

Kent Academic Repository

Full text document (pdf)

Citation for published version

Javadzadeh, Yousef and Jafari-Navimipour, Baharak and Nokhodchi, Ali (2007) Lquisolid technique for dissolution rate enhancement of a high dose water-insoluble drug (carbamazepine). *International Journal of Pharmaceutics*, 341 (1-2). pp. 26-34. ISSN 0378-5173.

DOI

<https://doi.org/10.1016/j.ijpharm.2007.03.034>

Link to record in KAR

<https://kar.kent.ac.uk/2027/>

Document Version

UNSPECIFIED

Copyright & reuse

Content in the Kent Academic Repository is made available for research purposes. Unless otherwise stated all content is protected by copyright and in the absence of an open licence (eg Creative Commons), permissions for further reuse of content should be sought from the publisher, author or other copyright holder.

Versions of research

The version in the Kent Academic Repository may differ from the final published version.

Users are advised to check <http://kar.kent.ac.uk> for the status of the paper. **Users should always cite the published version of record.**

Enquiries

For any further enquiries regarding the licence status of this document, please contact:

researchsupport@kent.ac.uk

If you believe this document infringes copyright then please contact the KAR admin team with the take-down information provided at <http://kar.kent.ac.uk/contact.html>

Liquisolid technique for dissolution rate enhancement of a high dose water-insoluble drug (carbamazepine)

Yousef Javadzadeh^{a,b}, Baharak Jafari-Navimipour^a, Ali Nokhodchi^{b,c,*}

^a Department of Pharmaceutics, Faculty of Pharmacy, Tabriz University of Medical Sciences, Iran

^b Drug Applied Research Center, Tabriz University of Medical Sciences, Iran

^c Medway School of Pharmacy, Universities of Kent and Greenwich, Central Ave., Chatham Maritime, Kent ME4 4TB, United Kingdom

Received 11 December 2006; received in revised form 23 March 2007; accepted 26 March 2007

Available online 30 March 2007

Abstract

Different liquisolid formulations of carbamazepine were accomplished by dissolving the drug in the non-toxic hydrophilic liquids, and adsorbing the solution onto the surface of silica. In order to reduce the amounts of carrier and aerosil in liquisolid formulations, some additives namely polyvinylpyrrolidone (PVP), hydroxypropyl methylcellulose (HPMC) and polyethylene glycol (PEG 35000) were added to liquid medication to increase loading factor. The effects of various ratios of carrier to coating material, PVP concentration, effect of aging and type of the carrier on dissolution rate of liquisolid compacts were studied. X-ray crystallography and differential scanning calorimetry (DSC) were used for evaluation of physicochemical properties of carbamazepine in liquisolid formulations. The results showed that the drug loading factor was increased significantly in the presence of additives. Liquisolid formulations containing PVP as additive, exhibited significantly higher drug dissolution rates compared to the compacts prepared by the direct compression technique. It was shown that microcrystalline cellulose had more liquid retention potential in comparison with lactose, and the formulations containing microcrystalline cellulose as carrier, showed higher dissolution rate. By decreasing the ratio of microcrystalline cellulose to silica from 20 to 10, an improvement in dissolution rate was observed. Further decrease in the ratio of microcrystalline cellulose:silica from 10 to 5 resulted in a significant reduction in dissolution rate. Increasing of PVP concentration in liquid medication caused a dramatic increase in dissolution rate at first 30 min. The results showed that the dissolution rate of liquisolid tablets was not significantly affected by storing the tablets at 25 °C/75% relative humidity for a period of 6 months. The results of DSC and X-ray crystallography did not show any changes in crystallinity of the drug and interaction between carbamazepine and excipients during the process.

© 2007 Elsevier B.V. All rights reserved.

Keywords: Carbamazepine; Liquisolid tablets; Dissolution rate; Polymorphic changes

1. Introduction

It is well established that the active ingredient in a solid dosage form must undergo dissolution before it is available for absorption from the gastrointestinal tract. The poor dissolution characteristics of water-insoluble drugs are a major challenge for pharmaceutical scientists. The absorption rate of a poorly water-soluble drug, formulated as an orally administered solid dosage form, is controlled by its dissolution rate in the fluid

present at the absorption site, i.e. the dissolution rate is often the rate-determining step in drug absorption. There are several methods for enhancing dissolution rate of poorly water-soluble drugs including: (a) reducing particle size to increase surface area, thus increasing dissolution rate of drug; (b) solubilization in surfactant systems; (c) formation of water-soluble complexes; (d) drug derivatization such as a strong electrolyte salt forms that usually have higher dissolution rate and (e) manipulation of solid state of drug substance to improve drug dissolution, i.e. by decreasing crystallinity of drug substance through formation of solid solutions (Kapsi and Ayres, 2001). The most common method is to increase surface area of the drug by micronization. But, in practice the effect of micronization is often disappointing, especially when the drugs are encapsulated

* Corresponding author at: Medway School of Pharmacy, Central Ave., University of Kent and Greenwich, Chatham, Kent ME4 4TB, United Kingdom. Tel.: +44 1634 883846; fax: +44 1634 883927.

E-mail address: a.nokhodchi@kent.ac.uk (A. Nokhodchi).

or tableted (Aguiar et al., 1979; Finholt and Solvang, 1968; Lin et al., 1968). Micronised drugs also have the tendency to agglomerate as a result of their hydrophobicity, thus reducing their available surface area (Finholt and Solvang, 1968). Several researchers have shown that the liquisolid technique is the most promising method for promoting dissolution rate of poorly water-soluble drugs (Javadzadeh et al., 2005; Nokhodchi et al., 2005b; Spireas and Sadu, 1998; Spireas et al., 1998, 1999). A “liquisolid system” refers to formulations formed by conversion of liquid drugs (such as vitamin A, clofibrate), drug suspensions or drug solution in non-volatile solvents into dry, nonadherent, free-flowing and compressible powder mixtures by blending the suspension or solution with selected carriers and coating materials (Spireas and Sadu, 1998). This technique was successfully applied for low dose water-insoluble drugs. However, formulation of the high dose insoluble-drugs as liquisolid tablets is one of the limitations of the liquisolid technique. In order to have acceptable flowability and compactability for liquisolid powder formulation, high levels of carrier and coating materials should be added and that in turn will increase the weight of each tablet above 1 g which is very difficult to swallow. Therefore, in practice it is impossible with conventional method to convert high dose drugs to liquisolid tablet with the tablet weight of less than 1 g. In fact, when the therapeutic dose of drug is more than 50 mg, dissolution enhancement in the presence of low levels of hydrophilic carrier and coating material is not significant. We believe that by adding some materials such as polyvinyl pyrrolidone (PVP) to liquid medication (microsystems), it would be possible to produce dry powder formulations containing liquid with high concentration of drug. By adding such materials to the liquid medication, low amount of carrier is required to obtain dry powder with free flowability and good compactability.

Carbamazepine (CBZ), 5H-dibenzazepine-5-carboxamide, is a sodium channel blocker that has been in routine use in the treatment of epilepsy and trigeminal neuralgia for over 40 years (Martindale, 1999). This agent belongs to class II drugs that its bioavailability is limited by its poor dissolution rate in GI. In fact, its solubility and dissolution rate are key factors in its bioavailability. In this study, carbamazepine was chosen as a model drug to examine capability of microsystems for obtaining liquisolid tablets with enhanced dissolution rate for drugs that have therapeutic dose more than 50 mg.

2. Materials and methods

2.1. Materials

Carbamazepine was provided by Sobhan Co. (Rasht, Iran). Coarse granular microcrystalline cellulose (Mingtai Chemical, Taiwan), sodium starch glycolate (Yung Zip Chemical, Taiwan), nm-sized amorphous silicon dioxide (Mingtai Chemical), polysorbate 80 (Merck, Germany), PEG 400 (Merck, Germany), glycerin (Merck, Germany), PEG 200 (Merck, Germany), PG (Merck, Germany), PVP K25 (BASF, Germany), HPMC K4M (Colorcon, England), lactose, starch, sorbitol and sodium chloride (Merck, Germany) were used.

2.2. Solubility studies

To select the best non-volatile solvent for dissolving or suspending of carbamazepine in liquid medication, solubility studies of carbamazepine were carried out in five different non-volatile solvents, i.e. PEG 200, PEG 400, glycerin, polysorbate 80 and PG. 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 through a 0.45 µm Millipore filter, diluted with distilled water containing sodium lauryl sulphate (SLS) and analysed by UV-spectrophotometer (Shimadzu, Japan) at a wavelength of 284.4 nm against blank sample (blank sample contained the same concentration of specific solvent used without drug). Three determinations were carried out for each sample to calculate the solubility of carbamazepine.

2.3. Calculation of the loading factor (L_f)

To calculate the loading factor, different concentrations (w/w) of polymers (PVP, HPMC K4M and PEG 35000) were dissolved in the PEG 200 (carbamazepine showed the highest solubility in PEG 200). Each of the above system (liquid medication without drug) was added to 30 g of microcrystalline cellulose–silica powder mixture or lactose as a carrier material and blended for 10 min. By using $L_f = W/Q$ formula (W : amount of liquid medication and Q : amount of carrier material), the drug loading factors were obtained and used for calculating the amount of carrier and coating materials in each formulation. The preliminary results showed that if the viscosity of the carrier was higher, lower amounts of microcrystalline cellulose powder are needed to produce flowable powder. The low viscosity grade of HPMC (HPMC LV100) was tried, but an appropriate powder flow was not achievable.

2.4. Flow properties of liquisolid powders

Two techniques were used to evaluate the flow properties of powders: hopper flow rate and angle of repose. In hopper flow rate technique, 100 cm³ of powders was placed in the funnel of flowmeter (Erweka, Germany). A simple shutter is placed over the hopper outlet (the orifice size was 6 mm) and the hopper filled with powder. The shutter is then removed and the time taken for the powder to discharge completely is recorded. By dividing the discharge powder volume by this time, a flow rate is obtained which can be used for quantitative comparison of different powders. The flow rate above 10 cm³/s was considered as acceptable flow rate for tableting purpose in this research.

Flow properties of the powders were also evaluated by determining the angle of repose. Static angle of repose was measured according to the fixed funnel and freestanding cone method. A funnel with the end of the stem cut perpendicular to the axis of symmetry is secured with its tip 10 cm height, H , above a graph paper placed on a flat horizontal surface. The powders were carefully poured through the funnel until the apex of the conical pile so formed just reaches the tip of the funnel. The mean diameter, $2R$, of H , base of the powder cone, was determined and the

tangent of the angle of repose was given by:

$$\tan \alpha = \frac{H}{R}$$

where α is the repose angle.

2.5. Preparation of conventional tablet and liquisolid compacts

Carbamazepine conventional tablets were produced by mixing the drug with microcrystalline cellulose–silica (with different ratios of microcrystalline cellulose to silica) and the additive for a period of 10 min in a cubic mixer (Erweka, Type UG, Germany). The mixture was mixed with sodium starch glycolate (5%, w/w, of the formulation) 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 56–70 N (Newton). This formulation was denoted as direct compression tablet (DCT) and each tablet contains 100 mg carbamazepine, 400 mg microcrystalline cellulose or lactose as a carrier material, 20 mg nm-sized silica as coating material (26.67 mg in formulations with ratio of 15:1 of carrier to coating material) and 25 mg sodium starch glycolate (as a disintegrating agent).

Several liquisolid compacts, denoted as LS-1 to LS-18 (Table 1) were prepared as follows. Carbamazepine was dispersed in PEG 200 (PEG 200 was used as the liquid vehicle to prepare the liquid medication). Then various polymers namely PVP, HPMC and PEG 35000 were dissolved in PEG 200 containing carbamazepine. Then a binary mixture of carrier-coating materials (microcrystalline cellulose or lactose, as the carrier powder and silica as the coating material) was added to the obtained liquid medication under continuous mixing in a mortar. Depending upon the type of carrier in formulation, different li-

quid loading factors were employed in our liquisolid preparations. 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 56–70 N. Important formulation characteristics of the prepared carbamazepine liquisolid formulations are shown in Table 1.

2.6. Dissolution studies

The USP paddle method (Erweka, DPT6R, Germany) was used for all the in vitro dissolution studies. In this method, distilled water containing 1% (w/v) sodium lauryl sulphate without enzyme, was used as dissolution media. The rate of stirring was 100 ± 2 rpm. The amount of carbamazepine was 100 mg in all formulations. The dosage forms were placed in 900 ml of distilled water containing 1% (w/v) SLS and maintained at 37 ± 0.1 °C. At appropriate intervals (5, 10, 15, 20, 30, 45, 60 and 90 min), 5 ml of the samples were taken and filtered through a 0.45 μ m Millipore filter. The dissolution media was then replaced by 5 ml of fresh dissolution fluid to maintain a constant volume. After proper dilution, the samples were then analysed at 284.4 by UV/vis spectrophotometer. The mean of six determinations was used to calculate the drug release from each of the formulations.

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 the %dissolved of one formulation at a given time point and T_t is the %dissolved of the formulation to be compared at

Table 1
Key formulation characteristics of prepared formulations

Formulation	Additive in liquid medication	Carrier	Ratio of carrier to coating material	Loading factor	Unit dose weight (mg)
LS-1	PVP	MCC ^a	20	0.42	735
LS-2	HPMC	MCC	20	0.52	636
LS-3	PEG35000	MCC	20	0.59	584
LS-4	PVP	MCC	15	0.43	731
LS-5	HPMC	MCC	15	0.53	633
LS-6	PEG35000	MCC	15	0.60	583
LS-7	PVP	Lactose	20	0.28	995
LS-8	HPMC	Lactose	20	0.35	840
LS-9	PEG35000	Lactose	20	0.42	735
LS-10	PVP	Lactose	15	0.28	1010
LS-11	HPMC	Lactose	15	0.35	850
LS-12	PEG35000	Lactose	15	0.43	731
LS-13	PVP	MCC	20	0.42	700
LS-14	HPMC	MCC	20	0.52	604
LS-15	PEG35000	MCC	20	0.59	556
LS-16	PVP	Lactose	15	0.28	947
LS-17	HPMC	Lactose	15	0.35	800
LS-18	PEG35000	Lactose	15	0.42	700

In all formulations, the concentration of drug in liquid medication was 50% and additive was 10%.

^a MCC is microcrystalline cellulose.

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.

2.7. X-ray powder diffraction

X-ray diffractometry of drug, excipient and formulations were done using Siemens diffractometer (Siemens, D5000-Germany). The cross section of samples was exposed to X-ray radiation (Cu K_{α}) with wavelength of 1.5406 Å. The rate of the scanning was 0.6°/min. Samples, ground into powders with an agate mortar and pestle, were measured on a low background quartz plate in an aluminum holder.

2.8. Differential scanning calorimetry (DSC)

Thermograms of the samples (carbamazepine, excipients and liquisolid formulations) were recorded on a DSC-60 (Shimadzu, Japan). Samples (3–5 mg weighed to a precision of 0.005 mg) were placed in aluminum pans and the lids were crimped using a Shimadzu crimper. Thermal behavior of the samples was investigated under at scanning rate of 20 °C/min, covering a temperature range of 30–200 °C. The instrument was calibrated with an indium standard.

2.9. 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

3.1. Solubility and dissolution studies

The solubility of carbamazepine in PG, PEG 400, PEG 200, glycerin and polysorbate 80 is given in Table 2. The table shows that the solubility of carbamazepine in PEG 200 is higher in comparison with other solvents. In fact, the higher fraction of drug in PEG 200 is in the molecular state in comparison with others solvents and this would help to increase dissolution rate of the drug because some percentages of drug is already dissolved.

It has been shown that in conventional liquisolid tablets, it is difficult to prepare formulation with good flowability and compactibility when loading factor is above 0.25 (Javadzadeh et al.,

Table 2
Solubility of carbamazepine in various solvents ($n = 3$)

Solvent	Solubility (mg/ml)
Propylene glycol	40.896 ± 0.525
PEG 400	71.820 ± 0.722
PEG 200	87.668 ± 1.101
Glycerin	7.789 ± 0.156
Polysorbate 80	45.831 ± 0.575

Table 3
Flow and release parameters of liquisolid and conventional formulations

Formulation	Flow rate (cm ³ /s)	Angle of repose (°)	$Q_{5\text{min}}$ (%)	$T_{50\%}$ (min)
LS-1	23.8	17	24 ± 1	18 ± 2
LS-2	11.1	27	14 ± 2	28 ± 2
LS-3	18.9	19	10 ± 1	21 ± 1
DCT1	18.5	18	17 ± 1	30 ± 2
LS-4	26.3	16	30 ± 2	14 ± 2
LS-5	13.5	23	19 ± 2	20 ± 2
LS-6	19.6	19	12 ± 1	19 ± 2
DCT2	20.1	16	14 ± 2	26 ± 3
LS-7	11.4	26	14 ± 2	21 ± 2
LS-8	10.3	29	14 ± 2	43 ± 3
LS-9	11.2	27	10 ± 2	24 ± 4
DCT3	30.4	25	18 ± 1	21 ± 3
LS-10	13.5	22	17 ± 5	22 ± 3
LS-11	11.2	27	18 ± 1	42 ± 5
LS-12	11.5	25	17 ± 1	20 ± 2
DCT4	26.0	16	17 ± 1	20 ± 2
LS-13	23.8	16	20 ± 1	25 ± 1
LS-14	11.1	25	12 ± 1	41 ± 2
LS-15	18.9	21	28 ± 2	15 ± 2
Powder mix	18.5	18	15 ± 1	41 ± 4
LS-16	13.5	24	29 ± 1	20 ± 2
LS-17	11.2	28	17 ± 2	40 ± 3
LS-18	11.5	26	34 ± 2	14 ± 1
Powder mix	26.0	16	13 ± 2	32 ± 2

2005; Nokhodchi et al., 2005a,b). We believe that by preparing microspheres (adding some additives such as PVP, HPMC or PEG 35000 into liquid medication), the loading factor can be increased above 0.25. The results showed that the loading factor for the samples containing PEG 35000 was 0.6 (Table 1) and still these formulations possess good flow properties (Table 3). The dissolution profiles of liquisolid formulations containing different types of additives are shown in Fig. 1. In all cases, 100% of dissolution occurred between 3 and 4 h. However, for a better comparison of the results using the graphs dissolution profiles after the release of 90% was excluded from the graphs (but not from the experiments). It is clear from Fig. 1 the formulations containing PVP as additive (LS-1) has a better dissolution rate in comparison with conventional direct compressed tablet (DCT),

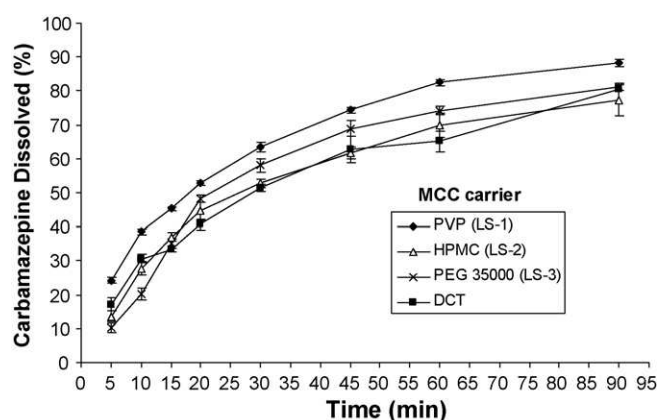


Fig. 1. Effect of various additives on dissolution profile of carbamazepine from liquisolid tablets (ratio of microcrystalline cellulose to silica is 20:1).

formulations containing HPMC (LS-2) and PEG 35000 (LS-3) as additives. Liquisolid tablets containing PEG 35000 had the lowest dissolution rate within the first 5 min. In order to have a better comparison, $Q_{5\text{ min}}$ (percent drug dissolved within 5 min) and $T_{50\%}$ (time required for the dissolution of 50% drug) were calculated (Table 3). Comparing $Q_{5\text{ min}}$ for these formulations revealed that liquisolid tablets containing PEG35000 (LS-3) were the slow release formulations (Table 3). This is due to the higher disintegration time of these tablets (14 min). When the disintegration of tablet was completed the dissolution rate was increased in comparison with DC tablet (compare $T_{50\%}$ values in Table 3). PEG 35000 is a waxy-like material and wetting of tablet by dissolution media is difficult. In other words, PEG 35000 might increase the viscosity of the stagnant diffusion layer and decrease dissolution rate of the drug and these can describe that why LS-3 had a lower dissolution rate in comparison with LS-1 tablet. Sample containing HPMC showed fast disintegration (less than 1 min) due to swelling behavior of HPMC. However, the low dissolution rate of LS-2 in comparison with LS-1 is due to gel forming properties of HPMC around the disintegrated particles. The high viscosity around drug particles may slow down the penetration of water into particles and this in turn will reduce the dissolution rate of drug from particles. The main reason for the increased dissolution of the drug in presence of PVP might be due to crystal growth inhibition. It has been shown that PVP may serve to inhibit precipitation of drug from the supersaturated solution (Simonelli et al., 1976; Usui et al., 1997). Another reason for the increased dissolution of drug in presence of PVP could be the increased surface area of the drug exposed to the dissolution medium as a result of the adsorption on carrier.

Similar results were obtained when ratio of microcrystalline cellulose to silica was altered from 20:1 to 15:1 (Fig. 2). Liquisolid compacts containing PVP with different ratios of microcrystalline cellulose:silica showed different dissolution rates. For example when the ratio of microcrystalline cellulose:silica was changed from 20:1 to 15:1, the dissolution rate of carbamazepine increased (compare LS-1 with LS-4). As silica has high surface area ($200\text{ m}^2/\text{g}$), then higher amounts of drug

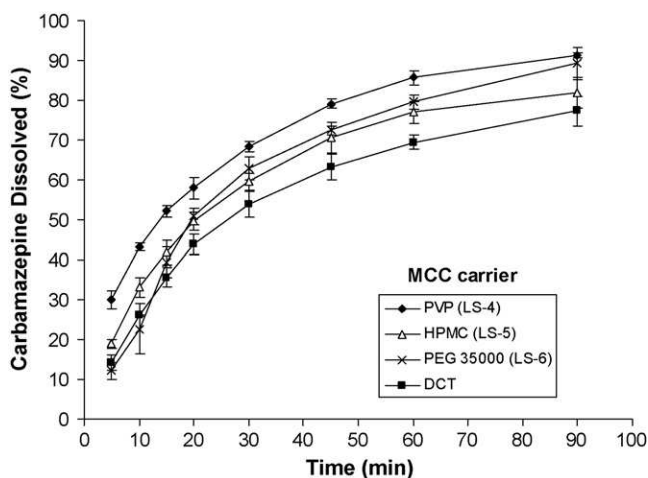


Fig. 2. Effect of various additives on dissolution profile of carbamazepine from liquisolid tablets (ratio of microcrystalline cellulose:silica is 15:1).

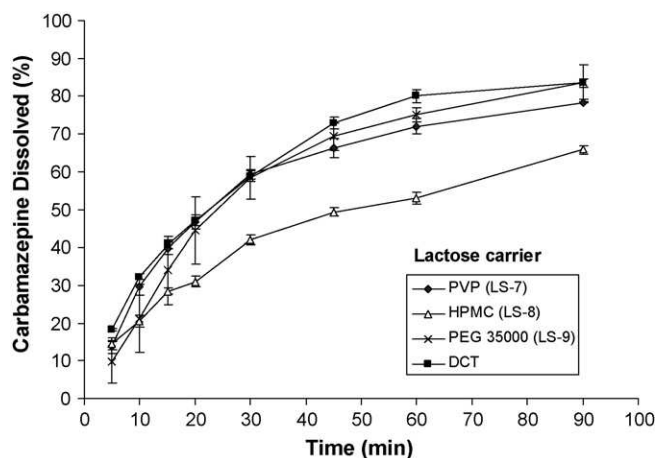


Fig. 3. Dissolution profiles of liquisolid tablets containing lactose (ratio of lactose:silica is 20:1).

in molecular state (dissolved in PEG 200) could be adsorbed on its surface. This status will expose more drugs to the dissolution media, and then higher dissolution rate of drug could be obtained.

To evaluate the effect of type of carrier on dissolution profile, several formulations were prepared using lactose as carrier and dissolution test were performed. As it is clear from Fig. 3, there is no significant difference between DCT tablet and liquisolid formulations containing PVP (LS-7), PEG 35000 (LS-9) as additive in liquid medication (similarity factor, $f_2 > 50$ also see $T_{50\%}$ in Table 3). Microcrystalline cellulose has disintegration property, which could facilitate disintegration of tablets and dissolution of drug. Because of the presence of a nonvolatile solvent acting as a binding agent in the liquisolid formulation, delayed disintegration time is expected. However, in the liquisolid tablets containing microcrystalline cellulose, a fast disintegration of tablet (less than 1 min) occurred which can be explained by the disintegrating property of microcrystalline cellulose with an exception of the tablets containing PEG 35000 (disintegration time was 16 min). All liquisolid tablets containing lactose as the carrier showed disintegration time above 13 min. Fig. 3 also showed that the LS-8 formulation containing HPMC as additive had a low dissolution rate. This could be due to the formation of gel around the disintegrated particles by HPMC, which builds a barrier against diffusion of the dissolved drug into dissolution medium. Similar results were obtained in 15:1 ratio of lactose to silica (Fig. 4).

As mentioned, the delayed disintegration time of tablets (for example, tablets containing PEG 35000 as additive or lactose as carrier material) could be the main reason for the lower dissolution rate of these formulations. To evaluate the hypothesis, dissolution test was carried out for the formulated liquisolid powders (without converting them into tablets, LS-13 up to LS-18). The results were summarized in Figs. 5 and 6. There were no significant differences between the conventional formulation and liquisolid powders containing HPMC ($p > 0.05$). In contrast to the liquisolid tablets, the liquisolid powder containing PEG 35000 showed higher dissolution rate among the formulations. This shows that the delayed disintegration could be a reason for

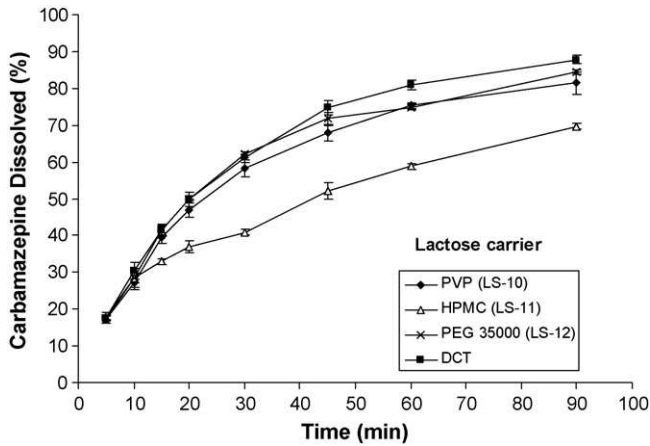


Fig. 4. Dissolution profile of liquisolid tablets containing lactose as carrier (ratio of lactose:silica is 15:1).

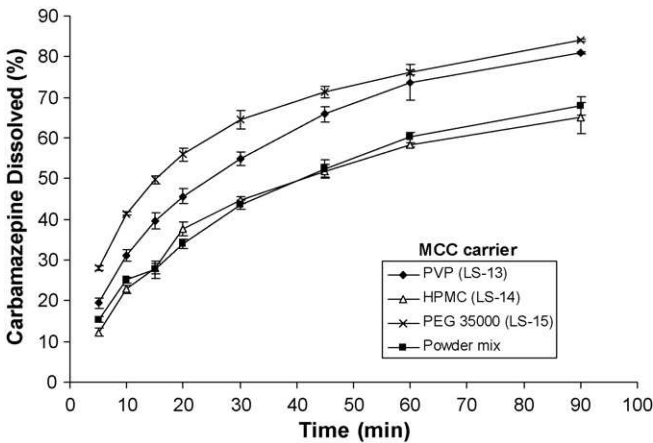


Fig. 5. Dissolution profiles of liquisolid powders containing microcrystalline cellulose as carrier.

lower dissolution rate of PEG liquisolid tablet especially within first 15 min. Comparing the dissolution rate of liquisolid powders containing microcrystalline cellulose (Fig. 5) and lactose (Fig. 6), showed no significant difference between their dissolution profiles indicating that the difference observed between

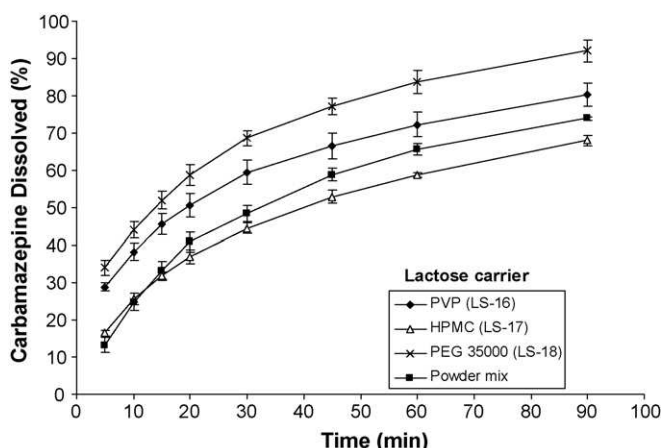


Fig. 6. Dissolution profile of liquisolid powders containing lactose as carrier.

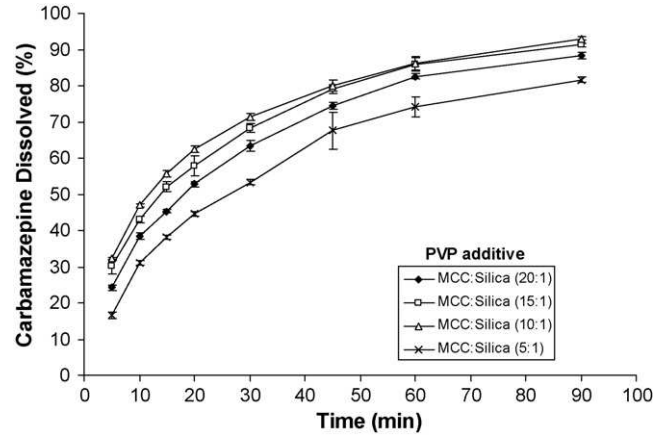


Fig. 7. Effect of various ratio of carrier to coating material (microcrystalline cellulose:silica) on dissolution profile of carbamazepine liquisolid tablets containing PVP as an additive.

the tablets made from these two formulations (see Figs. 1–6) is due to the disintegration property of microcrystalline cellulose (compare $Q_{5\text{ min}}$ and $T_{50\%}$ of these formulations in Table 3). For example, $Q_{5\text{ min}}$ values for LS-15 (liquisolid powder containing microcrystalline cellulose) and LS-18 (liquisolid containing lactose) were 14 and 15 min, respectively.

Fig. 7 shows the effect of various ratios of microcrystalline cellulose to silica. As it is clear from this figure, a reduction in the ratio of microcrystalline cellulose to silica from 20:1 to 10:1 showed a slight increase in the dissolution of carbamazepine within first 30 min, but when this ratio was reduced to 5, a lower dissolution rate was observed. Liquisolid compacts with lower R -values contain relatively smaller amounts of carrier powder (cellulose), and larger quantities of fine drug loaded silica particles, and the ratios of the amounts of their liquid medication per powder substrate are relatively higher. On the other hand, liquisolid compacts with higher R -values contain low liquid/powder ratios, high presence of cellulose and low presence of silica. This could be directly associated with enhanced wicking, disintegration and deaggregation properties. Therefore, the liquisolid tablets with low R -values showed relatively poor dissolution (Fig. 7). In addition, during the dissolution process, the primary particles produced after the disintegration of the liquisolid tablets with low R -values are overloaded with liquid medication. In such cases, even though the drug diffusion through the primary particles may be rapid, it might lead to overwhelming (solubility-wise) of the stagnant (adjacent to the primary particles) dissolution layers with drug, resulting in local precipitation of carbamazepine during the initial stages of the dissolution process, thereby presenting decreased dissolution rates (Spireas et al., 1999).

In order to study the effect of aging on hardness and dissolution profile of carbamazepine liquisolid compacts, six tablets from LS-4 series were kept at 25 °C/75% relative humidity for 6 months. Then hardness and dissolution rate were measured for these tablets. The results showed that there was no significant difference between the hardness of fresh ($62.3 \pm 7\text{ N}$) and aged ($59.5 \pm 7.7\text{ N}$) liquisolid tablets ($p > 0.05$). This indicated that the hardness of liquisolid compacts was not affected by aging.

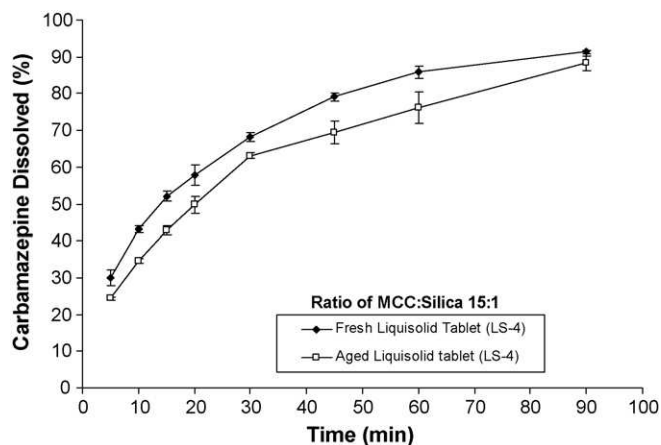


Fig. 8. Effect of aging on dissolution profile of carbamazepine liquisolid tablets.

Fig. 8 shows the dissolution profile of fresh and aged liquisolid tablets. Although the aged liquisolid tablets appear to have lower dissolution rate than fresh liquisolid tablets in the graph, similarity factor of the two release profiles was 57.7, indicating acceptably similar profiles. This means that aging has no effect on dissolution behavior of the carbamazepine liquisolid compacts. However, when $Q_{5\text{ min}}$ and $T_{50\%}$ were compared for freshly made liquisolid compacts and aged liquisolid compacts by t -test opposite results were obtained. However, still the aged liquisolid compacts have higher dissolution rate than the conventional tablets.

To assess the PVP effect on the dissolution rate, various formulations with different concentrations of PVP were prepared and dissolution tests were carried out (ratio of microcrystalline cellulose:silica was 15:1 in all these formulations). According to Fig. 9, the formulation containing 30% of PVP, had better dissolution rate within first 30 min, but after 30 min, there was no significant differences ($p > 0.05$) between percentages dissolved for carbamazepine liquisolid tablets containing different concentrations of PVP.

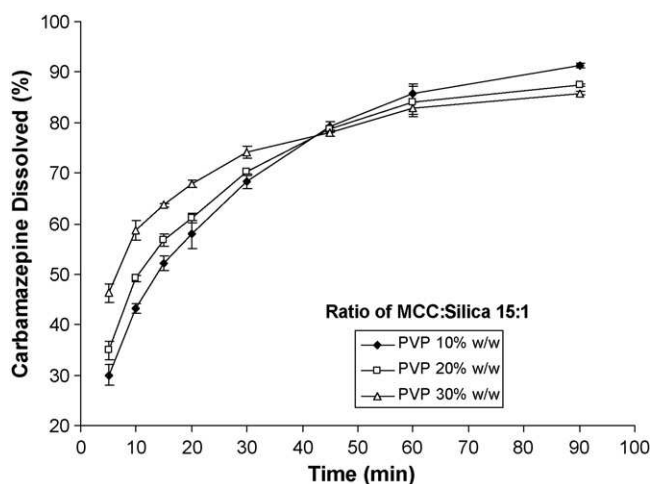


Fig. 9. Effect of various concentrations of PVP in liquid medication on dissolution profile of carbamazepine liquisolid tablets.

3.2. Solid state characterization of carbamazepine in liquisolid formulations

The drug might precipitate after adsorption of the drug solution onto the adsorbent. The potential precipitation is dependent on the solubility of the drug in the solvent and the degree of saturation of the drug solution or interaction between components. It has been shown that polymorphic changes of the drug are important factors that may affect the dissolution rate and bioavailability (Abdou, 1989). Therefore, it is important to study the polymorphic changes of carbamazepine in liquisolid formulations. Carbamazepine has been found to crystallize as four different anhydrous polymorphs (Himes et al., 1981; Lowes et al., 1987; Ceolin et al., 1997; Nokhodchi et al., 2005a; Bolourtchian et al., 2001). The most reliable way to distinguish between the four polymorphs of CBZ is with PXRD. Form I has diagnostic peaks at $2\theta = 7.92, 9.37, 12.28$ and 19.99 . Form II is recognizable because it has few high intensity peaks at $2\theta = 8.68, 13.26, 18.56$ and 24.54 . The indicative peaks for form III occur at $2\theta = 15.36, 19.56, 25.00$ and 27.47 . Form IV has characteristic peaks at $2\theta = 14.11, 17.89, 21.79$ and 33.11 .

Fig. 10 shows the X-ray diffractograms of the pure carbamazepine and pure excipients, physical mixture (carbamazepine, lactose, microcrystalline cellulose, PVP and silica) and liquisolid formulation. Carbamazepine diffractogram

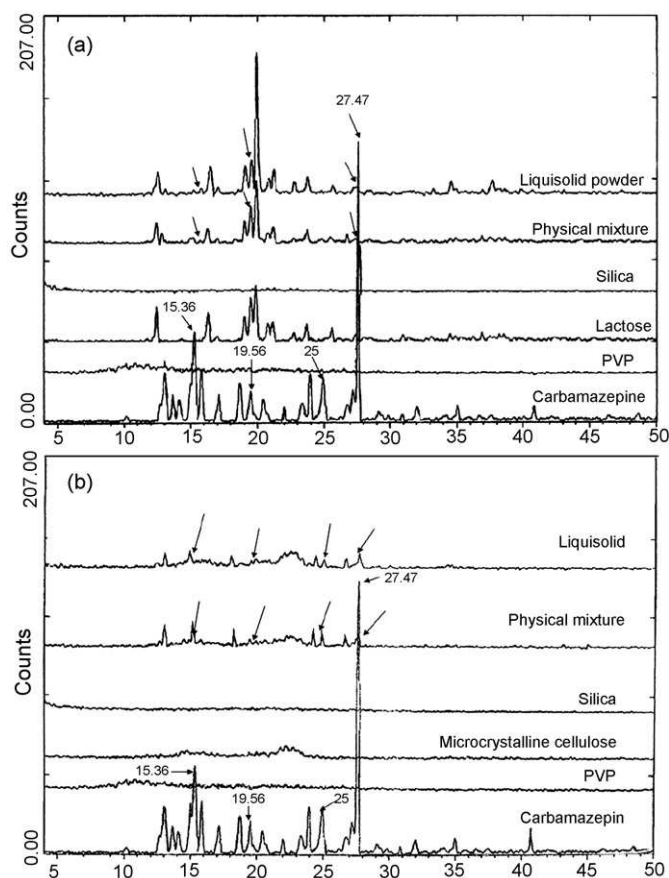


Fig. 10. X-ray diffractograms of pure carbamazepine, PVP, lactose, microcrystalline cellulose, silica, their physical mixture and liquisolid formulation.

showed sharp peaks, 2θ at 15.36, 19.56, 25 and 27.47. This corresponds to form III polymorph of carbamazepine (Grzesiak et al., 2003). As it is clear from Fig. 10, liquisolid and physical mixture formulations have the same diffraction patterns. It can be concluded that no alterations in crystallinity of carbamazepine or interaction between drug and excipients occurred during the formulation process. Diffractograms of other formulations showed the same results.

One useful technique to study of polymorphism is differential scanning calorimetry (DSC). DSC is usually combined with XRPD to determine the polymorphic composition of pharmaceutical powders, when the polymorphs present have different melting points. DSC thermograms of carbamazepine polymorph form I show no transformation and melts between 189 and 193 °C (Himes et al., 1981). Form II does not melt, but instead a transformation occurs between 135 and 170 °C and the new phase then melts between 188 and 192 °C. The large transformation range is due, in part, to higher initiation temperatures for crystals with fewer defects as determined by observing populations of crystals during heating. Form III melts and crystallizes to a new form nearly simultaneously between 162 and 175 °C. The new form subsequently melts between 189 and 193 °C. Form IV shows melting and partial crystallization to a new form between 178 and 187 °C, significantly higher than the transition temperatures of forms II or III. This is followed by further crystallization to produce a material that then melts between 190 and 192 °C. Based on the melting point of the form that is derived from the

others upon heating, it appeared that each had become form I (Himes et al., 1981).

The results of DSC thermograms confirmed the above conclusion (Fig. 11). According to the Fig. 11, carbamazepine showed an endothermic peak around its melting point. The liquisolid and physical mixture formulations showed the same peaks in this area, which indicates that there is no interaction between drug and excipients or changes in crystallinity of the drug during the formulation process. From above finding it can be concluded that the enhanced dissolution rate of carbamazepine liquisolid compacts is not due to the formation of complex between the drug and excipients or changes in crystallinity of the drug. It has already been shown that wetting of the tablets and drug particle had important impact on dissolution of poorly water-soluble drugs (Javadzadeh et al., 2007). We believe that, therefore, in the present study due to significantly improved wetting properties of liquisolid compacts and drug particles, liquisolid compacts display enhanced drug dissolution characteristics.

4. Conclusion

This study provided evidence that it is possible to load high amounts of drug into liquisolid tablets by addition of PVP to the liquid medication. This is valuable for the preparation of liquisolid tablets of high dose drugs. The liquisolid tablets prepared with PVP showed a remarkably improved dissolution rate in comparison with DC tablet and other formulations. The results showed that dissolution rate of the drug from liquisolid compacts or powders was affected by changing the ratio of the carrier (microcrystalline cellulose or lactose) to coating material (aerosil). Further, microcrystalline cellulose was a better carrier than was lactose in preparation of high dissolution rate liquisolid tablets. Increasing the amount of PVP also resulted in higher dissolution rate. Aging had no effect on hardness and dissolution profile of liquisolid tablets; no crystallinity changes or interaction was observed during the process.

References

- Abdou, H.M. (Ed.), 1989. Dissolution, Bioavailability and Bioequivalence. Mack Pub. Co., pp. 53–72.
- Aguiar, A.J., Zelmer, A.J., Kinkel, A.W., 1979. Deagglomeration behavior of relatively insoluble benzoic acid and its sodium salt. *J. Pharm. Sci.* 56, 1243–1252.
- Bolourtchian, N., Nokhodchi, A., Dinarvand, R., 2001. The effect of solvent and crystallization conditions on habit modification of carbamazepine. *Daru* 9, 12–22.
- Ceolin, R., Toscani, S., Gardette, M.F., Agafonov, V.N., Dyyabchenko, B., Bachet, B., 1997. X-ray characterization of the triclinic polymorph of carbamazepine. *J. Pharm. Sci.* 86, 1062–1065.
- Costa, P., 2001. An alternative method to the evaluation of similarity factor in dissolution testing. *Int. J. Pharm.* 220, 77–83.
- Finholt, P., Solvang, S., 1968. Dissolution kinetics of drugs in human gastric juice the role of surface tension. *J. Pharm. Sci.* 57, 1322–1326.
- Grzesiak, A.L., Lang, M., Kim, K., Matzger, A.J., 2003. Comparison of the four anhydrous polymorphs of carbamazepine and the crystal structure of form I. *J. Pharm. Sci.* 92, 2260–2271.
- Himes, V.L., Mighell, A.D., De Camp, W.H., 1981. Structure of carbamazepine 5Hdibenz [b,f]azepine-5-carboxamide. *Acta Crystallogr. B* 37, 2242–2245.

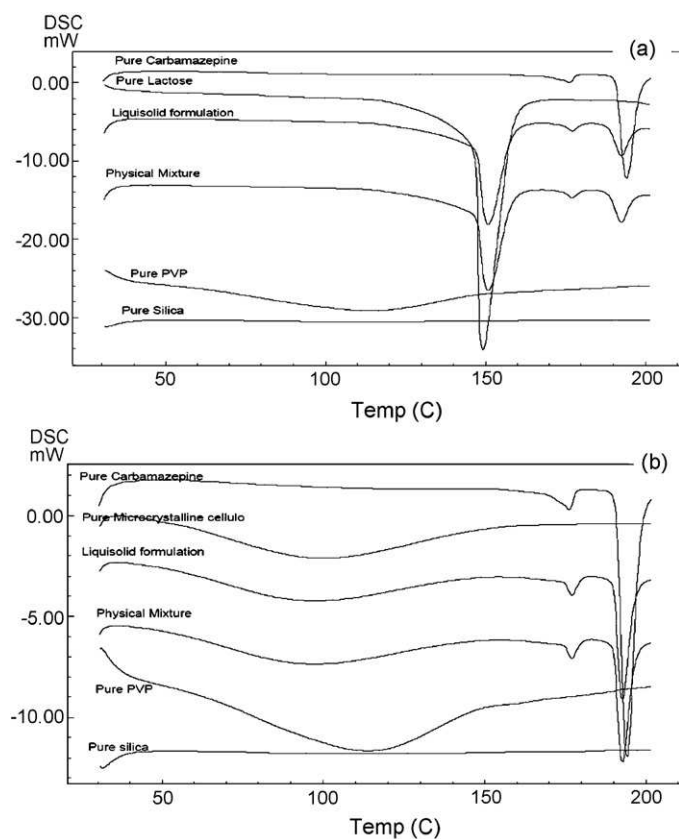


Fig. 11. Differential scanning calorimetry of silica, lactose, carbamazepine, physical mixture and liquisolid formulation (LS-7).

- Javadzadeh, Y., Siah, M.R., Barzegar Jalali, M., Nokhodchi, A., 2005. Enhancement of Dissolution Rate of Piroxicam Using Lquisolid Compacts, 60. *IL Farmaco*, pp. 361–365.
- Javadzadeh, Y., Siah, M.R., Asnaashari, S., Nokhodchi, A., 2007. An investigation on physicochemical properties of piroxicam liquisolid compacts. *Drug Dev. Technol.* (in press).
- Kapsi, S.G., Ayres, J.W., 2001. Processing factors in development of solid solution formulation of itraconazole for enhancement of drug dissolution and bioavailability. *Int. J. Pharm.* 229, 193–203.
- Lin, S.L., Menig, J., Lachman, L., 1968. Interdependence of physiological surfactant and drug particle size on the dissolution behavior of water insoluble drugs. *J. Pharm. Sci.* 57, 2143–2146.
- Lowe, M.M.L., Caira, M.R., Lotter, A.P., 1987. Physicochemical properties and X-ray structural studies of the trigonal polymorph of carbamazepine. *J. Pharm. Sci.* 76, 744–752.
- Martindale, 1999. *The Complete Drug Reference*, 32th ed. The Pharmaceutical Press, London, P 1473.
- Nokhodchi, A., Bolourchian, N., Dinarvand, R., 2005a. Dissolution and mechanical behaviors of recrystallized carbamazepine from alcohol solution in the presence of additives. *J. Crystal Growth* 274, 573–584.
- Nokhodchi, A., Javadzadeh, Y., Siah, M.R., Barzegar-Jalali, M., 2005b. The effect of type and concentration of vehicles on the dissolution rate of a poorly soluble drug (indomethacin) from liquisolid compacts. *J. Pharm. Pharmaceut. Sci.* 8, 18–25.
- Simonelli, A.P., Mehta, S.C., Higuchi, W.I., 1976. Dissolution rates of high energy sulfathiazole-povidon coprecipitates: II: characterization of form of drug controlling its dissolution rate solubility studies. *J. Pharm. Sci.* 65, 355–361.
- Spireas, S., Sadu, S., 1998. Enhancement of Prednisolone dissolution properties using liquisolid compacts. *Int. J. Pharm.* 166, 177–188.
- Spireas, S., Sadu, S., Grover, R., 1998. In vitro release evaluation of hydrocortisone liquisolid tablets. *J. Pharm. Sci.* 87, 867–872.
- Spireas, S., Wang, T., Grover, R., 1999. Effect of powder substrate on the dissolution properties of methochrothiazide liquisolid compacts. *Drug Dev. Ind. Pharm.* 25, 163–168.
- Usui, F., Maeda, K., Kusai, A., Ikeda, K., Nishimura, K., Yamato, K., 1997. Inhibitory effect of water-soluble polymers on precipitation of RS-8359. *Int. J. Pharm.* 154, 59–66.