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Liquisolid technique as a new approach to sustain propranolol hydrochloride release from tablet matrices

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ABSTRACT

It is suggested here that liquisolid technique has the potential to be optimized for the reduction of drug dissolution rate and thereby production of sustained release systems. In the present study, propranolol hydrochloride was dispersed in polysorbate 80 as the liquid vehicle. Then a binary mixture of carrier–coating materials (Eudragit RL or RS as the carrier and silica as the coating material) was added to the liquid medication under continuous mixing in a mortar. The final mixture was compressed using the manual tableting machine. The effect of drug concentration, loading factor, thermal treating and aging on release profile of propranolol hydrochloride from liquisolid compacts were investigated at two pH values (1.2 and 6.8). The release rate of propranolol HCl from liquisolid compacts was compared to the release of propranolol HCl from conventional tablets. X-ray crystallography and DSC were used to investigate the formation of any complex between drug and excipients or any crystallinity changes during the manufacturing process. Propranolol HCl tablets prepared by liquisolid technique showed greater retardation properties in comparison with conventional matrix tablets. This investigation provided evidence that polysorbate 80 (Tween 80) has important role in sustaining the release of drug from liquisolid matrices, and a reduction of T_g of the polymer can be the reason for the release prolongation of liquisolid tablets. The results also showed that wet granulation had remarkable impact on release rate of propranolol HCl from liquisolid compacts, reducing the release rate of drug from liquisolid compacts. The results showed that aging (liquisolid tablets were kept at 25 °C/75% relative humidity for 6 months) had no effect on hardness and dissolution profile of drug. The kinetics studies revealed that most of the liquisolid formulations followed the zero-order release pattern. X-ray crystallography and DSC ruled out any changes in crystallinity or complex formation during the manufacturing process of liquisolid formulations.

1. Introduction

Propranolol hydrochloride is a β-adrenergic blocking agent, i.e. a competitive inhibitor of the effects of catecholamines at β-adrenergic receptor sites. It is widely used in therapeutics for its antihypertensive and antiarrhythmic properties (Martindale, 1999). Furthermore, it has a short elimination half-life of 3 h, which makes it a suitable candidate to be delivered at a controlled rate (Gil et al., 2006).

Development of sustained release oral dosage forms is beneficial for optimal therapy in terms of efficacy, safety and patient compliance. Ideally, a controlled release dosage form will provide therapeutic concentration of the drug in the blood that is maintained throughout the dosing interval (Chien, 1990; Fukuda et al., 2006). There are several techniques for preparation of sustained release formulations, among which control of drug dissolution is one of the best and most successful methods due to its simplicity and low cost (Jantzen and Robinson, 1996). To achieve this aim, several methods have been developed such as preparation of salt form of drug, coating with special materials and incorporation of drugs into hydrophobic carriers (Jantzen and Robinson, 1996).

Liquisolid technique is a new and promising method that can change the dissolution rate of drugs. It has been used to enhance the dissolution rate of poorly water-soluble drugs (Javadzadeh et al., 2005, 2007; Nokhodchi et al., 2005; Spirease and Sadu, 1998; Spireas et al., 1998). A "liquisolid system" refers to formulations formed by conversion of liquid drugs, drug suspensions or drug solution in nonvolatile solvents into dry, non-adherent, free-flowing and compactible powder mixtures by blending the suspension or solution with selected carriers and coating materials. Simplicity, low cost and capability of industrial production are some of the advantages of this technique. It is claimed that if

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hydrophobic carriers such as Eudragit RL and RS are used instead of hydrophilic carries in liquisolid systems, sustained release systems can be obtained (Spireas and Bolton, 1998). There is no systematic publication regarding the use of this method for controlling the release rate of drug from polymeric matrices. Therefore, it is suggested here that the method have the potential to be optimized for the reduction of drug dissolution rate and thereby production of sustained release systems. To this end, propranolol hydrochloride was selected as a water-soluble drug and Eudragit RS and RL were used as carrier materials.

2. Materials and methods

2.1. Materials

Propranolol hydrochloride was provided by Darupakhsh Co. (Tehran, Iran), nm-sized amorphous silicon dioxide (Mingtai Chemical, Taiwan), polysorbate 80 (Merck, Germany), polyethylene glycol 400 (PEG 400) (Merck, Germany), glycerin (Merck, Germany), PEG 200 (Merck, Germany), propylene glycol (Merck, Germany), Eudragit RS and RL (Röhm, Germany), HPMC K4M (Colorcon, England), potassium dihydrogen phosphate and sodium chloride (Merck, Germany) were used.

2.2. Solubility studies

To select the best non volatile solvent for suspending of propranolol hydrochloride in liquid medication, solubility studies of propranolol hydrochloride were carried out in five different nonvolatile solvents i.e. PEG 200, PEG 400, glycerin, polysorbate 80 and propylene glycol (PG). Saturated solutions of propranolol hydrochloride were prepared by adding drug in excess amount 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 with distilled water (at least 1000 times) and analyzed by UV-spectrophotometer (Shimadzu 160A, Japan) at a wavelength of 288.5 nm. Three determinations were carried out for each sample to calculate the solubility of propranolol hydrochloride.

2.3. Dissolution studies

The in vitro dissolution tests were performed on the USP dissolution apparatus 1 (basket method) (Erweka, DPT6R, Germany), using 900 ml dissolution medium (pH 1.2 or pH 6.8) prepared according to USP propranolol HCl extended release capsules monograph (USP 26) with a rotation speed of 100 ± 2 rpm. The amount of propranolol hydrochloride was 80 mg in all formulations. The dissolution tests for all tablets were run for 2 h in a simulated gastric fluid (HCl solution, pH 1.2 without pepsin) at 37 ± 0.2 °C, and subsequently in a simulated intestinal fluid (phosphate buffer, pH 6.8 without pancreatin) at 37 °C for 6 h. Samples were collected at suitable time intervals (e.g. 15, 30, 60, 90 120, 180, 240, 300, 360, 420 and 480 min). Five milliliters of aliquot was removed from each dissolution vessel and filtered through a 0.45 μm filter (Millipore Corp., Bedford, MA, USA). The same amount of fresh dissolution fluid was added to replace the amount withdrawn. The samples were then analyzed at 288.5 nm by UV/visible spectrophotometer. The mean of three determinations was used to calculate the drug release from each of the formulation.

The in vitro release profiles of liquisolid tablets and conventional tablets were compared using similarity factors, f_2, as defined by the following equation (Costa, 2001):

$$f_2 = 50 \log \left\{ \left[1 + \frac{1}{n} \sum_{t=1}^{n} (R_t - T_t) \right]^{-0.5} \times 100 \right\}$$

where n is number of time points at which % dissolved was determined, R_t is the % dissolved of one formulation at a given time point, and T_t is the % dissolved of the formulation to be compared at the same time point. The similarity factor fits the result between 0 and 100. It is 100 when the test and reference profiles are identical and approaches 0 as the dissimilarity increases. An f_2 above 50 indicates that the two profiles are similar.

Table 1
Solubility of propranolol hydrochloride in various solvents

Solvent	Solubility (g/100 ml)
Propylene glycol	10.29
PEG 400	7.97
PEG 200	7.93
Glycerin	3.91
Poly sorbate 80	1.33

2.4. Calculation of loading factor (L_f)

As the aim of the present study was to produce sustained release formulation, polysorbate 80 was selected as the solvent because of the low solubility of propranolol HCl in this solvent (see Table 1). To calculate loading factor, polysorbate 80 as a nonvolatile solvent was added to 30 g of Eudragit–silica powder mixture (ratio of Eudragit:silica was 2:1) and blended for 10 min. Then flowability of this system was measured using flowmeter (Erweka, Germany). Flow rates higher than 10 cm^3/s were considered as acceptable flow rate in the present study. The above procedure was repeated with various amounts of nonvolatile solvent until a powder with flow rate of above 10 cm^3/s is obtained. By using $L_f = W/Q$ formula (W: amount of liquid medication and Q: amount of carrier material), the values of loading factor were obtained and used to calculate the amount of carrier and coating materials in each formulation.

2.5. Preparation of conventional tablet and liquisolid compacts

Several liquisolid compacts, denoted as LS-1–LS-8, (Table 2) were prepared as follows. Propranolol hydrochloride was dispersed in polysorbate 80 (polysorbate 80 was used as the liquid vehicle to prepare the liquid medication). Then a binary mixture of carrier–coating materials (Eudragit as the carrier and silica as the coating material) was added to the liquid medication under continuous mixing in a mortar. The final mixture was compressed using the manual tableting machine (Riken, Japan) to achieve tablet hardness of 53–62 N. Another formulation was prepared via wet granulation technique using an aqueous solution of HPMC 3% as a binder (5 ml HPMC 3% solution was used for 100 g powder mixture). After preparation of liquisolid systems, HPMC solution was added into the mixture to obtain wet mixture of powders. Then the mixture was granulated through 12 mesh sieve and kept at room temperature (25 ± 1 °C) for 24 h. After this period, the dried mixture was sieved using 20 mesh sieve. The final granules were compressed into the tablets using the manual tableting machine to achieve tablet hardness of 53–62 N. Compositions of the liquisolid formulations are shown in Table 2.

Propranolol hydrochloride conventional matrix tablets (CMT) were produced by mixing the drug with Eudragit–silica mixture for a period of 10 min in a cubic mixer (Erweka, Type UG, Germany). The mixture was compressed on a 10 mm punch and die using a man-