STUDY OF DISSOLUTION CHARACTERISTICS OF IBUPROFEN BY DIFFERENT POLYMERS AND SOLID DISPERSION TECHNIQUES

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Keywords: Solid Dispersion, Polymer, SEM, DSC, FTIR, Ibuprofen

ABSTRACT: Poor water solubility is characterized by low dissolution rate and consequently reduced bioavailability. Formulation of solid dispersion has attracted considerable interest where dispersing a poorly water soluble drug in a water soluble polymer matrix improves the dissolution characteristics and bioavailability of the drug. The aim of the present study was to enhance the dissolution rate and bioavailability of poor water soluble drug Ibuprofen (BCS class II) using solid dispersion techniques. Ibuprofen solid dispersion was prepared by melt dispersion and solvent evaporation method. Drug-carrier physical mixtures were also prepared to compare the dissolution characteristics. Effects of different polymer i.e. Polyvinylpyrrolidone (PVP) k12, Poloxamer 407, PEG 4000 and PEG 6000 were studied for solid dispersion and physical mixture. Solid dispersions were investigated for Drug content, dissolution characteristics. Scanning Electron Microscopy (SEM), Fourier Transform Infrared Spectroscopy (FTIR) and Differential Scanning Calorimetry (DSC) analysis. All the solid dispersions showed better dissolution rate than physical mixtures. Solid dispersion of Ibuprofen containing PEG 6000 in combination with Poloxamer 407 at the ratio of 1:1:1 prepared by melt dispersion method showed faster and higher drug release. After the study of SEM, FTIR and DSC it was found that solid dispersion of Ibuprofen using Poloxamer 407 and PEG 6000 show satisfactory results. So, solid dispersion may be an effective technique to enhance dissolution rate of Ibuprofen.

INTRODUCTION: A poorly water-soluble drug often shows insufficient bioavailability due to its poor solubility and low dissolution rate, especially for Biopharmaceutics Classification System (BCS) class II substances. This series of drugs possess low solubility but high penetration and the bioavailability can be greatly improved by accelerating the dissolution process in the gastrointestinal tract. For increasing the dissolution rate by enhancing its specific surface area or solubility has taken into consideration, such as micronization, enhancing the wettability and solid dispersion technology1. Therefore, poorly aqueous soluble drugs characterized by low bioavailability which is a major concern of pharmaceutical industries worldwide 2. With the recent advent of high throughput screening of potential therapeutic agents, the number of poorly soluble drug candidates has risen sharply and the formulation for oral delivery presents one of the most frequent and greatest challenges to formulation scientists 3. Among various approaches, the solid dispersion technique has been proved to be the most successful in improving the dissolution and bioavailability particularly of drugs having poor aqueous solubility4.

Present investigation explores the enhancement of solubility and dissolution of Ibuprofen. Ibuprofen was chosen as model drug because it is a phenyl propionic acid derivative, is widely used as first line non-steroidal anti-inflammatory (NSAID),
analgesic, and antipyretic agents with a half-life of 1.8-2 hours. It is also used to relieve headaches, muscle aches, tenderness, menstrual pain, aches and pains from the common cold, backache and pain after surgery or dental work and stiffness caused by arthritis and gout. Ibuprofen is a core medicine in the World Health Organization's "Essential Drugs List", that means it is in list of minimum medical needs for a basic health care system. It is poorly aqueous soluble and its oral absorption is dissolution rate limited, which leads to a potential bioinequality problem.

Thus, the improvement of Ibuprofen dissolution for its immediate release is desirable for rapid Ibuprofen absorption, which is prerequisite for quick onset of its pharmacological actions.

MATERIALS AND METHODS:

Materials:
Ibuprofen was obtained as a gift sample from ACI Pharmaceuticals Ltd, Bangladesh. PVP k12, Poloxamer 407, PEG 4000 and PEG 6000 were collected from Incepta Pharmaceuticals Ltd, Bangladesh. All other materials used were of Pharmacopoeial grade.

Preparation of Solid dispersion:
Ibuprofen solid dispersions were prepared by using two primary techniques melt dispersion or fusion method and solvent evaporation or co-precipitate method.

Melt dispersion Method:
The prerequisite for this technique is crystalline starting materials. The drug and carrier of definite quantity were taken in a glass beaker and heated in a hot plate at 80°C to melt both the drug and carrier. The molten mass was mixed thoroughly for uniform mixing. Then the mass was cooled at room temperature and sieved through ‘18’ mesh screen. The obtained dispersion was then stored in glass vial and placed into desiccator. Table 1 listed the solid dispersions prepared by this technique according to different ratios.

<table>
<thead>
<tr>
<th>Code</th>
<th>Ibuprofen (mg)</th>
<th>Poloxamer 407 (mg)</th>
<th>PVP k12 (mg)</th>
<th>PEG 4000 (mg)</th>
<th>PEG 6000 (mg)</th>
</tr>
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<tbody>
<tr>
<td>F1(1:3)MD</td>
<td>100</td>
<td>300</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>F2(1:3)MD</td>
<td>100</td>
<td>-</td>
<td>300</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>F3(1:5)MD</td>
<td>100</td>
<td>500</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>F4(1:5)MD</td>
<td>100</td>
<td>-</td>
<td>500</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>F5(1:1:1)MD</td>
<td>100</td>
<td>100</td>
<td>-</td>
<td>100</td>
<td>-</td>
</tr>
<tr>
<td>F6(1:2:2)MD</td>
<td>100</td>
<td>200</td>
<td>-</td>
<td>200</td>
<td>-</td>
</tr>
<tr>
<td>F7(1:1:1)MD</td>
<td>100</td>
<td>100</td>
<td>-</td>
<td>-</td>
<td>100</td>
</tr>
<tr>
<td>F8(1:2:2)MD</td>
<td>100</td>
<td>200</td>
<td>-</td>
<td>-</td>
<td>200</td>
</tr>
</tbody>
</table>

Solvent Evaporation Method:
In case of this method selection of solvent is of prime necessity and drug and carrier is dissolved in a volatile organic solvent. Accurately weighted amount of Ibuprofen and carrier were taken in a glass beaker and dissolved in minimum volume of methanol to obtain a clear solution. This solution was stirred robustly for uniform mixing and evaporated at room temperature by using a blower. The viscous residues thus obtained were allowed to solidify and were kept at room temperature for 72 hours. The solidified mixture was then powdered and passed through ‘18’ mesh screen and stored in glass vial and placed into desiccator. Table 2 listed the solid dispersions prepared by this technique.

<table>
<thead>
<tr>
<th>Code</th>
<th>Ibuprofen (mg)</th>
<th>Poloxamer 407 (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F9(1:1)SE</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>F10(1:3)SE</td>
<td>100</td>
<td>300</td>
</tr>
<tr>
<td>F11(1:5)SE</td>
<td>100</td>
<td>500</td>
</tr>
</tbody>
</table>

Preparation of Physical Mixture
Ibuprofen and carriers were crushed and mixed together by using mortar and pestle. The mixture was then sieved through ‘18’ mesh screen. Physical mixture was prepared by same ratios and equal amount as prepared by Melt dispersion method. The physical mixture were then stored in glass vial and kept in desiccator. Table 3 listed the physical mixtures of Ibuprofen with carriers.

<table>
<thead>
<tr>
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<th>Ibuprofen (mg)</th>
<th>Poloxamer 407 (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F9(1:1)SE</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>F10(1:3)SE</td>
<td>100</td>
<td>300</td>
</tr>
<tr>
<td>F11(1:5)SE</td>
<td>100</td>
<td>500</td>
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</table>
In vitro dissolution Studies:
The release profiles of solid dispersions were assessed using in-vitro dissolution devices and were conducted in USP XXI six stage dissolution rate test apparatus using 900 ml of dissolution medium (phosphate buffer pH 7.2). The temperature of the medium was maintained at 37±0.5°C throughout the experiment. From the samples containing 100 mg of Ibuprofen 10 mg were placed in the dissolution medium. Paddle was used at a stirring rate of 50 rpm. A 5 ml aliquot was withdrawn at predetermined time intervals of at 5, 15, 30, 45 and 60 minutes and then 5 ml of fresh dissolution medium was replaced to maintain the constant volume of dissolution medium.

From the collected samples the absorbance of the solutions were measured at 221 nm (λmax of Ibuprofen) using UV spectrophotometer. Percentage of drug release was calculated using the equation obtained from the standard curve prepared in dissolution media.

Scanning electron microscope (SEM):
Scanning electron microscopy was used to study the morphology and surface topology of the solid power particles. A scanning electron microscope (SEM) is a type of electron microscope that images a sample by scanning it with a high-energy beam of electrons in a raster scan pattern. The electrons interact with the atoms that make up the sample producing signals that contain information about the sample's surface topography, composition, and other properties such as electrical conductivity etc. The solid particles from the optimized batch were mounted on the SEM sample stab (aluminium stabs) which were coated with a double sided sticking tape, sealed and finally coated with gold (200Å) under reduced pressure(.001 tor) for 15 minutes using ion sputtering device. The samples were scanned using scanning electron microscope(s-3400N, Hitachi) under different magnification and photomicrographs of suitable magnification.

Fourier Transform Infrared Spectroscopy (FTIR):
The FTIR study was undertaken to assess the drug-polymer interaction. The FTIR spectrum of pure drug and formulations were studied by keeping sample in cell which is constructed of ionic substances like sodium chloride or potassium bromide. The characteristic absorption peaks of Ibuprofen were obtained at different wave numbers i.e. 4000-400 cm⁻¹ in different samples. The optical pathway produces a pattern called an interferogram.

This is complex signal, but its wave-like pattern contains all the frequencies that make up the infrared spectrum. The main aim of FTIR analysis is to determine the chemical functional groups and to investigate the composition in the samples. Since every type of bond has a different natural frequency of vibration no two molecules of different structure have exactly the same infrared absorption pattern.

Differential scanning calorimeter (DSC):
Thermal analysis methods involve a series of techniques that measure material properties as a function of externally applied temperature. Measurements of thermal analysis are conducted for the purpose of evaluating the physical and chemical changes that may take place in a heated sample. DSC was used to measure the specific heat and enthalpies of transition. Samples, sealed in an aluminium pan in a nitrogen atmosphere went through a thermal transition, the powder to the
heater was adjusted to maintain the temperature and a signed proportional to the powder difference was plotted on the second axis of the recorder known as thermogram. The area under the resulting curve is direct measure of the heat of transition. Thermograms were obtained by using a differential scanning calorimeter (Shimadzu DSC60) at a flow rate of 20ml/min and heating rate of 10°c/min over a temperature range of 30 to 300°c.

RESULTS AND DISCUSSION:
The In-Vitro dissolution characteristics of different types of preparations were compared with the pure drug. The solid dispersions of Ibuprofen prepared by different methods showed improved dissolution when compared with pure Ibuprofen.

Effect of Poloxamer 407 on release of Ibuprofen:
Solid dispersions F1(1:3)MD and F3(1:5)MD were prepared by using Poloxamer 407 by melt dispersion technique. In addition two physical mixtures F13(1:3)PM and F15(1:5)PM were also prepared to compare the solid dispersions against them. All the solid dispersions show a better release profile compare to the physical mixtures. Formulation F1(1:3)MD show better release 99% in 60 minutes than formulation F3(1:5)MD which shows 85% release of drug in 60 minutes. It was found that when the amount of polymer ratio increased in formulation the release rate of drug has been decreased.

In case of physical mixtures prepared in the ratio of 1:3 show better release than the ratio of 1:5. Figure 1(A) shows percent release of Ibuprofen from solid dispersions by melting method and physical mixtures using poloxamer 407.

Solid dispersions F9(1:1)SE, F10(1:3)SE and F11(1:5)SE were prepared by using Poloxamer 407 by solvent Evaporation technique. In addition three physical mixtures F12(1:1)PM, F13(1:3)PM and F15(1:5)PM were also prepared to compare the solid dispersions against them. All the solid dispersions show a better release profile compare to the physical mixtures. Among all solid dispersions of Ibuprofen prepared by solvent evaporation technique F9(1:1)SE shows 100% release of drug in 60 minutes where formulation F10(1:3)SE shows only 80% release and formulation F11(1:5)SE shows 85% release of the drug in 60 minutes. It was observed that the release rate has been decreased when the amount of polymer is increased in the formulation.

In case of physical mixtures prepared using poloxamer 407 in the ratio of 1:1 show better release than the ratio of 1:3 and 1:5. Figure 1(B) shows percent release of Ibuprofen from solid dispersions by solvent evaporation method and physical mixtures using Poloxamer 407.

Effect of PVP K12 on release of Ibuprofen:
Solid dispersions F2(1:3)MD and F4(1:5)MD were prepared by using PVP K12 by melt dispersion technique. In addition two physical mixtures F14(1:3)PM and F16(1:5)PM were also prepared to compare the solid dispersions against them. According to data all the solid dispersions show better release profile than physical mixtures. Formulation F2(1:3)MD prepared by melt dispersion method using PVP K12 shows 89%
release of drug in 60 minutes where formulation F4(1:5)MD shows 85% release of drug.

It was found that the release rate has been decreased when the amount of polymer is increased in the formulation. Physical mixtures prepared using PVP K12 in the ratio of 1:3 show better release than ratio 1:5. Figure 2 shows percent release of Ibuprofen from solid dispersions by melting method and physical mixtures using PVP K12.

**Effect of Poloxamer 407 and PEG 4000 on release of Ibuprofen:**
Solid dispersions F5(1:1:1)MD and F6(1:2:2)MD were prepared by using Poloxamer 407 and PEG 4000 by melt dispersion technique. In addition two physical mixtures F17(1:1:1)MD and F18(1:2:2)MD were also prepared to compare the solid dispersions against them. All the solid dispersions show a better release profile compare to the physical mixtures.

Here formulation F6(1:2:2)MD prepared by melt dispersion method using poloxamer 407 in combination with PEG 4000 shows 96% release in 60 minutes where formulation F5(1:1:1)MD shows 93% release of drug in 60 minutes. It was found that with the increase of polymer ratio in formulation release rate of drug has been increased. It was observed same in case of physical mixtures of Ibuprofen prepared using Poloxamer 407 in combination with PEG 4000 in the ratio of 1:2:2 shows better release than the ratio of 1:1:1. Figure 4 shows percent release of Ibuprofen from solid dispersions by melting method and physical mixtures using poloxamer 407 and PEG 4000.

**Comparison of Poloxamer 407 and PVP K12 on the release of Ibuprofen:**
Figure 3 shows the comparison of Poloxamer 407 and PVP K12 on the release of Ibuprofen. It was found that formulation F1(1:3)MD containing poloxamer 407 shows 100% drug releases after 60 minutes where F2(1:3)MD containing PVP K12 shows 89.02% release of Ibuprofen after 60 minutes. So, for further work was carried out with poloxamer 407 as the dissolution rate is higher than the PVP k12.

**Effect of Poloxamer 407 and PEG 6000 on release of Ibuprofen:**
Solid dispersions F7(1:1:1)MD and F8(1:2:2)MD were prepared by using Poloxamer 407 and PEG 6000 by melt dispersion technique. In addition two physical mixtures F19(1:1:1)PM and F20(1:2:2)PM were also prepared to compare the solid dispersions against them. All the solid dispersions show a better release profile compare to the physical mixtures.
mixtures. Here formulation F8(1:2:2)MD prepared by melt dispersion method using poloxamer 407 in combination with PEG 6000 shows 100% release within 45 minutes where formulation F7(1:1:1)MD shows 100% release of drug within 30 minutes. It was found that formulation F7(1:1:1)MD shows faster release than F8(1:2:2)MD and physical mixtures. Figure 5 shows percent release of Ibuprofen from solid dispersions by melting method and physical mixtures using poloxamer 407 and PEG 6000.

Comparison of PEG 4000 and PEG 6000 in combination with poloxamer 407 on the release of Ibuprofen:

Figure 6 shows that the comparison of PEG 4000 and PEG 6000 in combination with poloxamer 407 on the release of Ibuprofen. It was found that formulation F7(1:1:1)MD containing PEG 6000 in combination with poloxamer 407 shows 100% drug releases within 30 minutes where F5(1:1:1)MD containing PEG 4000 in combination with poloxamer 407 shows 93.56% release of Ibuprofen after 60 minutes. So, it was found that solid dispersions of Ibuprofen containing poloxamer 407 in combination with PEG 6000 in different ratios show faster release than in combination with PEG 4000.

From Figure 6 it was found that the solid dispersions prepared with poloxamer 407 in combination with PEG 6000 showed faster and higher drug release than prepared with poloxamer 407 in combination with PEG 4000 and with only poloxamer 407 and PVP K12. It might be caused by the structural composition and higher molecular weight of Poloxamer 407.

Poloxamers are nonionic polyoxyethylene-polyoxypropylene copolymers; the polyoxyethylene segment is hydrophilic while the polyoxypropylene segment is hydrophobic. Greater hydrophilic and hydrophobic content of Poloxamer 407 might be responsible for the better emulsifying property which in turn demonstrates higher solubility followed by better dissolution.

This highly water soluble polymer when used in combination with PEG 6000 results better dissolution than with PEG 4000. Because PEG 6000 has higher content of oxyethylene groups in its structure which in turn makes its molecular weight higher compared to the PEG 4000. PEG 6000 has molecular weight range of 7300-9300 and PEG 4000 has molecular weight of 3000-4800. Thus higher grades of PEG provide better solubilising effect in case of solid dispersions.

Poloxamer 407+PEG 6000> Poloxamer 407+ PEG 4000 >Poloxamer 407> PVP k12

In case of some formulations, F3(1:5)MD, F4(1:5)MD , F11(1:5)SE prepared by melt dispersion and solvent evaporation techniques it was found that as the proportion of polymer increased dissolution rates decreased. This may be due to the localization of higher amounts of carrier itself. Again all the solid dispersion formulations showed increased dissolution rates than their respective physical mixture formulations. This observation indicated that the increased dissolution...
rate of Ibuprofen from Ibuprofen solid dispersions may be due to the presence of drug in amorphous state as compared to the physical mixtures where drug is present in crystalline state.\(^{13}\)

**Surface morphology of solid dispersion**

Solid dispersion of Ibuprofen F1(1:3)MD containing Poloxamer 407 observed by SEM to see the morphological change that occurred due to formulation variation. SEM studies showed the surface morphological properties of the solid dispersion was in amorphous state. The surface morphology of F1(1:3)MD are observed and representative micrographs are shown in Figure 7.

This indicates that there was no interaction between Ibuprofen and polymers in the prepared solid dispersions. The spectra of solid dispersions were found to contain identical peaks of pure drug and carriers. In addition, no degradation of drug and carrier due to the high temperature during manufacturing was found from IR spectra.

**Fourier Transform Infrared Spectroscopy (FTIR):**

The IR spectrum shows the characteristic peaks of Ibuprofen indicating that the drug retains its identity in the formulation. Thus the FTIR spectra ensure the presence of drug in each formulation. IR spectrum of pure Ibuprofen (Figure 9) was identical with solid dispersions (Figures 9-11).
Differential scanning calorimetric (DSC) studies
The DSC thermograms of pure Ibuprofen and Ibuprofen solid dispersion using PEG 6000 and Poloxamer 407 combination are shown in Figure 8. The DSC thermogram of pure Ibuprofen used in this study showed an apparent sharp endothermic peak at 81.2°C and show melting point at 75°C corresponding to Ibuprofen (77-78°C).

On the other hand, the DSC thermograms of Ibuprofen solid dispersion using PEG 6000 and Poloxamer 407 combination showed an endothermic peaks, a small peak at 60.1°C and show melting point at 50.1°C corresponding to PEG 6000 (55-63°C) and Poloxamer 407 (52-57°C).

DSC curve of Ibuprofen solid dispersion, indicating the transformation of crystalline Ibuprofen (in pure drug) to amorphous Ibuprofen. This could be attributed more uniform distribution of the drug in crust of polymer.
CONCLUSION
For a formulation to be successful various parameters that play a crucial role are aqueous solubility, stability at ambient temperature and humidity, photo stability, compatibility with solvents and excipients etc of which solubility is the most important property for developing formulations. Ibuprofen is the most commonly used and most frequently prescribed NSAID and has been rated as the safest conventional NSAID by spontaneous adverse drug reaction reporting systems in the UK. So this is selected as the model drug in this study of increasing its solubility profile by solid dispersion technique dissolution rate will be evaluated. Solid dispersion is one of the most promising approaches for solubility enhancement. Solid dispersion of Ibuprofen was prepared with Poloxamer 407, PVP K12, PEG 4000 and PEG 6000 by melt dispersion and solvent evaporation technique to improve its physicochemical properties and dissolution characteristics.

The samples were investigated for drug content, dissolution characteristics, SEM, FTIR and DSC analysis. Drug content in the solid dispersions yielded a good result for all the solid dispersions. In vitro dissolution studies showed a remarkable improvement in the dissolution of Ibuprofen solid dispersions using PEG 6000 and Poloxamer 407 combination than solid dispersions of Ibuprofen using PEG 4000 and Poloxamer 407 combination and PVP K12 individually. SEM studies showed the surface morphological properties of the solid dispersion indicating that the solid dispersion was in amorphous state.

FTIR spectra confirmed the presence of the drug and there was no interaction between Ibuprofen and carriers in the prepared solid dispersions. DSC studies indicated the transformation of crystalline Ibuprofen (in pure drug) to amorphous Ibuprofen (in Ibuprofen solid dispersions using PEG 6000 and Poloxamer 407 combination) by the solid dispersion technology. This study concluded that the improved dissolution rate of Ibuprofen solid dispersions using PEG 6000 and Poloxamer 407 combination may be attributed to the improved wettability and decreased drug crystallinity, which can be modulated by appropriate level of hydrophilic carriers.

REFERENCES:

How to cite this article: