Skimmed milk mediated solubility enhancement of loperamide and development of mouth dissolving tablet

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Received: 01-08-2016 / Revised: 18-08-2016 / Accepted: 25-08-2016 / Published: 27-08-2016

ABSTRACT

Purpose of current research work was to develop mouth dissolving tablets of Loperamide HCl with enhanced solubility and palatable taste. Mouth dissolving tablets of Loperamide HCl were prepared by the direct-compression method. Skimmed milk was used as natural polymer. Improvement in dissolution rate of drug was observed in solid dispersion as compared to pure drug. All the batches of the tablets were preliminarily evaluated for various physical parameters such as hardness, friability, drug content, wetting time, disintegration and dissolution which were reported. Among the 6 formulations F5 showed better drug release (99.20%) and drug content (98.80%) than other formulations. Dissolution studies using the USP paddle method were performed for solid dispersions of loperamide at 37±0.50ºc and 50 rpm in Phosphate buffer pH 6.8. Fourier Transformer Infrared (FTIR) spectroscopy were performed to identify the Drug-Excipient interactions, hence its effect on dissolution rate. Furthermore, the drug release was found to be comparable to the marketed formulation.

Keywords: Solubility enhancement, skimmed milk, Loperamide, Solid dispersion

INTRODUCTION

Orally Disintegrating (ODT) Tablet technology has been approved by United States Pharmacopoeia (USP), by the Centre for Drug Evaluation and Research [1]. USFDA defined ODT tablet as “A solid dosage form containing medicinal substances, which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue”. Besides, this European Pharmacopeia has endorsed the term orodispersible tablet for a tablet that disintegrates in less than 3 minutes within the mouth before swallowing. Many dosage forms of therapeutic agents are designed to be administered orally [2]. This route of administration is convenient, economical and effective in quickly and easily placing the desired dosage of a therapeutic agent. Thus, it has been recognized that improving the taste of unpleasant-tasting therapeutic agents can affect patient compliance positively.

The Poorly water-soluble drug candidates often appear from current drug discovery programs and present formulators with considerable technical challenges [3]. The poor solubility and low dissolution rate of poorly water soluble drugs in aqueous gastro intestinal fluids often cause poor bioavailability. Consider the reformed Noyes-Whitney equation which gives some notion as how the dissolution rate of even very poorly soluble compounds might be enhanced to minimize the limitations to oral availability [4, 5]:

$$\frac{dC}{dt} = AD(Cs - C)$$

The Solubility is an important physicochemical factor affecting absorption of drug and its therapeutic effectiveness. Formulation advancement would lead to failure, if the drug is having poor aqueous solubility. The low dissolution rate and low solubility like drug substances in water in aqueous gastro fluid frequently leads to deficient bioavailability. The endeavour to improve solubility and dissolution of hydrophobic drugs remains one of the delicate tasks in the drug development [6]. Several methods have been introduced to elate over this problem Ford et al. (1986), Dressman et al. (2000). As long as enhancement of solubility and dissolution rate of poorly soluble drugs sufficient commercially applicable methods are available for e.g. Liquisolid method in which drug in solution state or softened drug is adsorbed over the impenetrable...
Solubility Enhancement: The Solubility is defined as the property of a solid, liquid or gaseous chemical materials labelled solute to dissolve in a solid, liquid or gaseous solvent to form alike solution of the maximum quantity of solute in a certain quantity of solvent at specified temperature and pressure [8].

Steps of solubilisation:
Process of solubilisation contains three steps [9]:
• The separation of the molecule of the solvent to provide slot in the solvent for solute.
• The splitting of intermolecular ionic bonds in the solute.
• The interaction between the solvent and the solute molecule or ion

Need for Solubility Enhancement: The drug absorption from the GI tract can be restricted by a variety of factors most important contributor being poor aqueous solubility and membrane permeability of the drug molecule, as solubility criteria shown in table 1. Thus two areas of pharmaceutical research that focus on enhancing the oral bioavailability of active agents include: enhancing of solubility and dissolution rate of poorly water soluble drugs [10,11]. BCS is a scientific scheme as shown in table 2, classifying a drug substance based on aqueous solubility and intestinal permeability [12]. The BCS II & IV class drugs are rate limiting step in drug release from the dosage form. As solubility increases in gastric fluid and not the absorption, thus, by increasing the solubility with the increase in bioavailability for BCS class II & IV drugs will result in enhanced solubility [13].

Solid Dispersion: Solid dispersion appertains to the dispersion of one or more active ingredients in an inert carrier or matrix at the solid state prepared by the melting solvent or the melting-solvent method [14]. The solid dispersion may also be called solid-state dispersion method [15].

Advantages: The encouraging results of solid dispersion in solubility and dissolution rate enhancement of poorly soluble drugs can be ascribed to various aspects:
• From amorphous structure replacing crystalline structure.
• To improve the local solubility and wettability of the poorly soluble drug in the solid dispersion-matrix [16].
• From the capacity of carrier functional groups to form interactions with the drug [17].

Role of Skimmed milk in Mouth Dissolving Tablets: The skimmed milk powder contained in the composition in an amount at least sufficient to mask the taste of the unpleasant therapeutic agent. The amount of skimmed milk powder will differ consonantly with a number of factors which includes, for e.g. the particular species of therapeutic agent used, ingredients, specific type of the oral dosage formulation and particular application in which the composition is expected to be used. It is considered that most of application ratios of skimmed milk powder to therapeutic agent will be from 1: 1 to about 1, 000,000: 1. In favoured form the ratios can be from about 1:1 to about 1,000:1, even more ideally from about 1:1 to about 100: 1, these normally weight ratios. Meanwhile not bound to be designed by any particular theory, it has been considered that the proteins in the skimmed milk powder acts to mask the taste of the therapeutic agent by altering the taste receptors. This hindering action may arise either by beneficial binding of proteins with the receptor sites acts by the formation of a film over the receptor site which strides as a physical impediment to the therapeutic agent [21]. Carbohydrates with sugars present in skimmed milk powder enhance the agreeable compositions and accords the physical characteristics of the composition. Therapeutic agents having unpleasant taste the powder form of skimmed milk with sufficient quantity can be utilized for masking the unpleasant taste of the therapeutic agent.

Importance in Pharmaceuticals:
1. It enhances the solubility and dissolution release profile [22]
2. It increases solubility of poorly soluble drugs [23].
3. It helps in overcome the gastric disturbances due gastric irritation of various API [24]
4. It is used to improve oral bioavailability [25].

MATERIALS AND METHOD

Preparation of Stock Solution and Calibration Curve: Accurately weighed 10mg Loperamide hydrochloride was weighed and transferred in to 100 ml volumetric flask. About 7 ml of solution (Distilled water, 6.8 pH Phosphate buffer) was added slowly to dissolve into pre-stock solution. Drug was properly dissolved in the solution. The
volume was prepared with drug concentration of 1000 µg/ml.

**Preparation of Calibration Curve of Loperamide Hydrochloride:** The stock solution was further diluted with distilled water. Serial no’s of dilutions were carried out so as to get different concentrations 2.4, 6.8, and 10 µg/ml. The absorbance was measured at $\lambda_{max}$ of 214 nm using double beam UV-VIS spectrophotometer against blank.

**Preparation of Calibration curve of Loperamide Hydrochloride in 6.8 pH PBS:** The stock solution was further diluted with 6.8 pH PBS. Serial dilutions were carried out so as to get different concentration 2.4, 6.8, and 10 µg/ml. The absorbance was measured at $\lambda_{max}$ using double beam UV-VIS spectrophotometer against blank.

**Preparation of Solid Dispersion:** (a)**Solvent Evaporation Method:** Loperamide Hydrochloride and Skimmed Milk were weighed accurately in the ratio of 1:1, 1:2, and 1:3 and triturated in a mortar pestle for 5 minutes and then were dissolved in 1 ml of ethanol with constant trituration. Solvent was evaporated at 40°C and dried in a desicator for 4 hours and passed through sieve No. 80.

**Preparation of Physical Mixture:** Loperamide Hydrochloride and Skimmed Milk in the ratio of 1:1, 1:2, and 1:3 and triturated in a mortar pestle for 10 minutes and kept in a desicator for its further use.

**Drug-Excipient interaction studies:** In order to check compatibility of drug with excipients used in the formulation drug excipient interaction study was carried out. In this method the drug and polymer were mixed together in the ratio 1:1, 1:2, and 1:3 to produce physical mixture. The Infrared Spectral analysis was obtained in the wave number of 3500-600 cm$^{-1}$ by using Bruker alpha spectrophotometer using ATR technique. These were than compared with earlier obtained spectrum of the pure drug and the polymer.

**Formulation of Mouth Dissolving Tablet:** Drug Polymer Complex (Solid Dispersion) and excipients were passed through sieve no. 80. Drug polymer complex, the directly compressible Mannitol, Superdisintegrants (Sodium Starch Glycolate and Microcrystalline cellulose), and Talc was mixed together for 15 min. Magnesium Stearate, was then added and mixed for 5 mins. Then these were compressed at required hardness and were collected on single punch machine. Ingredients of Mouth Dissolving tablets includes:-

- Loperamide HCl as a drug
- Skimmed Milk as polymer
- Sodium Starch Glycolate and Microcrystalline cellulose as Superdisintegrants
- Talc as glidant
- Magnesium Stearate as Lubricant

**Evaluation of MDT**

**General characteristics:**

**Drug Content Uniformity Test:** Tablets were kept in 100 ml volumetric flask containing buffer 6.8 pH for 24 hours. When they get completely dissolved the solution was centrifuged. After centrifuged the supernatant was collected. The absorbance was measured spectrophotometrically at 214 nm. Dilutions were made using phosphate buffer having pH 6.8

**Hardness and friability:** The hardness of the tablet was determined using Dr. Schleuniger Hardness tester. Six tablets were taken from each batch and were examined for friability using Roche Friabilator and the equipment was run for 4min at 25 revolutions per minute. The tablets were taken out, dedusted and reweighted and % friability was calculated.

\[
\text{% Friability} = \frac{\text{Loss in weight/Initial weight}}{100}
\]

**Disintegration test:** The disintegration test was performed using an USP disintegration apparatus, with distilled water at 37± 2°C. The time reported to obtain complete disintegration of six tablets were recorded and average was reported.

**Characterization of Solid Dispersion**

**FT-IR Studies:** The spectrum of Solid dispersion of Loperamide and Skimmed Milk was taken in a powder material form and was compared with pure Loperamide spectrum.

**In-vitro Drug Release Studies:** Dissolution studies were conducted for all the formulation using USP Type-II apparatus (paddle type). The dissolution test was performed using 900 ml of 6.8 pH phosphate buffer taken as dissolution medium at 50 rpm and 37 °C± 0.5 °C. 5 ml of aliquots were periodically withdrawn and the test samples volume was replaced with an equal volume of fresh dissolution medium. Test samples were collected in test tubes after filtration through Watt Mann filter paper. Amount of drug in aliquots was quantified taking the absorbance of sample at 214 nm using Phosphate buffer pH 6.8 (dissolution media) and analysed by UV-VIS. For comparison, dissolution studies of commercial tablets were also conducted.
RESULTS

Solubility Studies:
Solubility of Drug and Polymer: The observed result in case of pure drug and Polymer solubility in various solvents is given below (table 3 & 4):
Solubility study of Solid dispersions: Solid dispersions were prepared in the ratio of 1:1, 1:2 and 1:3 simultaneously they were observed in distilled water, a comparative study shows that solid dispersion having ratio 1:3 was having greater solubility in distilled water. As shown in (fig. 1):
UV Spectroscopy (λ max Determination): The standard solution of Loperamide hydrochloride in Ethanol (10µg/ml) was scanned (200-400) nm by use of UV spectrophotometer. The λ max was found to be 214 nm (fig 2):

FTIR SPECTROSCOPY STUDIES:
FTIR Spectrum of Pure Drug: FTIR spectrum of Loperamide hydrochloride was performed using wave number ranges. Observed wave numbers are shown in (fig 3), confirmed the presence of Loperamide Hydrochloride.

FTIR spectrum of Solid Dispersion (1:3):- FTIR spectrum of Solid Dispersion of Loperamide hydrochloride and skimmed milk is shown in (fig. 4), and interpretation was done using Standard Wave number ranges. Observed wave numbers along with assessment of specific chemical groups which shows all peaks of drug confirms there was no interaction between drug and polymer.

In-vitro Dissolution Studies:
In-vitro Drug release of Marketed Tablet of Loperamide Hydrochloride: Dissolution Profile of marketed formulation shows 72 % of drug release within in 10 minutes, as this was done to compare it with the formulated batches so that better release was observed. As shown in (fig. 5) below:

In-vitro Drug Release of Formulated Mouth Dissolving Tablet of Loperamide Hydrochloride: Dissolution profiles revealed that, after 10 minutes, formulations F1-F6 showed percentage drug release of 88, 90, 92, 95, and 88 % respectively. Among all the formulations, F5 formulation shows better dissolution efficiency and rapid disintegration with release of 95% within 10min. As shown in (Fig. 6 and 7) the comparative studies between F1, F2 and F3 and F4, F5 and F6 respectively with Marketed formulation. Above all formulations F5 shows better disintegration time and In-vitro drug release. As shown in table 5. The In-vitro drug release of the optimized formulation (F5) and marketed formulation was compared and it reveals that optimized formulation shows much better drug release than Marketed preparation. As shown in (fig. 8) below:

DISCUSSION
Approximately 1/3 of drugs in the development are water insoluble of which 1/2 fails in the trials because of destitute pharmacokinetics. Poorly water soluble drugs belong to BCS class II and Class IV group of compounds. In the process of absorption of drug from oral route dissolution is the rate limiting step for lipophilic drugs. Therefore it is necessary to enhance dissolution of these drugs to ensure maximum therapeutic utility of these drugs. Therefore, it is crucial to enhance dissolution of these drugs to assure maximum therapeutic benefit. Rapid dissolving drug-delivery systems was initiated and developed in the late 1970s as an alternative to tablets, capsules, and syrups for paediatric and geriatric patients who experiences difficulties in swallowing traditional oral solid-dosage forms. Taste being one of the most important vital patient acquiescence. Therefore, any pharmaceutical formulation with enhanced solubility and palatable taste would definitely be favoured over competitor’s product as taste being one of the most important vital patient acquiescence. The encouraging results of solid dispersion in solubility and dissolution rate enhancement of poorly soluble drugs attributes the better results. Loperamide hydrochloride orally disintegrating tablets were prepared by direct compression method. All the batches of the tablets were preliminarily evaluated for various physical parameters such as hardness, friability, drug content, disintegration and dissolution which were reported. All the above properties and value were near to boundary of standard limit. All above properties and value were near to borderline of standard limit. Batches of all tablets maintained hardness in the range 5.0 kg/cm². The debt in total weight of the tablets due to friability was found in the range of 0.56 to 0.88 %. The drug content in different formulation was highly reliable and in the range of 96.12-98.80 %. The result of in-vitro disintegration was within the prescribed limits and complies with the norms for orally disintegrating tablets and the value obtained were 16-18 seconds. Dissolution profiles revealed that, after 12 minutes, formulations F1-F6 showed percentage cumulative drug release of 91, 93, 95, 97, 99, and 96% respectively. Among all the formulations, F5 formulation shows better dissolution efficiency and rapid disintegration with release of 99.20% within 12min.

CONCLUSION
Mouth Dissolving tablets of Loperamide hydrochloride were formulated by using skimmed...
milk as polymer. The use of skimmed milk has enhanced the solubility of drug and also due to the bitter taste of drug, the drug was also masked by using skimmed milk. The proposed mouth dissolving formulation possessed an increased solubility and reproducible characteristics of disintegration time and drug release profile. The promising results of solid dispersion in solubility and dissolution rate enhancement of poorly soluble drugs attributes the better results. On the basis of these studies it can be conclude that Loperamide Mouth Dissolving tablet showed better in-vitro drug release of 90 to 99 percentages. All tablets showed good flow properties. So from this study it is concluded that enhanced solubility approach to be used as orally disintegrating drug delivery system.

CONFLICT OF INTERESTS:
The authors do not have any conflict of interest to declare.

Table 1: USP & IP Solubility criteria

<table>
<thead>
<tr>
<th>Descriptive term</th>
<th>Part of solvent required per part of solute</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very Soluble</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Freely Soluble</td>
<td>1-10</td>
</tr>
<tr>
<td>Soluble</td>
<td>10-30</td>
</tr>
<tr>
<td>Sparingly Soluble</td>
<td>30-100</td>
</tr>
<tr>
<td>Slightly Soluble</td>
<td>100-1000</td>
</tr>
<tr>
<td>Very slightly soluble</td>
<td>1000-10000</td>
</tr>
<tr>
<td>Practically Insoluble</td>
<td>&gt;10000</td>
</tr>
</tbody>
</table>

Table 2: BCS classification

<table>
<thead>
<tr>
<th>Class I</th>
<th>Class II</th>
<th>Class III</th>
<th>Class IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>High permeability</td>
<td>High permeability</td>
<td>Low permeability</td>
<td>Low permeability</td>
</tr>
<tr>
<td>High solubility</td>
<td>Low solubility</td>
<td>High solubility</td>
<td>Low solubility</td>
</tr>
</tbody>
</table>

Table 3: Solubility of Pure drug

<table>
<thead>
<tr>
<th>Sr. No</th>
<th>Solvent</th>
<th>Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Distilled water</td>
<td>Insoluble (0.221mg/ml)</td>
</tr>
<tr>
<td>2.</td>
<td>Ethanol</td>
<td>Soluble</td>
</tr>
<tr>
<td>3.</td>
<td>6.8 pH Phosphate Buffer</td>
<td>Soluble</td>
</tr>
</tbody>
</table>

Table 4: Solubility of Polymer:

<table>
<thead>
<tr>
<th>Sr. No</th>
<th>Solvent</th>
<th>Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
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<tr>
<td>3.</td>
<td>6.8 pH Phosphate Buffer</td>
<td>Soluble</td>
</tr>
</tbody>
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Shahid et al., World J Pharm Sci 2016; 4(9): 373-381

![Overlay of solubility studies of Solid Dispersion of Loperamide Hydrochloride and Skimmed milk in Distilled Water.](image1)

**Fig 1**: Overlay of solubility studies of Solid Dispersion of Loperamide Hydrochloride and Skimmed milk in Distilled Water.

![UV Spectrum of Loperamide Hydrochloride in Ethanol](image2)

**Fig 2**: UV Spectrum of Loperamide Hydrochloride in Ethanol

![FTIR spectrum of Loperamide Hydrochloride](image3)

**Fig 3**: FTIR spectrum of Loperamide Hydrochloride
Fig 4: FTIR spectrum of Skimmed Milk

Fig 5: FTIR spectrum of Physical Mixture

Fig 6: FTIR spectrum of Solid Dispersion (1:3)
Fig 7: In-vitro Drug Release of Marketed Formulation

Fig 8: Percentage Cumulative Release of F1, F2, F3, F4, F5 and F6 Formulations

Fig 9: Percentage Cumulative Release of Marketed Formulation against Optimized Formulation (F5).
REFERENCES


