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DESIGN AND DEVELOPMENT OF SUPERSATURATED DRUG DELIVERY SYSTEM OF METFORMIN HCL

Manoj R V[*1], Parthasarathi K Kulkarni[2], Nagendra R[3], Venkatesh K[4] and Hanumanthachar Joshi[5]

[1,2,3,4]Department of Pharmaceutics, Sarada Vilas College of Pharmacy, Mysore.
[5]Department of Pharmacognosy, Sarada Vilas College of Pharmacy, Mysore.

***Corresponding Author: Manoj R V**

Department of Pharmaceutics, Sarada Vilas College of Pharmacy, Mysore.

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ABSTRACT

The basic drugs tend to precipitate when it moves from acidic pH to basic pH that is from the stomach to the intestine which decreases the availability of the drug for absorption. Certain polymeric carriers such as HPMC, PVP, and HPC inhibit the precipitation and can be used as carriers so that the drug will be in a solubilized state and easier to absorb. Supersaturated drug delivery systems are a potentially effective and novel way in pharmaceutical sciences to increase the absorption of drugs. The study investigates the formulation and assessment of SDDS to reach and sustain a supersaturated condition by using solid dispersion techniques. The FT-IR studies showed that the drug and excipients were compatible. Nucleation and crystallization studies were carried out for the drug with different polymer grades PVP K25, PVP K30, and PVP K90 among these polymers a suitable polymer was selected and solid dispersion was prepared by solvent evaporation method. The final formulation was examined for morphology using scanning electron microscopy and for compatibility using Fourier-transform infrared spectroscopy and differential scanning calorimetry. Compared to the pure drug, in vitro dissolution experiments showed a marked improvement in drug solubility and dissolution rate. An extended duration of the supersaturated condition was sustained, suggesting that the drug precipitation was effectively inhibited.

KEYWORDS: Supersaturated drug delivery system, Basic dugs, Basic pH, Precipitation inhibitors.

INTRODUCTION

The oral route is widely favoured for drug administration worldwide because of its convenience and widespread acceptance.[1-2] A drugs must have specific qualities, such as acceptable permeability, high dissolving rate, and adequate water solubility, in order to be considered a desirable option for oral administration.[3]

Candidates for drugs with these qualities can enter the systemic circulation and have the intended therapeutic effect. Oral bioavailability is therefore greatly impacted by drug metabolism, permeability, and aqueous solubility. When a drug is taken orally, it must be dissolved in order for absorption to occur. Drugs with low water solubility must be taken at high doses in order to achieve the necessary plasma concentrations and to achieve the intended therapeutic effect, which ultimately increases the risk of dose-related side effects. The drug's absorption and, thus, its oral bioavailability are influenced by its gut wall permeability. These characteristics led G.L. Amidon to divide the therapeutic candidates into four divisions the biopharmaceutical classification system (BCS) classes I, II, III, and IV.[4]

Roughly 90% of compounds in the discovery pipeline and 40% of medications having market approval were found to be more lipophilic and poorly soluble in water.[5] The researchers had found a number of formulation techniques to address issues with drug solubility and dissolution rate-limited absorption. These methods include complexation, lipid-based drug delivery systems, nano-vesicular and nanoparticulate systems, amorphization of pharmaceuticals, molecular adduct creation, and solid-state changes.[6-11]

Solid dispersions and drug cyclodextrin complexes, two traditional drug delivery methods, have demonstrated encouraging outcomes in enhancing the biopharmaceutical performance of weakly water-soluble components.[9,12]

These formulation techniques are well-known for their ease of use in formulation creation, which eliminates the need for complex equipment and leads to a finished product with excellent performance and a low cost. These two systems are referred to as supersaturating drug delivery systems because it is known that they cause supersaturation drug concentrations higher than

saturation solubility at the site of absorption, which increases oral bioavailability.[13]

In order to improve oral bioavailability, one or two active pharmacological components are disseminated in a biologically inert matrix to create a dose form called SD. Water soluble polymers including polyethylene glycol, polyvinyl pyrrolidone, cellulose derivatives, polyvinyl alcohol, water insoluble polymers, and tiny molecular weight sugars are examples of the inert carriers that are frequently utilized.[14]

The medication will eventually reach a supersaturation condition in the gastrointestinal fluid due to amorphization and particle size reduction, which will increase solubility and rate of dissolution at the gastrointestinal tract. Increased absorption and ultimately bioavailability are caused by the increased supersaturation level at the absorption site.[15]

Super saturable formulation

When super saturable formulations come into contact with the aqueous environment of the gastrointestinal tract, they can cause a supersaturated drug concentration. For medications to be absorbed in the intended amount of time, supersaturation needs to be created and sustained. Several variables affect formulation performance, including the compound's physicochemical characteristics, the methods of processing employed, and the drug's propensity to generate and retain a supersaturated solution. Precipitation inhibitors are necessary to stop premature crystallization in the gastrointestinal system because precipitation from nucleation and crystal formation in these supersaturated states might restrict absorption.[16]

Saturated Drug Delivery System

When a medication delivery system reaches its maximum solubility limit, more drugs cannot be added to improve the drug's absorption or dissolution. The drug in these systems dissolves partially to saturation; after this happens, the drug will not dissolve any further under the specified circumstances. Because it guarantees a stable condition and known concentration of the medication, this saturation can be beneficial. Amorphous solid dispersions, Nano particulate systems, and lipid-based formulations are examples of supersaturated drug delivery systems that are intended to improve the oral bioavailability and solubility of poorly soluble drugs by sustaining drug concentrations above equilibrium solubility for long enough periods of time to permit absorption.[17-24]

Supersaturation

Supersaturation is the driving force for crystallization comprising two steps Nucleation & Crystal growth.

Crystallization

Nucleation, or the arranging of ions and molecules for crystal development, is the first step in the process of crystallization, which is the solute mass's transformation from a liquid to a solid state. When the number of nuclei approaches a critical amount, tiny crystals first form, and growth and nucleation happen at the same time, resulting in a polydisperse mixture of particle ages and sizes. Different polymorphs of compounds can crystallize, and the resulting polymorph is frequently kinetically preferred over the most stable one. The solubility of the solute, the degree of supersaturation, the pace at which supersaturation forms, diffusivity, temperature, and surface susceptibility to nucleation are some of the variables that affect crystallization.[25,26,27]

Nucleation: The process of solute molecules separating from the solution known as the "birth of small nuclei" is the first step in nucleation. Supersaturated solutions tend to crystallize and move toward equilibrium. Nucleation is further divided into primary and secondary nucleation. Primary nucleation lacks a crystalline surface whereas secondary nucleation occurs in the presence of a surface and is affected by environmental and processing conditions while the Secondary nucleation is the formation of new crystals through mechanisms involving existing solute crystals.[25]

Precipitation inhibitors

When PPIs are present, it is typical for crystal habits to change. It has been demonstrated that the selective adsorption of the polymer to distinct crystal faces is the cause of the change in crystal habit. This is the sole known instance in which the presence of a PPI led to the development of an amorphous drug precipitate.[29,30]

Polymeric precipitation inhibitors

For uses in oral drug delivery, PPIs seek to keep the medication in a supersaturated, thermodynamically unstable state for long enough duration to permit absorption. Because of this, their impacts are often kinetic and only serve to slow down the precipitation process by preventing nucleation or crystal formation. On the other hand, changes in the thermodynamic features of the system are less frequent. PPIs major method of action is consequently not via co-solvency and they do not often promote equilibrium solubility. In contrast, surfactants, for example, are also capable of avoiding drug precipitation but normally do so via increases in drug solubility arising from micellar solubilization.[31]

MATERIALS AND METHODS

MATERIALS: Metformin HCl, different grades of PVP (K 25, K30, K90) and other reagents and solvents are analytical grade chemicals were used.

The drug characterization was done and formulation was developed.

METHODS

Melting point: The drug was taken in a capillary tube with one end closed. It is then heated at a controlled rate

using an electric heating coil. The melting point of a drug is the temperature at which it starts to melt.

Fourier Transform-Infra Red (FT-IR): Both drug and solid dispersion were analysed. The sample is mixed with KBr and the mixture is compressed to get the pellet and then placed in the sample compartment of the FTIR instrument. The sample is scanned with infrared radiation over a specific wavelength range of 4000 to 400cm^{-1}.

Thermal analysis (DSC) analysis: The thermograms of the drug and solid dispersion were recorded in DSC. Accurately, 10 mg of the sample was weighed, taken in an aluminium pan, and sealed to prevent moisture loss. Then heated at a controlled rate of 10˚C/min over the temperature range of 30˚C to 300˚C.

Scanning electron microscopy: The SEM analysis studied the morphology and surface topography of Metformin HCl and solid dispersion at room temperature, using a voltage of 15 kV and appropriate magnification. Sample was mounted on 5 mm silicon wafers and coated with gold (Au) using sputter coating in an argon environment. The specimens were electrically grounded to prevent the formation of electrostatic charges on the surface. As a precaution, a carbon coating was applied before the sample was subjected to electron scanning.

Ultraviolet-Visible (UV-Visible) Spectrophotometry: The drug was dissolved in pH 1.2 and pH 6.8 and absorbance maxima of drugs were determined by UV Spectrophotometer. Dissolve known quantities of the Metformin HCl in the simulated fluid (pH 1.2, pH 6.8).

Calibration Curve: Prepare a series of standard solutions with increasing concentrations. Set the UV spectrophotometer to the wavelength of maximum absorbance of 234 nm. Measure the absorbance of each solution. Plot the absorbance of each solution on the y-axis and its concentration on the x-axis.

CRYSTALLIZATION STUDY

Nucleation and Induction Time Determination: Nucleation-Induction time determination Crystal formations were studied by Induction time (IT) from saturated drug solution. The super saturation generated by dissolving drugs in methanol (1 mg ml) was added into simulated fluid, analysed absorbance in UV Graph was plotted for absorbance vs. time. The intersection point between two regions was taken as induction time.

Solution mediated phase transfer: The purpose of this study is to investigate the effect of particles on the precipitation of Metformin HCl in the small intestine. The drug was dissolved in simulated gastric fluid of pH 1.2. The solution is then infused to simulated intestinal fluid of pH 6.8 and determined by UV Spectroscopy at frequent intervals.

FORMULATION AND EVALUATION OF SOLID DISPERSION

Preparation of Solid dispersion: The Solvent evaporation method was employed to formulate solid dispersion for Metformin HCl. The Hit Polymers were selected and screened for inhibition effect by recrystallization technique briefly. Drugs and polymer were weighed and dissolved in ethanol.

Percentage yield: Percentage yield was calculated from equation given below

$$\text{Practical yield (\%)} = \frac{\text{Mass of solid dispersion (practical mass)}}{\text{Mass of carrier and drug used 100 in formulation (Theoretical mass)}}$$

Drug content: 10 mg of solid dispersion was dissolved 10ml of methanol. The solution was analysed for drug content in UV spectrophotometer. The drug content was calculated using equation

$$\text{Drug content} = \frac{\text{Amount of drug in solid dispersion} \times 100}{\text{Theoretical amount of solid dispersion}}$$

In-vitro release study/Dissolution studies: USP Dissolution testing apparatus was used for solid dispersion. The 900ml simulated gastric fluid and 500 ml simulated intestinal fluid under non-sink condition at 37± 0.5°C at 50 rpm used for dissolution study and samples withdrawn at frequent intervals of time was measured in UV spectrophotometer, percentage drug release calculated by the absorbance obtained and graph was plotted against time versus cumulative drug release.

RESULTS AND DISCUSSION

1. Melting point: The purity and identity of the metformin HCl sample are confirmed by the observed melting point range of 222°C to 226°C, which is consistent with values reported in the literature. Any deviation from this range might point to the existence of contaminants or medication variants.

2. Fourier Transform-Infra red (FT-IR): The FTIR spectroscopy analysis of Metformin HCl sample typically reveals several characteristic absorption bands relative to the literature values.

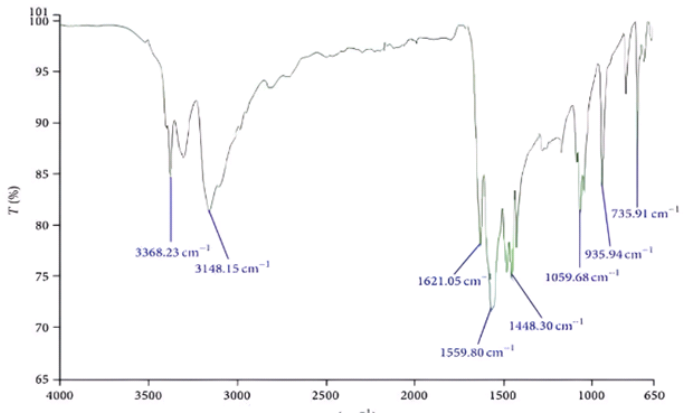

Figure 1: FT-IR of Metformin HCL.

3. Thermal analysis (DSC): Thermal characteristics of Metformin HCl can be better understood by using Differential Scanning Calorimetry (DSC) investigation. A strong endothermic peak, representing the melting point of pure metformin HCl, is visible on the DSC thermogram at about 224°C. This suggests that the medication is crystalline in structure.

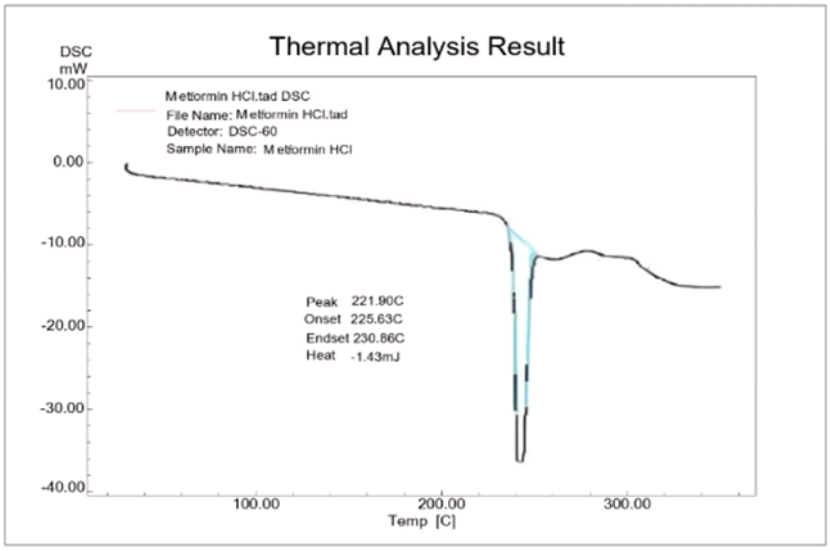

Figure 2: Differential Scanning Calorimetry of Metformin HCl.

4. Scanning electron microscopy: Scanning Electron Microscopy study offers comprehensive insights into the drug's surface shape and particle size. Smooth surfaces and well-defined edges are characteristic of crystalline formations seen in SEM images of pure metformin HCl. These attributes point to the high purity and crystalline form of the substance.

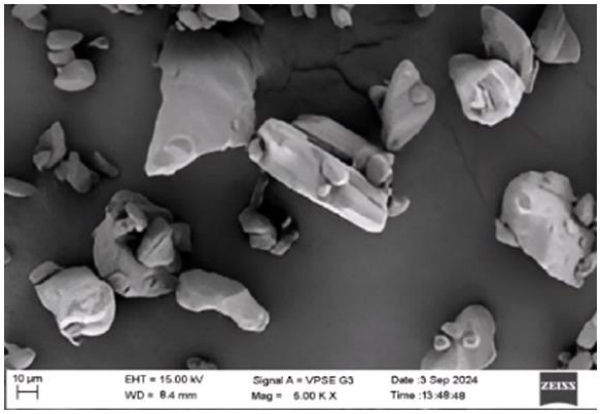

Figure 3: Scanning electron microscopy of Metformin HCl.

Ultraviolet-Visible (UV- Visible) Spectroscopy: The highest absorbance of metformin HCl in simulated gastric fluid and simulated intestinal fluid were determined. The λ max of pure Metformin HCl was found to be 234 nm and 232 nm in pH 1.2 and pH 6.8 after scanning on the spectrophotometer, which complies with the reference.

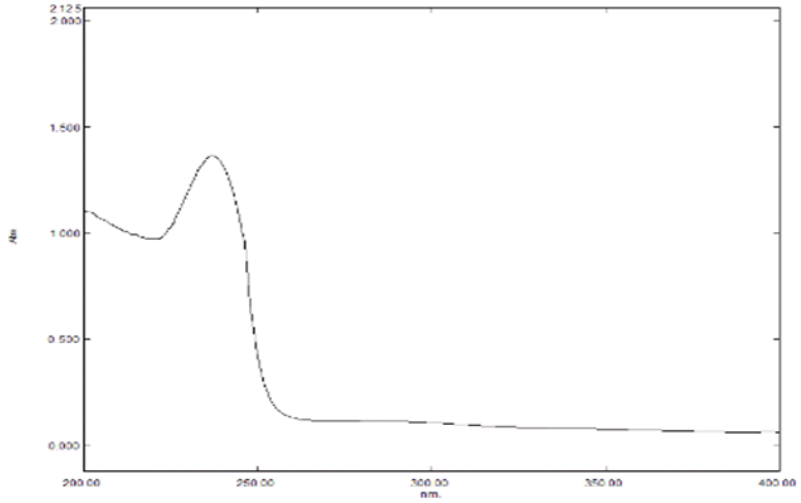

Figure 4: UV Spectrum of Metformin HCl in pH 1.2.

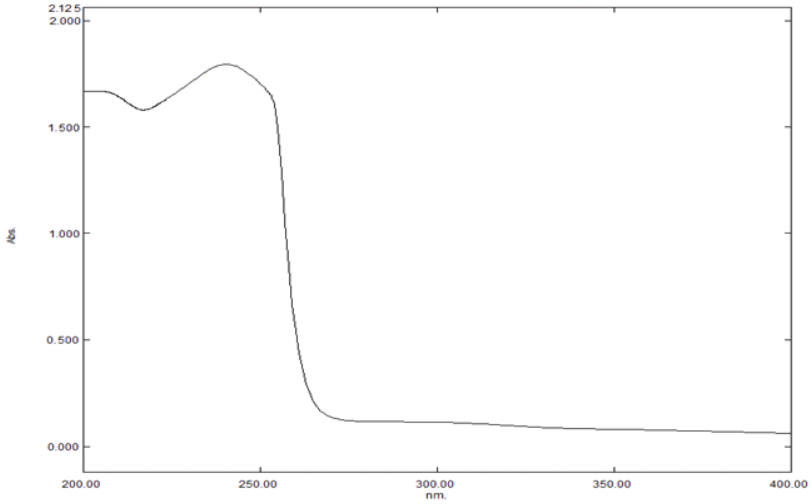

Figure 5: UV Spectrum of Metformin HCl in pH6.8.

STANDARD CALIBRATION CURVE OF METFORMIN HCl

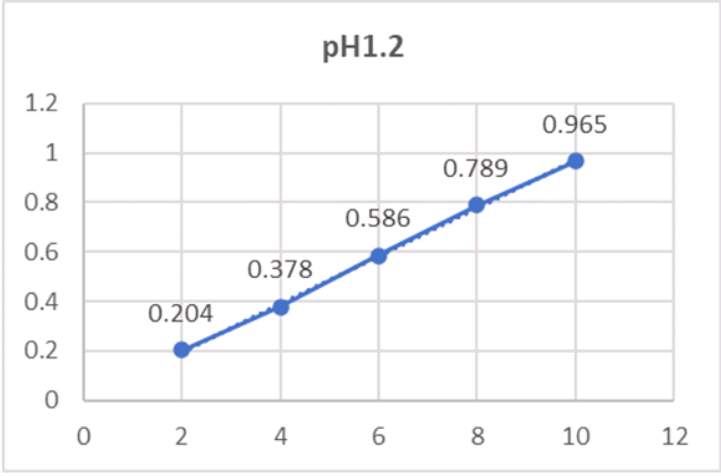

Figure 6: Standard Calibration curve of Metformin HCl in pH 1.2.

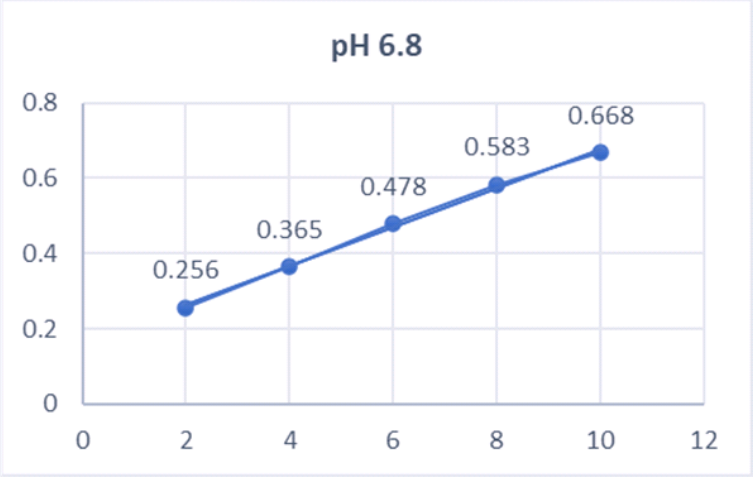

Figure 7: Standard Calibration curve of Metformin HCl in pH 6.8.

Crystallization study

Precipitation initiation time was found by adding the methanolic drug solution to the polymer solution and detectable change in the slope was considered. On the basis of this the induction time was estimated.

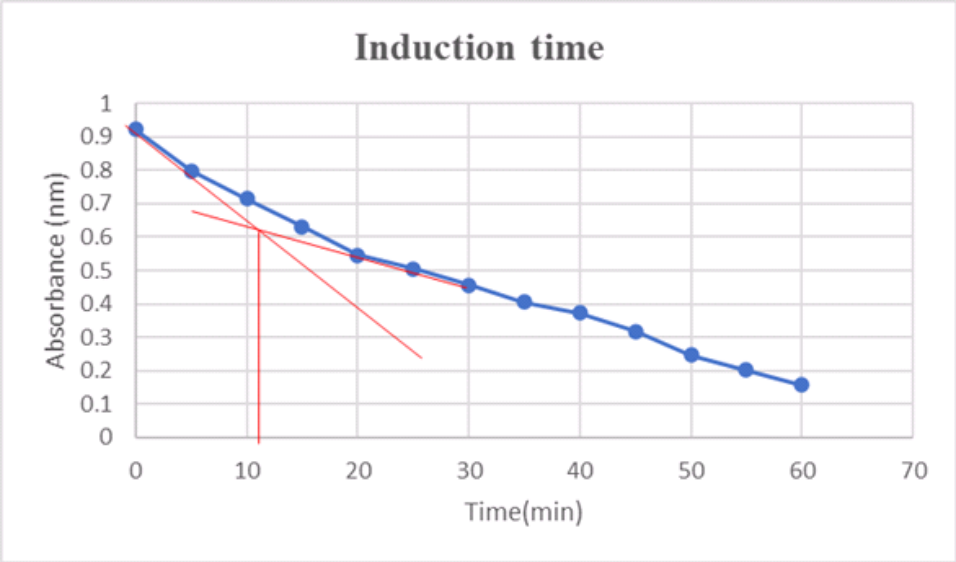

Figure 8: Representative plot for induction time.

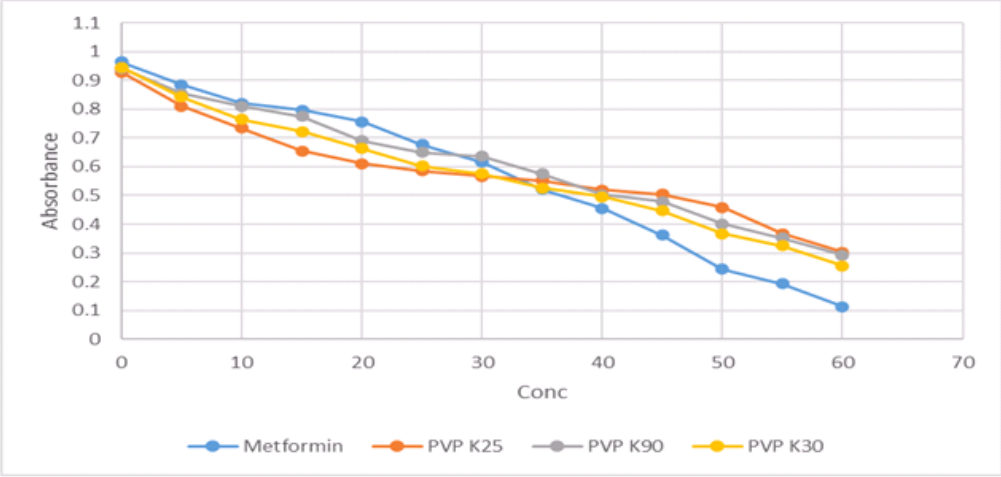

Figure 9: Metformin HCl Precipitation inhibition in presence of polymers.

Table 1: Metformin HCl precipitation inhibition in presence of polymers.

Polymer	PIT (min)	IT (min)	t_{10}	t_{50}	SHC
Metformin HCl	26	12.5	5	35.26	-
PVP K 25	34	15	11.12	44.68	1.26
PVP K 30	33	22	7.22	34.16	0.96
PVP K 90	27	17	7.88	39.41	1.11

Solution mediated phase transfer: During this the drug dissolved in acidic medium is transferred to basic medium mimicking the transfer of the drug from stomach to intestine. The polymer present in the solid dispersion inhibits the precipitation causes increased concentration of the drug.

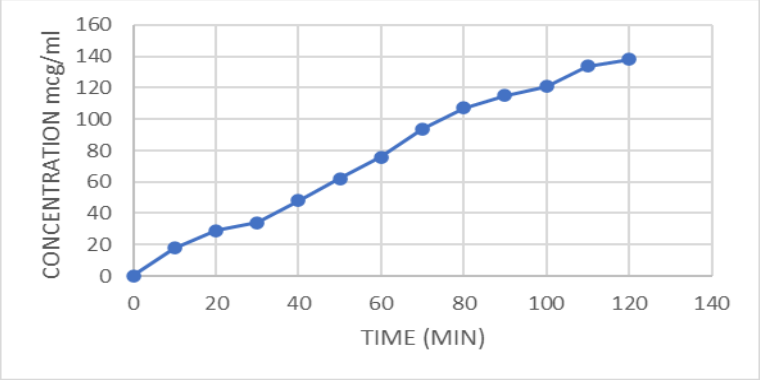

Figure 10: solution mediated phase transfer of Metformin solid dispersion

The solid dispersion was prepared and evaluated for the following parameters.

Percentage yield: Weighing the dried solid dispersion and comparing it to the starting weight of the medication and polymer employed allowed us to calculate the % yield. The percentage yield was found to be 95.68%.

Drug content: UV spectrophotometry was used to quantify the drug content in the solid dispersion at 234 nm following the proper dilution in distilled water. The findings demonstrated that the solid dispersions drug content was 97%.

Scanning electron microscopy analysis: Scanning Electron Microscopy study offers comprehensive insights into the drug's surface shape and particle size.

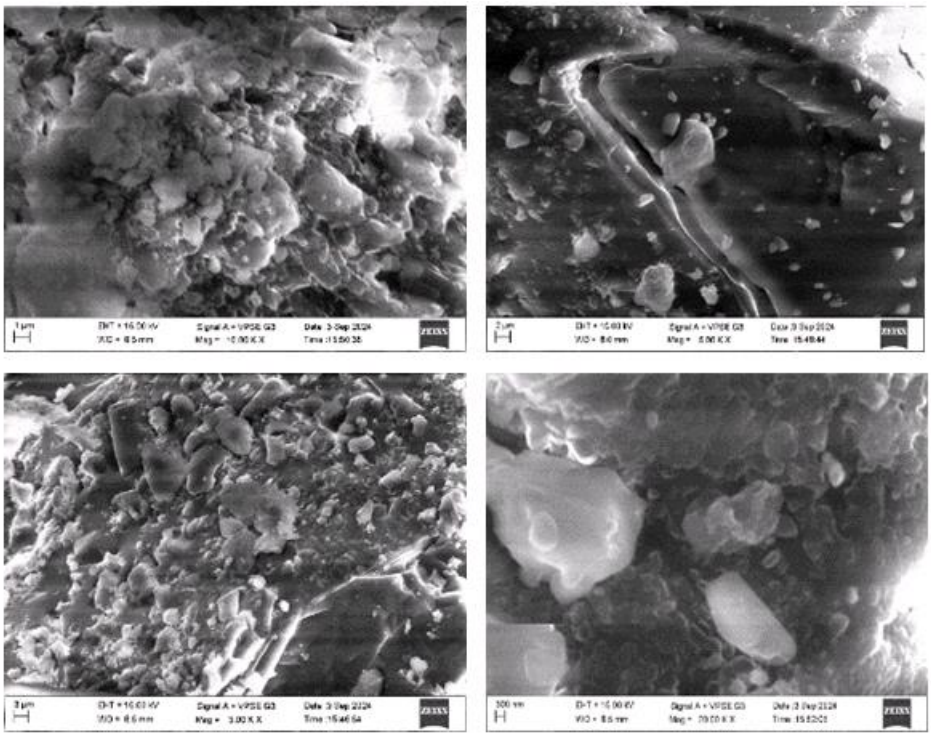

Figure 11: Scanning electron microscopy images of solid dispersion.

Differential Scanning calorimetry: The melting peaks shift or disappearance indicates that Metformin HCl and PVP 25 have significant interactions that cause the drug molecules to disperse within the polymer matrix. The alterations in the DSC thermogram validate the interaction between PVP 25 and metformin HCl. By keeping the medication in its amorphous form and inhibiting recrystallization, these interactions can increase its bioavailability. The use of PVP 25 as a carrier for metformin HCl in solid dispersions is supported by the DSC data. Better drug performance and efficacy may result from the dispersion's amorphous structure and enhanced thermal characteristics.

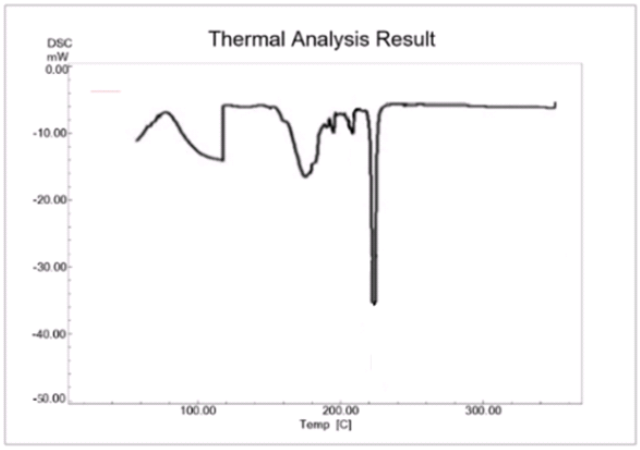

Figure 12: DSC of Metformin HCl Solid dispersion.

Fourier transforms infrared spectroscopy: When compared to the spectra of the pure components, the solid dispersion's FTIR spectrum exhibits notable modifications. There are the distinct peaks of PVP and metformin HCl, although they are slightly shifted and vary in intensity. The solid dispersion's appearance of distinct peaks for both PVP and metformin HCl attests to the drug's compatibility with the polymer. Compatibility is essential for solid dispersions to be successfully formulated.

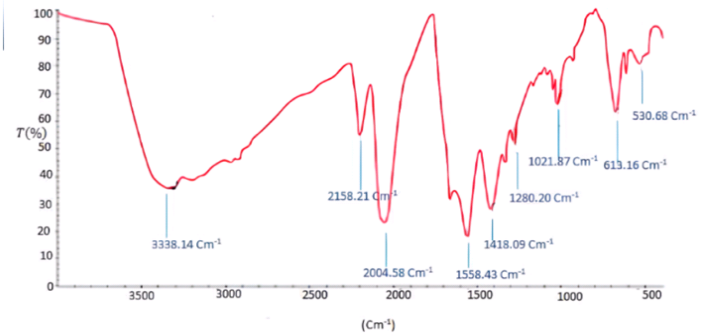

Figure 13: Fourier Transform-Infra red (FT-IR) of Metformin HCl solid dispersion.

In Vitro release study: The solid dispersion studied for the in vitro drug release in two distinct pH environments: phosphate buffer (pH 6.8) and acidic buffer (pH 1.2). The purpose of this work was to simulate the behaviour of drug release in intestinal and stomach environments, respectively. The drug release in pH 6.8 and pH 1.2 is shown in fig 14 and fig 15 respectively.

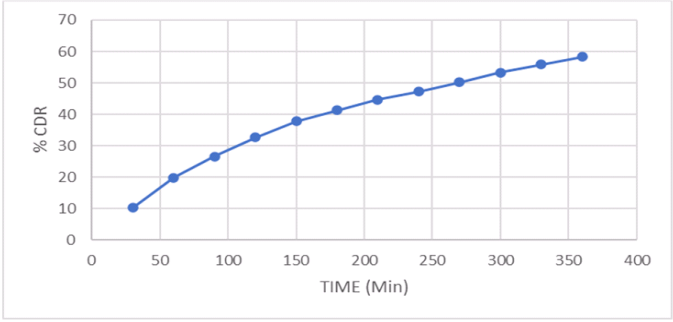

Figure 14: Cumulative drug release of solid dispersion in pH 6.8.

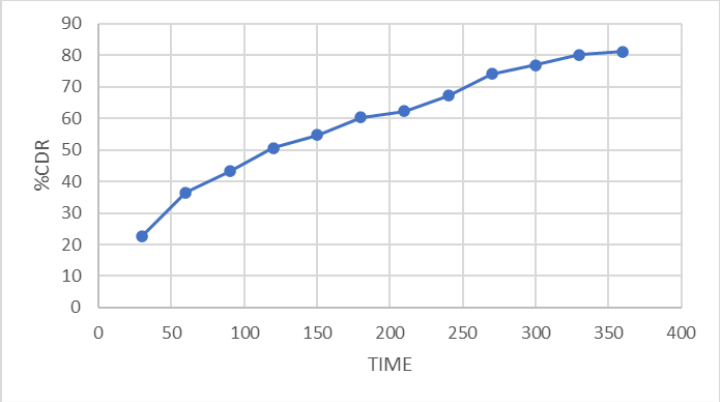

Figure 15: Cumulative drug release of solid dispersion in pH 1.2.

SUMMARY AND CONCLUSION

Supersaturated drug delivery system was prepared for the precipitation inhibition in the intestinal pH and to increase the drug absorption. Precipitation studies were carried to select the polymer having the more inhibition. The drugs and excipients were characterized and studied for the compatibility. FT-IR spectroscopy used for the compatibility studies and drug and excipients found to be compatible, SEM used for the morphological characteristics, DSC used for the thermal analysis, UV Visible spectroscopy used to determine the absorption maxima and calibration curve for the further drug determinations. The absorption maxima found to be 234 nm and 234 nm in pH 1.2 and pH 6.8 respectively. Solid dispersion of metformin HCl was prepared by selecting the suitable polymer by solvent evaporation method. Percentage yield for the obtained product is 95.68% and Drug content was found to be 97%. The in-vitro drug release studies show that the increase in the drug release from the solid dispersion compared to the drug.

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