Abstract
Improving oral bioavailability of drugs those given as solid dosage forms remains a challenge for the formulation scientists due to solubility problems. The dissolution rate could be the rate-limiting process in the absorption of a drug from a solid dosage form of relatively insoluble drugs. Therefore increase in dissolution of poorly soluble drugs by solid dispersion technique represents a challenge to the formulation scientists. Solid dispersion techniques have attracted considerable interest of improving the dissolution rate of highly lipophilic drugs thereby improving their bioavailability by reducing drug particle size, improving wettability and forming amorphous particles. The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic inert carrier or matrix and a hydrophobic drug.

Keywords: Poorly soluble drug; solid dispersion; solubility enhancement.

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INTRODUCTION

Oral bioavailability of drugs depends on its solubility and/or dissolution rate, therefore major problems associated with these drugs was its very low solubility in biological fluids, which results into poor bioavailability after oral administration [1-5]. A drug with poor aqueous solubility will typically exhibit dissolution rate limited absorption, and a drug with poor membrane permeability will typically exhibit permeation rate limited absorption [6]. Therefore, pharmaceutical researchers’ focuses on two areas for improving the oral bioavailability of drugs include: (i) enhancing solubility and dissolution rate of poorly water-soluble drugs and (ii) Enhancing permeability of poorly permeable drugs [7]. It has been estimated that 40% of new chemical entities currently being discovered are poorly water soluble. [8, 9] Unfortunately, many of these potential drugs are abandoned in the early stages of development due to the solubility problems.

It is therefore important to realize the solubility problems of these drugs and methods for overcoming the solubility limitations are identified and applied commercially so that potential therapeutic benefits of these active molecules can be realized [10,11]. Therefore lots of efforts have been made to increase dissolution of drug. Methods available to improve dissolution include salt formation, micronization and addition of solvent or surface active agents. Solid dispersion (SD) is one of such methods and involves a dispersion of one or more active ingredients in an inert carrier or matrix in solid state prepared by melting, dissolution in solvent or melting-solvent method.[11] The formulation of drugs having low aqueous solubility using solid dispersion technology has been an active area of research since 1960.[12]

The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles. The first drug whose rate and extent of absorption was significantly enhanced using the solid dispersion technique was sulfathiazole by Sekiguchi and Obi [1]. This technique has been used by many researchers/scientists for a wide variety of poorly aqueous soluble drugs to enhance the solubility of the drugs and hence bioavailability [13, 14, 15].

Clarithromycin is used for the treatment of infections including those of the chest, skin and ear. It is also used for some types of stomach ulcer. Even if your condition improves, it is important to complete the prescribed course unless you are told to stop. Otherwise your infection could come back. Any side-effects are usually mild. The most common are feeling or being sick, indigestion,
and diarrhea. Clarithromycin is used to treat a variety of bacterial infections. It works by killing the bacteria that cause the infection [16,17].

Clarithromycin is stable in gastric medium and has a narrow absorption in gastrointestinal tract, rapid intestinal absorption, highly solute at gastric pH, no effect of food on absorption and it has higher eradication rate in vivo to H.pylori. Based on this, an attempt was made through this investigation to formulate floating matrix tablets of clarithromycin using different polymers and their combinations. [18,19]

**Clarithromycin** is a macrolitic antibiotic used to treat pharyngitis, tonsillitis, acute maxillary sinusitis, acute bacterial exacerbation of chronic bronchitis, pneumonia (especially atypical pneumonias associated with Chlamydia pneumonia or TWAR), skin and skin structure infections. In addition, it is sometimes used to treat Legionellosis, Helicobacter pylori, and Lyme disease [20].

Clarithromycin prevents bacteria from growing by interfering with their protein synthesis. It binds to the subunit 50S of the bacterial ribosome and thus inhibits the translation of peptides. Clarithromycin has similar antimicrobial spectrum as erythromycin, but is more effective against certain Gram-negative bacteria, particularly *Legionella pneumophila*. Besides this bacteriostatic effect, Clarithromycin also has bactericidal effect on certain strains, such as *Haemophilus influenzae*, *Streptococcus pneumoniae* and *Neisseria gonorrhoeae*. [21]

To reduce the development of drug-resistant bacteria and maintain the effectiveness of clarithromycin extended-release tablets and other antibacterial drugs, clarithromycin extended release tablets should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy. [21-25].

**MATERIALS AND METHODS**

**Materials**

Clarithromycin was a kind gift from Torrent Pharmaceuticals Pvt. Ltd., India. Citric acid was procured from (Loba chemie, Mumbai, India). Sodium Starch glycolate (Signet Chemicals (Thomas baker(chemicals) Pvt limited), Citric acid (Thomas baker (chemicals) Pvt Ltd).
Equipments

Melting point apparatus (PERFIT, India), Hot air oven (Microsil, India), Electronic Weighing Balance (Shimadzu Japan), U.V spectroscopy (Shimadzu, Japan).

API characterization

Characterization of API was done by development of calibration curve and also pre-formulation studies. This was mainly done to ensure that the API which is to be used is of the optimum quality and its properties could be judged.

Calibration curve of Clarithromycin

-Calibration curve of Clarithromycin: Calibration curve was prepared in two solvents for the API. These were Methanol and HCl. The procedure for determining absorbance maxima was done by using two solvents explained as follows:

- Methanol – 100 mg clarithromycin was dissolved in 100 ml methanol to prepare stock solution. Now take out 1ml, 2ml, 3ml, 4ml, 5ml 6ml, 7ml, 8ml, 9ml and 10ml of stock solution to prepare different concentrations of 100µg/ml, 200µg/ml, 300µg/ml, 400µg/ml, 500µg/ml, 600µg/ml, 700µg/ml, 800µ/ml, 900µg/ml and 1000µg/ml respectively. The base line was corrected and lambda max was determined on UV spectrophotometer at 282 nm. Absorbance of drug at different concentrations was calculated and graph was plotted.

- Hydrochloric acid (HCl) -100 mg Clarithromycin acid was dissolved in 100 ml HCl to prepare stock solution. Now take out 1ml, 2ml, 3ml, 4ml, 5ml 6ml,7ml, 8ml, 9ml and 10ml of stock solution to prepare different concentrations of 100µg/ml, 200µg/ml, 300µg/ml, 400µg/ml, 500µg/ml, 600µg/ml, 700µg/ml, 800µ/ml, 900µg/ml and 1000µg/ml respectively. The base line was corrected and lambda max was determined on UV spectrophotometer at 288 nm. Absorbance of drug at different concentrations was calculated and graph was plotted.

Pre-formulation Studies

Before starting with the formulation development the pre-formulation studies were conducted to characterize the drug and the selection of Excipients was also based on the pre-formulation studies. [27,28] It mainly involved two parameters Organoleptic and physicochemical properties of the API used. This was mainly done to check the purity of the drug and any deviation could also help to know if there is any deterioration involved.
a) Organoleptic properties (API)

- Appearance
- Colour
- Odour

All the above studies were carried out by using no special equipment these were done by visual assessment.

b) Physicochemical Properties (API)

- Melting point:
  For determination of melting point of Clarithromycin a melting point apparatus of capillary type was used. The capillary filled with API was inserted and the temperature at which the API started to melt was noted down as melting point of the API.

- Partition coefficient:
  The partition coefficient is the parameter used to determine the lipophilicity of the API. The API with high lipophilic nature has high lipophilicity and thus a high partition coefficient and vis- versa. The logarithm of the ratio of the concentrations of the un-ionized solute in the organic and aqueous solvents is called $\log P$: The log P value is also known as a measure of lipophilicity (partition coefficient). It provides a means of characterizing the lipophilic/hydrophilic nature of the drug. [29-32]

  Drugs having values of P much greater than 1 are classified as lipophilic, whereas those with partition coefficient much less than 1 are indicative of a hydrophilic drug. [33, 34] The partition coefficient is commonly determined using an oil phase of n-Octanol and water.

  It can be determined by the formula: [35]

  \[ K_{o/w} = \frac{\text{Concentration of drug in non aqueous phase}}{\text{Concentration of drug in aqueous phase}} \]

- Solubility Studies:
  These pre-formulation studies formed the most important part of the formulation development; as it formed the base for selection of excipients which had high solubility of the API. The procedure followed was the shake flask method. [36-38] The solubility of Clarithromycin in various solvents was determined by dissolving excess amount of API in 5ml of each of the selected solvents in 10ml capacity stoppered vials separately. The mixture vials were then kept at
37±1.0 °C in a shaker bath for 24 h to get equilibrium. The concentration of API was determined in each solvent by UV spectrophotometer by scanning from 200-400nm (wavelength 282nm).

[39-42]

Method of preparation of Solid dispersion

Preparation of solid dispersion (kneading technique)

Preparation of Binary System

Binary mixtures was prepared by mixing accurate weight of Clarithromycin with sodium starch glycolate in drug: polymer ratio of 1:1, 1:2, 1:3, 1:4, and 1:5 for 5 min using glass mortar and pestle. The physical mixture was triturated using a small volume of water and Hcl (1:1) solution to give a thick paste, which was kneaded for 30 minutes, and then dried at 45°C in an oven. The dried mass was pulverized, passed through 60 mesh sieve size, then weighed, transferred to airtight container and stored, and the percentage drug content was determined.

Preparation of Ternary system

Ternary mixtures was prepared by mixing accurate weight of Clarithromycin with sodium starch glycolate and citric acid in Drug: polymer ratio of 1:5:2,1:5:4, and 1:5:5 for 5 min using glass mortar and pestle. The physical mixture was triturated using a small volume of water and Hcl (1:1) solution to give a thick paste, which was kneaded for 30 minutes, and then dried at 45°C in an oven. [43,44] The dried mass was pulverized, passed through 60 mesh sieve size, then weighed, transferred to airtight container and stored, and the percentage drug content was determined.

Characterization of Solid Dispersion

- Percentage yield

Percentage practical yield were calculated to know about percent yield or efficiency of any method, thus it helps in selection of appropriate method of production. Solid dispersions were collected and weighed to determine practical yield (PY) from the following equation [45-49].

\[
\text{Percentage yield} = \frac{\text{Practical mass (solid dispersion)}}{\text{Theoretical mass (drug + carrier)}} \times 100
\]

- Drug content

The Physical mixture of solid dispersion equivalent to 50 mg of drug were taken and dissolved separately in100 ml of Hcl. The solutions were filtered and were further diluted such that the absorbance falls within the range of standard curve [50-52] The absorbance of solutions were
determined at 288 nm by UV-visible spectrophotometer. The actual drug content was calculated using the following equation as follows

\[
\% \text{ Drug content} = \frac{\text{Practical drug content}}{\text{Theoretically drug content}} \times 100
\]

- **Fourier Transform Infra red spectroscopy (FTIR)**
  The IR analysis of sample drug was carried out for qualitative compound identification. The infrared spectra of Clarithromycin was performed on Fourier transformed infrared spectrophotometer. This technique shines a beam containing many frequencies of light at once, and measures how much of that beam is absorbed by the sample. Next, the beam is modified to contain a different combination of frequencies, giving a second data point. This process is repeated many times [53-58].

- **X-Ray Diffraction (XRD)**
  X-ray powder diffraction patterns were recorded on X-ray powder diffraction system, PAN analytical spectris Pvt.Ltd., [59,60] Singapore using copper target, a voltage of 40 Kv and a current of 30 mA. The scanning was done over 2θ range of 5º to 60º.

- **Scanning Electron Microscopy (SEM)**
  Photomicrographs of clarithromycin and Best ternary SD formulation were obtained by SEM (JSM-6360; JEOL Ltd., Japan). The powder were mounted on double-sided adhesive tape and sputtered with gold for 2 min using SPI sputter. Scanning Electron photographs were taken at an accelerating voltage of 15 kV [61,62].

- **In vitro release studies**
  The drug release rate from solid dispersion was determined using USB apparatus Type II paddle type dissolution apparatus. Weighed amount of formulation was filled into the capsule then it was being placed in the basket. 0.1N Hcl was used as dissolution medium at 37±5ºc at a rotating speed of 100 rpm.
  Volume of dissolution media was kept at 900ml .5ml sample was withdrawn at predetermined time. First sample was withdrawn at 10 min interval.
  The samples were analysed spectrophotometrically at 288 nm to determine the concentration of drug present. The initial volume of dissolution fluid was maintained by adding 5ml of fresh dissolution [63-66].
RESULT AND DISCUSSION

Calibration curve of Clarithromycin

Calibration curve was prepared in two solvents for the API these were Methanol and Hcl. These were determined in 100ug/ml-1000ug/ml for both the solvents.

Determination of absorbance maxima:

The procedure for determining absorbance maxima was done by using two solvents explained as follows:

- **Methanol**
  100 mg clarithromycin was dissolved in 100 ml methanol to prepare stock solution. Now take out 1ml, 2ml, 3ml, 4ml, 5ml 6ml, 7ml, 8ml, 9ml and 10ml of stock solution to prepare different concentrations of 100µg/ml, 200µg/ml, 300µg/ml, 400µg/ml, 500µg/ml, 600µg/ml, 700µg/ml, 800µg/ml, 900µg/ml and 1000µg/ml respectively. The base line was corrected and lambda max was determined on UV spectrophotometer at 282 nm. Absorbance of drug at different concentrations was calculated and graph was plotted.

- **Hydrochloric acid (Hcl)**
  100 mg Clarithromycin acid was dissolved in 100 ml HCl to prepare stock solution. Now take out 1ml, 2ml, 3ml, 4ml, 5ml 6ml, 7ml, 8ml, 9ml and 10ml of stock solution to prepare different concentrations of 100µg/ml, 200µg/ml, 300µg/ml, 400µg/ml, 500µg/ml, 600µg/ml, 700µg/ml, 800µg/ml, 900µg/ml and 1000µg/ml respectively. The base line was corrected and lambda max was determined on UV spectrophotometer at 288 nm. Absorbance of drug at different concentrations was calculated and graph was plotted.
Pre-formulation studies

The Preformulation studies were carried out for the API in use which involved the organoleptic and physicochemical properties of the drug. The results obtained were used in the formulation development process.

a) Organoleptic properties: The basic properties of the API were tested as appearance, colour and odour. It was observed as a powder which was white in colour having no odour and bitter in taste.

b) Physico-chemical properties: The physicochemical properties were analysed to estimate its ability to be used in the formulation. The various properties studied were as follows;

- **Melting point:**
  There is a linear correlation between log flux and reciprocal of melting point, indicating that the lower melting point the better penetration [68]. The melting point of Clarithromycin was found to be 210-222°C.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Melting point observed</th>
<th>Reported value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clarithromycin</td>
<td>217-220°C</td>
<td>210 -222°C</td>
</tr>
</tbody>
</table>

- **Partition coefficient:**
  Partition coefficient was determined as ratio of concentration of drug in octanol to the concentration of drug in water and the value were reported as log P [69,70]

\[
K_{O/W} = \frac{\text{Concentration of drug in non aqueous phase}}{\text{Concentration of drug in aqueous phase}}
\]
Table 2: Partition coefficient of Clarithromycin

<table>
<thead>
<tr>
<th>Drug</th>
<th>Partition coefficient observed</th>
<th>Reported value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clarithromycin</td>
<td>2.91±01</td>
<td>2.92</td>
</tr>
</tbody>
</table>

Solubility studies:

The solubility studies conducted have the following results. The shows the solubility results and also as per IP have been determined. The highlighted solvents are selected for further study. The saturation solubility of Clarithromycin was calculated.

Table 3: Solubility profile of Clarithromycin in different solvents

<table>
<thead>
<tr>
<th>S.no</th>
<th>Solvent</th>
<th>Amount in mg/ml</th>
<th>Inference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Acetone</td>
<td>136.36±0.22</td>
<td>Soluble</td>
</tr>
<tr>
<td>2</td>
<td>Water</td>
<td>1.09±0.17</td>
<td>Insoluble</td>
</tr>
<tr>
<td>3</td>
<td>Methanol</td>
<td>4.27±0.46</td>
<td>Partially soluble</td>
</tr>
<tr>
<td>4</td>
<td>Ethanol</td>
<td>3.85±0.15</td>
<td>Partially soluble</td>
</tr>
</tbody>
</table>

Evaluation of solid dispersion

Percentage Drug yield

Percentage drug content was in the range of 90% to 98%

Table 4: Percentage drug yield of solid dispersion

<table>
<thead>
<tr>
<th>S.no</th>
<th>Batch no</th>
<th>% yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TD1</td>
<td>98%</td>
</tr>
<tr>
<td>2</td>
<td>TD2</td>
<td>89%</td>
</tr>
<tr>
<td>3</td>
<td>TD3</td>
<td>85%</td>
</tr>
</tbody>
</table>

TD-Ternary solid dispersion

Percentage drug content

Percentage drug content was in the range of 60% to 97.5%

Table 5: Percentage drug content of solid dispersion

<table>
<thead>
<tr>
<th>S.no</th>
<th>Batch no</th>
<th>% drug content</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TD1</td>
<td>97.5%</td>
</tr>
<tr>
<td>2</td>
<td>TD2</td>
<td>60.0%</td>
</tr>
<tr>
<td>3</td>
<td>TD3</td>
<td>85.6%</td>
</tr>
</tbody>
</table>
Scanning electron microscopy (SEM)

Surface characteristics of ternary solid dispersion were analysed using a scanning electron microscope. This technique is useful in the examination of internal and external morphology of solid dispersions. The SEM analysis of the samples was performed to investigate the surface morphology and homogeneity of the particles. The samples of optimized solid dispersion were sputter-coated with gold at room temperature before examination to render the surface of particles Electroconductive [71-76]. The SEM analysis of the sample was done by Jeol JSM-840 (Japan) scanning electron microscope. SEM analysis of clarithromycin was shown in fig 5.10 and SEM of final formulation (1:5:2) ternary solid dispersion was shown in fig 5.11.

![Fig 1: Scanning electron micrographs of final formulation](image1)

![Fig 2: Scanning electron micrographs of Clarithromycin](image2)

XRD (X-ray Diffractometry)

X-ray diffractometry (XRD) spectra Drug and ternary systems with carriers are presented in Figure 3. The x-ray diffractogram of clarithromycin has sharp peaks at diffraction angles (2θ) 12.26-, 15.88-, 19.88-, 22.08-, and 23.92- showing a typical crystalline pattern. However, all major characteristic crystalline peaks appear in the diffractogram of both physical mixtures and solid dispersion system. Moreover, the relative intensity and 2θ angle of these peaks remains practically unchanged [77-80]. Thus it can be clearly suggestive from x-ray data that there is no amorphization of clarithromycin and aliquots were withdrawn, filtered (0.22 μm pore size) and spectrophotometrically assayed if it is still in its original crystalline form.
Table 6: In vitro release studies

<table>
<thead>
<tr>
<th>S.No</th>
<th>Time (in min)</th>
<th>% cumulative drug release (1:5:2)</th>
<th>% cumulative drug release (1:5:4)</th>
<th>% cumulative drug release (1:5:5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>10</td>
<td>67.85±1.02</td>
<td>20.743±0.63</td>
<td>33.7±0.57</td>
</tr>
<tr>
<td>2</td>
<td>20</td>
<td>69.86±0.04</td>
<td>23.23±1.09</td>
<td>36.13±1.08</td>
</tr>
<tr>
<td>3</td>
<td>30</td>
<td>70.19±0.51</td>
<td>26.22±1.87</td>
<td>38.6±1.93</td>
</tr>
<tr>
<td>4</td>
<td>40</td>
<td>72.07±1.07</td>
<td>28.9±0.27</td>
<td>39.27±2.08</td>
</tr>
<tr>
<td>5</td>
<td>50</td>
<td>75.95±0.08</td>
<td>29.23±1.71</td>
<td>40.5±1.52</td>
</tr>
<tr>
<td>6</td>
<td>60</td>
<td>77.72±1.6</td>
<td>32.78±1.77</td>
<td>41.5±0.57</td>
</tr>
<tr>
<td>7</td>
<td>70</td>
<td>79.61±1.12</td>
<td>36.12±0.18</td>
<td>42.21±0.48</td>
</tr>
<tr>
<td>8</td>
<td>80</td>
<td>80.5±1.08</td>
<td>41.81±0.71</td>
<td>52.69±0.67</td>
</tr>
<tr>
<td>9</td>
<td>90</td>
<td>83.49±0.07</td>
<td>44.4±0.61</td>
<td>61.2±0.51</td>
</tr>
<tr>
<td>10</td>
<td>100</td>
<td>84.49±1.73</td>
<td>45.39±0.34</td>
<td>65.12±0.98</td>
</tr>
<tr>
<td>11</td>
<td>110</td>
<td>89.38±0.92</td>
<td>45.44±0.77</td>
<td>71.01±1.1</td>
</tr>
<tr>
<td>12</td>
<td>120</td>
<td>90.34±0.52</td>
<td>45.49±1.09</td>
<td>75.6±1.52</td>
</tr>
<tr>
<td>13</td>
<td>130</td>
<td>91.38±0.19</td>
<td>46.47±0.55</td>
<td>76.9±1.5</td>
</tr>
<tr>
<td>14</td>
<td>140</td>
<td>94.49±0.05</td>
<td>46.99±0.67</td>
<td>78.8±0.26</td>
</tr>
<tr>
<td>15</td>
<td>150</td>
<td>95.6±0.12</td>
<td>47.51±0.78</td>
<td>80.83±1.1</td>
</tr>
<tr>
<td>16</td>
<td>160</td>
<td>96.8±1.15</td>
<td>48.97±0.89</td>
<td>83.0±0.57</td>
</tr>
<tr>
<td>17</td>
<td>170</td>
<td>98.6±0.09</td>
<td>52.69±1.21</td>
<td>85.06±0.32</td>
</tr>
</tbody>
</table>
Fig 4: Cumulative Percent Release of Clarithromycin from ternary Solid Dispersions

Series1: Ternary solid dispersion 1:5:2
Series2: Ternary solid dispersion 1:5:4
Series3: Ternary solid dispersion 1:5:5

CONCLUSION
The result of the present study showed that the solid dispersion had enhanced the dissolution of drug. Solid dispersions of Clarithromycin were prepared by using sodium starch glycolate and citric acid showed better drug release. On the basis of result of Clarithromycin, sodium starch glycolate and citric acid solid dispersions in 1:5:2 ratio (TD1) revealed better solubility and dissolution rate. This study was started to establish the possibility of preparing solid dispersions with improved aqueous solubility and dissolution rate, which will solve the difficulties in the development of pharmaceutical dosage forms of Clarithromycin, poorly water soluble drug due to their limited water solubility, slow dissolution rate and low bioavailability. Solid dispersion was prepared by Kneading method thus may be an ideal means of drug delivery system for poorly water soluble drugs.

REFERENCES


23. Remington- The Science & Practice of Pharmacy, Published by Lippincott Williams & Wilkins, 21st Edn., 229-230.


51. Leunar C, Dreessan J, Improving drug solubility for oral delivery using solid dispersion, European journal of Pharmaceutics and Biopharmaceutics, 50, 2000, 47-60.


73. Sheu MT, Chen SY, Chen LC. Influence of micelle solubilization by tocopheryl polyethylene glycol succinate (TPGS) on solubility enhancement and percutaneous penetration of estradiol. J. Controlled Release 2003; 88: 355-368.
