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

Yousef Javadzadeh[a], Leila Musaalrezaei[a], Ali Nokhodchi[b,*]

[a] Faculty of Pharmacy and Drug Applied Research Centre, Tabriz University of Medical Sciences, Tabriz 51664, Iran
[b] Chemistry and Drug Delivery Group, Medway School of Pharmacy, Central Avenue, Universities of Kent and Greenwich, Chatham, Kent ME4 4TB, United Kingdom

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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

* Corresponding author. Tel.: +44 1634 883846; fax: +44 1634 883927.
E-mail address: a.nokhodchi@kent.ac.uk (A. Nokhodchi).

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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-

Table 2
Key formulation characteristics of liquisolid formulations*

Formulation	Drug concentration in liquid medication (g/100 ml)	Carrier	Method of preparation	Unit dose weight (mg)	Amount of polysorbate 80 (mg)	Amount of Eudragit (mg)	Amount of silica (mg)	Hardness (N)
LS-1	30	Eudragit RL	Direct compression	933	187	444	222	58 ± 2
LS-2	30	Eudragit RS	Direct compression	933	187	444	222	57 ± 2
LS-3	30	Eudragit RL	Granulation	933	187	444	222	62 ± 4
LS-4	40	Eudragit RL	Granulation	700	120	333	167	60 ± 2
LS-5	50	Eudragit RL	Granulation	560	80	267	133	57 ± 3
LS-6	30	Eudragit RS	Granulation	933	187	444	222	60 ± 2
LS-7	40	Eudragit RS	Granulation	700	120	333	167	55 ± 3
LS-8	50	Eudragit RS	Granulation	560	80	267	133	53 ± 3

* In all formulations, the ratio of carrier to coating material is 2, loading factor is 0.600 and each formulation contains 80 mg propranolol hydrochloride.

ual tableting machine. Sufficient compression load was applied in order to produce tablets with the hardness of 42–56 N. Each tablet contained 80 mg propranolol hydrochloride, 444 mg Eudragit RL or RS as a carrier material, 222 mg of nm-sized silica as coating material. Other formulations with the same contents were prepared using wet granulation method to compare with liquisolid tablets, as mentioned above.

2.6. X-ray powder diffraction

X-ray diffractometry of drug, excipient and liquisolid formulations were performed using Siemens diffractometer (Siemens, D5000-Germany). The cross section of samples was exposed to x-ray radiation (Cu Kα) with wavelength of 1.5406 Å. The rate of the scanning was 0.6°/min at a range of 5–50 2θ. Samples, ground into powders with an agate mortar and pestle, were measured on a low background quartz plate in an aluminum holder.

2.7. Differential scanning calorimetry (DSC)

Thermograms of the samples (propranolol hydrochloride, excipients and liquisolid formulations) were recorded on a DSC-60 (Shimadzu, Japan). Samples (3–5 mg, accurately weighed to 0.01 mg) were placed in aluminum pans and the lids were crimped using a Shimadzu crimper. Thermal behavior of the samples was investigated under nitrogen gas at scanning rate of 10 °C/min, covering a temperature range of 30–300 °C. The instrument was calibrated with an indium standard.

2.8. Statistical analysis

All the data were statistically analyzed 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 propranolol hydrochloride in PG, PEG 400, PEG 200, glycerin and polysorbate 80 is given in Table 1. The table shows that propranolol hydrochloride has lowest solubility in polysorbate 80. Since the aim of this study was to slow down the dissolution rate of drug, polysorbate 80 was exploited as a nonvolatile solvent in preparation of liquisolid systems.

Dissolution profiles of liquisolid compacts and conventional tablets prepared by direct compression method were shown in Fig. 1. It is clear from the figure that the tablets prepared by liquisolid technique (LS-1 and LS-2) show greater retardation properties in comparison with conventional matrix tablets ($f_2 = 35$). Similar results were obtained for formulations containing Eudragit RL as the carrier material. The results showed that the percentage of drug released from liquisolid matrices containing Eudragit

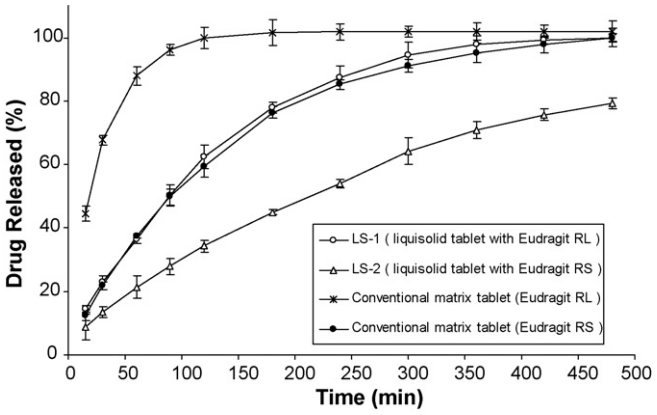

Fig. 1. Effect of liquisolid technique on retardation properties of propranolol hydrochloride from tablets that prepared by direct compression method.

RL is greater than liquisolid matrices containing the same amount of Eudragit RS. This could be due to difference in water permeability of these two polymers as water can permeate more freely into Eudragit RL than it can into Eudragit RS, due to the relative hydrophilicity of the RL polymer (Azarmi et al., 2002; McGininty, 1989). This could be main reason for the low dissolution rate of propranolol HCl from liquisolid compacts containing Eudragit RS.

To obtain a greater retardation property for liquisolid matrices, wet granulation method was used for the preparation of tablets. Figs. 2 and 3 show the effect of granulation technique on the release of propranolol HCl from liquisolid tablets containing Eudragit RL and RS, respectively. It can be seen that wet granulation had remarkable impact on release rate of propranolol HCl from liquisolid

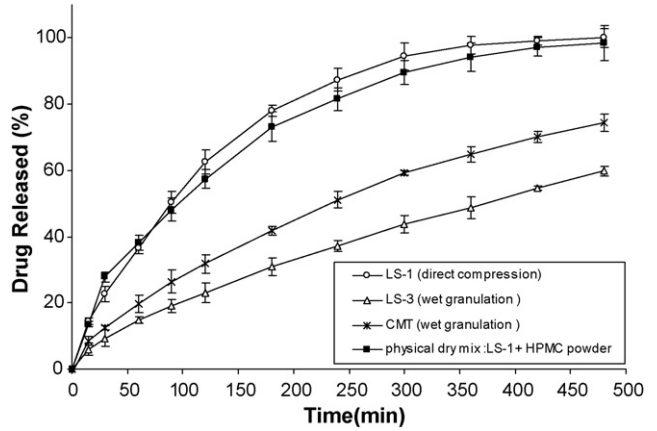

Fig. 2. Effect of liquisolid technique on retardation properties of propranolol hydrochloride from tablets that prepared by wet granulation method (Eudragit RL was used as a carrier).

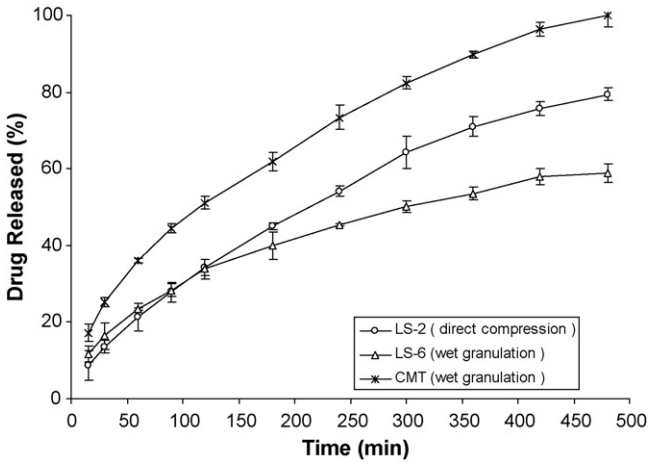

Fig. 3. Effect of liquisolid technique on retardation properties of propranolol hydrochloride from tablets that prepared by wet granulation method (Eudragit RS was used as a carrier).

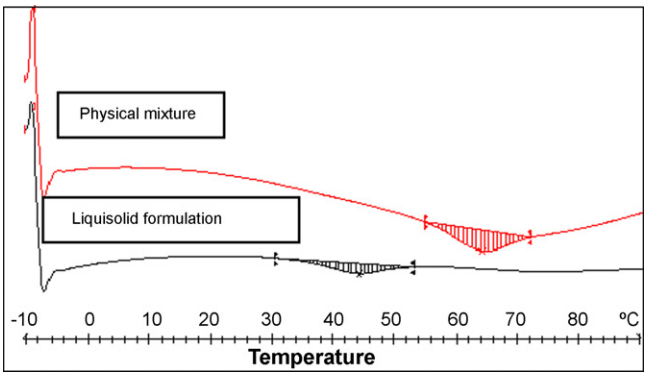

Fig. 4. Differential scanning calorimetery of liquisolid formulation (LS-1) and physical mixture for T_g studies of Eugragit RL.

compacts. A greater retardation effect was obtained when granulation technique used to obtain liquisolid compacts particularly for the liquisolid tablets containing Eudragit RL. Similar results were obtained on diclofenac sodium release from tablet matrices where granulation technique was compared to dry technique (Savas et al., 2005). It was reported that granulation of diclofenac sodium using HPMC can slow down the release of drug in comparison with dry technique. This could be due to the coating of drug particles by HPMC during granulation process which in turn slows down the penetration of water into the granules and/or reduces the direct contact of the drug with dissolution medium. In order to find whether it was the granulation process that induced the slow release effect or that was the retarding effect of HPMC, physical dry mix formulation of LS-1 and HPMC was prepared and the results of dissolution tests were compared (Fig. 2). The results showed that there was no significant difference between the release profile of LS-1 and LS-1 + HPMC (f_2 = 75). On the other hand, a significant difference was observed between LS-3 and LS-1 + HPMC liquisolid compacts (f_2 = 20). These results confirmed the impact of granulation process on sustained release behavior of liquisolid tablets. Conventional matrix tablets prepared via dry mix using Eudragit RL show a faster release rate than those prepared using Eudragit RS; in other cases the matrix tablets made via granulation Eudragit RL lead to slower release tablets (Figs. 2 and 3). This could be due to effect of granulation process which changes the release pattern as a result of the coating of drug particles by HPMC. This efficient coating might not happen in the matrix tablets containing Eudragit RS. Kinetics analysis of the release data between 15 and 480 min revealed that formulations LS-3 and LS-6 followed zero-order kinetics (correlation coefficients, *r*, for LS-3 and LS-6 were 0.998 and 0.997, respectively).

In preparation of liquisolid tablets, liquid medications containing drug were adsorbed on the surface of carrier materials. Then, when this system is exposed to the dissolution medium, drug located onto the surface of tablets dissolves fast and diffuses into dissolution medium. This can be assumed to be the cause of the burst release effect observed within the first 15 min (compare the slope of release data from 0 to 15 min and 15 to 480 min).

The mechanism of release prolongation is likely to be a more efficient encapsulation of drug particles by the hydrophobic polymers. However, a major difference between physical mixture and liquisolid formulations is the presence of polysorbate 80 in the liquisolids. An interesting property of polysorbate 80 is the plasticizer effect (Gruetzmann and Wagner, 2005) by which it can reduce the glass transition temperature of polymers and impart flexibility. The plasticizers affect the intermolecular bonding between polymer chains, thereby increasing flexibility (Porter and Bruno, 1990). Therefore, reduction of T_g of the polymer might be the reason for the release prolongation of liquisolid tablets. In the temperature above the T_g, a better coalescence of the polymer particles occurs that forms a fine network and a matrix with lower porosity and higher tortuosity. In this way, the drug is surrounded and entangled by the polymer network, resulting in the restricted leaching of the drug (Azarmi et al., 2002). It was reported that the minimum polymer-softening temperature or T_g for Eudragit powders was higher than the glass transition temperature of the organic-cast Eudragit films (Pearnchob and Bodmeier, 2003). For example with 20% triethyl citrate (TEC), the minimum polymer-softening temperature was reduced from 60 to 20–30 °C, whereas the T_g of Eudragit cast films containing 20% TEC was around 15 °C. Our results showed that the T_g of Eudragit RL in the liquisolid formulation (LS-1) was 44 ± 2 °C whereas in the physical mixture without polysorbate 80 the T_g was 63 ± 3 °C (Fig. 4). Gruetzmann and Wagner (2005) reported that T_g of Eudragit samples in the presence of 30% polysorbate 80 (similar concentration as in the liquisolid formulations in the present study) was reduced to around 15 °C. This is due to the use of different forms of Eugragit in these two studies. In the present investigation fine Eudragit powders was used for DSC studies whereas in Gruezman and Wagner studies casting Eudragit film was used.

Thermal treating was used as a tool for preparing sustained release dosage forms of several drugs using Eudragit RS and RL (Billa et al., 1998; Azarmi et al., 2005a,b). On the other hand, plasticizers are able to reduce the glass transition temperature of amorphous polymers and impart flexibility. The plasticizers, by their interaction with the polymer, affect the intermolecular bonding between polymer chains (Porter and Bruno, 1990). Such a temperature could be achieved during the tableting process. Therefore, at this temperature the fine network and matrix with lower porosity and higher tortuosity could be formed and the drug particles are surrounded by the polymer network resulting in the lower diffusion of the drug. This could be a reason for the observed greater retardation properties of the liquisolid tablets compared to the conventional matrix tablets. Although leaching of plasticizer from Eudragit films to dissolution medium could happen within the first 30 min of increasing the T_g of Eudragit films increased rapidly from 7 to 46 °C (Gruetzmann and Wagner, 2005), this was not the case in this study, as water cannot penetrate into liquisolid tablets easily and quickly.

To provide further evidence for this hypothesis, LS-3 formulation was kept at 70 °C (above the T_g of Eudragits) for 24 h and after this period, dissolution test was carried out. The results of dissolution for the thermal treated liquisolid formulations are shown in Fig. 5. As it is clear from this figure, there is no significant difference

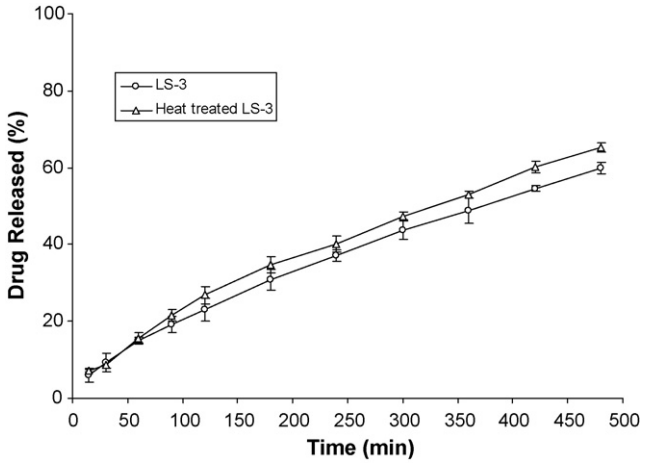

Fig. 5. Effect of heat treating on dissolution profile of propranolol hydrochloride from liquisolid tablets.

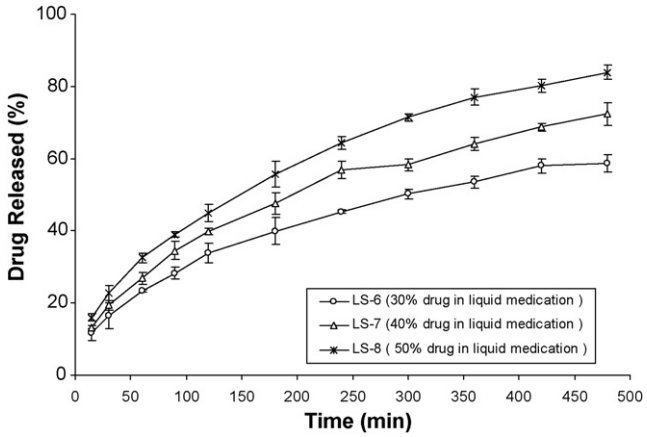

Fig. 7. Effect of drug concentration in liquid medication on release profile of propranolol hydrochloride from liquisolid tablets containing Eudragit RS as carrier material.

between fresh and heat treated formulation ($f_2 = 67$). This indicates that the thermal treatment had no further effect to slow down the release of the propranolol hydrochloride from liquisolid tablets.

The concentration of the drug in liquid medication has an important effect on the release profile of the drug. With increasing drug concentration in liquid medication, lower fraction of the drug would be present in the molecular state and, according to the Noyes–Whitney equation, lower dissolution rate is expected (Javadzadeh et al., 2005). On the other hand, with decreasing drug concentration, higher amount of Eudragit is needed in order to convert the liquid medication into dry and flowable powder. Therefore, it is expected that the liquisolid tablets containing high concentration of Eudragit show slow release behavior. In this study, several formulations with different concentrations of the drug in liquid medication were prepared and their release behaviors were studied and the results were shown in Figs. 6 and 7. The figures show that the greater retardation effect is observed in LS-3 and LS-6 (containing 30% drug in the liquid medication); these formulations have higher amounts of carrier in comparison with other formulations. Thus, the amount of Eudragit is high enough to slow down the release from these liquisolid tablets. Although the high concentration of drug is able to slow down the release, this result indicates that the retarding effect of Eudragit is higher than the retarding effect of the drug concentration in the liquisolid formulation. This is the reason for formulations LS-3 and LS-6 showing slower release behavior than formulations LS-5 and LS-8.

Effect of aging on hardness and dissolution profile of propranolol hydrochloride liquisolid compacts was also investigated. To this end, six tablets from LS-3 series were kept at 25 °C/75% relative humidity for 6 months. Then hardness and dissolution rate were measured for the aged tablets. The results showed that there was no significant difference between the hardness of fresh (61 ± 4 N) and aged (62 ± 2 N) liquisolid tablets ($p > 0.05$). Fig. 8 shows similar dissolution profiles between the fresh and aged liquisolid tablets, with a calculated similarity factor of 70. This means that aging had no significant effect on dissolution profile of the propranolol hydrochloride sustained release tablets. Then, we can expect that propranolol hydrochloride liquisolid tablets will maintain their initial hardness and sustained releasing character after 6 months.

It has been shown that polymorphic changes of the drug are important factors that may affect the dissolution rate and bioavailability (Abdou, 1989). On the other hand, the importance of polymorphism on the therapeutic effectiveness of a drug and the pharmaceutical implication of the presence of meta stable crystalline forms in the bulk powder are well recognized. It has also been shown that the crystal structure could affect tablet porosity and density, the mechanism of disintegration and aggregation, as well as the plastic and elastic properties of solid dosage forms (Bartolomei et al., 1999). Therefore, it is important to study polymorphic changes of propranolol hydrochloride in liquisolid formulations. Bartolomei et al. (1999) reported that (*R*, *S*) propra-

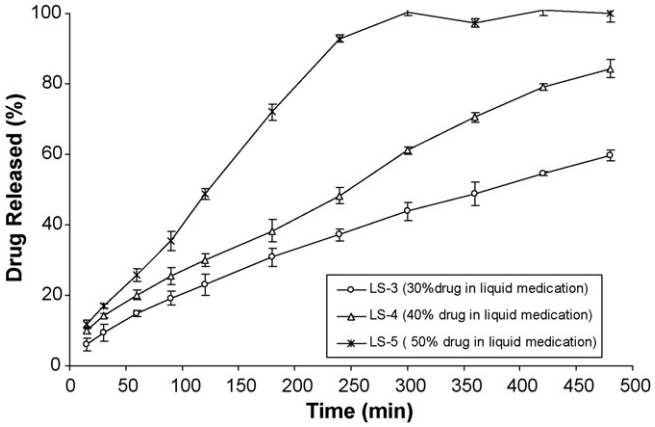

Fig. 6. Effect of drug concentration in liquid medication on release profile of propranolol hydrochloride from liquisolid tablets containing Eudragit RL as carrier material.

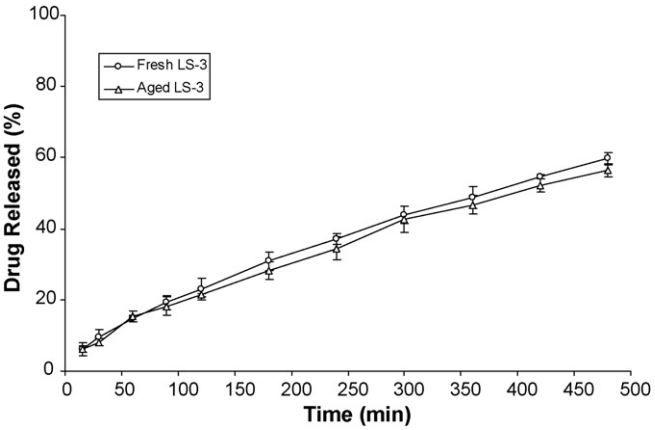

Fig. 8. Effect of aging on dissolution profile of propranolol hydrochloride liquisolid tablets.

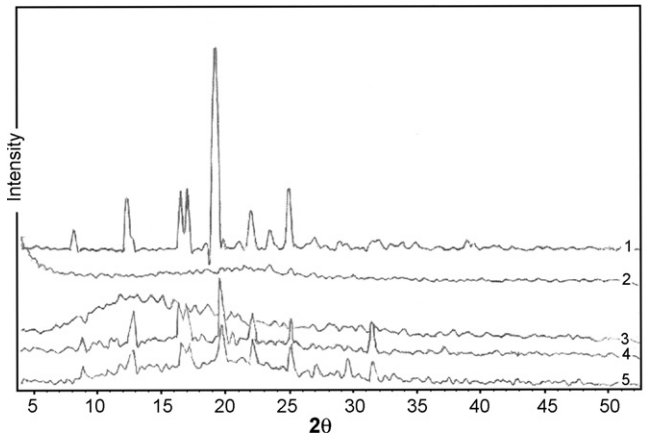

Fig. 9. X-ray diffractograms of: (1) pure propranolol hydrochloride; (2) silica; (3) Eudragit RL; (4) physical mixture and (5) liquisolid formulation (LS-1).

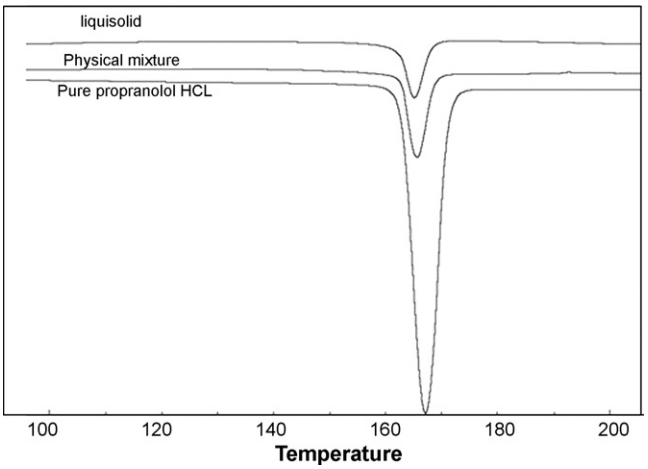

Fig. 10. Differential scanning calorimetery of liquisolid formulation (LS-1), physical mixture and pure propranolol hydrochloride for melting point of propranolol HCl.

nolol hydrochloride existed in two crystalline forms, designated I and II. In X-ray diffraction patterns, form I has diagnostic peaks at $2\theta = 14.26^\circ$, 17.65°, 19.77°, and 23.22°. The indicative peaks for form II occur at $2\theta = 12.51^\circ$, 16.74°, 17.20°, and 25.09°. Fig. 9 shows the X-ray diffractograms of the pure propranolol hydrochloride and pure excipients, physical mixture (propranolol hydrochloride, Eudragit RL and silica) and liquisolid formulation (LS-1). Propranolol hydrochloride diffractogram showed sharp peaks at 12.51°, 16.73°, 17.19°, 19.76°, 23.22°, 25.08° and 27.47° 2θ. This corresponds to mixture polymorphs of propranolol hydrochloride as reported by Bartolomei et al. (1999). As it is clear from Fig. 9, liquisolid and physical mixture formulations have relatively the same diffraction pattern with minor changes; some of them could be due to peak noises. A reduction in height of peaks might be due to lower concentration of drug in these formulations in comparison with pure propranolol hydrochloride powder or dissolution of some fraction of drug in nonvolatile solvent. Comparing the ratio of peaks at 19.76° 2θ (polymorph I) to 25.08° 2θ (polymorph II) for pure propranolol HCl and liquisolid formulations showed that this ratio for formulations is lower than the ratio for pure propranolol HCl indicating a change in polymorphic ratio of the drug in the formulations. It can be concluded that no significant interaction between drug and excipients occurred during the formulation process. Diffractograms of other formulations resulted in similar findings.

The results of DSC thermograms confirmed the above conclusion (Fig. 10). The DSC profiles of form I and II, recorded at a heating rate of $10\,^\circ$C/min, showed quite sharp fusion endotherms: form I with an onset temperature of $163.0 \pm 0.3\,^\circ$C (peak temperature: $166 \pm 0.5\,^\circ$C), while form II showed an onset temperature of $161.8 \pm 0.1\,^\circ$C (peak temperature: $163.6 \pm 0.2\,^\circ$C). According to the Fig. 10, propranolol hydrochloride showed an endothermic peak around its melting point. The liquisolid (LS-1) and physical mixture formulations showed the same peaks in this area, which indicates that there is no interaction between drug and excipients during the formulation process. From above finding it can be concluded that the delayed dissolution rate of propranolol hydrochloride liquisolid compacts is not due to the formation of complex between the drug and excipients or changes in crystallinity of the drug.

4. Conclusion

The present work showed that liquisolid technique can be optimized for the production of sustained release matrices of water-soluble drugs. Polysorbate 80 was used as the liquid vehicle. The release of drug from these formulations followed zero-order release kinetics. This investigation provided evidence that polysorbate 80 (Tween 80) has important role in sustaining the release of drug from liquisolid matrices. Heat treatment had no effect on release profile of drug from liquisolid tablets. Hardness and dissolution profile of drug were not affected by aging. No crystallinity change was observed during the process of liquisolid formulation. The proposed new technique can be used in the preparation of sustained release formulations of water-soluble drugs such as propranolol hydrochloride.

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