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A REVIEW ON FORMULATION OF GLICLAZIDE NANOSUSPENSION BY PRECIPITATION METHOD

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ABSTRACT

In the present study, an attempt was made to prepare Nanosuspension of Gliclazide which is an oral antihyperglycemic agent used for the treatment of non-insulin-dependent diabetes mellitus (NIDDM). Nanosuspension containing the drug was prepared by precipitation method using combination of polymers such as PVP K-30, poloxamer (407), Sodium lauryl sulphate (SLS), and acetone. Estimation of Gliclazide was carried out spectrophotometrically at 232nm. The Oral Nanosuspension were evaluated for various physical and biological parameters, drug content uniformity, particle size analysis, zeta potential, in-vitro drug release, short-term stability, drug-excipient interactions (FTIR). IR spectroscopic studies indicated that there are no drug-excipient interactions. The formulations F1 to F9 (containing PVP K-30, Eudragit S 100, SLS, Poloxamer (407), and Acetone) used different ratio were found to be promising, of that formulation F9 containing Eudragit S 100 and PVP K-30 releases 99.43% at the end of 20min & it follows first order drug release kinetics. These formulations have displayed good Nanosuspension strength.

KEYWORDS: Gliclazide, Nanosuspension, PVP K-30, SLS, poloxamer (407), and Methanol.

INTRODUCTION

Nanosuspension

The nanotechnology is presently gaining attention from researchers and pharmaceutical world. In the pharmaceutical field, the term “nanoparticle” is usually used to describe submicron sized particles. The drug of interest is dissolved, entrapped or encapsulated within

the particles. Nanoparticle technologies have been used as important strategies to deliver drugs, including peptides and proteins, vaccines and more newly nucleotides.[1] In pharmaceutical field, nanosuspension, nanoemulsion, self nanoemulsifying drug delivery system, solid lipid nanoparticle (SLN) etc are covered under nanotechnology area.

A nanosuspension consists of drug nanocrystals, stabilizers, typically surfactants or polymeric stabilizers, and a liquid dispersion medium. Drug nanocrystals are pure solid drug particles with a mean particle size less than 1 μm, generally between 200 nm and 500 nm.6 Although the term nanocrystals implicates a crystalline structure, the particles can be crystalline, partially crystalline or absolutely amorphous. The dispersion medium can be water, mixtures of water and other non-aqueous media or non-aqueous media. Nanosuspension permits delivery of drugs that are poorly soluble in water or unstable in biological fluids.

Nanosuspensions are colloidal dispersions of nanosized drug particles stabilized by surfactants. They can also be defined as a biphasic system consisting of pure drug particles dispersed in an aqueous vehicle in which the diameter of the suspended particle is less than 1μm in size. Reduction of drug particles to nanometer range leads to an enhanced dissolution rate not only because of increased surface area but also because of saturation solubility. The increase in the saturation solubility and solution velocity of nanoparticle is due to increase of vapour pressure of the particles.[2]

Method of Preparation of Drug Nanosuspension

Nanosuspensions can be prepared using different techniques, which could be classified generally in two groups based on the principle on which the nanorange is achieved. Top down production, in which the size of drug macrosuspension is reduced up to nanosuspension and second is bottom up technique in which the drug nanoparticles are assembled from a solution of drug by controlling the rate and growth of nuclei formed.[3]

Bottom up technique

a) Nanoprecipitation

b) Supercritical fluid technology

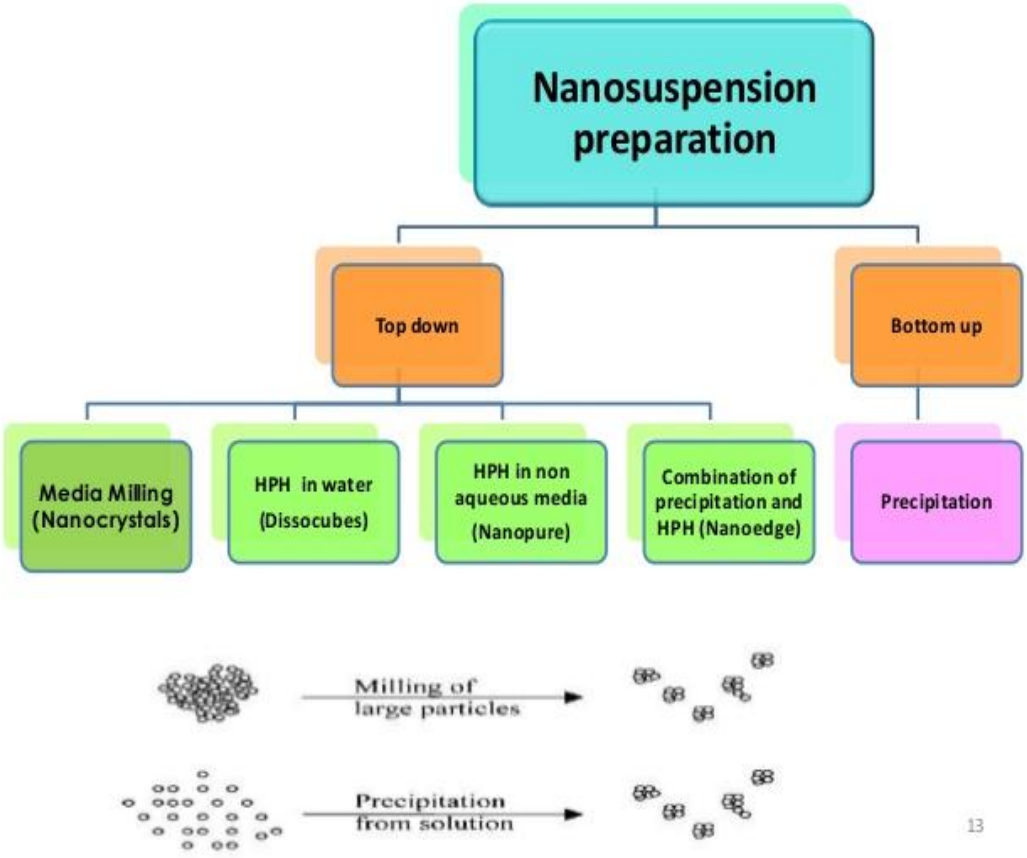
c) Using microemulsions and emulsions as templates.

Top down technique

a) Media milling

b) Dry co-grinding

c) High pressure homogenization



Schematic representation of nano-suspension preparation

Bottom up Technique

Nanoprecipitation

In the precipitation method the poorly water-soluble drugs are dissolved in a suitable solvent and the solution is added into a miscible anti-solvent with stirring and/or agitation. Stabilizers are used to avoid the spontaneous aggregation of molecules. Final morphology of nanoparticles are affected by factors such as types of solvents, the volume ratio of antisolvent to solvent, stirring speed, amount of drug etc.[4]

Nucleation and crystal (particles) growth of drug particles from a supersaturated solution involves in the precipitation process. The supersaturated solution is a solution in which the concentration of solute exceeds the saturation or equilibrium solute concentration at a given

temperature. Thus, a supersaturated solution is not at equilibrium, and crystallization of the solute occurs in order to move about the solution towards equilibrium. After initial particle nucleation, both nucleation and crystal growth attempt to take the supersaturated solution to equilibrium. The time required for crystallization depends on the driving force of supersaturation.

The nucleation velocity decreases with increasing surface energy and increases with increasing temperature and degree of supersaturation. High nucleation rates offer the potential to create a large number of submicron particles in the final dispersion, as long as the growth can be seized by stabilizers. Precipitation method is used in both the chemical and pharmaceutical industries for the production of nanoparticles.[5] Solvent evaporation and salting out are the usual precipitation technologies, having common the drawbacks of poor control over particle morphology and particle size and size distribution producing a wide range of particle sizes.[6]

Precipitation process has also been joined with high shear processing. Precipitation of friable materials for subsequent fragmentation under conditions of high shear and/or thermal energy covered under the NANOEDGE technique a registered trademark of Baxter International Inc. and its subsidiaries.[7] It is accomplished by a combination of rapid precipitation and high-pressure homogenization. Rapid adding of a drug solution in to an antisolvent direct to sudden supersaturation of the mixed solution, and generation of fine crystalline or amorphous solids. Precipitation of an amorphous material may be favored at high supersaturation when the solubility of the amorphous state is exceeded. It has been reported that nanosuspensions are successfully prepared by precipitation techniques.[8]

Advantage

- Simple process
- Ease of scale up
- Low cost equipment

Disadvantage

- Drug has to soluble at least in one solvent and that this solvent needs to be miscible with a non-solvent.
- Growing of drug crystals needs to be limit by surfactant addition

Chemically Gliclazide is [1-(3-azabicyclo (3,3,0) oct- 3-yl)-3-p-tolylsulfonylurea]. It is a second generation hypoglycemic sulfonylurea which is useful in the treatment of non-insulin dependent diabetes mellitus (NIDDM). Gliclazide is a white crystalline powder, relatively insoluble in water. The pKa of Gliclazide is 6.6. It exhibits slow GI absorption rate and inter individual variations of its bioavailability. Oral bioavailability of drug in rang of 79 to 81 percent. Half-life of drug is about 10hr. Thus solubility enhancement and dissolution enhancement of Gliclazide from its dosage form is an important issue for its in vivo bioavailability and therapeutic efficacy.[9]

AIM AND OBJECTIVES

AIM

The aim of the present work is to develop oral Nanosuspension of Gliclazide by precipitation method and to evaluate it.

OBJECTIVES

- To perform Preformulation studies for the pure drug.
- To construct standard calibration curve for gliclazide.
- To perform Drug-Excipient Compatibility Studies.
- To formulate and develop the Nanosuspension and formulations.
- To find out drug content for all the prepared nanosuspensions.
- To determine drug entrapment efficiency for all the prepared nanosuspensions.
- To evaluate the formulation by establishing drug release kinetics using various dissolution models.
- To establish *In–vitro* drug release compliance with the established criteria.
- To establish stability studies of the final formulation, for the selected oral Nano suspension.

MATERIALS AND METHODOLOGY

Materials

Excipients and Chemicals

All the materials used in the formulations, evaluation and other experiments are listed below. The chemicals procured for the study are of laboratory reagent grade. The double distilled water was used in all experiments.

List of Materials Used

S.NO	Materials	Manufactured by
1	Gliclazide	Sri Krishna Pharmaceuticals, Hyderabad
2	Eudragit S 100	Colorcon , Goa
3	Poloxamer 407	Colorcon, Goa
4	Sodium Lauryl Sulphate	SD Fine chem., Mumbai
5	PVP K30	SD Fine chem., Mumbai
6	Acetone	Rankem chemicals, Hyderabad
7	Hydrochloric Acid	Rankem chemicals, Mumbai
8	Potassium Dihydrogen phosphate	Merck, Mumbai
9	Sodium hydroxide	Merck, Mumbai
10	Distilled Water	SD Fine chem., Mumbai

Equipments used: Following equipments were used for preparation and evaluation.

List of Equipment and Instruments

S.NO	Equipment	Manufacturer	Model No
1	Electronic Weighing Balance (0.001mg-200gm)	Shimadzu, Japan	BL-220H
2	Digital melting point apparatus	Contech instruments	CDMP-300
3	Dissolution test apparatus	Electrolab, TDT-06N	
4	UV- Visible spectrophotometer	Shimadzu, Japan	UV-1700
5	Magnetic stirrer	Remi, Ahmedabad	1MLH
6	FTIR spectroscopy	Shimadzu, Japan	1700S
7	Digital pH meter	ELICO	101
8	DSC	Shimadzu	DSC-60
9	SEM	JEOL, Japan	JSM 5200
10	PCS	Malvern Zetasizer	
11	Zeta potential	Malvern Zetasizer	
12	Stability Chamber	Thermolabs	TH 80S/G

PLAN OF WORK

Methods

Pre-formulation studies

Prior to the development of nanosuspension form, it is essential that certain fundamental physical and chemical properties of the drug molecule alone and when combined with excipients are determined. This first learning phase is known as pre-formulation. The overall objective of the pre-formulation is to generate information useful to the formulator in developing stable and bioavailable dosage forms which can be mass produced. The goals of pre-formulation studies are.

- To evaluate the drug substance analytically and determine its necessary characteristics, and
- To establish its compatibility with different excipients.

- Spectroscopic study
- Identification of pure drug

Organoleptic properties

The colour, odour and taste of the drug were recorded using descriptive terminology.[10]

Determination of Melting Point

The temperature at which the first particle of the substance completely melts is regarded as melting point of the substance. The temperature at which the first particle starts to melt and last particle completely melts is regarded as the range of melting point. Melting point of the drug was determined by capillary tube method.

Solubility studies of Gliclazide

Solubility of Gliclazide was carried out in different buffers as follows.

1) Purified water

2) 0.1 N hydrochloric acid (HCl), (pH 1.2) USP

3) Phosphate buffer pH 6.8, USP

Preparation of different buffer media

pH 1.22 buffer: 85 ml of 0.2 M HCl was added to 50 ml of 0.2 M potassium chloride solution and volume was made up to 200 ml in volumetric flask.

pH 6.8 Phosphate Buffer: Placed 50.0 ml of 0.2 M potassium dihydrogen phosphate in a 200-ml volumetric flask and 22.4 ml 0.2 M sodium hydroxide was added, then made up the volume with water.

0.2M Potassium Dihydrogen Phosphate: Dissolved 27.218 g of potassium dihydrogen phosphate in water and dilute with water to 1000 ml.

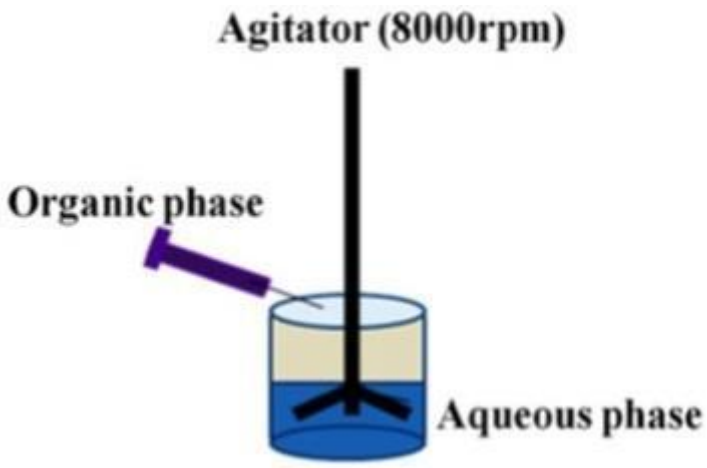
0.2M Sodium Hydroxide: Dissolved 8.0 g of sodium hydroxide in 1000 ml.

Saturated solutions were prepared by adding excess drug to the vehicles and shaking on the shaker for 24 hrs at 25^0C under constant vibration. Solubility of Gliclazide was determined at 25 ± 1^0C. The solubility of Gliclazide in distilled water and different buffers was determined by shake flask method. According to this method the drug was added in surplus to different aqueous mediums like distilled water, 0.1N HCl, pH6.8 Phosphate buffer. The flasks were closed with aluminium foil and constantly agitated at room temperature 25 ± 1^0C for 24 hrs using mechanical shaker. After 24hrs, the solution was filtered through a 0.45 µm membrane

filter. The filtrates were diluted suitably, and amount of drug solubilised was then estimated by measuring the absorbance at 232nm using UV-VIS spectrophotometer against corresponding solvent blank.

Preparation of Nanosuspension

Nanosuspensions were prepared according to nanoprecipitation method given by Fessi et al. with slight modification. ERLPO polymer and specified quantity of drug were dissolved in acetone at 40°C to form uniform organic solution. The prepared organic solution was then injected slowly dropwise with the help of a syringe into an aqueous phase containing 2%(w/v) P-188 kept under high-speed mechanical agitation of 8,000 rpm to get desired nanodispersion (Fig. 1). Prepared nanosuspension was then stirred magnetically at 500 rpm at room temperature for 12 h to evaporate organic solvent. Complete evaporation of acetone was determined by spectrophotometric method using vanillin. The volume was then adjusted with the addition of triple distilled water to recover loss in volume. All samples were prepared in triplicate. Drug/polymer ratio and agitation time was varied keeping other parameters constant.[11]



Setup used for the preparation of nanosuspension.

Evaluation Parameters of Nanosuspensions: To perform

- Particle size analysis
- Particle Charge (Zeta Potential)
- % Drug Content
- Apparent Solubility
- Dissolution Studies

- Scanning Electron Microscopy (SEM)
- Powder X-Ray Diffraction (PXRD)
- Stability studies.
- Flow Properties
- Stability of Nanosuspensions

SUMMARY

Gliclazide is an oral antihyperglycemic agent used for the treatment of non-insulin-dependent diabetes mellitus (NIDDM). It belongs to the sulfonylurea class of insulin secretagogues, which act by stimulating β cells of the pancreas to release insulin. Sulfonylureas increase both basal insulin secretion and meal-stimulated insulin release. Gliclazide has been shown to decrease fasting plasma glucose, postprandial blood glucose and glycosolated hemoglobin (HbA1c) levels (reflective of the last 8-10 weeks of glucose control). Gliclazide is extensively metabolized by the liver; its metabolites are excreted in both urine (60-70%) and feces (10-20%).

Nanosuspension containing drug was prepared by precipitation method by using combinations of polymers PVP K-30, Eudragit S 100, acetone, SLS, Poloxamer 407, and quantity sufficient of distilled water. Estimation of Gliclazide was carried out spectrophotometrically at 232 nm.

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