The aim of this work is to formulate and evaluate Cefepime by using solid dispersion technique. The present investigation involves the enhancement of solubility and dissolution rate of Cefepime. Cefepime is slightly soluble an orally active fourth generation cephalosporin it is active against gram positive and gram-negative bacteria.

All the prepared solid dispersions were found to be fine free flowing powders and drug content was uniform in all formulations. In order to increase the solubility of cefepime by solid dispersion were prepared by solvent evaporation. The prepared solid dispersions were evaluated for their physicochemical characteristics such as drug content, and in vitro drug release studies.

The result of solubility study revealed that solubility increases with increases in concentration of carrier. In vitro release studies revealed that there is marked increase in the dissolution rate of cefepime solid dispersion when compared to pure drug. As the amount of some carrier was increased dissolution rate was decreased this may be due to increased viscosity of coating materials.
INTRODUCTION:
Today, optimizing the use of older and novel antibiotics in the treatment of disease is required primarily due to the increased medication resistance of new antibiotics to protect worldwide health. Increasing consciousness is vital in order to optimize a therapy to improve the therapeutic result and minimize the drug’s resistivity throughout the treatment [1]. Cefepime is a mildly soluble drug [2] that belongs to antibiotic class IVth. Cefepime has a widespread spectrum activity against gram positive and gram-negative bacteria with higher activity against both organism types than agents of the third generation.

![Fig. 1 Chemical structure of Cefepime](image)

Chemical and physical data

**Formula:** C19 H24 N6 O5 S2  
**Molar mass:** 480.56 g/mol. Mol

**IUPAC Name:**  
(6R,IR, Z)-7(2(2aminomithiazol 4-yl)-2-(methoxyimino)acetamido)- 3 ((1 methyl. Pyrrolidinium -1 yl) methyl) -8oxo - 5 this -1 azo - bicyclo [4.2.0] oct - 2 ene - 2 carboxylate.

**Medical use:**  
Cefepime is generally reserved for the therapy of mild to serious mosocomial pneumonia, multi drug resistant microbial disease (e.g. Pseudomonas aeruginosa ) and febrile neutropenia therapy . Cefepime works well against major pathogen including Pseudomonas aerginosa. Staphylococcus pneumonia. It was used to treat bacteria that caused pneumonia and skin and urinary tract infection [3].

**Mechanism of Action:**  
Like β lactams, in the final stage of peptide glycol synthesis, cephalosporins interfere with PBP (penicillin binding protein) activity. PBP’s are enzymes that catalyze a crosslink of pentaglyline between residues of alanine and lysine giving extra power to the cell wall. The integrity of the cell wall is significantly comprised without a pentaglycine crosslink and eventually leads to cell lysis and death. Cephalosporins resistance frequently due to plasmid-encoded cells β lactamases. Interestingly, cefepime is resistant to different β lactamases encoded by strains of β lactam bacteria otherwise resistant[2 ].

**Objective:**  
Solubility is greater formulation challenges that can be explained by different technological approaches during the pharmaceutical product development and improving water solubility and drug release respectively [4] poorly water soluble drugs could generate problem with reduced drug efficacy. Most drugs, which are soluble in tiny quantities. Most drugs, which are soluble in small quantities in small quantities of water, have low bioavailability [5].Water solubility and dissolution are two of the key variables that influence drug absorption from the gastrointestinal tract. A drug’s solubility conduct is the main determinant of its oral bioavailability [6].Many methods are used to increase drug dissolution rates, including solid dispersion, chemical modification, micronization, cosolvency, complexation, pH adjustment and micellar solubilization. In the present study solubility enhancement methods are employed for increasing the poor solubility, dissolution rate by solid dispersion method and in effect to check if its antibacterial activity is also increased or not. Recently, the formulation of poorly soluble compounds for oral delivery is one of the most frequent and major problems facing formulation researchers in the pharmaceutical industry[5].
Techniques for the solubility enhancement

1) Use of surfactant:
   To boost drug dissolution, surfactant is used. The fundamental mechanism behind surfactant action is that wetting is first promoted so that the penetration of dissolution fluid into strong drug particles can be improved. Soluble drug was researched which is used as a sequence of co-solvent and surfactant and ionic surfactants were preferred to other for better solubilizing agents. For solubility improvement, anionic surfactants such as sodium dodecyl sulphate were discovered to offer better outcomes compared to cationic surfactant (such as acetyldimethyl ammonium bromide).

2) Physical mixture:
   In this, the drug and appropriate polymer in different proportion is triturated in a mortar for about an hour, then the blend is sieved through sieve no 80 and placed in fused NaCl desiccators.

3) Kneading method
   In this technique drug and appropriate polymer are mixed in a mortar in different proportion and triturate to prepare slurry with a small amount of solvent. The drug is then added with constant stirring slowly to the slurry. The slurry we prepared and sifted through sieve number 80 and stored with NaCl in desiccators.

4) Co-Precipitation method:
   In this technique the active drug and the appropriate polymer are combined with distinct molar ratios. Then it is dissolved at room temperature in solvent and distilled water and the solvent is evaporated the precipitated gathered as crystalline powder are pulverized and sieved through sieve no 80 and stored in desiccators.

5) Co - Solvency:
   Organic solvent such as water miscible solvent is used to improve water solubility in soluble medication. Water and solvent soluble in water form a solution called a co-solvent. PEG 300, ethanol, propylene glycol is some of solvents used in the preparing of co solvent mixtures.

6) Solid dispersion:
   To increase the absorption, dissolution and therapeutic efficacy of the drug in dosage forms a commonly used and most appropriate pharmaceutical method is solid dispersion the word SD can be described as the allocation of one or more active components (hydrophobic) in a solid state inactive carrier or matrix (hydrophilic) [7]. However, the most appealing choice for increasing the art is to improve solubility through formulation methods. Although salt formation solubilization and reduction of particle size have been commonly used to increase the rate of dissolution and hence oral absorption and bioavailability of poor water soluble drugs, these techniques are practically limited. A technique known as Solid Dispersion (SD) [6] was developed in 1961 by Sekiguchi and Obi. Solid dispersion method has been used for a broad variety of poorly water soluble drugs such as irbesartan (Adeli, 2015), nimesulide (Bbu et al., 2003), and ursodeoxycholic acid (Okonogi et al, 1997), which are slightly soluble in biological fluids due to poor bioavailability. In this research the technique of solid dispersion was used to increase cefepime dissolution frequency and solubility[5].SD relates to the solid product group composed of at least two distinct parts , usually a hydrophilic matrix and hydrophobic drug, the matrix may be either crystalline or amorphous[8].the word SD can be described as the allocation of one or more active components in the active carrier matrix in a solid condition. The mechanism by which the solubility and dissolution rate of the drug is improved involves first when the solid solution is acquired the particle size of a drug is lowered to submicron size or molecular size. The decrease of particle size usually improves the rate of dissolution, secondly the drug is altered from crystalline to amorphous shape, the extremely soluble energetic state, lastly the dissolve carrier improves the wet capacity of the particle.

Importance of Solubility Enhancement includes.

1) Solubility is one of the significant parameters for obtaining desired medication concentration in systemic circulation to obtain the necessary pharmacological reaction
2) Poor water-soluble medication often involves elevated doses and elevated dosage regimen to affect therapeutic plasma level after oral administration.
3) For orally administered drugs solubility is one of the significant rates restricting parameters to achieve their required concentration in completely pharmacological reaction circulation.
4) Water is an outstanding solvent for liquid pharmaceutical formulations
5) Low aqueous solubility is the primary issue with the formulation and development of new chemicals as well as generic drugs
5) Poorly water-soluble medication with slow drug absorption leads to inadequate and gastrointestinal toxicity and varying bioavailability. [7]

Advantages of Solid Dispersion

1) Particles with reduced particle size:
Molecular dispersions constitute the last state of particle size decrease as solid dispersions, and the drug is molecularly dispersed in the dissolution medium after carrier dissolution. Solid dispersions apply this principle to drug release by generating a combination of poorly water-soluble drug and extremely soluble carriers. A elevated surface area is created, leading in an enhanced rate of dissolution and, subsequently, enhanced bioavailability.

2) Particles with improved wet ability:
A powerful contribution to enhancing drug solubility is linked to the drug moist capacity improvement verified in solid dispersions. It was noted that even carriers without surface activity, such as urea, enhanced drug moist capacity. It has been noted that even carriers without surface activity, such as urea, have enhanced drug wet capacity. Moreover, by direct dissolution or co-solvent impacts, carriers can affect the drug dissolution profile.

3) Particles with higher porosity:
Particles in solid dispersions have a greater degree of porosity. The rise in porosity also depends on the carrier characteristics; for example, solid dispersions comprising linear polymers generate bigger and more porous particles than those containing reticular polymers, resulting in a greater dissolution rate. The enhanced porosity of strong dispersion particles also accelerates the drug release profile.

4) Drugs in amorphous state:
Poorly water-soluble crystalline medications tend to have greater solubility in the amorphous state. Drug release enhancement can usually be achieved using the drug in its amorphous state, as no energy is required to break up the crystal lattice during the dissolution process. In solid dispersions, drugs are described as super-saturated alternatives after system dissolution, and it is speculated that if drugs precipitate, it is a metastable polymorphic form with greater solubility than the most stable crystal form. For drugs with low crystal energy (low melting temperature or fusion heat), the amorphous structure is mainly detected by the difference in melting temperature between drug and carrier. For drugs with high crystal energy, greater amorphous compositions can be acquired by selecting carriers that display particular interactions with them [9].

Methods for the preparation of solid dispersion:

1) Melting method:
Water soluble carrier (PEG 4000) is taken in a China dish and heated at 60 °C in a water bath until the mixture totally melts. The drug is added to the molten carrier and carefully blended. The dispersion is closed to the condition of the ambient environment. Solidified mass is crushed, pulverized, passed through sieve no. 60 and stored in desiccators. The dispersion is closed to the condition of the environment. Solidified mass is crushed, pulverized, passed through sieve no. 60 and stored in desiccators.

2) Kneading method:
A combination of drug and carrier in distinct proportions is wetted with solvent (methanol) and water and carefully conducted in a glass mortar for 30 minutes. The paste created is dried for 24 hours under the vaccine. Dried powder is scraped, crushed, pulverized through sieve no. 60 and placed in desiccators.

3) Solvent Evaporation method:
Solid dispersion is prepared using solvent evaporation technique in proportion viz (1:1, 1:2, 1:3, 1:4, & 1:5). The drug and carrier are dissolved in methanol in a China dish and the mixture is heated until the solvent evaporation and clear film of drug and carrier is with a spatula. Solid dispersion is pulverized in a mortar and pestle and passed through a 60 sieve before being packed in an airtight container.

4) Preparation of physical mixture:
The physical combination is prepared by combining drug and carrier in a glass mortar. Solid mass is pulverized and passed through sieve no. 60 to obtain standardized particles of size [10].

5) Freezing drying method:
Hydrophilic carriers dissolved in organic solvent (methanol), a poorly water-soluble drug is added individually and dissolved. The resulting ternary system of organic solvent, hydrophilic carrier and drug is freeze dried at -45 °C and a compression pressure of 0.5 torr. The vials are removed after full drying and the dried item is separated from the vials. The formulation is powdered and packaged in glass vials [11].
6) **Spray drying:**
Each spray drying solution was prepared by adding distinct ratios of drug and polymer to 200ml of methanol. It was subjected to ultrasonics by a bath sonicator for about 10min. After that spray drying was performed in a lab spray dryer with a drying capacity of 1 L/h. The parameters set for spray drying were like using a flow rate of 4ml/min, an inlet temperature of 80 °C, an outlet temperature of 60-70 °C, and an aspirator value of about 40 m3/h [12].

**MATERIALS AND METHODS:**
**Materials Used:** Cefepime (Lupin Pharma Ltd), Distilled Water, Methanol, Dichloro methane, Lactose, Mannitol, Polyethylene Glycol 4000 (PEG4000) [8], Sodium Carboxyl methyl cellulose [12].
**Instruments Used:** Digital Balance, Dissolution Apparatus, U_V spectrophotometer.

**Method:**
Solid dispersion of cefepime was prepared in drug: carrier weight ratio as 1:1, 1:2, 1:3, and 1:4, using solvent evaporation method. 100 mg of cefepime was dissolved in 10 ml of methanol in a beaker and the carrier was added to mix to dissolve at 40 °C on a hot plate to obtain a clear solution. The solvent was then permitted to evaporate. The resulting strong dispersion is scrapped with a spatula. The prepared strong dispersions were gathered and stored in air tight containers for subsequent evaluation. Cefepime was evaluated using a spectrophotometer at 483 nm [13].

<table>
<thead>
<tr>
<th>Polymer/carrier</th>
<th>Drug (mg)</th>
<th>Carrier (mg)</th>
<th>Drug: carrier</th>
<th>Batches for solid dispersion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pure drug</td>
<td>100</td>
<td>0</td>
<td>1:0</td>
<td>Pure drug</td>
</tr>
<tr>
<td>Mannitol</td>
<td>100</td>
<td>100</td>
<td>1:1</td>
<td>SD1</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>200</td>
<td>1:2</td>
<td>SD2</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>300</td>
<td>1:3</td>
<td>SD3</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>400</td>
<td>1:4</td>
<td>SD4</td>
</tr>
<tr>
<td>Lactose</td>
<td>100</td>
<td>100</td>
<td>1:1</td>
<td>SD5</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>200</td>
<td>1:2</td>
<td>SD6</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>300</td>
<td>1:3</td>
<td>SD7</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>400</td>
<td>1:4</td>
<td>SD8</td>
</tr>
<tr>
<td>Na-CMC</td>
<td>100</td>
<td>100</td>
<td>1:1</td>
<td>SD9</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>200</td>
<td>1:2</td>
<td>SD10</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>300</td>
<td>1:3</td>
<td>SD11</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>400</td>
<td>1:4</td>
<td>SD12</td>
</tr>
<tr>
<td>PEG 4000</td>
<td>100</td>
<td>100</td>
<td>1:1</td>
<td>SD13</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>200</td>
<td>1:2</td>
<td>SD14</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>300</td>
<td>1:3</td>
<td>SD15</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>400</td>
<td>1:4</td>
<td>SD16</td>
</tr>
</tbody>
</table>

**Characterization of sample:**
**Percent practical yield:**
The percentage of practical yields were calculated to learn about the percentage yield or effectiveness of any technique, thus helping to select the suitable manufacturing technique. Solid dispersion was gathered and weighed to determine practical yield by following equation [14].

\[
PY\% = \frac{\text{Practical mass (SD) } \times 100}{\text{Theoretical mass (drug + carrier)}}
\]

**Drug content:**
Solid dispersions equal to 10 mg cefepime were measured correctly and dissolved in 10 ml of methanol. The solution is filtered, diluted appropriate, and UV-spectrophotometer [8, 10] analyzes the drug content at 483 nm.
Actual amount of drug in solid dispersion
\[
\% \text{Drug content} = \frac{\text{Actual amount of drug in solid dispersion}}{\text{Theoretical amount of drug in solid dispersion}} \times 100
\]

**Saturation solubility studies:**
Saturation solubility testing was conducted to assess the rise in drug solubility, strong dispersions, and physical mixtures. Excess amounts (approximately 50 mg) of the drug have been added to 50mL of distilled water. Samples were stirred at room temperature for 24 hours, filtered through whatman filter paper, diluted and analyzed at 483 nm by a UV spectrophotometer.

**Dissolution studies:**
In vitro release studies of cefepime and solid dispersions were performed in a USP rotating paddle device at 100 rpm in 900 ml of water maintained at 37.0 ± 0.5 °C. Dissolution studies were conducted using 100 mg of pure drug and an equivalent amount of individual sample preparations. Aliquots of 5 ml were withdrawn at specified time intervals of 5, 10, 15, 20, 30, 45 and 60 min and replaced with equal volumes of fresh medium. The resulting samples were filtered through Whatman filter paper and spectrophotometrically evaluated at 483 nm to determine the dissolved drug. Studies of dissolution were conducted in triplicate.

**RESULT AND DISCUSSION**

**Percent practical yield and Drug content of solid dispersion:**
The percentage of practical yield and drug content in all formulations was estimated spectrophotometrically at 483 nm. The drug content of the prepared solid dispersions was discovered to be between 95 percent to 98.80 percent and 89 percent to 95 percent, respectively, showing the uniform distribution of the drug in the formulation (Table 2).

**Table 2. Percent practical yield and Drug content of solid dispersion**

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>% Practical yield</th>
<th>Drug content</th>
</tr>
</thead>
<tbody>
<tr>
<td>SD1</td>
<td>95.00</td>
<td>89.64</td>
</tr>
<tr>
<td>SD2</td>
<td>95.50</td>
<td>89.51</td>
</tr>
<tr>
<td>SD3</td>
<td>95.30</td>
<td>89.26</td>
</tr>
<tr>
<td>SD4</td>
<td>95.20</td>
<td>91.81</td>
</tr>
<tr>
<td>SD5</td>
<td>96.70</td>
<td>94.81</td>
</tr>
<tr>
<td>SD6</td>
<td>96.40</td>
<td>90.27</td>
</tr>
<tr>
<td>SD7</td>
<td>96.60</td>
<td>91.73</td>
</tr>
<tr>
<td>SD8</td>
<td>97.00</td>
<td>95.56</td>
</tr>
<tr>
<td>SD9</td>
<td>96.40</td>
<td>90.14</td>
</tr>
<tr>
<td>SD10</td>
<td>97.20</td>
<td>92.18</td>
</tr>
<tr>
<td>SD11</td>
<td>96.10</td>
<td>94.67</td>
</tr>
<tr>
<td>SD12</td>
<td>95.30</td>
<td>90.89</td>
</tr>
<tr>
<td>SD13</td>
<td>98.01</td>
<td>91.52</td>
</tr>
<tr>
<td>SD14</td>
<td>98.50</td>
<td>95.73</td>
</tr>
<tr>
<td>SD15</td>
<td>98.10</td>
<td>94.18</td>
</tr>
<tr>
<td>SD16</td>
<td>98.70</td>
<td>94.46</td>
</tr>
</tbody>
</table>

**Standard curves:**
In the concentration range of 10-40(μg / ml), which obeys Lambert Beer Law, the normal curve of the absorbance at distinct and the graph was plotted for absorbance versus cefepime concentration Fig 2. [15]. Cefepime was discovered to be linear at 483 nm in (Distilled Water).
Solubility Study:
Cefepime's solubility experiments were conducted in distilled water. The result of solubility study revealed that solubility increases with increases in concentration of carrier. The maximum solubility of 4.804µg/ml was found to be in PEG 4000 based on solid dispersion 1:4 ratio. The solubility of pure is less compared to its solid dispersion. The solubility profile shown in Fig 3-6 of all solid dispersion in distilled water which shows the graphic representation of all formulations.

Fig 3: Solubility of Mannitol Based Solid Dispersion in Distilled Water
Fig 4: Solubility of Lactose based solid dispersion in distilled water

Fig 5: Solubility of Na-CMC based solid dispersion in distilled water

Fig 6: Solubility of PEG 4000 based solid dispersion in distilled water
**Dissolution study:** In vitro release studies were carried out for the cefepime solid dispersion prepared by solvent evaporation method. In this method drug and Carrier ratio used was 1:1, 1:2, 1:3 and 1:4 of mannitol, lactose, Na- CMC, PEG4000. The release profile of drug with carries was found to be as given in Fig7-10.

*Fig 7 : in vitro dissolution profile of 1:1 ratio of all Drug: Carrier solid dispersion in water.*

*Fig 8 : in vitro dissolution profile of 1:2 ratio of all Drug: Carrier solid dispersion in water.*

*Fig 9: in vitro dissolution profile of 1:3 ratio of all Drug: Carrier solid dispersion in water.*

*Fig 10: in vitro dissolution profile of 1:4 ratio of all Drug: Carrier solid dispersion in water.*
vitro release studies revealed that there is marked increase in the dissolution rate of cefepime solid dispersion when compared to pure drug. From the in vitro release studies, it can be observed that SD16 Containing (1:4 drug: carrier) exhibited maximum release of 27.10% after one hour and so it was considered as the overall good formulation. As the amount of some carrier was increased dissolution rate was decreased this may be due to increased viscosity of coating materials.

CONCLUSION:
In the present study an attempt was made to enhance the solubility and dissolution of Cefepime. The cefepime solid dispersion was prepared by solvent evaporation method using mannitol, lactose, Na-CMC and PEG4000 (weight ratio). The solubility of cefepime was enhanced in presence of carrier (Mannitol, Lactose, Na-CMC, and PEG4000). It was concluded that the solvent evaporation method is useful for the successful enhancement of solubility of cefepime with faster dissolution rate. The highest solubility was found in Cefepime: PEG4000 solid dispersion in 1:4 ratios in water. The dissolution rate of Cefepime from all solid dispersion was significantly higher than that of pure Drug. The general trend indicated that there was increase in dissolution rate for solid dispersion in the following order PEG4000>Na- CMC> Lactose>Mannitol. The In vitro comparison of all solid dispersion showed that the highest dissolution was observed with PEG4000 solid dispersion in ratio 1:4 as compared to Na-CMC, Lactose, Mannitol.

REFERENCE:
Antihypertensive Drug using Solid Dispersion Technique, Asian Journal of Pharmaceutics, 10(4) S676, pg.no.2

How To Cite This Article:

Source of Support: Nil

Your next submission with British BioMedicine Publishers will reach you the below assets
• Quality Editorial service
• Swift Peer Review
• E-prints Service
• Manuscript Podcast for convenient understanding
• Global attainment for your research
• Manuscript accessibility in different formats (Pdf, E-pub, Full Text)
• Unceasing customer service

Track the below URL for one-step submission
http://www.britishbiomedicine.com/manuscript-submission.aspx