ENHANCEMENT OF DISSOLUTION RATE OF DICLOFENAC SODIUM USING LIQUISOLID COMPACT METHOD

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KEYWORDS:
Diclofenac sodium, Avicel, Aerosil, Liquisolid compacts.

ABSTRACT

The technique of liquisolid compacts is a promising method towards enhancing the dissolution of poorly soluble drugs. In the present study, the potential of liquisolid systems to improve the dissolution properties of water-insoluble agents were investigated using diclofenac sodium as the model drug. Several formulations of liquisolid compacts having same drug concentration were prepared. The aim of the present study was to improve the dissolution rate of diclofenac sodium using liquisolid techniques. Propylene glycol (PG) was used as a liquid vehicle. Various formulations are prepared by using various carriers like MCC, Starch and Lactose and colloidal silica is used as coating material in all formulations. The dissolution profile of liquisolid tablets was compared with each other and also with pure drug (control formulation). The effect of added liquid on the flowability and compressibility of the final admixture was studied and the effect of carrier on the dissolution pattern of diclofenac sodium was investigated. Liquisolid compacts demonstrated significantly higher drug release rates than the pure drug.
INTRODUCTION:
Over the years, various solid dosage formulation techniques, to enhance the dissolution of poorly soluble substances, have been introduced with different degrees of success [1-3]. Liquisolid compacts are acceptably flowing and compressible powdered forms of liquid medications [4, 5]. The term liquid medication implies oily, liquid drugs and solutions or suspensions of water-insoluble solid drugs carried in suitable nonvolatile solvent systems termed the liquid vehicles [6]. Using this new formulation technique, a liquid medication may be converted into a dry-looking, non-adherent, free-flowing, and readily compressible powder by a simple blending with selected powder excipients referred to as the carrier and coating materials [7-9]. Mcc, starch, lactose are used as the carriers, whereas very fine-particle-size silica powders may be used as the coating (or covering) materials [10, 11]. In liquisolid compacts, even though the drug is in a tabletted or encapsulated dosage form, it is held in a solubilized liquid state, which consequently contributes to increased drug wetting properties, thereby enhancing drug dissolution. Another advantage of liquisolid systems is that their production cost is lower than that of soft gelatin capsules because the production of liquisolid systems is similar to that of conventional tablets than that of soft gelatin capsules because the production of liquisolid systems is similar to that of conventional tablets [7-9].

Diclofenac sodium is a non-steroidal drug having a potent anti-inflammatory, analgesic, and antipyretic effect. It is an inhibitor of prostaglandin synthetase and is also used for the relief of pain and inflammation in conditions such as rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, acute gout, and following some surgical procedures. [12-14]. It is sparingly soluble in water [12]. Based on the Biopharmaceutics Classification System (BCS), it can be classified as a Class II drug. Class II drugs are defined as those with high permeability but whose solubility in aqueous media is not sufficient for the whole dose to be dissolved in the gastrointestinal tract. Diclofenac sodium was chosen for the work because of its poor tableting properties and hence requires a binder among other excipients to form satisfactory tablets. For these substances dissolution is therefore the rate-limiting step to absorption. The choice of medium for in vitro dissolution tests is therefore expected to play a very important role in the dissolution of Class II drugs [15].

MATERIALS AND METHODS:
Materials:
Diclofenac sodium was collected from NATCO, Hyderabad and MCC, Starch, Lactose, colloidal silica, PG, and sodium starch glycolate (SSG), magnesium stearate, talc were obtained from S.D. Fine chemicals, Mumbai. All other reagents and solvents used were of analytical grade. A multi-station tablet press (CDM-3-16, Cadmach machinery Co. Pvt. Ltd., Ahmedabad); disintegration test apparatus (2-USP-305,
Camphbell electronics, Mumbai); dissolution test apparatus (DT 03071009, lab India- Mumbai, 2000); and UV-visible spectrophotometer (SL159, Elico Ltd., Hyderabad) were used in research work.

**Methods:**

**Application of the Mathematical Model for designing the Liquisolid Systems:**[16-18]

A powder can retain only limited amounts of liquid while maintaining acceptable flow and compression properties. To calculate the required amount of excipients (carrier & coating materials), a mathematical approach is used for the formulation of liquid-solid systems. This approach is based on the flowable (Φ) and compressible (Ψ number) liquid retention potential introducing constants for each powder/liquid combination. The Φ-value of a powder represents the maximum amount of a given non-volatile liquid that can be retained inside its bulk (w/w) while maintaining an acceptable flowability. The Ψ-number of powder is defined as the maximum amount of the liquid that the powder can retain inside the bulk (w/w) while maintaining acceptable compactability resulting in compacts of sufficient hardness with no liquid leaking out during compression.

Depending upon the excipient ratio (R) of the powder substrate an acceptable flowing and compressible liquid-solid system can be obtained only if a maximum liquid load and the carrier material is not exceeded. This liquid-carrier ratio is termed as “Liquid load factor” and is defined as the weight ratio of the liquid formulation (W) and the carrier material (q) in the system.

\[ Lf = \frac{W}{Q} \]

‘R’ represents the ratio between the weights of the carrier (Q) and coating (q) material present in the formulation.

\[ R = \frac{Q}{q} \]

The liquid load factor that ensures acceptable flowability (Lf) can be determined by

\[ Lf = \Phi + \Psi \left( \frac{1}{R} \right) \]

**Preparation of Liquisolid Compacts:**[19, 20]

The diclofenac sodium was dissolved in PG and a homogenous drug solution was prepared. Next, the calculated weights (W) of the resulting liquid medications were incorporated into the calculated quantities of the carrier material and were mixed thoroughly. The resulting wet mixture was then blended with the calculated amount of the coating material using a standard mixing process to forms simple admixture. The prepared liquisolid powder systems were manually compressed into multi stationary punching machine of desired weight by using 5mm punch.
Solubility Studies:
Solubility studies of diclofenac sodium were carried out in five different nonvolatile solvents: PG, polyethylene glycol 400, polyethylene glycol 200, Tween 80, and glycerin. Saturated solutions were prepared by adding excess quantities of drug to the vehicles. The mixtures were sonicated for 3-5 hrs. Then it was filtered and supernatant solutions were analyzed spectrophotometrically at λmax of 276 nm for their drug content.

EVALUATION OF DICLOFENAC SODIUM LIQUISOLID COMPACTS:
The prepared liquisolid compacts were evaluated for the following parameters:

Friability:
The friability of the compacts was measured using a “Roche Friabilator” which is rotated at a speed of 25 rpm per minute. The tablet samples were weighed accurately and placed in the drum. The drum was rotated for 4 min (100 rotations) and the tablets were then removed. Any loose dust from the tablets was removed and again weighed accurately and the percentage friability was calculated from the weight of the tablets before and after the test according to the equation given below.

Hardness:
Tablets should be sufficiently hard to resist breaking during normal handling and yet soft enough to disintegrate properly after swallowing. The hardness of the liquisolid compacts prepared was evaluated using a Monsanto hardness tester. The tablet to be tested is placed between the spindle and the anvil. The desired pressure needed to hold the tablet in position is applied by moving the screw knob in a clockwise direction. The scale is moved so that the indicator is fixed at zero. The pressure is then applied until the tablet breaks. The reading is noted, which indicates the pressure that is needed to break the tablet. The mean hardness of each formula was determined and expressed in kilograms per square centimeter (kg/cm²).

In Vitro Drug Release:
In-vitro dissolution studies were performed for all the prepared tablets by using USP dissolution apparatus II. The dissolution test was carried for a period of 20 min., at 50 rpm using 900ml of 6.8 pH phosphate buffer as the dissolution medium at 37±0.5°C. At appropriate time intervals (5minutes), 5ml of the sample was withdrawn and replaced with the same volume of dissolution medium. The absorbance of the samples was measured at 276 nm against blank using UV spectrophotometer to determine the amount of drug release.

Percentage moisture absorption, wetting time was calculated for the optimized formulation ‘F1’
**Percentage moisture absorption:**

Initial tablet weight was noted and the tablet was subjected for wetting time and the weight of the tablet was noted and calculated by using the formula.

\[
\text{% Moisture absorption} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100
\]

**Wetting time:**

10 ml of water was taken in a Petri plate. Then five folds of filter paper were placed in that Petri plate and the tablet was placed on that filter paper. Then the time taken to wet the complete tablet was noted.

**RESULTS AND DISCUSSION:**

The method called “Liquid solid compaction” is mainly useful for class II drugs which are poorly water soluble. In the above work we have selected diclofenac sodium to increase the solubility and therefore there is a further increase in the bioavailability of the drug.

**Solubility Studies**

The solubility of diclofenac sodium in PG, polyethylene glycol 400, polyethylene glycol 200, Tween 80, and glycerin was tabulated in the table no: 1 shows that diclofenac sodium has the lowest solubility in glycerin. The solubility of diclofenac sodium was considerably increased in the presence of PG. The solubility of the drug strongly depends on the solvent used, therefore; PG was selected as a nonvolatile solvent.

Φ-value of carrier and coating material in propylene glycol were cited in the table no: 2. According to mathematical model was based on new fundamental powders properties by Spireas et al equations for carrier and coating materials were calculated and the results were shown in the table no: 2

Various flow properties were determined for the granules prepared by liquid solid compaction technique, and the results were shown in the table no: 3. The optimized formulation was found to be F1 which is having improved floe properties when compared with other formulations. Percentage friability of the optimized formulation F1 was found to be 0.34, disintegration time was found to be 37 seconds foe the formulation F1 which was shown in the table no:4. Dissolution studies were conducted for the tablets prepared by the technique and also for the control tablet. The drug was completely released from the tablets within 20 minutes and the rate of drug release was found to be more for the tablets prepared by liquid solid compaction than compared with the control tablet. The results and dissolution profile was shown in the table no:5 and fig no: 1. The percentage drug release for F1 was more than compared with the others and was found to be 98.14 and follows first order kinetics.
CONCLUSION:
The new technique of liquisolid compacts appears to be a promising alternative for the formulation of water insoluble drugs. A technique called liquid solid compaction is very much useful for the drugs having poor aqueous solubility. In the above work we have selected diclofenac sodium which is a poorly water soluble drug. The higher dissolution rate displayed by liquisolid compacts is due to the increased wetting properties and surface of the drug available for dissolution. With an increase in Lf-value, flow property was found to be reduced. It also resulted in a decrease in the compressibility of the final admixture. The prepared tablets showed rapid disintegration and acceptable dissolution rate compared with the control tablet.

Table 1: Solubility of Diclofenac sodium in various solvents

<table>
<thead>
<tr>
<th>S.No</th>
<th>Solvent</th>
<th>Solubility(mg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PG</td>
<td>41.34</td>
</tr>
<tr>
<td>2</td>
<td>PEG 400</td>
<td>6.138</td>
</tr>
<tr>
<td>3</td>
<td>PEG 200</td>
<td>22.97</td>
</tr>
<tr>
<td>4</td>
<td>Tween 80</td>
<td>29.41</td>
</tr>
<tr>
<td>5</td>
<td>Glycerin</td>
<td>23.41</td>
</tr>
</tbody>
</table>

Table 2: Composition of different Diclofenac sodium liquisolid formulation prepared using PG as a liquid vehicle according to mathematical model

<table>
<thead>
<tr>
<th>Formulation</th>
<th>R=Q/q</th>
<th>Lf=W/Q</th>
<th>Carrier material</th>
<th>Coat</th>
<th>SSG</th>
<th>UNIT DOSE WEIGHT(mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>15</td>
<td>0.0110</td>
<td>93.75</td>
<td>6.25</td>
<td>10</td>
<td>200</td>
</tr>
<tr>
<td>F2</td>
<td>7.5</td>
<td>0.0117</td>
<td>88.23</td>
<td>11.76</td>
<td>10</td>
<td>382</td>
</tr>
<tr>
<td>F3</td>
<td>15</td>
<td>0.0122</td>
<td>85</td>
<td>5.66</td>
<td>10</td>
<td>352</td>
</tr>
<tr>
<td>F4(control)</td>
<td>13</td>
<td>-</td>
<td>65.0</td>
<td>5.0</td>
<td>10</td>
<td>132</td>
</tr>
</tbody>
</table>

Table 3: Flowability Parameters of Diclofenac Sodium Liquid solid Compact Systems

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Bulk density</th>
<th>Tapped density</th>
<th>Carr’s index (%)</th>
<th>Hausner’s ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>0.50</td>
<td>0.572</td>
<td>12.58</td>
<td>1.14</td>
</tr>
<tr>
<td>F2</td>
<td>0.44</td>
<td>0.506</td>
<td>13.04</td>
<td>1.15</td>
</tr>
<tr>
<td>F3</td>
<td>0.39</td>
<td>0.502</td>
<td>22.31</td>
<td>1.25</td>
</tr>
<tr>
<td>F4</td>
<td>0.37</td>
<td>0.488</td>
<td>24.18</td>
<td>1.31</td>
</tr>
</tbody>
</table>
Table 4: Evaluation of liquid solid compacts

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Friability (%)</th>
<th>Disintegration time(sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>0.34</td>
<td>37</td>
</tr>
<tr>
<td>F2</td>
<td>0.46</td>
<td>44</td>
</tr>
<tr>
<td>F3</td>
<td>0.71</td>
<td>67</td>
</tr>
<tr>
<td>F4</td>
<td>0.66</td>
<td>93</td>
</tr>
</tbody>
</table>

Table 5: Cumulative percent Drug Release of diclofenac sodium

| Table 5: Cumulative percent Drug Release of diclofenac sodium
| Liquisolid Formulations |
|-------------------------|-------------------------|
| Time(min) | F1 | F2 | F3 | F4 |
| 5         | 81.50 | 90.47 | 77.08 | 40.56 |
| 10        | 84.85 | 81.89 | 79.44 | 65.52 |
| 15        | 87.67 | 88.64 | 82.31 | 74.61 |
| 20        | 98.14 | 95.50 | 93.64 | 85.91 |

Percentage moisture absorption and wetting time for optimized formulation ‘F1’ was found to be 12.37% and 43 seconds.

Fig 1: Comparative dissolution profile of Diclofenac Sodium tablets.

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