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Effect of Some Commercial Grades of Microcrystalline Cellulose on Flowability, Compressibility, and Dissolution Profile of Piroxicam Liquisolid Compacts

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The technique of liquisolid compacts is a promising method toward enhancing the dissolution of poorly soluble drugs. Lower flowability and compressibility is one of the limitations of this technique. The evaluation of effects of different grades of microcrystalline cellulose (MCC) on flowability, compressibility, and dissolution of liquisolid systems were the aims of this study. For this means, several formulations were prepared using various grades of MCC as carrier. Propylene glycol (PG), silica, and sodium starch glycolate were used as nonvolatile solvent, coating material, and disintegrant, respectively. Then flowability, friability hardness, and dissolution rate of prepared formulations were studied. The effect of tablet aging on mentioned properties was also investigated. The results showed that among the evaluated different grades of MCC, compacts containing MCC PH 101 and 102 showed better dissolution profiles. Harder compacts were obtained using MCC PH 101 and 200 as carriers. Better flowability was observed in compacts containing MCC PH 101. Also, these compacts demonstrated acceptable friability. Aging had no effect on hardness and dissolution profile of liquisolid tablets. It could be concluded that MCC PH 101 is a suitable carrier for preparing liquisolid systems for having acceptable flowability, friability, hardness, and dissolution profile.

Keywords liquisolid compact; piroxicam; microcrystalline cellulose; dissolution rate; flowability; hardness

INTRODUCTION

Piroxicam is a member of the oxicam group of nonsteroidal anti-inflammatory drugs (NSAIDs). NSAIDs are widely used for rheumatoid arthritis, osteoarthritis, various other acute and chronic musculoskeletal disorders, and dysmenorrhea, and as ordinary analgesics (Andersson, Bredberg, Lagerström, Naesdal, & Wilson, 1998; PDR, 2002). According to the Biopharmaceutics Drug Classification System (BCS) proposed by Amidon et al. (Amidon, Lennernäs, Shah, & Crison, 1995), piroxicam is from class 2 drugs with low solubility and high permeability. Its pharmacokinetic pattern is characterized by slow and gradual absorption via the oral route and a long half-life of elimination, rendering a prolonged therapeutic action but also a delayed onset of anti-inflammatory and analgesic effect (Tagliati, Kimura, Nothenberg, Santos, & Oga, 1999).

Recently, considerable attention has been focused on the improvement of bioavailability and clinical efficacy of poorly water-soluble, lipophilic drugs given orally. Numerous techniques have been used to improve the oral bioavailability of these drugs by enhancing their solubility. The most popular approaches are the incorporation of the drugs into inert lipidic vehicles such as oils, surfactant dispersions, and self-emulsifying formulations (Gershanik & Benita, 2000; Humberstone & Charman, 1997; MacGregor et al., 1997). The preparation of solid dispersion based on cyclodextrin inclusion complexes (Cavallari, Abertini, González-Rodríguez, & Rodriguez, 2002; Kimura, Bersani-Amado, Sudo, Santos, & Oga, 1997), polyvinylpyrrolidone (Tantishaiyakul, Kaewnopparat, & Ingkatawornwong, 1999), and polyethylene glycols 4000 and 6000 (Bhattacharyya et al., 1993; Fernández, Margarit, Rodríguez, & Crezo, 1993) is another popular approach to increase dissolution/solubility of poorly water-soluble drugs. Reducing particle size (Kubo, Osawa, Takashima, & Mizobe, 1996), formation of water-soluble complexes (Cassella, Williams, & Jambhekar, 1998), use of pro-drug and drug derivatization such as strong electrolyte salt forms (Trapani et al., 1998), and manipulation of solid state of drug substance are some other methods for improving drug dissolution and oral bioavailability. Each of

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these methods has own problems and their use in industrial field have been limited. 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 or tableted (Aguiar, Zelmer, & Kinkel, 1979; Finholt & Solvang, 1968; Lin, Menig, & Lachman, 1968). Micronized drugs also have the tendency to agglomerate as a result of their hydrophobicity, thus reducing their available surface area (Finholt & Solvang, 1968).

Several researchers have shown that the liquisolid technique is the most promising method for improving dissolution rate of poorly water-soluble drugs (Javadzadeh, Jafari-Navimipour, & Nokhodchi, 2007a; Javadzadeh, Siahi, Asnaashari, & Nokhodchi, 2007b, 2007c; Javadzadeh, Siahi, Barzegar-Jalali, & Nokhodchi, 2005; Nokhodchi, Javadzadeh, Siahi, & Barzegar-Jalali, 2005; Spireas & Sadu, 1998; Spireas, Sadu, & Grover, 1998; Spireas, Wang, & Grover, 1999). A "liquisolid system" refers to formulations formed by conversion of liquid drugs (such as vitamin A, clofibrate), drug suspensions, or drug solution in nonvolatile solvents into dry, nonadherent, free-flowing, and compressible powder mixtures by blending the suspension or solution with selected carriers and coating materials (Spireas & Sadu, 1998). One of the limitations of this technique is its free flowability and compressibility. 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 which is very difficult to swallow.

The flowability generally depends on the physical properties of the powder, such as particle size and shape, surface morphology, particle density, bulk density, moisture content, and fat content (Kim, Chen, & Pearce, 2005). Choosing the appropriate excipient to perform a specific function in a tablet formulation can be critical to achieving acceptable manufacturing performance.

Microcrystalline cellulose (MCC) is a very popular pharmaceutical excipient in direct compression. The compactibility of MCC is mostly offered by plastic deformation and mechanical interlocking between particles (Nyström, Alderborn, Duberg, & Karehill, 1993). This excipient has been used as a major carrier material in the preparation of liquisolid compacts due to having high surface area for adsorbing drug solutions or suspensions. MCC is available in many grades that differ from each other by their particle size, particle shape, and moisture content. The initial size of the particles constituting powder form is an important factor in determining its flow and compaction behavior. For most powder materials, compaction of the smaller particles results in stronger tablets because of the large surface area available for binding (Sun & Grant, 2001). Then it was suggested that using the best grade of MCC in view of having better flowability and compressibility in liquisolid systems could solve the limitations of this technique. In this study, three kinds of MCC—i.e., PH 101, 102, and 200—were employed as a carrier material in liquisolid compacts to compare the effect of several structural factors on flowability, compressibility, and dissolution rate of drug from these systems. Piroxicam was used as model drug with poor solubility and dissolution rate. Liquid medication was prepared in two different concentrations (10 and 50% drug in liquid medication), and flowability, compressibility, and dissolution rate of drug were investigated after preparing liquisolid systems using different grades of MCC. Finally, the effect of aging on hardness and dissolution profile was also studied.

MATERIAL AND METHODS

Materials

Piroxicam was provided by Shahid Razakani Co. (Tehran, Iran). Coarse granular MCC (Mingtai Chemical, Bah-Der, Taiwan), sodium starch glycolate (Yung Zip Chemical, Tachia, Taiwan), nanometer-sized amorphous silicon dioxide (Mingtai Chemical), propylene glycol (PG) (Merck, Germany), sodium hydroxide (Merck), potassium phosphate monobasic (Merck), and sodium chloride (Merck) were used.

Spectrophotometric Analysis

The spectrophotometric analysis of all piroxicam samples in aqueous solutions (pH 1.2 or 7.2) was performed at 334.4 and 353.6 nm, respectively (UV/visible spectrophotometer, Shimadzu-120, Tokyo, Japan). Standard curves were constructed by serially diluting an aqueous stock solution of the drug (at pH 1.2 and 7.2) to obtain concentrations in the range of 2.5–50 μg/mL using simulated gastric fluid (SGF) or simulated intestine fluid (SIF) without enzymes as the diluents. Each sample was analyzed in triplicate.

Preparation of Piroxicam Liquisolid Tablets

Several liquisolid compacts (denoted as PLS-1 to PLS-6) were prepared as follows. Piroxicam was dispersed in PG (PG was used as the liquid vehicle to prepare the liquid medication of the different drug concentrations) with two different concentrations, i.e., 10 and 50% drug in liquid medication. Then a binary mixture of the different grades of MCC–silica (MCC as the carrier powder and silica as the coating material with a ratio of 20, R [R = weight of the carrier powder/weight of coating material]) was added to the mixture containing the drug and PG under continuous mixing in a mortar. Depending on the ratio of the drug and PG in the formulation, different liquid load factors (the liquid load factor, L_f, is the weight ratio of the liquid medication and carrier powder in the liquisolid formulations) were employed in our liquisolid preparations. These amounts of the carrier and coating materials were enough to maintain acceptable flow and compression properties. Finally, 5% (wt/wt) of sodium starch glycolate as the disintegrant was mixed with the mixture (Erweka, Type UG, Heusenstamm, Germany) for a period of 10 min. The final mixture was compressed using the manual tableting machine (Riken, P-16B, Tokyo, Japan)

TABLE 1
Key Formulation Characteristics of Liquisolid Formulations

Formulation	Carrier	% Drug in Liquid Medication
PLS-1	Microcrystalline cellulose PH 101	10
PLS-2	Microcrystalline cellulose PH 101	50
PLS-3	Microcrystalline cellulose PH 102	10
PLS-4	Microcrystalline cellulose PH 102	50
PLS-5	Microcrystalline cellulose PH 200	10
PLS-6	Microcrystalline cellulose PH 200	50

with different pressures (20, 40, 60, 80, and 100 kg/cm^2). Important formulation characteristics of the prepared piroxicam liquisolid compacts have been shown in Table 1.

Dissolution Study

The USP paddle method (Erweka, DPT6R) was used for all the in vitro dissolution studies. In this method, distilled water with SGF (pH 1.2) and intestinal fluid (pH 7.2) without enzyme were used as dissolution media. The rate of stirring was 50 ± 2 rpm. The amount of piroxicam was 10 mg in all formulations. The dosage forms were placed in 900 mL of gastric fluid (HCl solution) or intestinal fluid (phosphate buffer) and maintained at 37 ± 0.1°C. At appropriate intervals (10, 20, 30, 60, and 90 min), 5 mL of the samples were taken and filtered through a 0.45-mm Millipore filter. The dissolution media were then replaced by 5 mL of fresh dissolution fluid to maintain a constant volume. The samples were then analyzed by UV/visible spectrophotometer. The mean of three determinations was used to calculate the drug release from each of the formulations. For assessment and comparison, drug dissolution rates (D_R) of drug were used.

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 the 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 two dissolution profiles are identical and approaches 0 as the dissimilarity increases. An f_2 above 50 indicates that the two profiles are similar.

Determination of Particle Sizes of MCC

Size distributions of different grades of MCC were determined by the laser diffraction particle size analyzer (Shimadzu-SALD 2101).

Flowability of Liquisolid Systems

Two techniques were used to evaluate the flow properties of powders: hopper flow rate and angle of repose. In hopper flow rate technique, 100 cm^3 of powders was placed in the funnel of flowmeter (Erweka). 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 was used for quantitative comparison of different powders. The flow rate above 10 cm^3/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 with 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 the equation

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

where α is the repose angle.

Compressibility of the Liquisolid Systems

Appropriate amount of the liquisolid systems containing 10 mg of piroxicam was compressed by using lubricated punch and die set installed in a manual tablet machine (Riken, P-16B). Tablets were prepared under conditions where maximum compression pressure (P_{max}) ranged from 20 to 100 kg/cm^2. The compression pressure was released immediately after the pressure reached P_{max}, that is, an upper punch was not kept holding at P_{max}. Tablets were stored in airtight vials for 24 h and then their final thickness (T_t) and tablet tensile strength (T)

were measured. T was evaluated by the method of Fell and Newton through below equation (Obae, Iijima, & Imada, 1999):

$$T = \frac{2H}{\pi D_t T_t}$$

where H is the hardness of the tablet, D_t is the tablet diameter, and T_t is the tablet thickness (cm). H, D_t, and T_t were measured by a tablet hardness tester (Erweka TBH 30MD), which is also used to determine the diameter and thickness of the tablets. Ten determinations were carried out for each batch to calculate the tensile strength.

Friability of the Liquisolid Tablets

The friability of the compacts was measured using a dual-chamber drum friability tester (Erweka) set at a rotation speed of 25 rpm. Twenty tablets were weighed accurately, placed in the chamber, and rotated for 4 min (100 rotations). At the end of the run, the dusts on the tablet were cleaned carefully, weighed accurately again, and the percent friability (f) was computed from the weight of tablets before and after the test according to the below equation:

$$f = \left[1 - \frac{W}{W_0}\right] \times 100$$

where W_0 and W are the weights of tablets before and after the test, respectively.

Evaluation of the Aging on Hardness and Dissolution Profiles

In order to study the effect of aging on hardness, friability, and dissolution profile of piroxicam liquisolid compacts, six tablets from PLS-1, PLS-3, and PLS-5 series were kept at 25°C/75% relative humidity for 6 months. Then hardness and dissolution rate were measured for these tablets according to the mentioned procedures.

Statistical Analysis

All the data were statistically analyzed by analysis of variance or Tukey's multiple comparison test. Results are quoted as significant where $p < .05$.

RESULTS AND DISCUSSION

To evaluate the drug release from liquisolid compacts, we performed dissolution studies for tablets prepared at low compaction pressure of 20 kg/cm^2. The dissolution profiles of piroxicam from the liquisolid compacts in different media have been shown in Figures 1 and 2. Our previous studies (Javadzadeh et al., 2005, 2007b) have demonstrated that the liquisolid compacts produced higher dissolution rates in comparison with the conventional tablets at both the dissolution media (i.e., pH 1.2 and 6.8). Such enhanced drug dissolution rate may be mainly attributed to the fact that this poorly water-soluble drug is already in solution in PG, while at the same time, it is carried by the powder particles (MCC–silica) of the liquisolid vehicle. Thus, its release is accelerated due to its markedly increased wetability and surface availability to the dissolution medium. According to the classic dissolution equation (Noyes & Whitney, 1897):

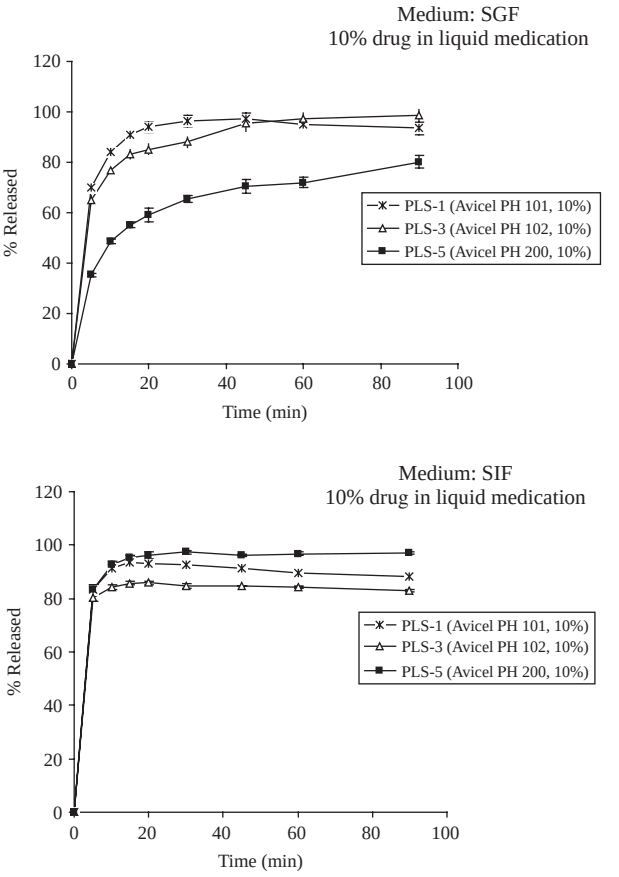

FIGURE 1. Dissolution profile of piroxicam liquisolid tablets containing 10% drug in their liquid medications prepared from different grades of microcrystalline cellulose in two different media: simulated gastric fluid (SGF) and simulated intestinal fluid (SIF) (n = 3).

$$D_R = \frac{D}{h} S (C_s - C)$$

The drug dissolution rate (D_R) of a drug is directly proportional to its concentration gradient ($C_s - C$) in the stagnant diffusion layer and its surface (S) available for dissolution. C_s is the saturation solubility of the drug in the dissolution medium,

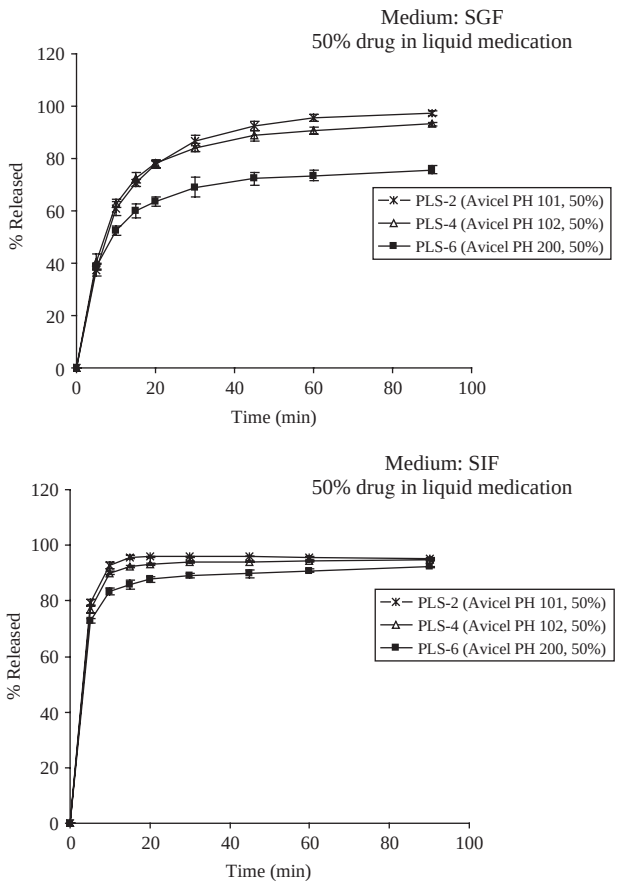

FIGURE 2. Dissolution profile of piroxicam liquisolid tablets containing 50% drug in their liquid medications prepared from different grades of microcrystalline cellulose in two different media: simulated gastric fluid (SGF) and simulated intestinal fluid (SIF) (n = 3).

and thus, it is a constant characteristic property related to the drug and dissolving liquid involved. Because all of dissolution tests for formulations were done at a constant rotational paddle speed (50 rpm) and identical dissolving media, we can assume that the thickness (h) of the stagnant diffusion layer and the diffusion coefficient (D) of the drug molecules remain almost identical. Therefore, the observed higher dissolution rates of piroxicam from liquisolid tablets are due to the significantly increased surface of the molecularly dispersed piroxicam. In addition, the saturation solubility of the drug in the microenvironment (C_s) might be increased in the liquisolid systems due to the presence of PG. So, such an increase in C_s, in a larger drug concentration gradient, increases the dissolution rate of piroxicam according to the Noyes–Whitney equation. Figures 1 and 2 showed that the drug concentration in the liquid medication could be one of the main factors affecting the performance of a liquisolid compact and has considerable effect on the piroxicam dissolution rate. It can be seen that D_R decreased with an increase in the concentration of drug or reduction in the concentration of PG. Such differences in the D_R values of piroxicam from liquisolid compacts may be justified by the differences in the amount of soluble form of the drug or molecular dispersion states of the drug in the formulations (Javadzadeh et al., 2005).

As it is clear from Figures 1 and 2, in SIF medium, there are not any significant differences between dissolution profiles of piroxicam from formulation prepared using different grades of MCC ($f_2 > 50$). This could be attributed to a higher solubility and fast dissolution rate of the drug in this medium (Javadzadeh et al., 2005). In other words, the dissolution profile of drug was not affected by the size and grade of MCC. But in SGF medium, it appeared that dissolution is dependent on the MCC particle size. As it is clear from Figures 1 and 2, tablets containing MCC PH 200 as a carrier material has lower dissolution rate in comparison with others ($f_2 < 50$), but significant differences were not seen between formulations containing MCC PH 101 and 102 ($f_2 > 50$). According to the laser diffraction data shown in Table 2, particle sizes of the carriers (MCC PH 101, 102, and 200) were 74, 108, and 182 μm, respectively. As solution or suspension state of the drug was adsorbed on the surface of the these carriers, and according to the results of their particle sizes, it could be concluded that after disintegration of tablets, increased surface area to the medium fluid is available in PLS-1 to PLS-4 formulations. Then, according to the Noyes–Whitney equation (Noyes & Whitney, 1897), higher dissolution rate is expected from these formulations. Similar dissolution profiles of PLS-1 to PLS-4 formulations may be due to smaller particle sizes of their carriers, which is in agreement with previous study performed by Nazzal, Zaghbol, and Akhan (2002).

The tensile strength results are shown in Figure 3. A linear relationship between tensile strength and compression pressure was observed for all carriers under the condition of the test, except for MCC PH 101, which shows a reduction in tensile strength value after a compression pressure of 80 kg/cm^2. Sun and Grant (2001) showed that the tensile strength of tablets prepared by compacting smaller particles reaches its plateau value at a lower compaction pressure than for larger particles because of the greater compressibility of the smaller particles. As MCC PH 101 has smaller particle size (Table 2), the mentioned hypothesis may describe this event. As it is clear from Figure 2, at the same compression force, PLS-2, PLS-4, and PLS-6 formulations containing 50% drug in their liquid

TABLE 2
Particle Sizes of Different Grades of Microcrystalline Cellulose Obtained Using Laser Diffraction Technique (n = 6)

Carrier	Mean (μm)	*SD*
Microcrystalline cellulose PH 101	47.92	0.92
Microcrystalline cellulose PH 102	108.8	0.30
Microcrystalline cellulose PH 200	182.51	0.26

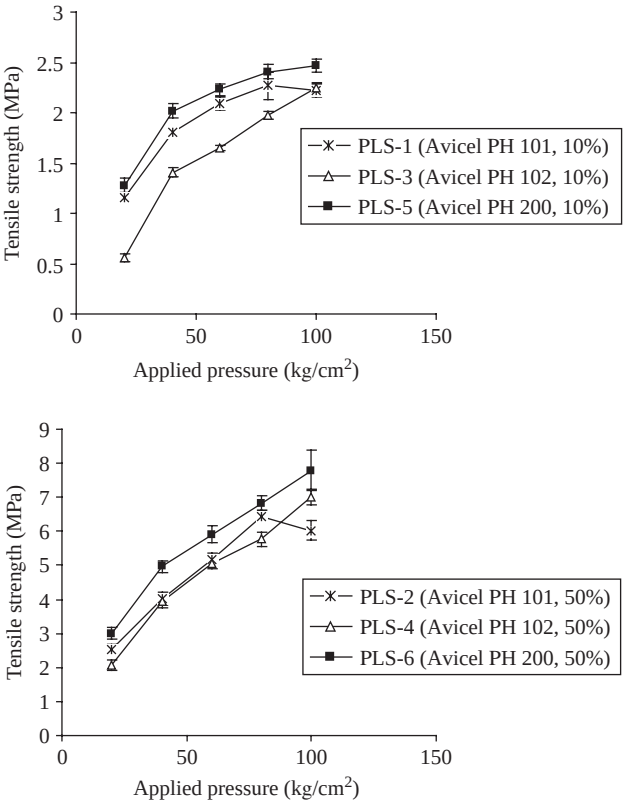

FIGURE 3. Relationship between tensile strength of the liquisolid compacts and compaction pressure for different grades of microcrystalline cellulose (n = 10).

medications produced harder compacts in comparison with their counterparts (PLS-1, PLS-3, and PLS-5 have 10% drug in their liquid medications). Former formulations contained 9% of nonvolatile solvent, whereas this level was 15.46% in last compacts. PG as nonvolatile solvent can act as a binder in low concentration, but it can have a negative effect on mechanical properties of liquisolid compacts in higher concentrations. Excessive nonvolatile solvent produces the capillary state of powder aggregation, and therefore the surface tension effect becomes less significant in bringing the particles together, hence poor bonding. Another possible explanation for a decrease in tensile strength at high level of nonvolatile solvent is the formation of multilayers of PG at the particle surfaces. These layers may disturb or reduce inter-molecular attraction forces and thereby reduce tablet strength (Nokhodchi, Rubinstein, Larhrib, & Gyout, 1995). It means that in higher concentration, nonvolatile solvent could be able to cover contact points between particles and act as a lubricant and does not allow particles to bind each other. These could be main reasons for a reduction in tensile strengths of tablets made from PLS-1, PLS-3, and PLS-5 formulations.

According to Figure 3, MCC PH 200 and 101 produced hard compacts, whereas MCC PH 102 produced softest compacts. Sun and Grant (2001) demonstrated that the tensile strength of tablets increased with decreasing particle size due to a larger number of contact points between smaller particles. Generally, during direct compression, the tensile strength increases by decreasing the size of the MCC due to an increase in binding area available for bonding (McKenna & McCafferty, 1982). Then higher tensile strength of liquisolid tablets containing MCC PH 101 as carrier in comparison with MCC PH 102 may be due to this fact.

One of the limitations of liquisolid technique is the poor flow of the powdered mass that holds the solution or suspension of drug. The flowability results shown in Table 3 for the liquisolid formulations were obtained by measuring hopper flow rate and angle of repose. In repose angle method, values for angles of repose ≤30º usually indicate a free-flowing material and angles ≥40º suggest a poorly flowing material (Banker & Anderson, 1986). Considering high loading of suspension on the surface of carriers, the flow values obtained are reasonably good. According to the Table 3, formulations containing MCC PH 101 as a carrier showed better flow properties in comparison with other formulations ($p < .05$). The flow properties of a material result from many forces. Solid particles attract one another, and forces acting between particles when they are in contact are predominately surface forces. There are many types of forces that can act between solid particles: (a) frictional forces, (b) surface tension forces, (c) mechanical forces caused by interlocking of particles of irregular shape, (d) electrostatic forces, and (e) cohesive or van der Waals forces. All of these forces can affect flow properties of a solid. With fine particles

TABLE 3
Results Showing Flow Properties of Liquisolid Formulations (n = 10)

Formulation	Carrier	Flow Rate (cm^3/s)	Angle of Repose (°)
PLS-1	Microcrystalline cellulose PH 101	6.54 ± 1.29	35.4 ± 0.6
PLS-3	Microcrystalline cellulose PH 102	5.90 ± 0.31	37.67 ± 0.87
PLS-5	Microcrystalline cellulose PH 200	4.47 ± 0.52	38.2 ± 0.49
PLS-2	Microcrystalline cellulose PH 101	5.17 ± 0.64	36.33 ± 0.44
PLS-4	Microcrystalline cellulose PH 102	4.64 ± 0.20	37.19 ± 0.6
PLS-6	Microcrystalline cellulose PH 200	4.36 ± 0.40	39.13 ± 0.54

(≤150 μm), the magnitude of the frictional and van der Waals forces usually predominate. For larger particles (≥150 μm), frictional forces normally predominate over van der Waals forces. Also, as particle size increases, mechanical or physical properties of particles and their packing become important.

Usually bigger particles show better flowability. Flow rate of different grades of pure MCC were 7.32, 8.00, and 14.64 cm^3/s for MCC PH 101, 102, and 200, respectively, indicating that bigger particles show high flow rate which is in agreement with previous studies (Zhang, Law, & Chakrabarti, 2003).

Our liquisolid formulations showed a reduction in flowability in comparison with pure carriers. This could be due to the presence of viscose liquid medication (PG) on the surface of the carriers in liquisolid formulations. Furthermore, the added liquid could increase cohesive and adhesive forces between particles due to the wall effect. Therefore, a reduction in flow rate is expected for liquisolid formulations which is in agreement with other study (Nazzal et al., 2002). As it is clear from Table 3, formulations consisting MCC PH 101 show better flow rate than that of MCC PH 200. As the particle size of MCC PH 200 is large, the carrier particles will have a low surface area which can accommodate a thicker layer of liquid medication distributed around its surface. Therefore, the liquid around these particle surfaces will be thicker than if the particles were small. This will increase the tendency of particles to stick together, hence poor flowablity of powder.

Friability of liquisolid compacts as a function of compaction pressure is shown in Figure 4. The results showed that friability decreased gradually with an increase in compression load. This can be correlated well with the compressibility and tabletability data. The compacts containing 50% drug in their liquid medications showed lower friability in comparison with their counterparts liquisolid compacts having 10% drug in their liquid medication. Latter formulations containing higher level of nonvolatile solvent were able to reflect greater interparticulate bonding between particles, resulting in low friability. But unit dose weights of these compacts are about five-fold heavier than former compacts (582 and 109 mg for 10 and 50%, respectively), and differences in mass of each tablet could be the reason for high friability percentage of heavier liquisolid tablets. In friability tester, tablets fall from about 15 cm in height to the bottom of instrument. It is obvious that those tablets with high mass will collide with the surface of the friability tester with higher forces than those for tablets with low masses. Therefore, formulations with higher masses are expected to show high friability.

According to the Figure 4, compacts containing MCC PH 102 showed the highest friability that could be correlated well with the results obtained for hardness of tablets. In other words, the liquisolid tablets with low hardness showed high percentage of friability.

In order to study the effect of aging on hardness and dissolution profile of liquisolid compacts, six tablets from PLS-1, PLS-3, and PLS-5 series were kept at 25°C/75% relative humidity for 6 months. Then tablets were evaluated from points of leakage of solvent (appearances of tablets were evaluated optically for any leakage of the solvent to the surface of them), hardness, and dissolution profiles. After this period, there was not any solvent leakage in compacts. Hardness results were summarized in Table 4.

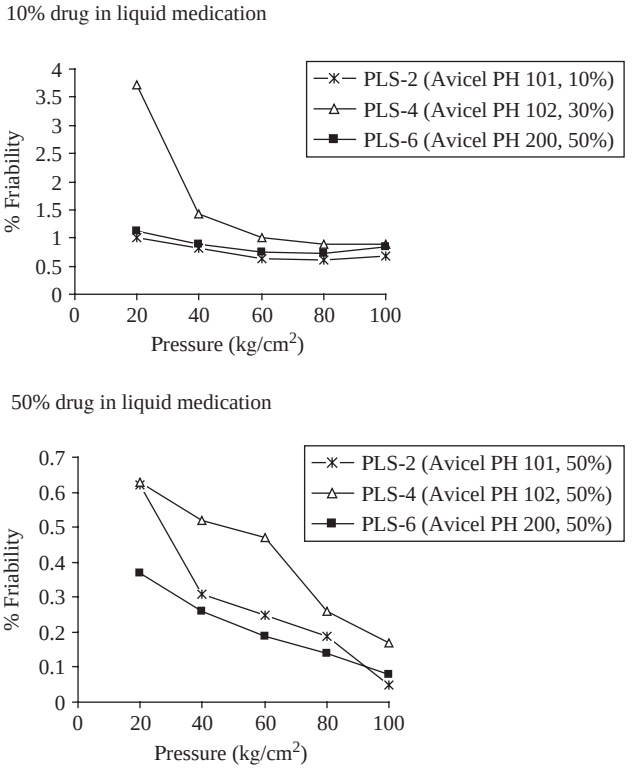

FIGURE 4. Plots of percent friability against compaction pressure of liquisolid formulations prepared using grades of microcrystalline cellulose ($n = 20$).

The results showed that there was no significant difference between the hardness of fresh (69 ± 2.49 N) and aged (62.25 ± 12.09 N) liquisolid tablets ($p > .05$) in PLS-1 series prepared from MCC PH 101, and this was in agreement with our previous studies (Javadzadeh et al., 2007a, 2007c). Whereas

TABLE 4
Hardness Results of Fresh and Aged Liquisolid Compacts ($n = 6$)

Formulation	Hardness (N)	*SD*
PLS-1 (fresh)	69	2.49
PLS-1 (aged)	62.2	12.41
PLS-3 (fresh)	34.5	2.17
PLS-3 (aged)	31	3.22
PLS-5 (fresh)	69.2	4.18
PLS-5 (aged)	56.3	3.36

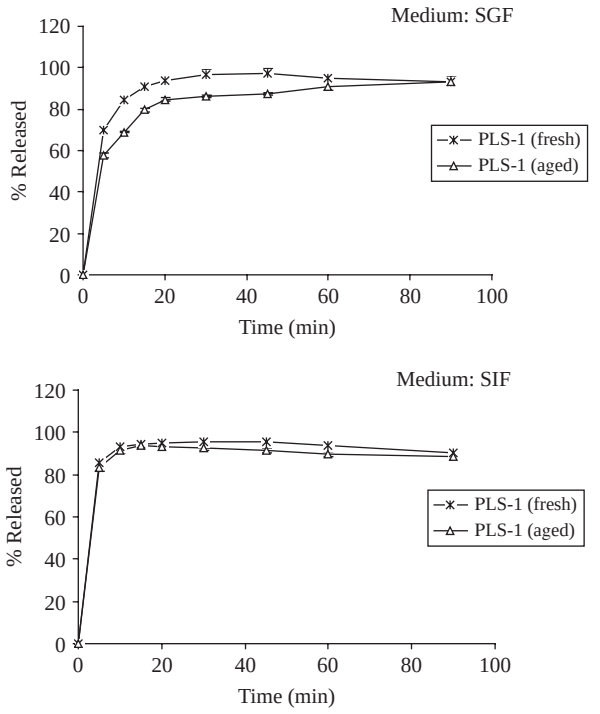

FIGURE 5. Effect of aging on dissolution profile of liquisolid tablets ($n = 3$).

the hardness of liquisolid tablets series PLS-3 and PLS-5 was decreased by aging ($p < .05$).

Figure 5 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 SGF medium in the graph, similarity factor of the two release profiles was higher than 50, indicating acceptably similar profiles. This means that aging has no effect on dissolution behavior of the liquisolid compacts.

CONCLUSION

This study provide evidence that among the evaluated different grades of MCC, compacts containing MCC PH 101 and 102 showed better dissolution profile. Harder compacts were obtained using MCC PH 101 and 200 as carriers. Better flowability was observed in compacts containing MCC PH 101. Also these compacts demonstrated acceptable friability. Aging had no effect on hardness and dissolution profile of liquisolid tablets prepared from MCC PH 101. Then it could be concluded that MCC PH 101 is a suitable carrier for preparing of liquisolid systems in terms of having acceptable flowability, friability, hardness, and dissolution profile.

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