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Enhancement of prednisolone dissolution properties using liquisolid compacts

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Abstract

The in-vitro release characteristics of prednisolone, a very slightly water soluble glucocorticoid, formulated in directly compressed tablets and liquisolid compacts, were studied at different dissolution conditions. According to the new formulation method of liquisolid compacts, liquid medications such as solutions or suspensions of water insoluble drugs in suitable non-volatile liquid vehicles, can be converted into acceptably flowing and compressible powders by blending with selected powder excipients. It has been speculated that such systems exhibit enhanced release profiles due to the increased wetting properties and surface of drug available for dissolution. In the present study, the potential of liquisolid systems to improve the dissolution properties of water-insoluble agents was investigated using prednisolone as the model drug. Several liquisolid tablet formulations were prepared using a new mathematical model to calculate the appropriate quantities of powder and liquid ingredients required to produce acceptably flowing and compressible admixtures. Liquisolid compacts demonstrated significantly higher drug release rates, in different dissolution media and volumes, compared to tablets prepared by the direct compression method. It was also observed that the drug dissolution rate from liquisolid tablets was independent of the volume of dissolution medium, in contrast to the plain tablets which exhibited declining drug release patterns with decreasing dissolution volumes.

Keywords: Prednisolone; Water insoluble drugs; Dissolution conditions; Liquisolid compacts; Liquisolid systems; Liquisolid tablets; Liquid vehicle; Drug concentration; Carrier; Coating powder materials; Fraction molecularly dispersed; Liquid medication

1. Introduction

The poor dissolution rates of water insoluble drugs is still a substantial problem confronting the

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pharmaceutical industry. A great number of new and, possibly, beneficial chemical entities do not reach the public merely because of their poor oral bioavailability due to inadequate dissolution. Over the years, various solid dosage formulation techniques, to enhance the dissolution of poorly soluble substances, have been introduced with different degrees of success. The technique of 'liquisolid compacts' is a new and promising addition towards such a novel aim.

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

The industrial application of liquisolid compacts, however, can be hampered by the poor and erratic flow and compaction properties of the final liquid/powder admixtures. In previous work (Spireas et al., 1992) only the flowability of these systems, which were then termed 'powdered solutions', had been addressed. In more recent studies (Spireas, 1993), however, the flowability and compressibility of liquisolid compacts were addressed simultaneously resulting in the new formulation-mathematical model of liquisolid systems, which enables one to calculate the appropriate quantities of excipients required to produce acceptably flowing and compressible powders.

Due to significantly increased wetting properties and surface area of drug available for dissolution, liquisolid compacts of water-insoluble substances may be expected to display enhanced drug release characteristics and, consequently, improved oral bioavailability. Since dissolution of a non-polar drug is often the rate limiting step in gastrointestinal absorption, better bioavailability of an orally administered water-insoluble drug is achieved when the drug is already in solution, thereby displaying enhanced dissolution rates (Nelson, 1962). That is why soft gelatin elastic capsules containing solutions of such medications demonstrate higher bioavailability when compared to conventional oral solid dosage forms (Ebert, 1977). A similar principle underlies the mechanism of drug delivery from liquisolid compacts and is chiefly responsible for the improved dissolution profiles exhibited by these preparations. In this case, even though the drug is in a solid dosage form, it is held within the powder substrate in solution or, in a solubilized, almost molecularly dispersed state, which contributes to the enhanced drug dissolution properties.

In the present work, prednisolone, USP, a very slightly water soluble corticosteroid, was formulated into 5-mg liquisolid tablets consisting of similar powder excipients and different liquid vehicles and drug concentrations in their liquid medications. The in-vitro drug dissolution rates of such preparations were compared to those of conventionally prepared, directly compressed, tablets using a USP dissolution apparatus II and different dissolution media and volumes, namely, 900, 450 and 300 ml distilled water or 0.1 N HCl aqueous solution.

2. Theoretical aspects

In previous studies (Spireas, 1993), fundamental flow and compression issues have been addressed with the introduction of the new formulation-mathematical model of liquisolid systems, which is based on the flowable (Φ-value) and compressible (Ψ-number) liquid retention potentials of the constituent powders. According to the new theories, the carrier and coating powder materials can retain only certain amounts of liquid while maintaining acceptable flow and compression properties. Depending on the excipient ratio (R) of the powder substrate, where:

$$R = Q/q \tag{1}$$

which is the fraction of the weights of the carrier (Q) and coating (q) materials present in the formulation, an acceptably flowing and compressible

liquisolid system can be prepared only if a maximum liquid load on the carrier material is not exceeded. Such a characteristic amount of liquid is termed the liquid load factor (L_f) and defined as the weight ratio of the liquid medication (W) and carrier powder (Q) in the system, i.e.:

$$L_f = W/Q \quad (2)$$

It should be emphasized that the terms 'acceptably flowing' and 'acceptably compressible' imply preselected and desirable levels of flow and compaction which must be possessed by the final liquid/powder admixtures. Essentially, the acceptable flow and compaction characteristics of liquisolid systems are ensured and, in a way, built in during their manufacturing process via the Φ-value and Ψ-number concepts, respectively. These are recently introduced (Spireas et al., 1992; Spireas, 1993) fundamental properties of powders and are referred to as their flowable and compressible liquid-retention potentials, respectively.

The Φ-value of a powder represents the maximum amount of a given non-volatile liquid (e.g. propylene glycol) that can be retained inside its bulk (w/w) while maintaining acceptable flowability. The Ψ-number of a powder is defined as the maximum amount of liquid that a powder can retain inside its bulk (w/w) while maintaining acceptable compactability, namely, producing cylindrical compacts of adequate crushing strengths and acceptable levels of friability without presenting any 'liquid-squeezing-out' phenomena during compression.

The Φ-value of powders may be determined using a new procedure referred to as the liquisolid flowability (LSF) test, which employs recording powder flowmetry (Gold et al., 1966) for the flow characterization of the tested liquid/powder admixtures (Spireas, 1993). The limits of acceptable flow properties of the finished liquisolid systems may be adjusted during LSF testing according to the intended process and equipment requirements and are built in the magnitude of the determined Φ-values of the carrier (Φ) and coating (ϕ) powder materials.

The Ψ-number of powders may be determined using a new method termed the liquisolid compressibility (LSC) test or 'pactisity testing', which employs the recently proposed 'pactisity theories' (Spireas, 1993; Grover, 1998) to evaluate the compaction properties of the liquid/powder admixtures. Accordingly, the pactisity (Ω) or maximum crushing strength of the liquisolid compacts consisting of certain liquid and powder, is inversely proportional to the liquid/solid weight ratio (C_w) of the preparations. The desired compression properties of the finished liquisolid systems may be adjusted during pactisity testing according to the requirements of the individual target product and are, in essence, built in the magnitude of the determined Ψ-numbers of the carrier (Ψ) and coating (ψ) powders.

It has been established (Spireas, 1993) that, for a given powder substrate consisting of a certain carrier and coating powders mixed at various powder excipient ratios (R), there are specific maximum liquid load factors (L_f) which must be employed in order to produce acceptably flowing liquisolid systems. Such flowable L_f values, denoted as ${}^{\Phi}L_f$, are related to the R-values of their powder blends by:

$${}^{\Phi}L_f = \Phi + \phi(1/R) \quad (3)$$

where, as mentioned earlier, Φ and ϕ are the Φ-values of the carrier and coating powder materials, respectively.

Similarly, the compressible liquid load factors, ${}^{\Psi}L_f$, required to produce liquisolid compacts with acceptable compaction properties, are related to the excipient ratios (R) of their powder substrates as follows:

$${}^{\Psi}L_f = \Psi + \psi(1/R) \quad (4)$$

where Ψ and ψ are the Ψ-numbers of the carrier and coating powders, respectively.

Therefore, for any liquid medication incorporated onto a given powder substrate consisting of certain carrier and coating materials (e.g. microcrystalline cellulose and silica) blended at a specific excipient ratio (R), there exists an optimum liquid load factor, L_O, required to produce acceptably flowing and, simultaneously, acceptably compressible liquisolid preparations. In essence, the L_O value required at a given powder excipient ratio for any system is equal to either its ${}^{\Phi}L_f$ or ${}^{\Psi}L_f$ value, whichever is less; thus:

$$L_O = {}^{\phi}L_f \quad \text{when: } {}^{\Phi}L_f < {}^{\Psi}L_{\phi f} \tag{5}$$

or

$$L_O = {}^{\psi}L_f \quad \text{when: } {}^{\Phi}L_f > {}^{\Psi}L_f \tag{6}$$

Based on Eqs. (1) and (2), as soon as the optimum liquid load factor of a given excipient ratio system is established, the appropriate quantities of carrier (Q_O) and coating (q_O) powder materials required to convert a given amount of liquid medication (W) into an acceptably flowing and compressible liquisolid system, may be calculated as follows:

$$Q_O = W/L_O \tag{7}$$

and

$$q_O = Q_O/R \tag{8}$$

The validity of the preceding principles has been repeatedly tested and verified by producing liquisolid compacts possessing acceptable (or anticipated at a desired level) flow and compaction properties. Several lab-scale and pilot batches of commercial and experimental drugs have been prepared yielding tablets of acceptable crushing strength, friability, weight variation and content uniformity, even for liquisolid compacts of a very low dose.

3. Materials and methods

3.1. Materials

The following materials were used as received: prednisolone, USP, micronized powder (Geneva Pharmaceuticals, Greenfield, CO); lactose monohydrate (Zeparox®, EM Industries, Hawthrone, NY); coarse granular microcrystalline cellulose (Avicel® PH 200, FMC, Philadelphia, PA); sodium starch glycolate (Explotab®, Edward Mendell, Carmel, NY); nm-sized amorphous silicon dioxide (Cab-O-Sil® M5, Spectrum, Gardena, CA); polysorbate 80 (Tween® 80), polyethylene glycol 400 and glycerin (Ruger, Irvington, NJ); propylene glycol (Sigma, Irvington, NJ); and hydrochloric acid 37% A.C.S. grade (Aldrich, Milwaukee, WI).

3.2. Directly compressed tablets

A conventional formulation of micronized prednisolone, USP, (denoted as DC-1) was directly compressed into cylindrical tablets, each containing 5 mg drug. In addition, each DC-1 tablet contained the following powder excipients: 70 mg coarse granular microcrystalline cellulose (Avicel® PH 200), 35 mg lactose monohydrate (Zeparox®), 5 mg nm-sized silica (Cab-O-Sil® M5) and 10 mg sodium starch glycolate (Explotab®). A 50 tablet batch was mixed in a Turbula mixer (Glen Mills, Maywood, NJ) for 10 min and compressed using a semiautomatic Carver system (Fred S. Carver, Wabash, IN) consisting of a Model-C hydraulic laboratory press interfaced with a MotorPak motorized unit with automatic time and pressure release. Sufficient compression loads were applied in order to produce tablets of 5–6 kp hardness, as determined using a Schleuniger Model 6-D Hardness Tester (Dr Schleuniger Pharmatron, Manchester, NH).

3.3. Liquisolid compacts

Several liquisolid systems of prednisolone (denoted as LS-1–LS-14) were prepared in 50 tablet batches and compressed into cylindrical tablets of 5 mg strength each, using the semi-automatic Carver system and a target hardness of 7–8 kp. All liquisolid formulations contained microcrystalline cellulose as the carrier powder and silica as the coating (covering) material at a fixed powder excipient ratio (R) of 20. Propylene glycol was used as the liquid vehicle to prepare the liquid medications of the different drug concentrations, ranging from 5 to 50% w/w, included in the formulations LS-1–LS-11. On the other hand, formulations LS-11–LS-14 contained liquid medications with a fixed 5% (w/w) drug concentration in different liquid vehicles, namely, propylene glycol (LS-11), glycerin (LS-12), polyethylene glycol 400 (LS-13) and polysorbate 80 (Tween® 80) (LS-14). Depending on the liquid vehicle and drug concentration in the liquid medication used, different liquid load factors (L_f) ranging from 0.195 to 0.25 (w/w) were employed in our liquisolid preparations. Finally, a standard 5% (w/w) of the

Table 1
Key formulation characteristics of prepared prednisolone liquisolid compacts (see text for theoretical definitions)

Liquisolid system[a]	Liquid vehicle[b]	Drug concentration (% w/w) in liquid medication (C_d)[c]	Liquid load factor (L_f)[d]	Unit dose weight (mg)[e]	Molecular fraction (F_M)[f]
LS-1	PG	10	0.230	270.4	1.000
LS-2	PG	12.5	0.232	233.0	0.748
LS-3	PG	15	0.235	193.1	0.698
LS4	PG	17.5	0.238	163.2	0.599
LS-5	PG	20	0.240	141.6	0.524
LS-6	PG	22.5	0.243	124.5	0.466
LS-7	PG	25	0.245	111.4	0.419
LS-8	PG	30	0.250	91.3	0.349
LS-9	PG	40	0.250	68.5	0.262
LS-10	PG	50	0.250	54.8	0.210
LS-11	PG	5	0.225	597.3	1.000
LS-12	GLY	5	0.210	632.4	1.000
LS- 13	PEG	5	0.205	645.3	0.947
LS-14	T80	5	0.195	672.9	0.728

[a] A fixed powder excipient ratio ($R = Q/q$) equal to 20 was used (see Section 2 for the symbol definitions).
[b] Liquid vehicles: propylene glycol (PG), glycerin (GLY), polyethylene glycol 400 (PEG), polysorbate 80 (T80).
[c] An appropriate amount of liquid medication containing 5 mg of drug was incorporated in each tablet.
[d] The liquid load factor is defined as $L_f = W/Q$ (see Section 2 for the symbol definitions).
[e] Includes a 5% (w/w) per tablet of the disintegrant sodium starch glycolate.
[f] The fraction (F_M) of molecularly dispersed drug in the system was calculated based on Eq. (12) and the drug solubilities in the liquid vehicles given in Table 2 (see Section 4).

disintegrant sodium starch glycolate was added to all systems. Important formulation characteristics of the prepared prednisolone liquisolid compacts are shown in Table 1.

3.4. Solubility studies

The solubility of prednisolone in water and the four liquid vehicles used to prepare the liquisolid systems, namely, propylene glycol, polyethylene glycol 400, glycerin and polysorbate 80, were studied by preparing saturated solutions of the drug in these solvents and analyzing their drug content spectrophotometrically. Specifically, prednisolone was mixed in 10 ml test tubes with such amounts of each of the above solvents in order to produce systems containing an excess of drug. The mixtures were sonicated for 24 h and then cooled down to 25°C under constant vibration. After centrifugation, accurately weighed quantities of the filtered supernatant solutions were further diluted with methanol and analyzed spectrophotometrically at 245 nm for their drug content. The results were extrapolated to determine the percent w/w of prednisolone in its saturated solution with the solvent under investigation.

3.5. Dissolution studies

The in-vitro release profiles of prednisolone from the tablets were obtained using a model 2100A Distek dissolution system (Distek, North Brunswick, NJ) equipped with seven vessels and sampling probes. Each time, six tablets from each formulation were tested by placing one unit dose (5 mg prednisolone tablet) in each vessel of the Distek dissolution apparatus II (paddle method). The run was repeated using two different dissolution media, namely, distilled water and 0.1 N HCl aqueous solution, at three different volumes per vessel, i.e. 900, 450 and 300 ml. The dissolving medium was maintained at 37°C and stirred at a paddle speed of 50 rpm. Samples were collected for up to 30 min at 10-min intervals, filtered through a 0.45 μm, type HA, nylon membrane

filter (Millipore, Bedford, MA), and analyzed spectrophotometrically at 245 nm. After their assay the dissolution samples were returned to their original vessels.

3.6. Spectrophotometric analysis and standard curves

A model U2001 double beam Hitachi UV/visible spectrophotometer (Hitachi, Danbury, CT) was used for the spectrophotometric analyses of all prednisolone samples in methanolic (solubility studies) or aqueous solutions (dissolution studies) at 245 nm which was previously established as the wavelength of the drug's maximum absorbance. Standard curves were constructed by serially diluting a methanolic stock solution of the drug to obtain concentrations in the range of 2–17 μg/ml using methanol, distilled water or an aqueous 0.1 N HCl solution as the diluents. Each concentration was analyzed in triplicate.

3.7. Assessment of cumulative percent drug dissolved

During each dissolution run, a standard solution of prednisolone (in the medium used) with a drug concentration equal to the one expected to be obtained at the 100% dissolution level, was placed in the seventh dissolution vessel of the Distek system. The percent drug dissolved in each sample was determined by comparing it's spectrophotometric absorbance (Ab_{sample}) to that of the standard solution ($Ab_{standard}$), as follows:

$$\%\ \text{Drug dissolved} = \frac{Ab_{sample}}{Ab_{standard}} \times 100 \qquad (9)$$

3.8. Assessment and comparison of drug dissolution rates

The dissolution rates (D_R) of prednisolone, in the form of amount of drug (in μg) dissolved per min, presented by each tablet formulation during the first 10 min of the dissolution process, were calculated as follows:

$$D_R = 5 \times (\%\ \text{drug dissolved in first 10 min}) \qquad (10)$$

The statistical significance of differences in the dissolution rates of liquisolid and directly compressed tablets was tested by conducting a double-sided t-test for the means of two-independent groups with unknown variance (Bolton, 1990). In all cases, pooled variances were computed from the sample data and used to estimate the t statistics and p-values.

4. Results and discussion

Prednisolone was selected as the model drug for these studies, since it is a very slightly water soluble substance and, thus, an ideal candidate for testing the potential of rapid-release liquisolid compacts. In addition, it can be easily assayed and quantitated in solution using spectrophotometric principles and procedures. Beer's law was obeyed by all the standard curves of our prednisolone solutions which were linear in the concentration range tested, i.e. from 2 to 17 μg/ml. The solubilities of prednisolone in water, propylene glycol, polyethylene glycol 400, glycerin and polysorbate 80, determined in these studies, are given in Table 2.

Fig. 1 shows the drug dissolution profiles from the liquisolid compacts (LS-1) and the directly compressed (DC-1) tablets of micronized prednisolone. When 900 ml (per vessel) of distilled water or 0.1 N HCl aqueous solution was used as the dissolving medium, liquisolid tablets displayed slightly better in-vitro release characteristics than those of their directly compressed counterparts. However, when smaller volumes, namely, 450 and 300 ml, of dissolution media were used, the liquisolid tablets demonstrated significantly improved drug dissolution properties ($p < 0.01$).

Table 2
Solubility of prednisolone in various solvents

Solvent	Solubility (% w/w)
Distilled water	0.0142
Propylene glycol	10.4772
Glycerin	5.8227
Polyethylene glycol 400	4.7348
Polysorbate 80 (Tween 80)	3.6420

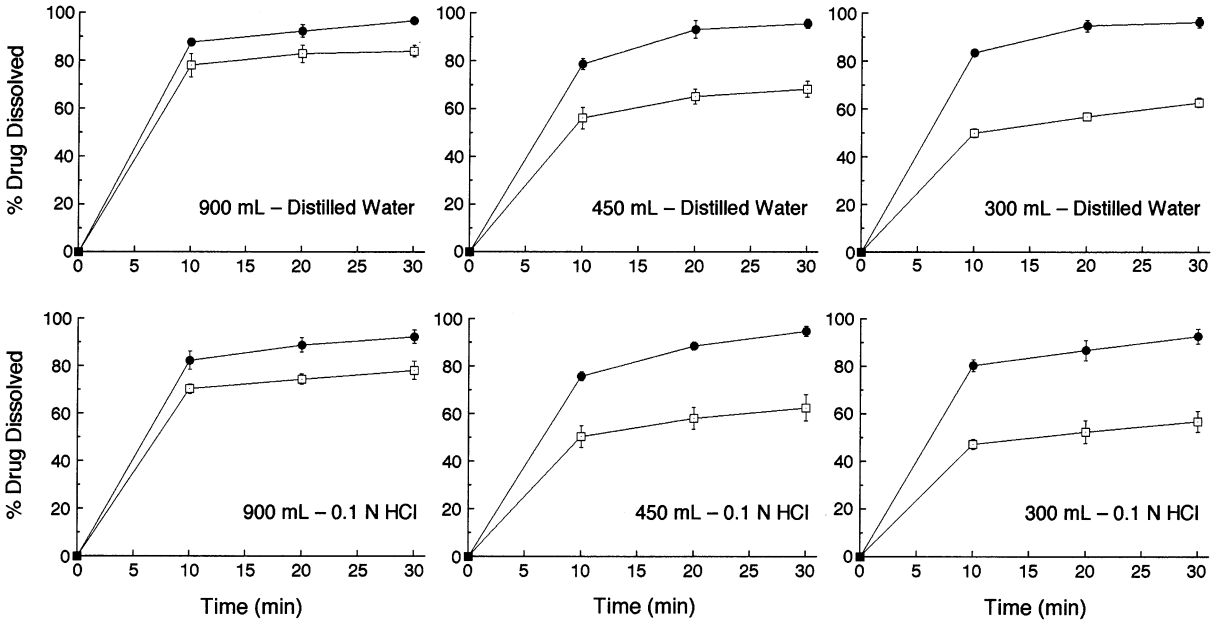

Fig. 1. Comparison of prednisolone dissolution profiles displayed by the liquisolid compacts and directly compressed tablets at different dissolution media and volumes. Significantly enhanced drug dissolution properties have been displayed by the liquisolid tablets ($p < 0.01$) at all dissolution conditions tested. Key: ●, liquisolid compacts; □, directly compressed tablets.

The higher prednisolone dissolution rates displayed by the liquisolid tablets are clearly observed in Fig. 2, where the dissolution rate (D_R in μg of drug dissolved per min) observed during the first 10 min of the dissolution process is plotted against the volume of dissolution medium. It seems that the drug dissolution rate of liquisolid compacts is significantly faster than that of the plain tablets ($p < 0.01$), and it is independent of the volume of the dissolving liquid used. Furthermore, it is apparent that decreasing dissolution volumes result in a proportional decrease of the in-vitro drug release rates displayed by the directly compressed tablets.

According to the 'diffusion layer model' dissolution theories (Martin, 1993; Hoener and Benet, 1996), the dissolution rate of a drug is directly proportional to its concentration gradient ($\Delta C = C_s - C$) in the stagnant diffusion layer formed by the dissolving liquid around the drug particles. C_s is the saturation solubility of the drug in the dissolution medium and thus, it is a constant characteristic property related to the drug and dissolving liquid involved. On the other hand, C, the drug concentration in the bulk of the dissolving medium, increases with decreasing volumes of dissolution fluid used. Therefore, the ΔC values existing in the three different dissolution volumes of our tests decrease with decreasing volumes of dissolution medium. Consequently such ΔC reduction is directly related to the decreased drug dissolution rates of the conventional tablets with decreasing volumes of both dissolution media used (Fig. 2).

On the other hand, as illustrated in Fig. 2, decreasing dissolution volumes do not affect the drug release rate from the liquisolid compacts. Since the liquisolid tablets contain a solution of the drug in propylene glycol (10% w/w), the drug surface available for dissolution is tremendously increased. In essence, after disintegration, the liquisolid primary particles suspended in the dissolving medium contain the drug in a state of molecular dispersion, whereas the directly compressed tablets are merely exposing micronized drug particles. Therefore, in the case of liquisolid tablets, the surface of drug available for dissolution is related to its specific molecular surface

which, by any means, is much greater than that of the prednisolone particles delivered by the conventionally made, directly compressed tablets.

According to the classic dissolution equation (Noyes and Whitney, 1897):

$$D_R = (D/h)S(C_s - C) \quad (11)$$

the drug dissolution rate (D_R) is directly proportional not only to the concentration gradient ($C_s - C$) of the drug in the stagnant diffusion layer, but also to its surface (S) available for dissolution. Moreover, since all of our dissolution tests for both prednisolone preparations were conducted at a constant rotational paddle speed (50 rpm) and identical dissolving media, it is safe to assume that the thickness (h) of the stagnant diffusion layer and the diffusion coefficient (D) of the drug molecules transported through it, remain almost identical under each dissolution condition. Therefore, the hypothesis that the significantly increased surface of the molecularly dispersed prednisolone in the liquisolid tablets may be chiefly responsible for their observed higher and consistent dissolution rates, appears to be fundamentally valid.

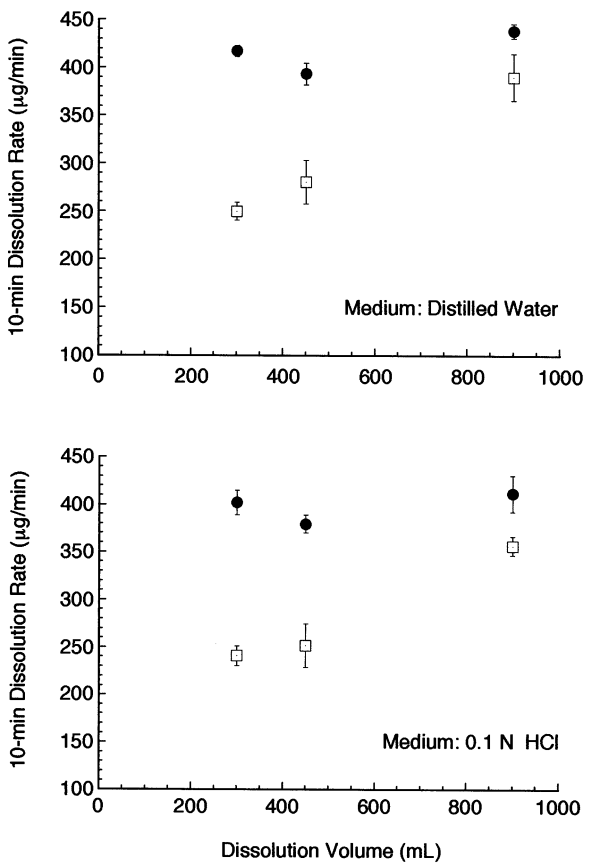

Fig. 2. Effect of the dissolution volume on the initial dissolution rate of prednisolone exhibited by the liquisolid compacts and directly compressed tablets using different dissolution media. Significantly enhanced drug dissolution rates have been obtained from the liquisolid tablets ($p < 0.01$) at all dissolution conditions tested. Key: ●, liquisolid compacts; □, directly compressed tablets.

In addition to the preceding theory, it might be also speculated that C_s, the saturation solubility of the drug in the micro-environment, might be increased in the case of liquisolid systems. Admittedly, the relatively small amounts of liquid vehicle (propylene glycol) contained per liquisolid compact, are not sufficient to increase the overall saturation solubility of prednisolone in the aqueous dissolution medium. At the local level, however, the solid/liquid interface between an individual liquisolid primary particle and the dissolving fluid involves minute quantities of aqueous medium clinging onto the particle surface to form the stagnant diffusion layer. At such a micro-environment, it is quite possible that the infinite amounts of propylene glycol diffusing with the drug molecules out of a single liquisolid particle, might be adequate to enhance the solubility of prednisolone acting as a cosolvent with the aqueous dissolution medium of the stagnant diffusion layer. Such an increase in C_s will result, of course, in a larger drug concentration gradient (ΔC) thereby increasing the dissolution rate as defined by the Noyes–Whitney equation (Eq. (11)).

The consistent and higher dissolution rates displayed by liquisolid compacts may also imply enhanced oral bioavailability. In this study, prednisolone was used as a representative water insoluble model. From a physicochemical point of view, it is well established that the inadequate dissolution of water insoluble drugs is the major reason for their poor and erratic bioavailability, since it is the rate determining step in the absorption of non-polar molecules. As shown in Fig. 2, adverse conditions result in a significant dissolu-

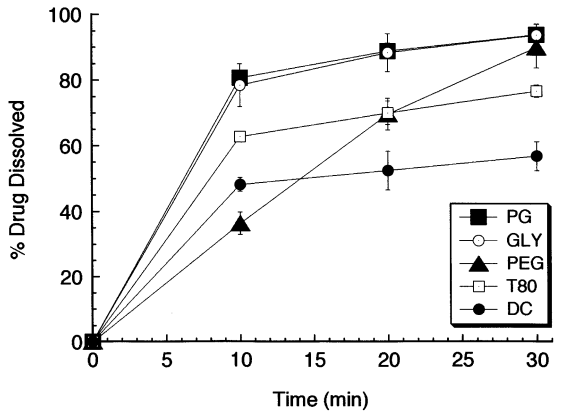

Fig. 3. Prednisolone dissolution profiles of directly compressed tablets (DC) and liquisolid compacts containing different liquid vehicles and a fixed 5% (w/w) drug concentration in their liquid medications. The dissolution results were obtained using 300 ml aqueous 0.1 N HCl solution as the dissolution medium. Significantly enhanced 30 min drug dissolution has been displayed by all the liquisolid tablets as compared to that of their directly compressed counterparts ($p < 0.01$). Key for the liquid vehicle in the liquisolid compacts: PG, propylene glycol; GLY, glycerin; PEG, polyethylene glycol 400; T80, polysorbate 80.

tion rate decrease of this very slightly water soluble drug formulated in conventional tablets. It is quite possible that in vivo conditions and gastric variations may be simulated by the various dissolution conditions used in this study. Should this be the case, liquisolid compacts of prednisolone may be expected to produce more consistent and enhanced in vivo dissolution and absorption characteristics. In other studies currently being prepared for publication, liquisolid systems of several water insoluble drugs, namely, nifedipine, gemfibrozil, ibuprofen and the liquid clofibrate, have exhibited significantly higher bioavailability in rats as compared to their commercial counterparts such as tablets and soft gelatin capsules.

The liquid vehicle contained in the prepared liquisolid systems seems to have some effects on their drug dissolution properties, as shown in Fig. 3. Specifically, similar prednisolone release profiles from liquisolid tablets containing identical drug concentrations (5% w/w) in their liquid medications and prepared with two different liquid vehicles, namely, propylene glycol and glycerin, were observed when 300 ml of a 0.1 N aqueous HCl solution was used as the dissolving medium. On the other hand, compacts containing polyethylene glycol 400 or polysorbate 80 (Tween® 80) as the liquid vehicles displayed relatively slower drug release rates for the first 10 and 20 min of dissolution. However, all liquisolid preparations exhibited significantly faster 30 min dissolution than that of the conventional tablets ($p < 0.01$).

The relatively poorer dissolution properties of the polyethylene glycol 400 (PEG) and the polysorbate 80 (T80) liquisolid compacts may be mainly attributed to the lower solubilities of prednisolone in these liquid vehicles as compared to those in propylene glycol (PG) and glycerin (GLY), shown in Table 2. Since all liquisolid formulations compared in Fig. 3 contain liquid medications with a fixed drug concentration equal to 5% w/w, prednisolone is not entirely in solution in all the compacts. In essence, the drug is in a partly dissolved state in the liquid medications of LS-13 (PEG) and LS-14 (T80) tablets, since the solubilities of prednisolone in PEG and T80 were found to be 4.735 and 3.642% w/w, respectively. On the other hand, the drug is completely in solution in the liquid medications of the LS-11 (PG) and LS-12 (GLY) compacts, thereby presenting improved dissolution properties.

However, the solubilization state of the drug in the liquid vehicle of the liquisolid compacts does not entirely justify the initial drug release patterns observed in Fig. 3. For instance, even though prednisolone is almost fully in solution in the liquid medication carried by the PEG tablets, their 10 min dissolution is much slower than that of similarly prepared T80 compacts containing the drug in a lesser solubilization state. Admittedly, this phenomenon dissipates as the dissolution process continues resulting into higher 30 min dissolution rates obtained by the PEG liquisolid tablets. However, it seems that, in addition to the drug solubility in the liquid vehicles, other physicochemical characteristics of the solvents used such as polarity, viscosity, molecular weight, chemical structure and hydrophylicity, may also have affected, to different extents, the availability of the drug molecules to the dissolving medium, the disintegration and deagreggation properties of mi-

crocrystalline cellulose included in our systems, and the diffusion of the liquid medication through the primary carrying particles during the dissolution process. Further studies on the effects of various properties of the liquid vehicle including drug solubility and dielectric constant, and on the release rate characteristics of liquisolid systems are under way.

The drug concentration in the liquid medication (C_d ranging from 5 to 50% w/w) has an apparent effect on the prednisolone 10 min dissolution rates displayed by the liquisolid compacts of propylene glycol, as shown in Fig. 4. Systems carrying liquid medications with 5 and 10% w/w drug concentrations (C_d), displayed similar drug dissolution rates when 300 ml of 0.1 N aqueous HCl solution was used as the dissolving medium. However, at the same dissolution conditions, compacts containing liquid medications with increasing C_d values exhibited declining in vitro release properties until reaching a minimum plateau dissolution rate displayed by the liquisolid systems containing more than 25% w/w of drug in their liquid medications.

Such differences in the drug dissolution rates of the PG liquisolid compacts possessing different C_d values, observed in Fig. 4, may be justified using the previous hypothesis of the available drug surface effects on dissolution. Apparently, the solubilization and molecular dispersion states of the drug in our liquisolid systems are different. For instance, since the saturation solubility of prednisolone in PG is 10.477% w/w (Table 2), the drug is partly dissolved in the liquid medication of our LS-5 liquisolid compacts containing 20% w/w prednisolone concentration, whereas it is completely dissolved in the LS-1 system containing 10% w/w of drug in PG.

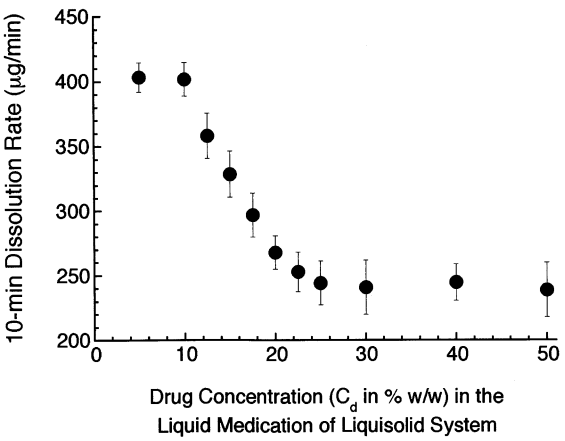

Fig. 4. The effect of the drug concentration in the liquid medication on the initial dissolution rate of prednisolone displayed by the liquisolid compacts of propylene glycol. The dissolution results were obtained using 300 ml aqueous 0.1 N HCl solution as the dissolution medium.

In other words, the ratio of the drug's saturation solubility (C_L) in the liquid vehicle over the drug concentration (C_d) in the liquid medication carried by each system denotes the fraction (F_M) of the dissolved, or molecularly dispersed, drug in the liquid medication of the prepared liquisolid tablets. Therefore:

$$F_M = C_L/C_d \quad (12)$$

(where $F_M = 1$ when $C_L/C_d > 1$)

Based on the above equation, the F_M values of each liquisolid preparation have been calculated in Table 1. It should be noted here that the fraction of the molecularly dispersed drug in any system can not exceed unity and, thus, in the cases at which C_L was greater than C_d, the value of F_M was made equal to 1. Moreover, since no liquid vehicle is involved in the case of directly compressed tablets which contain plain micronized prednisolone powder, their F_M value was taken equal to 0.

The dissolution rates obtained from directly compressed tablets and PG liquisolid compacts possessing different C_d values, are plotted against their corresponding F_M values in Fig. 5. As shown there, after remaining at a minimum plateau level (about 240 μg/min) for F_M values ranging from 0 to 0.5, the 10 min dissolution rate of the drug increased in a linear manner with increasing F_M values of the liquisolid systems. Therefore, for PG liquisolid tablets, one may be able to predict the dissolution rate (D_R in μg/min) of prednisolone which will be obtained within the initial 10 min of the dissolution process conducted using 50 rpm as the paddle speed and 300 ml of 0.1 N HCl solution as the dissolution medium. As shown in Fig. 5, for systems with F_M values ranging from 0.5 to 1.0, the dissolution rate of prednisolone may be given by:

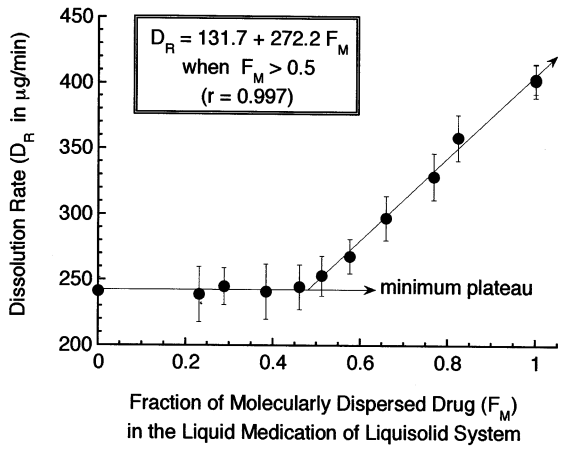

Fig. 5. Effect of the fraction (F_M) of the molecularly dispersed drug in the tablet formulations on the 10 min dissolution rate (D_R) of prednisolone displayed by the directly compressed tablets and the liquisolid compacts of propylene glycol containing various drug concentrations (C_d) in their liquid medications. The F_M values of all the liquisolid preparations are included in Table 1. They were calculated using Eq. (12) and the drug solubilities (C_L) are given in Table 2. The F_M value of the directly compressed tablets was taken as equal to zero.

$$D_R = 131.7 + 272.2F_M \quad (13)$$

5. Conclusions

(1) The new technique of liquisolid compacts appears to be a promising alternative for the formulation of water insoluble drugs, such as prednisolone, into rapid release tablets which may present improved oral bioavailability. (2) As compared to conventional directly compressed tablets, the liquisolid compacts of prednisolone display significantly enhanced in vitro release properties ($p < 0.01$) in different dissolution media, probably, due to the increased wetting properties and surface of drug available for dissolution. (3) The dissolution rate of prednisolone from the liquisolid compacts is independent of the dissolution volume, whereas the plain directly compressed tablets of the micronized drug display declining dissolution rates with decreasing volumes of the dissolving medium. (4) It seems that propylene glycol is the liquid vehicle of choice which may produce prednisolone liquisolid compacts possessing minimum tablet size and maximum drug dissolution rate. (5) The liquisolid compacts of prednisolone containing propylene glycol as their liquid vehicle and different drug concentrations in their liquid medications, exhibit drug dissolution rates which are directly proportional to the fraction, F_M, of the molecularly dispersed drug in their liquid medication.

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Appendix A. Index of symbols

W	weight of liquid medication
Q	weight of carrier powder material
q	weight of coating powder material
R	powder excipient ratio (Q/q)
L_f	liquid load factor (W/Q)
C_w	liquid/solid weight ratio
Φ	flowable liquid retention potential (Φ-value) of the carrier powder
ϕ	flowable liquid retention potential (Φ-value) of the coating powder
Ψ	compressible liquid retention potential (Ψ-number) of the carrier powder
ψ	compressible liquid retention potential (Ψ-number) of the coating powder
Ω	pactisity of a liquisolid compact
C_d	drug concentration in the liquid medication
C_L	saturation solubility of the drug in the liquid vehicle
F_M	fraction of molecularly dispersed drug in the liquisolid system (C_L/C_d)
D_R	10 min drug dissolution rate (in μg/min)
C_s	saturation solubility of the drug in the dissolution medium
C	drug concentration in the bulk of the dissolution medium
ΔC	drug concentration gradient in the stagnant dissolution layer ($C_s - C$)
S	surface of drug available for dissolution
h	thickness of the stagnant diffusion layer

D diffusion coefficient of the solute (drug molecules) in solution

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