amorphous dispersions, particle size is reduced. This may result in enhanced dissolution rate due to increase in the surface area. Similarly, it has been suggested that the presentation of particles to dissolution medium as physically separate entities may reduce aggregation.

b) Solubilization Effect
The carrier material, as it dissolves, may have a solubilization effect on the drug.Enhancement in solubility and dissolution rate of poorly soluble drugs is related to the ability of carrier matrix to improve local drug solubility as well as wettability.

c) Wettability and Dispersibility
The carrier material may also have an enhancing effect on the wettability and dispersibility of the drug due to the surfactant action reducing the interfacial tension between hydrophobic drug particle and aqueous solvent phase, increasing the effective surface area exposed to the dissolution medium. This also retards agglomeration or aggregation of the particles, which can slow down the dissolution.

d) Conversion of Polymorphic Nature of Solute
Energy required to transfer a molecule from crystal lattice of a purely crystalline solid is greater than that required for non-crystalline (amorphous) solid. Hence amorphous state of a substance shows higher dissolution rates.

Polymers Used in Solid Dispersions
A) Polyethylene Glycols (PEG)
The term polyethylene glycols refer to compounds that are obtained by reacting ethylene glycol with ethylene oxide. PEGs with molecular weight more than 300,000 are commonly termed as polyethylene oxides.

B) Polyvinyl Pyrrolidone (PVP)
PVPs have molecular weights ranging from 10,000 to 700,000. It is soluble in solvents like water, ethanol, chloroform and isopropyl alcohol.

C) Polymers and Surface Active Agent Combinations
The addition of surfactants to dissolution medium lowers the interfacial tension between drug and dissolution medium and promotes the wetting of the drug thereby they enhance the solubility and dissolution of drug.

D) Cyclodextrins
Cyclodextrins are primarily used to enhance solubility, chemical protection, taste masking and improved handling by the conversion of liquids into solids by entrapment of hydrophobic solute in hydrophilic cavity of CD.

E) Phospholipids
Phospholipids are major structural components of cell membranes. Phosphotidylcholine was first isolated from egg yolk and brain. In phosphatidyl ethanolamine and phosphatidyl serine, the choline moiety is replaced by ethanolamine and serine respectively. Other phospholipids that occur in tissues include phosphotidyl ethanolamide, phosphotidyl serine and phosphotidyl glycerol.

Methods of Preparation of Solid Dispersions
A) Fusion Process: Drug and carrier mixture of eutectic composition is molten at temperature above its eutectic temperature. Then molten mass is solidified on an ice bath and pulverized to a powder. The solidification is often performed on stainless steel plates to facilitate rapid heat loss. A modification of the process involves spray congealing from a modified spray drier onto cold metal surfaces. Decomposition should be avoided during fusion but is often dependent on composition and affected by fusion time, temperature and rate of cooling.

B) Solvent Evaporation Process
The solvent evaporation process uses organic solvents, the agent to intimately mix the drug and carrier

molecules and was initially used by Tachibana and Nakamura where, chloroform was used to co-dissolve β-carotene and PVP to form Co-evaporate. The choice of solvent and its removal rate are critical parameters affecting the quality of the solid dispersion. Vacuum evaporation may be used for solvent removal at low temperature and also at a controlled rate. More rapid removal of the solvent may be accomplished by freeze-drying.

C) Fusion Solvent Method

This method consists of dissolving the drug in a suitable solvent and incorporating the solution directly in the melt of carrier. If the carrier is capable of holding a certain proportion of liquid yet maintains its solid properties and if the liquid is innocuous, then the need for solvent removal is eliminated.

D) Supercritical Fluid Process

The process consists of the following steps

i. Charging the bioactive material and suitable polymer into the autoclave.
ii. Addition of supercritical CO2 under precise conditions of temperature and pressure, that causes polymer to swell
iii. Mechanical stirring in the autoclave
iv. Rapid depressurization of the autoclave vessel through a computer controlled orifice to obtain desired particle size.

The temperature condition used in this process is fairly mild (35-75°C), which allows handling of heat sensitive biomolecules, such as enzymes and proteins.

Advantages of Solid Dispersions

- The advantages of solid dispersion include the rapid dissolution rates that result in increased bioavailability and a reduction in pre-systemic metabolism.
- The latter advantage may occur due to saturation of the enzyme responsible for biotransformation of the drug or inhibition of the enzyme by the carrier, as in the case of morphine-tristearin dispersion.
- Both can lead to the need for lower doses of the drug.

Plan of Work

1. Literature survey
2. Procurement of materials
3. Experimental

A. Drug authentication
B. Compatibility study
C. Calibration curve of gliclazide
D. Phase solubility study
E. Formulation of solid dispersion.
F. Evaluation and characterization of solid dispersion:
a. Drug content
b. Interaction study
c. Thermal study
d. Assessment of crystallinity
e. In vitro dissolution study
f. In vivo pharmacodynamic study

4. Stability study of optimized formulation
5. Compilation of data

Experimental

Materials: Gliclazide was a generous gift from Lupin Research Park, Pune, India. Pluronic F68 and Pluronic F127 were kindly supplied as gift samples by BASF, Mumbai, India All other chemicals and solvents were of analytical reagent grade.

Drug Authentication

Melting Point: Primary authentication of GLZ was done by melting point determination. Melting point was checked by conventional capillary method and reported uncorrected.

FTIR Spectroscopy: FTIR Spectroscopy of GLZ was done by using FTIR Spectrophotometer (Schimadzu FTIR 8400S, Japan). The samples were scanned over wave number region of 4000 to 400 cm-1 at resolution of 4 cm-1. Samples were prepared using KBr (spectroscopic grade) disks with hydraulic pellet press at pressure of 7-10 tons.

UV Spectroscopy: A solution of 100 µg/ml concentration of GLZ in 0.1N hydrochloric acid was prepared for determination of λmax. The sample was scanned on Double beam UV-VIS spectrophotometer (Systronics -Double Beam Spectrophotometer- 2201).

Calibration Curve of Gliclazide: Calibration curve of absorbance vs. concentration of GLZ was plotted in 0.1N hydrochloric acid. The solutions of different concentrations (0-20 µg/ml) were prepared from stock solution of 100 µg/ml concentration in triplicates. The absorbances of solutions were read spectrophotometrically at 228.8 nm.

Solubility Study: Absolute solubility of GLZ was carried out by the method reported by Higuchi and Connor in distilled water and 0.1N HCl. Excess of GLZ was added to 10 ml study fluid in a screw capped vial. Samples were shaken on rotary shaker at constant speed at 25°C±2°C for 48 hr. The saturated solutions after equilibration for 24 hr were filtered through a membrane filter having pore size of 0.45 µm. Filtrates were suitably diluted and estimated spectrophotometrically for GLZ content at 228.8 nm.

Compatibility Study: The drug and excipients in different ratios were equally distributed in glass ampoules. They were kept at 37°C, 45°C, 60°C and room temperature of 25°C. The samples were analyzed for its physical appearance, UV scanning to examine the compatibility. Possibility of interaction was also studied by FTIR spectroscopy with 1:1 physical mixture of drug and excipients.

Phase Solubility Study: The phase solubility analysis for GLZ was done by Higuchi-Connor‟s method with two grades of poloxamer viz. Pluronic F68 and Pluronic F127. Excess amount of GLZ was added to screw-capped vials containing 10 ml of aqueous solutions of Pluronic F68 and Pluronic F127 with varying concentrations (5% to 30%). Vials were shaken with rotary shaker for 48 hr at a controlled temperature at 25ºC±2ºC. Supernatant was centrifuged after equilibration period for 24 hr. Aliquots were analyzed by UV- spectrophotometry at 228.8 nm.

RESULTS AND DISCUSSION

Authentication of Drug

Melting point: Melting point of GLZ was found to be in a range of 178 to 1810C. The reported value is 180-182°C. Thus, the melting point of GLZ sample complies with the standard reported value.

UV Spectra Analysis: The UV spectrum of GLZ in 0.1N HCl showed that the λmax was found to be at 228.8 nm which was in accordance with the previously reported values.

FTIR Spectroscopy

It shows an intense peak at 3272.54 cm-1 corresponding to N-H stretch; 1712.24 cm-1 attributed to carbonyl. functionality. Sulphonyl group in pure GLZ can be characterized by strong symmetric stretching peak at 1163.27 cm-1 and anti-symmetric vibration peak at 1348.98 cm-1. The observation of characteristic peaks of GLZ in FTIR spectra of sample authenticates the sample as pure GLZ.

Solubility Study

The solubility of GLZ in distilled water is found to be 57.607±3.677 µg/ml; while the solubility in 0.1N HCl was 82.43±0.67 µg/ml.

Compatibility Study

Compatibility Study by UV spectroscopy

Compatibility study shows that the physical appearance of the mixture remains unaffected on storage in different temperature condition. Compatibility was also examined by using UV spectrophotometry at initial, second week and fourth week. The scanning values were found in the range of 228.8 nm

Compatibility Study by FTIR Spectroscopy

Compatibility study was carried out by using FTIR spectroscopy. Drug and excipients with equal proportions showed all the characteristic peaks of their respective functional groups. Hence, it can be considered that the drug and poloxamers are chemically compatible and can be togetherly incorporated together in the formulation.

Standard Calibration Curve of Gliclazide

The standard calibration curve of UV absorption vs. concentration of GLZ at 228.8 nm showed very good linearity characterized by good coefficient of correlation (R2= 0.9999) over the concentration range of 0-20 µg/ml. Thus it was found to obey Beer- Lambert‟s law over this range. The line equation of standard calibration curve for estimation of GLZ in 0.1 N HCl can be given by equation. Y = 0.0481X - 0.0015

Phase Solubility Study

Poloxamers are water-soluble non-ionic surface active agents, which have been widely used in pharmaceutical applications as emulsifier and solubilizing agents. As stated in preformulation study, the intrinsic solubility of GLZ was 1.781 X 10-4 M/ml, which is in accordance with the reviewed literature[158]. At 25°C, aqueous solubility of GLZ was found to be increasing with increased poloxamer concentration as the carrier concentration increased both grades of poloxamer at the tested concentrations with AL type of solubility phase diagram[154]. Phase solubility curves with Pluronic F68 and Pluronic F127 are shown respectively. The significant enhancement in the solubility of GLZ might be attributed to the surfactant effect due to polymeric phase which creates a favorable environment around drug particles reducing the interfacial tension and enhancing wettability of the hydrophobic drug. Thus, the use of poloxamer for designing solid dispersion for solubility enhancement of GLZ appears to be a promising approach.

CONCLUSION

The aim of present investigation was to increase dissolution rate of gliclazide by application of the approach of solid dispersion. In present work, preformulation study was carried out to authenticate drug and to profile its solubility and phase solubility study. Hence, from preformulation study it was concluded that the drug was authentic based on the data obtained in FTIR spectrum and UV analysis. The solubility of GLZ in distilled water is found to be 57.607±3.677 µg/ml; while it was 82.43±0.67 µg/ml in 0.1N HCl. Dissolution of GLZ alone was very slow and incomplete up to 120 min. According to the obtained results, only 35.61±0.24 % of drug was dissolved after 2 hr. Hence, as the intrinsic solubility as well as rate of drug dissolution is poor, there is strong need to enhance its solubility and dissolution. Phase solubility study indicates that solubility of GLZ increased with poloxamer concentration. The improvement in solubility can be attributed to effect of poloxamer. Hence, poloxamer has ability to increase dissolution rate and can be considered as a suitable carrier for formulation of solid dispersion. Solid dispersions were formulated by solvent evaporation and melt fusion techniques. For the comparative study, corresponding physical mixtures were also prepared. Solid dispersions were characterized for chemical stability by Differential Scanning Calorimetry, Fourier Transform Infra-Red Spectroscopy and Thin Layer Chromatography and found to be stable.

REFERENCE

1. Aggarwal S, Gupta G D, Chaudhary S. Solid Dispersion as an Eminent StrategicApproach in Solubility Enhancement of Poorly Soluble Drugs. IJPSR, 2010; 1: 1-13.
2. Arno A. Enose, Priya K. Dasan, H. Siva Ramakrishnan and Sanket M. Shah. Formulationand Characterization of Solid Dispersion Prepared by Hot Melt Mixing: A Fast Screening Approach for Polymer Selection. J Pharma, 2014; 1-13.
3. Arora S.C., Sharma P.K, Irchhaiya R, Khatkar A. Development, Characterization andSolubility Study of Solid Dispersion of Cefpodoxime Proxetil by Solvent Evaporation MethodIJCRGG, 2010; 2: 1156-1162.
4. Dalwadi S, Soni T, Thakkar V, Tejal G. Silymarin-solid dispersions: Characterization andinfluence of preparation methods on dissolution. Acta Pharma, 2010; 60: 427-444.
5. Dhillon B, Goyal N, Malviya R, Sharma P (2014). Poorly Water-Soluble Drugs: Change inSolubility for Improved Dissolution Characteristics a Review. Global J Pharmacology.
6. Shinde S.S, Patil S.S., Mevekari F. I, Satpute A.S. An approach for solubilityenhancement: solid dispersion. Int J Adv Pharma Sci. 2010; 1: 299-308.
7. Sridhar I, Doshi A, Bhagyashri J, Wankhede V, Doshi J (2013). Solid Dispersions: AnApproachto Enhance Solubility of poorly Water-Soluble Drug. Journal of Scientific and Innovative Research.
8. Yadav B and Tanwar Y.S. Application of solid dispersions: J. Chem. Pharm.Department of Pharmaceutics Sultan-Ul-Uloom College of Pharmacy, 2015; 56.
9. Vemula V, Venkateshwarlu L, Lingala S, (2010). Solubility Enhancement Technique. Int.J.Pharma. Sciences Review.
10. Saharan V, Kukkar V, Kataria M, Gera M, Choudhury P (2009). Dissolution Enhancement ofDrugs. Part I: Technologies and Effect of Carriers. Int J Health Res.