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Original article

Enhancement of dissolution rate of piroxicam using liquisolid compacts

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Abstract

Piroxicam is a poorly soluble, highly permeable drug and the rate of its oral absorption is often controlled by the dissolution rate in the gastrointestinal. The poor dissolution rate of water-insoluble drugs is still a major problem confronting the pharmaceutical industry. There are several techniques to enhance the dissolution of poorly soluble drugs. Among them, the technique of liquisolid compacts is a promising technique towards such a novel aim. In this study, the dissolution behaviour of piroxicam from liquisolid compacts was investigated in simulated gastric fluid (SGF, pH 1.2) and simulated intestinal fluid (SIF, pH 7.2). To this end, several liquisolid tablets formulations containing various ratios of drug:Tween 80 (ranging from 10% to 50% w/w) were prepared. The ratio of microcrystalline cellulose (carrier) to silica (coating powder material) was kept constant in all formulations. The results showed that liquisolid compacts demonstrated significantly higher drug release rates than those of conventionally made (capsules and directly compressed tablets containing micronized piroxicam). This was due to an increase in wetting properties and surface of drug available for dissolution.

Keywords: Liquisolid compacts; Piroxicam; Dissolution rate; Tween 80; Liquid medication

1. Introduction

Piroxicam is an oxicam derivative with potent non-steroidal anti-inflammatory activity (NSAID). It is used in various acute and chronic musculoskeletal and joint disorders such as ankylosing spondylitis, osteoarthritis and rheumatoid arthritis and in acute gout, dysmenorrhoea and sometimes for pain associated with inflammation [1]. For poorly soluble, highly permeable (class II) drugs (like piroxicam), the rate of oral absorption is often controlled by the dissolution rate in the gastrointestinal (GI) tract [2]. Therefore, together with permeability, the solubility and dissolution behaviour of a drug are key determinants of its oral bioavailability. This undesired property, may also increase the amount of GI damage, due to long contact of drug with the mucous of GI. Thus, it is an ideal candidate for testing the potential of rapid-release liquisolid compacts.

Different approaches have been attempted to increase aqueous solubility of poorly soluble drugs, such as conversion of a crystalline molecule to its amorphous state [3], a particle size reduction via micronization [4–9] or nanosuspensions [10–12] and liquisolid compacts [13–15]. Among them, the technique of "liquisolid compacts" is a new and promising technique towards such a novel aim.

Liquid compacts are acceptably flowing and compressible powdered forms of liquid medications. The term "liquisolid medication" implies oily liquid drugs and solutions or suspensions of water-insoluble solid drugs carried in suitable non-volatile solvent systems. Using this new formulation technique, a liquid medication may be converted into a dry-looking, non-adherent, free flowing and compressible powder by a simple blending with selected powder excipients referred to as the carrier and coating materials. Various grades of cellulose, starch, lactose, etc., may be used as the carrier, whereas very fine particle size silica powder may be used as the coating material.

The aim of this study was to increase dissolution rate of piroxicam using liquisolid technique. In this study piroxicam, a poorly water-soluble, non-steroidal anti-inflammatory drug was formulated into 10 mg liquisolid tablets consisting of similar powder excipients and Tween 80 with different drug

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concentrations in their liquid medications. The in vitro drug dissolution rates of liquisolid formulations were compared to those of conventionally prepared (hard gelatine capsule and directly compressed tablets) using a USP dissolution apparatus Π at different dissolution media (pH 1.2 and 7.2).

2. Materials and methods

2.1. Materials

Piroxicam was provided by Industrial Shahid Razakani (Tehran, Iran). Coarse granular microcrystalline cellulose (Mingtai Chemical, Taiwan), sodium starch glycolate (Yung Zip Chemical, Taiwan), nm-sized amorphous silicon dioxide (Mingtai Chemical, Taiwan) and Tween 80 (Merck, Germany) were used.

2.2. Preparation of conventional tablet, capsule, and liquisolid compacts

Piroxicam conventional tablets were produced by mixing the drug with microcrystalline cellulose–silica (ratio of microcrystalline cellulose:silica was 20:1) for a period of 10 min in a cubic mixer (Erweka, Type UG, Germany). The mixture was mixed with sodium starch glycolate (as disintegrating agent) for 10 min. The mixture was compressed on a 10-mm punch and die using a manual-tableting machine (Riken, Japan). Sufficient compression load was applied in order to produce tablets with the hardness of 6–7 kp. This formulation was denoted as directly compressed tablets (DCT) and each tablet contains 10 mg piroxicam, 100 mg microcrystalline cellulose, 5 mg of nm-sized silica and 5 mg sodium starch glycolate. The same formulation that was used to make DCT formulation was filled in hard gelatine capsule without disintegrating agent (sodium starch glycolate).

Several liquisolid compacts (denoted as LS-1 to LS-9) were prepared as follows. Piroxicam was dispersed in Tween 80 (Tween 80 was used as the liquid vehicle to prepare the liquid medication of the different drug concentrations) with different ratios ranging from 1:1 to 1:9 (drug:Tween 80). Then a binary mixture of microcrystalline cellulose–silica (microcrystalline cellulose as the carrier powder and silica as the coating material with a ratio of 20, R) was added to the mixture containing the drug and Tween 80 under continuous mixing in a mortar. Depending on the ratio of drug:Tween 80 in formulation, different liquid load factors (the liquid load factor, L_f, is the weight ratio of the liquid medication and carrier powder in the liquid solid formulations) ranging from 0.200 to 0.225 (w/w) were employed in our liquisolid preparations. These amounts of the carrier and coating materials are enough to maintain acceptable flow and compression properties. Finally, 5% (w/w) of sodium starch glycolate as the disintegrant was mixed with the mixture for a period of 10 min. The final mixture was compressed using the manual tableting machine to achieve tablet hardness of 6–7 kp. Important formulation characteristics of the prepared piroxicam liquisolid compacts are shown in Table 1.

2.3. Spectrophotometeric analysis

The spectrophotometeric analysis of all piroxicam samples in aqueous solutions (pH 1.2 or 7.2) was performed at 333.6 nm (UV/visible spectrophotometer, Shimadzu-120, Japan). Standard curves were constructed by serially diluting an aqueous stock solution of the drug (at pHs 1.2 and 7.2) to obtain concentrations in the range of 2.5–40 μg/ml using simulated gastric fluid (SGF) or simulated intestine fluid (SIF) as the diluents. Each sample was analysed in triplicate.

2.4. Solubility studies

Solubility studies of piroxicam were carried out in SGF, SIF and the Tween 80. Saturated solutions were prepared by adding excess drug to the vehicles and shaking on the shaker (Velp, Italy) for 48 h at 25 °C under constant vibration. After this period, the solutions were filtered, diluted and analysed by UV-spectrophotometer (Shimadzu, Japan). Three determinations were carried out for each sample to calculate the solubility of piroxicam.

2.5. Dissolution studies

The USP paddle method (Erweka, DPT6R, Germany) was used for all the in vitro dissolution studies. In this method, distilled water which SGF (pH 1.2), and intestinal fluid (pH

Table 1
Key formulation characteristics of prepared piroxicam liquisolid compacts

Liquisolid system	Drug concentration (% w/w) in liquid medication	Liquid load factor (L_f)	Unit dose weight (mg)	Molecular fraction (F_M)
LS-1	10	0.200	657.9	0.586
LS-2	12.5	0.203	519.8	0.469
LS-3	15	0.205	429.6	0.391
LS-4	17.5	0.207	365.3	0.335
LS-5	20	0.210	315.8	0.293
LS-6	25	0.215	247.7	0.234
LS-7	30	0.220	202.6	0.195
LS-8	40	0.225	149.1	0.146
LS-9	50	0.225	119.3	0.117

7.2) without enzyme, were used as dissolution media. The rate of stirring was 50 ± 2 rpm. The amount of piroxicam was 10 mg in all formulations. The dosage forms were placed in 900 ml of gastric fluid (HCl solution) or intestinal fluid (phosphate buffer) and maintained at 37 ± 0.1 °C. At appropriate intervals (10, 20, 30 and 60), 5 ml of the samples were taken and filtered through a 0.45 mm Millipore filter. The dissolution media was then replaced by 5 ml of fresh dissolution fluid to maintain a constant volume. The samples were then analysed at 333.6 by UV/visible spectrophotometer. The mean of six determinations was used to calculate the drug release from each of the formulations.

For assessment and comparison, drug dissolution rates (D_R) of drug were used. For this mean, amount of drug (in μg) dissolved per min that presented by each tablet formulation during the first 10 min were calculated as follows:

$$D_R = (M \times D)/1000$$

where M is the total amount of piroxicam in each tablets (in this study, it is 10,000 μg) and D denotes percentage of drug dissolved in first 10 min.

2.6. Statistical analysis

All the data were statistically analysed by analysis of variance or Tukey's multiple comparison test. Results are quoted as significant where $P < 0.05$.

3. Results and discussion

The solubility of piroxicam in SGF, SIF and Tween 80 is given in Table 2. The table shows that the solubility of piroxicam was markedly increased by the presence of Tween 80. The table also shows that an increase in pH resulted in an increase in the solubility of piroxicam.

The dissolution profiles of piroxicam from the liquisolid compacts (LS-1) and conventional formulations (tablets and capsules) in different media are shown in Fig. 1. In vitro dissolution profiles of piroxicam showed that the liquisolid compacts produced higher dissolution rates in comparison with the conventional tablet and capsule formulations at the both dissolution media (Fig. 1). For example, the percentages of drug released from LS-1, conventional tablet and capsule after 10 min were 100%, 60% and 50% at pH 7.2 (SIF medium), respectively. This shows that the tablets containing Tween 80 (liquisolid compacts) produced faster dissolution rate in comparison with other formulations. Similar results were obtained in SGF (pH 1.2).

Table 2
Solubility of piroxicam in various solvents

Solvent	Solubility (% w/w)
Stimulated gastric fluid (SGF)	0.00744
Stimulated intestinal fluid (SIF)	0.03172
Polysorbate 80 (Tween 80)	5.861

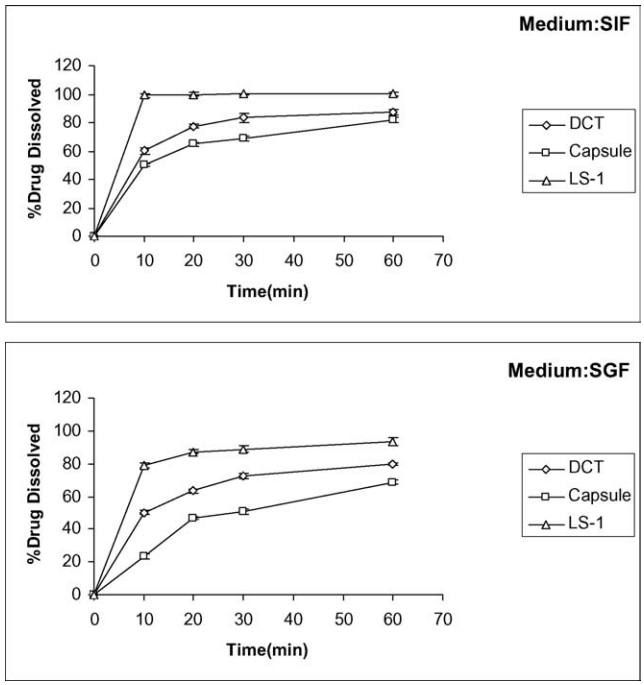

Fig. 1. Dissolution profiles of liquisolid compacts (LS-1), conventional capsule and directly compressed tablets (DCT) at different dissolution media.

Such enhanced drug dissolution rate may be mainly attributed to the fact that this poorly water-soluble drug is already in solution in Tween 80, while at the same time, it is carried by the powder particles (microcrystalline cellulose–silica) of the liquisolid vehicle. Thus, its release is accelerated due to its markedly increased wetability and surface availability to the dissolution medium.

Fig. 2 shows the drug dissolution rate (D_R) of piroxicam from LS-1 (this formulation contains 10% w/w piroxicam and 90% w/w Tween 80), conventional capsule and directly compressed tablet in first 10 min. As it is clear from this figure, at any dissolution media, the liquisolid tablets (LS-1) displayed higher dissolution rate than those of directly compressed (DCT) and capsule formulations ($p < 0.05$).

According to the classic dissolution equation [16]:

$$D_R = (D/h)S(C_S - C)$$

The drug dissolution rate (D_R) of a drug is directly proportional to its concentration gradient (C_s–C) in the stagnant diffusion layer and its surface (S) available for dissolution. C_s is the saturation solubility of the drug in the dissolution medium and, thus, it is a constant characteristic property related to the drug and dissolving liquid involved. Since all of dissolution tests for formulations were done at a constant rotational paddle speed (50 rpm) and identical dissolving media, we can assume that the thickness (h) of the stagnant diffusion layer and the diffusion coefficient (D) of the drug molecules remain almost identical. Therefore, the observed higher dissolution rates of piroxicam from liquisolid tablets are due to the significantly increased surface of the molecularly dispersed piroxicam [14].

In addition, the saturation solubility of the drug in the microenvironment (C_s) might be increased in the liquisolid

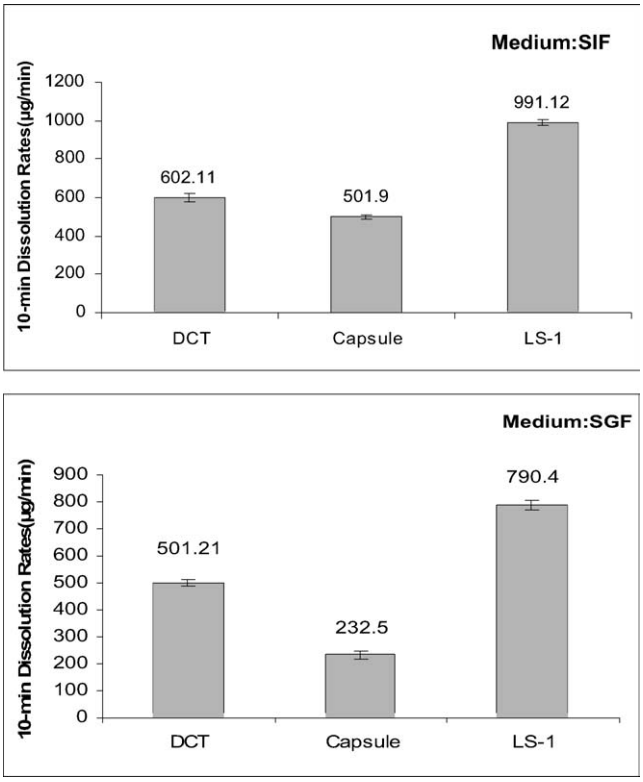

Fig. 2. Comparison of the 10-min dissolution rate of piroxicam exhibited by liquisolid compacts (LS-1), conventional capsule and directly compressed tablets (DCT).

systems due to the presence of Tween 80. So, such an increase in C_s, in a larger drug concentration gradient, increases the dissolution rate of piroxicam according to the Noyes Whitney equation [13,14].

The effect of drug concentration (C_d) in the liquid medication (Tween 80) on the 10-min dissolution rate (D_R) of piroxicam from the liquisolid compacts in SGF and SIF media is shown in Fig. 3. The figure shows that the drug concentration in the liquid medication is one of the main factors on the performance of a liquisolid compact and has considerable effect on the piroxicam 10-min dissolution rate. It can be seen

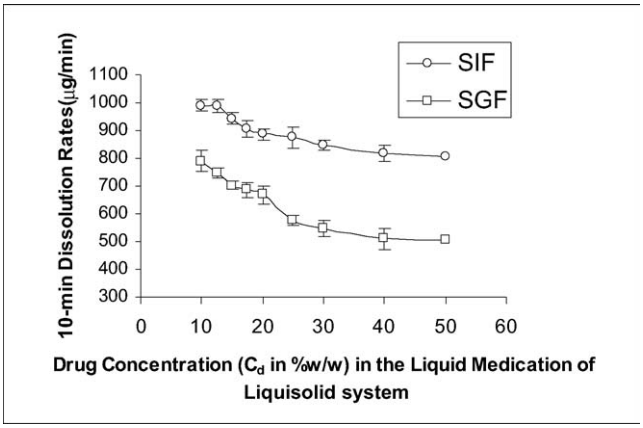

Fig. 3. Effect of drug concentration (C_d) in the liquid medication on the 10-min dissolution rate (D_R) exhibited by different liquisolid formulations at various dissolution media.

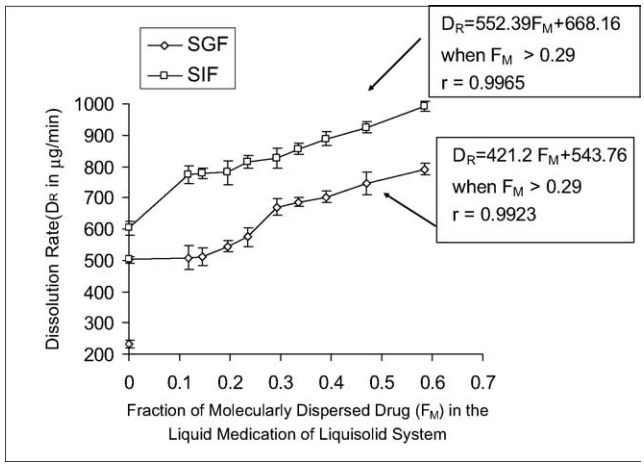

Fig. 4. Effect of the fraction (F_M) of molecularly dispersed drug in the systems on the 10-min dissolution rate (D_R) of piroxicam exhibited by various liquisolid formulations at different dissolution media.

that D_R decreased with an increase in the concentration of drug or reduction in the concentration of Tween 80. However, when the concentration of piroxicam was increased from 30% to 50% w/w, there was no significant difference in D_R values ($P > 0.05$). Such differences in the D_R values of piroxicam from liquisolid compacts observed in Fig. 3, may be justified using the differences in the amount of soluble form of the drug or molecular dispersion states of the drug in the formulations. For instance, since the saturation solubility of piroxicam in Tween 80 is 5.86% w/w (Table 2), about 52.7% of the drug is as soluble form in LS-1 formulation (this formulation containing 10% drug and 90% Tween 80). Whereas in LS-6 formulation, about 17.6% of piroxicam is as soluble form (LS-6 formulation containing 25% piroxicam and 75% Tween 80).

In Fig. 4, the dissolution rates of conventional capsules, DC tablets and liquisolid compacts that possessing different drug concentrations (C_d) are plotted against their corresponding fraction of the dissolved or molecularly dispersed of drug in the liquid medication (F_M) for different liquisolid tablets. F_M can be defined as the ratio of the drug's saturation solubility (C_L) in the liquid vehicle to the drug concentration (C_d) in the liquid medication. Therefore:

$$F_M = C_L/C_d$$

where $F_M = 1$ when $C_L/C_d > 1$.

Based on the above equation, the F_M values of our formulations are listed in Table 1. Since no Tween 80 (the liquid vehicle) is involved in the case of capsules and directly compressed tablets, their F_M values was taken equal to 0.

It can be seen from Fig. 4, in SGF or SIF media, after remaining at a minimum plateau level for F_M values ranging from 0 to 0.23, the D_R in 10-min, increased in a linear manner, with increasing F_M values of the liquisolid systems. Therefore, it is possible to predict the dissolution rate (D_R in µg/min) of piroxicam liquisolid compacts containing Tween 80 liquisolid tablets, which will be obtained within the initial 10 min of the dissolution process. A plot of the D_R against

F_M (when $0.29 < F_M < 0.59$) shows that the D_R changes linearly with F_M. The high correlation coefficients of 0.9923 and 0.9965 provide a value that characterizes the effect of F_M on piroxicam release from Tween liquisolid compacts at SGF and SIF, respectively.

As shown in Fig. 4, for systems with F_M values ranging from 0.29 to 0.59, the dissolution rate of piroxicam may be given by:

$$D_R = 421.2F_M + 543.76 \quad \text{in SGF medium}$$

$$D_R = 552.39F_M + 668.16 \quad \text{in SIF medium}$$

4. Conclusions

The liquisolid compacts technique can be a promising alternative for the formulation of water-insoluble drugs, such as piroxicam into rapid release tablets. The higher dissolution rates displayed by liquisolid compacts may also imply enhanced oral bioavailability due to the increased wetting properties and surface of drug available for dissolution. It can also be concluded that from this study, the liquisolid compacts of piroxicam that polysorbate 80 is their liquid vehicle, in different drug concentrations in their liquid medications, exhibit drug dissolution rates which are directly proportional to the fraction, F_M, of the molecularly dispersed drug in their liquid medication.

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