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Effect of solvent type on retardation properties of diltiazem HCl form liquisolid tablets

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ABSTRACT

Liquisolid technique is a new approach to formulate sustained release dosage forms. It seems that the solubility of an active ingredient in solvent plays an important role in drug release profile. The aim of present study was to investigate the effect of solvent type on diltiazem hydrochloride release profile from liquisolid compacts. To examine aforementioned idea, the drug solubility was studied in several conventional nonvolatile solvents. Liquisolid formulations of diltiazem HCl in the different solvents were prepared and their release profiles were also obtained. Effect of aging on the hardness and drug release profile was studied as well. X-ray crystallography and differential scanning calorimetry (DSC) were used to investigate the formation of any complex between drug and carrier or any crystallinity changes during the manufacturing process. The results showed that diltiazem HCl had lowest solubility in polysorbate 20. Highest amount was devoted to polysorbate 80 and propylene glycol. Type of nonvolatile solvent and its physicochemical properties as well as solubility of the drug in the applied solvent found to have important role on release profile of the drug from liquisolid compacts. Hardness and dissolution profile of the drug were not affected by aging. Amorphous form was obtained during the process of liquisolid formulation. It follows that the optimized new technique can be used to prepare sustained release formulations of water-soluble drugs.

1. Introduction

Development of sustained release oral dosage forms is favorable for optimal therapy in terms of efficacy, safety and patient compliance. Ideally, a controlled release dosage form will present therapeutic concentration of the drug in the blood that is maintained all over the dosing interval [1,2]. Numerous techniques have been used for preparation of sustained release formulations, among which, control of drug dissolution, due to its simplicity and low cost, is one of the superlative and most successful methods [3]. To realize this aim, several methods such as preparation of salt form of the drugs, coating with special materials and incorporation of the drugs into hydrophobic carriers have been developed [3].

Liquisolid technique is a capable method that could be used for changing of the dissolution rate of drugs. 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. Low cost and potential of industrial production are some of the advantages of this method. It has been used to enhance the dissolution rate of poorly water soluble drugs [4–9]. Meanwhile, in a proper manner, it was also used to retard release of soluble drugs. It is claimed that if hydrophobic carries such as Eudragit RL and RS are used instead of hydrophilic carries in liquisolid systems, sustained release systems can be obtained [10–13]. In our previous study [10], sustained release formulation of propranolol hydrochloride was prepared using nonvolatile solvent applying Eudragit RS and RL as hydrophobic carriers. According to another hypothesis, any increase of drug solubility in a certain solvent will enhance the solvent capability for retaining the drug molecules, and subsequently lowered amount of the drug will be release in the dissolution medium. Then it seems that the solubility of active ingredient in the solvent may play an important role in the drug release pattern. The aim of present study was to investigate the effect of solvent type on diltiazem HCl release, as a model water soluble drug. Diltiazem HCl, a calcium channel blocker, is commonly used for its peripheral and vasodilator

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properties. It is administrated as an oral dosage form for treatment of angina pectoris and the management of hypertension. Because of its short biological half-life (3–5 h), high aqueous solubility, and frequent administration (usually three to four times a day), preparation of its sustained release formulation seems to be favorable [14,15].

2. Materials and methods

2.1. Materials

Diltiazem hydrochloride was provided by Darupakhsh Co. (Tehran, Iran), nm-sized amorphous silicon dioxide (Mingtai Chemical, Taiwan), polysorbate 20 and 80 (Merck, Germany), polyethylene glycol (PEG 200 and 400) (Merck, Germany), glycerin (Merck, Germany), propylene glycol (Merck, Germany), Eudragit RS and RL (Röhm, Germany), HPMC K4M (Colorcon, England), potassium di-hydrogen phosphate and sodium chloride (Merck, Germany) were used.

2.2. Solubility studies

Six different commonly used nonvolatile solvents i.e. PEG 200, PEG 400, glycerin, polysorbate 20, polysorbate 80 and propylene glycol (PG) were used to carry out solubility studies of diltiazem HCl. Saturated solutions of diltiazem HCl 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 with distilled water (at least 1000 times) and analyzed by UV-spectrophotometer (Shimadzu 160A, Japan) at a wavelength of 236 nm. To calculate the solubility of diltiazem hydrochloride, three determinations were carried out for each sample.

2.3. Dissolution studies

The in vitro dissolution tests were performed on the USP dissolution apparatus II (paddle method) (Erweka, DPT6R, Germany), using 900 ml dissolution medium (pH 1.2 or pH 6.8) with a rotation speed of 75 rpm. The total amount of diltiazem HCl was 60 mg in the all formulations. The dissolution tests for the all tablets were run for two hours in a simulated gastric fluid (HCl solution, pH 1.2 without pepsin, 5.3 ml HCl 37% (w/w) in a 1 L water) at 37 °C, and subsequently in a simulated intestinal fluid (phosphate buffer, pH 6.8 without pancreatin containing monobasic potassium phosphate and NaOH 0.2 N) at 37 °C for 6 h. Samples were collected at suitable time intervals. 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 236 nm by UV–vis spectrophotometer. The mean of 6 determinations was used to compute the drug release from each of the formulation.

The in vitro release profiles of the prepared formulations were compared using similarity factors, f_2, as defined by the following equation [16].

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

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. When the test and reference profiles are identical it will be 100 and approaches 0 as the dissimilarity increases. An f_2 above 50 points out that the two profiles are similar.

2.4. Calculation of the loading factor (L_f)

To calculate the loading factor, 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 were acceptable when they were higher than 10 cm^3/s. This process was repeated with various amounts of nonvolatile solvent until a powder with flow rate of above 10 cm^3/s was obtained (see Table 1). By using $L_f = W/Q$ formula (W: amount of liquid medication and Q: amount of carrier material), the values of loading factor were calculated and used to determine the amount of carrier and coating materials in each formulation.

2.5. Preparation of the conventional tablets and liquisolid compacts

Several liquisolid compacts, symbolized as LS-1 to LS-6 (Table 1) were prepared. Diltiazem HCl was dispersed in nonvolatile solvent. Then under continuous mixing in a mortar, a binary mixture of carrier–coating materials (Eudragit as the carrier and silica as the coating material) were added to the liquid medication. After preparation of liquisolid systems, HPMC solution (3% (w/v) as a binder) was added into the mixture to obtain wet mixture of powders. The mixture was granulated through 12 mesh sieve afterwards 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 57–70 N. Compositions of the liquid formulations are shown in Table 1.

Diltiazem HCl 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). Granules were formulated by the same procedure of liquisolid formulation. The prepared granules were compressed on a 10 mm punch and die using a manual-tableting machine. Adequate compression load was applied in order to produce tablets with the hardness of 57–70 N. Each tablet contained 60 mg diltiazem HCL.

Table 1
Key formulation characteristics of liquisolid formulations.

Formulation	Type of non-volatile solvent	Diltiazem HCl (mg)	Solvent (mg)	Silica (mg)	Eudragit RS (mg)
LS-1	PEG 200	60	204	243	487
LS-2	PEG 400	60	204	243	487
LS-3	Polysorbate 80	60	204	243	487
LS-4	Polysorbate 20	60	204	243	487
LS-5	Glycerin	60	204	243	487
LS-6	PG	60	204	243	487