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FORMULATION AND DEVELOPMENT APPROACH FOR TABLETS BY SOLID DISPERSION METHOD

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ABSTRACT

Authentication of the drugs was done by analytical techniques using FTIR, UV, and DSC. Further drug excipients compatibility was done and found that drugs are very well compatible with the other selected specified excipients. The Solid Dispersion technique has been performed as promising valued and cost effective technique for enhancing Solubility and Dissolution rate, compressibility and micrometric properties. "Solid Dispersion is an extension of spherical crystallization technique, which enables simultaneous crystallization and agglomeration of two or more drugs or crystallization of a drug and its simultaneous agglomeration with another drug or excipient." The selected drug was characterized and identified by melting point : Solubility, partion coefficient, IR, DSC, XRD and for analysis of drug uv spectroscopy is done . For Solid Dispersion polymers and solvent system are selected and used with different concentration. Solid Dispersion are obtained with help of polymer, good solvent and bad solvent etc. Initial batches of Solid Dispersion were obtained of different concentration of PVP K90, PVP K30 and PVP K25. Solubility data was obtained in triplicate of preliminary batches. Optimization is done on 8 batches and further evaluated for its Solubility and % Drug Release. Out of 8 optimized batches batch was further used for study depending on Solubility data. Solid Dispersion showed enhancement in physicochemical and micrometric properties. From the above optimized Solid Dispersion batch Fast dissolving tablets were formulated by using various concentration of Polymer and wetting agent by direct compression method and different batches were studied for Dissolution study and disintegration time. From above discussion it was concluded that Fast dissolving tablet were prepared by direct compression method exhibited disintegration time 5 min and improved Dissolution rate.

KEYWORD: Drug, Solid Dispersion, Fast dissolving tablet, crystallization, micrometric.

INTRODUCTION

The simplest and easiest way of administering drugs is through oral route. Over other types of dosage forms the oral dosage forms have many advantages like accurate dosage, less bulk, greater stability and easy production is possible. At present, to the formulation scientists in the pharmaceutical industry one of the most major challenges is formulation of poorly soluble compounds for oral delivery. Nearly 40% of identified potential new drug by pharmaceutical industry are poorly water soluble. Poor water soluble compounds. Large dose is required to produce desirable effect for the poor water soluble drug because they show decreased release rate and poor bioavailability but large dose may leads to toxicity of the drug. So the best option for increasing release rate is improvement of the solubility through formulation approaches.[1] When aqueous solubility of a drug is less than 100µg/ml, Poor dissolution: Intrinsic dissolution rate ow permeability. Solubility of drug can be increase by increasing of dissolution rate.

Solubility is defined in quantitative terms as the concentration of solute in a saturated solution at a certain temperature, and qualitatively, it can be defined as the spontaneous interaction of two or more substances to form a homogeneous molecular dispersion. Practically the Solubility of a solute in a solvent at a specific temperature is the number of grams of the solute essential to saturate 100 gm of the solvent at that temperature. Considering Solubility properties will offer a basis for understanding the excellent rule of Solubility- "Like dissolves like"(Brahmankar D.M. Jaiswal S.B. 2002).[1]

When a solute is in equilibrium with the solute is called saturated solution and unsaturated or sub saturated solution is one comprising the dissolved solute in a concentration below that essential for complete saturation at a sure temperature. A supersaturated solution contains more dissolved solute than it would usually hold at a definite temperature, where the undissolved solute is also present(SINKO 2006).[2]

The Solubility of a drug can be expressed quantitatively in several modes like in terms of molality, molarity, mole fraction, parts per million,etc(Lieberman H.A., Lachman Leon 1992a)(A. Jouyban-Gharamaleki 1998).[3,4] A pharmaceutically active compound is traditionally categorized as highly soluble when the largest dose of a drug is soluble in less than 250ml water over a pH range from 1 to 6.8. Soluble drugs have a Solubility range of greater than or equal to 33mg/ml. sparingly soluble drugs have a range from 10 to 33mg/ml, slightly soluble drugs from 1 to 10mg/ml and drugs with solubilities below 1mg/ml are ordered as practically insoluble. Sparingly soluble or less than sparingly soluble drugs mentioned to as "low Solubility" drugs are recurrently problematic to formulate into liquid dosage forms(Waterbeemd 2000).[5] The U.S. P. National Formulary describes the Solubility of drugs as the number of milliliters of solvent essential to solubilize one gram of solute. For constituents whose solubilities are not certainly known, the values are described in pharmaceutical compendia by the use of assured common terms.

- **Solubility enhancement techniques**

○ **Nanonization:** Nanoemulsions present large o/w interfacial areas and radically low interfacial tensions. They have greater capacity to solubilize than simple solution of micelles. Being thermodynamically stable, Nanoemulsions hold an edge over unstable dispersions. The ability of o/w Nanoemulsions to integrate hydrophobic drugs into the oil phase lends them more solubility. As per the literature, Nano-emulsions have made plasma concentration and bioavailability profiles of drugs more consistent. Nanonization are used for conversion of drug particle in to nano-crystals having the size of 200-600nm.

○ **Supercritical fluid recrystallization (SCF):** Those fluids have temperature and pressure greater than its critical temperature and pressure so as properties of gas and liquid. Example of supercritical fluid is carbon dioxide. These are compressible at temperature and pressure so as allow for alteration in density and mass transfer. By this method drugs are solubilize. It can be re-crystallized with reduction of particle size of pharmaceutical chemicals.[6]

○ **Use of surfactant:** Permeability and dissolution rate can be increased be surfactant. Absorption rate also be enhance due to increasing of particle size. Mechanism involves firstly wettability and then penetration of solvent in the particles of drug. Solubility of much poorly water soluble anti-microbial drugs can be increased by use of surfactant. Surfactant are three types; anionic, cationic and non-ionic. Anionic and cationic select over the non-ionic surfactant. It acts as good solubilizing agent.

○ **Evaporative precipitation**: This method involves phase separation for nucleation and growth of micro or nano particle occurs. For this technique low boiling point of solvents are selected and sufficient amount of drug is added after that solution is passed and pumped through tube which is heated under suitable temperature. Heated solution sprayed through atomizing nozzle and surfactants are added for reduction of particle size. Fine particles are generated which improve the solubility and permeability of drug.[7]

○ **Micronization:** Reduction of particle size occur so as increase of surface area which increase the dissolution rate and bioavailability of drug .The particle size after micronization is 1-10 microns. This method involves spray drying and attrition method.

○ **Sonocrystallisation:** This method used for the reduction of particle size by use of ultrasound and liquid solvent. It is a new method for increasing of solubility.[8]

○ **Nanomorph technology:** In this method crystalline state of less water soluble drugs change in to amorphous state.[9,10]

○ **Homogenization:** Drug particles are reduced under high pressure and high velocity by applying of shear force. By this phenomenon drugs particles get dispersed. Homogenization depends on pressure and nature of drug.[10]

○ **Solid dispersion:** Chiou and Riegelman dispersions as "the dispersion of one or more active Ingredients in an inert excipient or matrix, where the active ingredients could exist in finely crystalline, solubilize, or amorphous stat''.

Solid dispersion is the most important method for improving of solubility of poorly water soluble drugs. It also increases the bioavailability by physical modification. Solid dispersion classified in to six categories; solid solution, eutectic mixtures, glass suspensions, amorphous precipitates, complex and above combinations.

Solid dispersion improves the solubility and dissolution rate by reducing of wettability and porosity. Solid dispersion can be prepared by solvent evaporation, hot melt extrusion, co-grinding and supercritical method and etc.

EXPERIMENTAL PROTOCOLS

- **Physicochemical Characterization of Drug (API)**

○ Saturation Solubility

The saturation Solubility is used to predict the Solubility of the drug. The saturation Solubility of Drug was determined in water. The Saturation Solubility studies were conducted according to the method given by Higuchi and Connors in triplicate. To determine saturation Solubility, an excess amount of Drug was added to vials having 10 ml of distilled water. The vials are subjected to rotary shaking for 6 hours and then allowed to stand for equilibrations for 24 hrs. After that Samples were filtered through Whatmann filter paper and remainder was analyzed by UV Spectrophotometer after appropriate dilutions.

○ Partition coefficient

The partition coefficient for the drug was determined in Octanol and Water and it was taken each 5ml and 10mg of the drug was added and the mixture was shaken for 5-6 hrs and then kept for 24 hrs for equilibrium. From the

mixture, octanol was separated and then absorbance of the remaining mixture is taken and the partition coefficient was calculated.

- **Melting Point**

The melting point of Drug was determined by the Digital melting point apparatus (LAB TRONICS Ltd). The capillaries filled with powder were placed in the Melting point apparatus containing liquid paraffin. The melting point of the drug powder was noted. Each observation was made in triplicate determination.

- **Optimization of Solid Dispersions**

Optimization of SDs is done with studying one factor at a time and Characterization of Solid Dispersions performed

- **Saturation Solubility of SDs**

The saturation Solubility of SDs was determined by the method given using SDs as a sample.

- **Melting point determination**

The melting point of SDs was done by the same procedure carried out for melting point determination of drug and SDs.

- **Pre-formulation characterization of Solid Dispersions**

After SDs was performed the pre-formulation characterization of SDs and their comparison with Drug was done. The pharmaceutical processing properties i.e. angle of repose, bulk density; tapped density, Carr's index and Hausner's ratio were studied in comparison to pure Drug.

- **Bulk Density**

Bulk density or apparent density is defined as the ratio of mass of a powder to the bulk volume. The + of a powder depends primarily on particle size distribution, particle shape, and the tendency of the particles to adhere to one another. Accurately weighed quantity of sample (10 gm) was placed in 50 ml measuring cylinder. The volume occupied by powder was determined without disturbing the cylinder. Bulk density for pure drug and all SDs was calculated using following equation.

- **Tapped Density**

Accurately weighed quantity of sample (10gm) was placed in 50 ml measuring cylinder. The measuring cylinder was tapped for fixed number of taps to obtain constant volume of powder bed. The final volume was noted and tapped density was determined by using following equation.

- **Carr's compressibility index (C.I)**

The compressibility index measures of the propensity of powder to be compressed. The packing ability of drug was evaluated from change in volume, which is due to rearrangement of packing occurring during tapping. C.I is frequently used as an indication of flowability of powder. It is indicated as Carr's compressibility index (CI) and was determined by using following equation.

- **Hausner's ratio**

Hausner's ratio gives an idea regarding the flow of the blend. It is the ratio of tapped density to the apparent density. Hausner's ratio was determined by using following equation.

- **Angle of Repose**

The angle of repose is an indication for flow ability of powder. The lower tip of funnel was kept at 2.5 cm from the surface of table. 5 gm of drug and SDs powder was poured from funnel to form a pile. Then funnel was adjusted up to height of pile and a circle was drawn around the pile. The height of tip from surface of table was measured as pile height (h) and diameter of pile (d) was measured taking average of three average diameter of circumference of the circle. The angle of repose was calculated by using following equation.

- **Process yield and Drug content**

For determination of drug content in SDs were powdered from which eqvivalent to 100 mg of Drug was weighed and added in solvent methanol and then filtered through whatman filter paper and drug in solvent was determined spectrophotometrically at 239 λ .The percentage drug content was calculated using following formula.

- **Evaluation of Prepared Immediate Release Tablets**
  - **Thickness**

The thickness of tablet is important for uniformity of tablet size. The thickness of the tablets was determined using a Vernier Calliper. Three tablets from each batch were used.

- **Weight variation test I.P.**

The procedure mentioned in I. P. was selected for uniformity of weight. Ten tablets were selected randomly and weighed. Average weight of the tablet was determined. The tablets were weighed individually and the weight variation was determined. The limits of weight variation test according to I.P (2010).

- **Friability**

Friability is the measure of tablet strength. In this test whole tablets corresponding to about 6.5 gm subjected to combined effect of shock abrasion by utilizing a plastic chamber which revolves at a speed of 25rpm, dropping the tablets at a distance of 6 inches in each revolution. A sample of pre-weighed tablets was placed in Roche Friability tester (Veego Instruments Ltd. Mumbai). This was then operated for 100 revolutions. The tablets then dedusted and reweighed. Permitted friability limit is 1.0%. Tablets were then weighed and friability values were determined.

- **Hardness (Crushing strength)**

The term hardness indicates the ability of a tablet to

withstand mechanical shocks while handling. It is generally expressed in Kg/cm2 or in Newton (N) and the hardness of about 30-60 N. Hardness of a tablet was measured using hardness testers.

In vitro Disintegration time

The disintegration time of Immediate Release tablets was determined in conventional disintegration test apparatus in agreement with the official European Pharmacopoeia monograph Immediate Release tablets.

The in-vitro disintegration studies were carried out using Tablet Disintegration Test Apparatus. One tablet was placed in each of the six tubes of the basket assembly and disk was added to each tube. This assembly was then suspended in one-liter beaker containing water maintained at 37±20C. The basket was then moved up and down through a distance of 5 to 6 cm at a frequency of 28 to 32 cycles per minutes. The time required for complete disintegration of the tablet was recorded.

- **In vitro Dissolution test**

Dissolution profiles of immediate release tablets were determined using the USP Method II with paddle spindle, speed at 50 rpm. Dissolution was performed in 900 ml of 6.8 PBS containing 1% SLS, maintained at 37 ± 0.5°C. 5 ml of samples were withdrawn at specified time intervals. The volume of Dissolution fluid was adjusted to 900 ml, by replacing each 5 ml aliquot withdrawn with 5 ml of 6.8 PBS containing 1% SLS solution, pre- warmed at 37±0.5°C. Samples were withdrawn and analyzed at 239 nm, using UV spectrophotometer (SHIMADZU 1800). The data presented is the average of 3 individual determinations.

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