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RESEARCH PAPER

Development and Evaluation of Glyburide Fast Dissolving Tablets Using Solid Dispersion Technique

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ABSTRACT

Glyburide is a poorly water-soluble oral hypoglycemic agent, with problems of variable bioavailability and bio-inequivalence related to its poor water-solubility. This work investigated the possibility of developing glyburide tablets, allowing fast, reproducible, and complete drug dissolution, by using drug solid dispersion in polyethylene glycol. Phase-solubility studies were performed to investigate the drug-carrier interactions in solution, whereas differential scanning calorimetry, X-ray powder diffraction, and infrared spectroscopy were used to characterize the solid state of solid dispersions. The effects of several variables related to both solid dispersion preparation (cofusion or coevaporation technique, drug-to-carrier ratio, polyethylene glycol molecular weight) and tablet production (direct compression or previous wet-granulation, tablet hardness, drug, and solid dispersion particle size) on drug dissolution behavior were investigated. Tablets obtained by direct compression, with a hardness of 7–9 Kp, and containing larger sized solid dispersions (20–35 mesh, i.e., 850–500 μm) of micronized glyburide in polyethylene glycol 6000 prepared by the cofusion method gave the best results, with a 135% increase in drug dissolution efficiency at 60 min in comparison with a reference tablet formulation containing the pure micronized drug. Moreover, the glyburide dissolution profile from the newly developed tablets was clearly better than those from various commercial tablets at the same drug dosage.

Key Words: Glyburide; Polyethylene glycol; Solid dispersions; Tablets; Dissolution rate.

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INTRODUCTION

For most therapeutic agents used to produce systemic effects, the oral route still represents the preferred way of administration owing to its several advantages and high patient compliance compared to alternate routes. However, poorly water-soluble drugs, when administered orally, have been shown to be slowly and unpredictably absorbed since their bioavailability is largely dependent on the dissolution process in the gastrointestinal tract.[1] Glyburide is an oral hypoglycemic agent whose low aqueous solubility gives rise to unsatisfactory dissolution profiles leading to potential problems of poor bioavailability and bioinequivalence of its dosage forms. A multinational postmarket comparative study pointed out the presence of marked differences concerning the in vitro dissolution properties and the in vivo performance of commercial glyburide products.[2] Drug amorphization by spray-drying was experimented with as a method of increasing the drug dissolution rate, but the amorphous form was instable and rapidly deactivated into the crystalline form.[3] Recent works demonstrated the possibility of increasing the dissolution performance of glyburide via the solid dispersion technique.[4–6] However, although the use of solid dispersions in hydrophilic carriers has been largely and successfully applied for improving the solubility of poorly water-soluble drugs,[7–10] the number of marketed products derived from this approach is very limited, mainly because of both manufacturing and scale-up difficulties and physical stability problems.[10,11] It must be taken into account that the dissolution behavior of a drug formulated in tablets as solid dispersion is difficult to predict. In fact, it is influenced by several factors—on the one hand the variables related to the technology employed to prepare the dispersion, the proportion and properties of the carrier used, the solid state and surface properties of solid dispersion particles, etc.,[12,13] and, on the other, the variables related to the tablet manufacturing process, such as the method of production, compression force, disintegrant type, powder particle size, etc.[14–17] Moreover, problems related to difficulty of pulverization and sifting of solid dispersions, poor compressibility, changes of properties with time, the high carrier amount needed to obtain the required increase in the release rate and consequent excessive increase in tablet size can make the development of convenient dosage forms impractical.[10,18]

In the present work we investigated the possibility of developing glyburide tablets, allowing fast, reproducible, and complete drug dissolution, by using drug solid dispersion in a high hydrophilic carrier such as polyethylene glycol.

Phase-solubility studies were performed to investigate the drug-carrier interactions in solution, whereas differential scanning calorimetry, X-ray powder diffraction, and infrared spectroscopy were used to characterize the solid state of the solid dispersions. The effects of varying the solid dispersion preparation method (cofusion or coevaporation), drug-to-carrier ratio, polyethylene glycol molecular weight, as well as the influence of tablet production technique (direct compression or previous wet-granulation), tablet hardness, drug, and solid dispersion particle size on drug dissolution behavior, were studied. The effect of 1 year of aging at room temperature in closed glass containers on drug release rate from the tablets was also evaluated. The drug dissolution performance of the newly developed tablets was compared with that of marketed tablets of glyburide.

MATERIALS AND METHODS

Materials

Micronized (2 μm) and not micronized (10 μm) glyburide (GLY) was obtained from Guidotti Laboratori S.p.A. (Pisa, Italy). Polyethylene glycols (PEG) at different molecular weights (4000, 6000, 20000) were purchased from BASF (Ludwigshafen, Germany). The excipients used were: microcrystalline cellulose (Avicel PH102, F.M.C., Philadelphia, PA); spray-dried lactose monohydrate (Pharmatose® DCL11, DMV Int. Pharma, Veghel, The Netherlands); maize starch and pregelatinized starch (Cerestar, Castelmassa, Italy); colloidal silicon dioxide (Aerosil® 200, Degussa, Marl, Germany); and Mg stearate (Usines Chimiques d'Ivry-La Bataille, Anet Centre, France). The commercial glyburide tablets selected for comparison purposes were: Euglucon® (Boehringer Mannheim), Daonil® (Hoechst), Gliben® (Gentili), and Gliboral® (Guidotti), all coming from the Italian market.

Phase-Solubility Studies

An excess of drug (50 mg) was added to 10 mL of pH 7.4 phosphate buffer solution containing increasing amounts of PEG 4000, 6000, or 20000 (0–10% w/v), in sealed glass containers stirred at 37±0.5°C until equilibrium (2 days). An aliquot was then withdrawn, filtered (pore size 0.45 μm), and spectrophotometrically assayed for drug concentration at 300 nm (Perkin Elmer Lambda2, Perkin Elmer, Norwalk, CT, USA).

Thermal Studies

Differential Scanning Calorimetry (DSC) analysis of pure GLY, PEG (4000, 6000, 20000), and their physical mixtures and solid dispersions at different drug:carrier (w/w) ratios was performed with a Mettler TA4000 apparatus equipped with a DSC 25 cell on 5–10-mg samples (Mettler M3 microbalance, Mettler Toledo S.p.A., Novate Milanese, Milano, Italy) scanned in pierced Al pans at 10°C min^{-1} between 30° and 200°C under static air. The instrument was calibrated using Indium (melting point, 156.61°C; enthalpy of fusion, 28.71 $J.g^{-1}$). Hot Stage Microscopy (HSM) analysis was performed using an Olympus BH-2 microscope fitted with a Mettler FP-82 hot-stage. A 5–10-mg sample was placed on the stage and heated at 5°C min^{-1} in the 30–200°C temperature range.

X-Ray Powder Diffractometry

X-ray powder diffraction (XRPD) patterns of pure GLY, PEG (4000, 6000, 20000), and selected samples of their physical mixtures and solid dispersions at different drug:carrier (w/w) ratios were collected with a Philips PW 1130 powder diffractometer under the following conditions: CuKα radiation, voltage 40 kV, current 30 mA; 10–50 2Θ range; scan rate 1° 2Θ min^{-1}.

Infrared Spectroscopy

Infrared absorption spectra of pure GLY, PEG (4000, 6000, 20000), and selected samples of physical mixtures and solid dispersions at different drug:carrier (w/w) ratios were obtained on KBr disks, under static air, using a Perkin-Elmer Mod. 1600 FTIR spectrophotometer. In order to obtain good quality spectra, a minimum of 15 scans were accumulated.

Preparation of Binary Systems

Drug-PEG physical mixtures (PM) at different drug-to-polymer (w/w) ratios were prepared from the individual components by tumble mixing with a turbula mixer for 10 min at 50 rpm.

Solid dispersions at different drug-to-carrier (w/w) ratios (1:5, 1:10, or 1:20) were prepared according to both the melt and the solvent methods. In the melt method the drug was incorporated, under stirring, into the melted carrier (70±5°C), heating until a homogeneous melt was obtained and then cooling at room temperature (cofused products, COF). In the solvent method drug and carrier were dissolved in chloroform and then the solvent was removed using a rotary evaporator (coevaporated products, COE). In both cases, the resulting solid dispersions were stored for 24 h in a desiccator at room temperature before pulverization and sieving. The 20–35, 35–45, 45–80, and >80-mesh ASTM sieve granulometric fractions were collected (corresponding, respectively, to 850–500 μm, 500–355 μm, 355–180 μm, <180 μm).

Tablet Preparation

Tablets containing 5 mg of glyburide were prepared by direct compression or previous wet-granulation. Excipients were chosen among those present in marketed glyburide tablets, in order to obtain a suitable reference formulation. The composition of the tablets is reported in Table 1.

In the direct compression method, the drug (as such or in solid dispersion or physical mixture with PEG) and all the other components, except Mg stearate, were accurately mixed in a tumbler mixer; the resulting mixture was calibrated through a 35-mesh ASTM screen and, after Mg stearate addition and further mixing, tabletted using a single-punch tablet press (Manesty E2, Manesty, Knowsley, Merseyside, UK).

In the wet-granulation method drug, spray-dried lactose monohydrate and half of microcrystalline cellulose and maize starch were mixed in a zeta arms kneading mixer. Granulation was performed for 10 min using water (20–25 mL) as solvent. Wet granulate was dried at 40°C for 2 hours in a static oven and then calibrated through a 35-mesh ASTM screen. Other excipients, excluding Mg stearate, were added and accurately mixed; finally, after Mg stearate addition and further mixing, tabletting was performed as above. The reason for granulating the drug with only a part of the selected formulation excipients and adding the others afterwards was to obtain a final mixture with good flow properties and to assure a good disintegration of the obtained tablets.

Tablets were evaluated for hardness, weight, friability, and disintegration time according to the United States Pharmacopoeia (USP) 24. The results (reported in Table 1) are the mean of 10 tablets for each formulation.

Tablet samples were stored for 12 months in closed glass bottles at room temperature (25°C) to check their stability.

Dissolution Studies

Dissolution tests were performed with a USP Paddle Apparatus (Sotax AT7, Sotax S.r.L., Basel,

Table 1. Tablet formulations and properties.

	Ingredients (mg)										Properties				
Tablet code	LY	PEG 6000	PEG 4000	PEG 20000	Avicel	DCL11	Maize starch	Preg. starch	Aerosil	Mg stear	Sol. disp. part. size (mesh)	Hardness (Kp)	Disint. time (sec)	Friab. (%)	Weight (mg ± s.d.)
1a	5	–	–	–	52	50	15	10	1	2	–	7–9	60	0	134 (0.75)
1b[a]	5	–	–	–	52	50	15	10	1	2	–	7–9	120	0	134 (0.75)
2a[b]	5	50	–	–	104	100	30	20	2	4	35–45	7–9	60	0	313 (0.64)
2b[c]	5	50	–	–	104	100	30	20	2	4	35–45	7–9	120	0.32	313 (0.84)
2c[d]	5	50	–	–	104	100	30	20	2	4	35–45	7–9	120	0	314 (0.32)
3a[b]	5	25	–	–	52	50	15	10	1	2	35–45	7–9	60	0.60	159 (1.02)
3b[b]	5	100	–	–	208	200	60	40	4	8	35–45	7–9	60	0.30	625 (0.80)
4[b]	5	50	–	–	20	20	10	40	20	20	35–45	11–13	180	0.32	315 (0.64)
5[b]	5	–	50	–	104	100	30	20	2	4	35–45	7–9	60	0.60	313 (0.90)
6[b]	5	–	–	50	104	100	30	20	2	4	35–45	7–9	60	0.60	313 (1.02)
7[b]	5	50	–	–	104	100	30	20	2	4	20–35	7–9	60	0	314 (0.91)
8[b]	5	50	–	–	104	100	30	20	2	4	45–80	7–9	120	0	312 (0.77)
9[b]	5	50	–	–	104	100	30	20	2	4	>80	7–9	360	0.31	315 (0.63)
10[c]	5	50	–	–	104	100	30	20	2	4	20–35	7–9	60	0	314 (1.05)
11[c]	5	50	–	–	104	100	30	20	2	4	45–80	7–9	60	0.32	314 (0.96)
12[c]	5	50	–	–	104	100	30	20	2	4	>80	7–9	780	0	316 (1.03)

[a]Wet-granulation.
[b]Cofused solid disp.
[c]Coevaporated sol. disp.
[d]Physical mixture.

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Switzerland) according to the procedure previously described by Blume, Ali, and Siewert in their multinational postmarket comparative study of commercial glyburide products.[2] Briefly, glyburide tablets were added to 900 mL pH 7.4 phosphate buffer, thermostated at 37±0.5°C, and stirred at 75 rpm; the concentration of dissolved drug was spectrophotometrically monitored at 300 nm (Perkin Elmer Lambda2). Each test was simultaneously performed on six samples (coefficient of variation <1.5%). Dissolution efficiency was calculated from the area under the dissolution curve at time t (measured using the trapezoidal rule) and expressed as a percentage of the area of the rectangle described by 100% dissolution in the same time.[19]

RESULTS AND DISCUSSION

Phase-Solubility Studies

Phase-solubility studies performed in the presence of PEG 4000, 6000, and 20000 showed in all cases a linear increase of glyburide solubility as the polymer concentration increased. The linear A_L type phase-solubility diagrams obtained were indicative of a definite interaction in solution between drug and polymer and of soluble complex formation.[20] No attempt was made to calculate the apparent stability constants, since the exact stoichiometrical relationship of drug/polymer concentration ratio should be known. Based on data from solubility diagrams, for example, the ratio for the number of PEG 6000 molecules required to solubilize one molecule of GLY was 200, indicating the formation of very weak complexes with high dissociation constants.[21] The slopes of the straight line relationships, assumed to be indicative of the relative solubilizing efficiency,[22] were very similar, independent of the PEG molecular weight: about a four-fold increase in drug solubility was obtained in the presence of 10% w/v of each polymer, passing from the initial value of 15 mg/L up to about 55 mg/L. Moreover, no differences were observed in the drug solubility values at equilibrium (after 2 days) between the micronized or not micronized sample. Polyethylene glycol 6000 was then selected for further formulation studies.

Solid-State Studies

The DSC curves of the pure components and of some representative drug-PEG physical mixtures and solid dispersions are shown in Fig. 1. The thermal profiles of the pure products exhibited a single endothermic effect, corresponding to the melting of glyburide (T_{fus} 175°C, ΔH_{fus} 95 $J.g^{-1}$) or polymer (T_{fus} 62.9°C, ΔH_{fus} 180 $J.g^{-1}$), respectively. The DSC curves of binary systems of drug with PEG 6000 showed a progressive broadening and lowering of drug melting temperature and a concomitant reduction of its enthalpy with the increase of carrier content in the mixture, until total disappearance of the drug melting endotherm for PEG content equal or higher than 70%. This finding could be considered indicative of drug amorphization as a consequence of interaction between the components.[23] However, in the present case, the

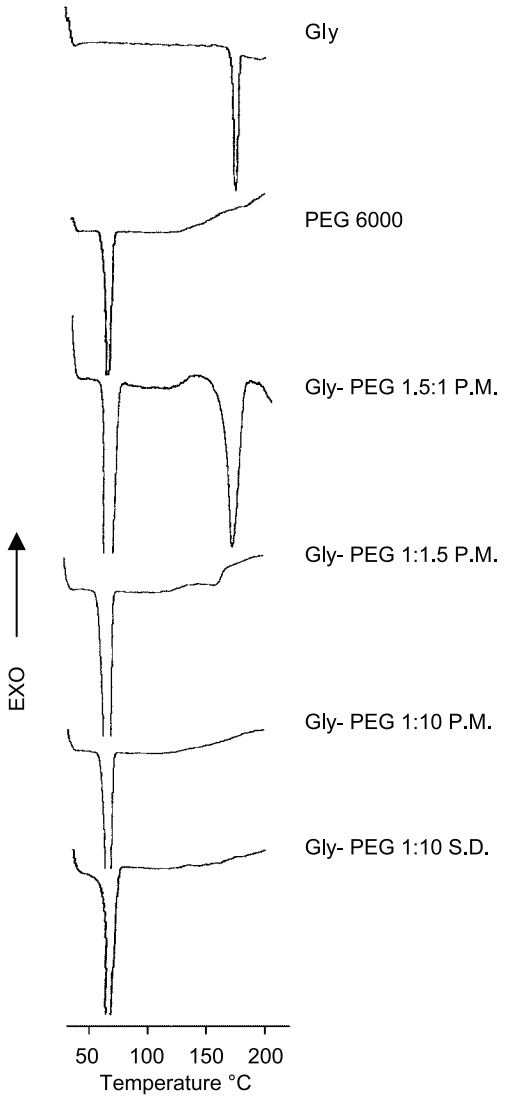

Figure 1. DSC curves of pure glyburide (GLY) and PEG 6000, and some drug-PEG physical mixtures (PM) and solid dispersions (SD) (obtained by cofusion or coevaporation) at different w/w ratios.

particular thermal behavior recorded, can more probably be ascribed, rather than to a loss of drug crystallinity, to the progressive drug dissolution in the melted carrier before achieving its melting temperature, as was previously observed for other drug-PEG combinations.[8,24] This hypothesis was confirmed by HSM analysis, which reliably allowed the detection of fine glyburide crystals after the melting of PEG; subsequently, as the heating program continued, the gradual dissolution of such crystals was observed. Moreover, solid dispersions (either cofused or coevaporated systems) showed the same thermal behavior as the physical mixtures of the same composition, indicating the absence of a well-defined chemical interaction between drug and PEG. The only difference observed during HSM analysis was the reduced GLY particle size obtained in both coevaporated and cofused products (independent of the solid dispersion preparation method) with respect to the corresponding physical mixtures, which allowed a faster dissolution of the drug in the melted carrier.

In agreement with the results of HSM studies, X-ray diffraction analysis showed that the typical drug crystallinity peaks were still detectable (even though of reduced intensity, due to the low drug content) in both the 1:4 (w/w) physical mixture and solid dispersion

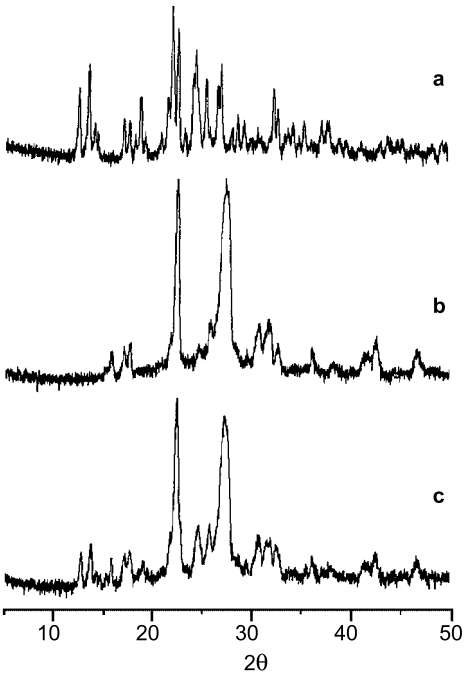

Figure 2. Powder X-ray diffraction patterns of pure glyburide (a) and PEG 6000 (b) and their 1:4 (w/w) cofused product (c).

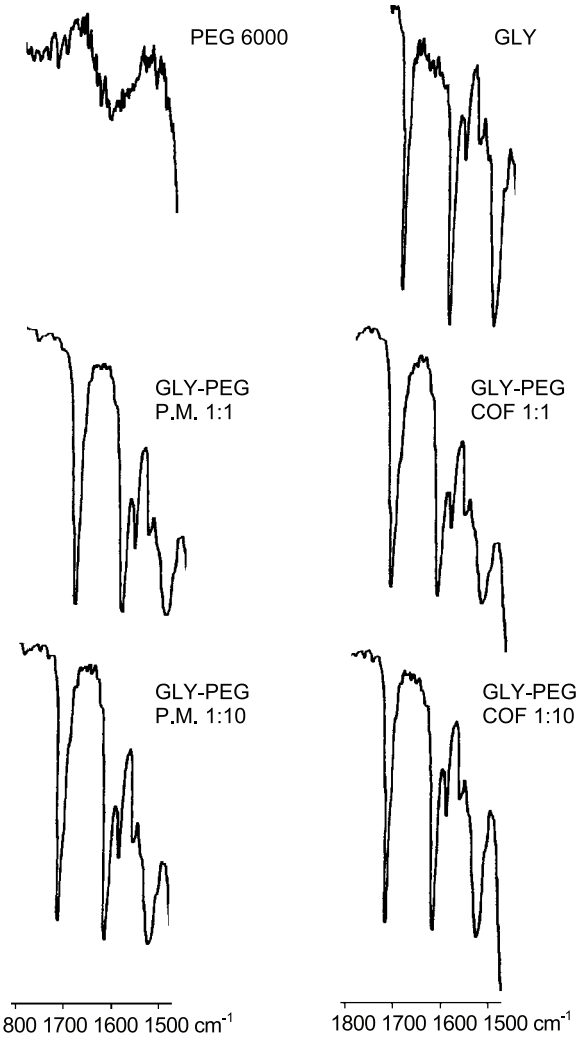

Figure 3. FT-IR spectra of pure glyburide (GLY) and PEG 6000 and their 1:1 and 1:10 (w/w) physical mixtures (PM) and cofused products (COF).

(whether as coevaporated or as cofused product), i.e., in the presence of 80% carrier (Fig. 2). This finding confirmed the presence of crystalline drug in such samples despite the complete disappearance of its melting peak in the corresponding DSC curves. Moreover, the spectra of coevaporated and cofused products were very similar and substantially superimposable on those of the corresponding physical mixtures, excluding possible formation of polymorphs and indicating no significant loss of drug crystallinity as a consequence of solid dispersion preparation, independent of the preparation technique used.

The infrared (IR) spectra of solid dispersions, independent of the preparation method, were identical to those of the corresponding physical mixtures; the

main glyburide absorption bands at 1713, 1615, and 1524 cm^{-1} attributed to the amide carbonyl group, urea carbonyl group, and urea N-H bending, respectively,[25] were unchanged (Fig. 3). These results were consistent with those of the thermal and X-ray diffraction studies and confirmed the absence of chemical interaction between glyburide and polymer.

Dissolution Rate Studies

A reference tablet formulation was prepared (with the same drug dosage and the same excipients present in marketed glyburide tablets) and utilized for comparison purpose with the newly developed tablets, whose composition and properties are collected in Table 1.

The results of dissolution studies for the different examined formulations are shown in Table 2 in terms of percent dissolved at 10 (PD_{10}) and 30 (PD_{30}) min, dissolution efficiency at 60 min (DE), time to dissolve 50% drug ($t_{50\%}$), and relative dissolution rate at 5 min in comparison with the reference formulation (1a, Table 1).

Preliminary studies performed with the reference formulation (1a, Table 1) showed that, as expected, micronized drug ($\approx$2 μm) exhibited better dissolution properties than the unmicronized one ($\approx$10 μm), owing to the greater surface exposed to the dissolution medium. Therefore, micronized glyburide was used in all following studies. Drug dissolution profiles from tablets of the same composition (1a, 1b, Table 1), prepared by direct compression or previous wet-granulation, showed in both cases unsatisfactory dissolution performance (Fig. 4). However, the direct compression technique was about two-fold more effective in terms of DE, and, therefore, this technique was chosen for tablet production in later formulation studies.

With the aim of improving the drug dissolution behavior, tablets containing 1:10 (w/w) drug-to-polymer solid dispersions (obtained by both cofusion and coevaporation methods) or physical mixture were prepared (2a, 2b, 2c, Table 1) and tested for dissolution properties (Fig. 5). As is evident, the presence of PEG as a physical mixture with the drug did not cause any variation of the drug dissolution profile. On the contrary, a clear improvement was observed for tablets containing coevaporated and, even more so, cofused products, where 30% and 115% increases of DE values were obtained with respect to the reference tablet 1a. These results showed the importance of using drug solid dispersions and the influence of their preparation method on their effectiveness. The mechanisms by which drug dissolution enhancement occurs from solid dispersions are numerous and not yet well understood; however, factors such as improved wettability, reduced aggregation and/or agglomeration, increased effective surface area, loss of drug crystallinity, and

Table 2. Percent drug dissolved (PD) at 10 and 30 min, dissolution efficiency (DE), time (min) to dissolve 50% drug ($t_{50\%}$), and relative dissolution rate (RDR) of glyburide from tablets (see Table 1 for tablet compositions).

Tablet	PD_{10}	PD_{30}	D.E.[a]	$t_{50\%}$	RDR[b]
1a	17.1	33.0	28.1	>60	1.0
1b	5.50	17.7	14.5	≫60	0.2
2a	56.9	66.2	60.7	5	5.0
2b	30.6	41.4	36.6	60	1.7
2c	18.9	31.9	28.3	>60	1.1
3a	48.9	62.9	55.5	<10	3.5
3b	59.6	64.1	60.1	<5	6.2
4	7.60	39.5	32.6	<60	0.2
5	55.1	64.4	58.8	<10	4.8
6	57.1	66.5	60.9	5	5.2
7	59.4	73.8	65.9	5	5.2
8	50.7	57.2	51.7	<10	3.2
9	19.2	53.2	42.3	20	0.6
10	29.3	43.2	37.3	30	2.4
11	28.1	36.0	33.8	60	1.7
12	0.0	30.6	25.4	>60	0.0

[a]Calculated from area under the dissolution curve at 60 min (% area of the rectangle described by 100% dissolution in the same time).
[b]Ratio between amount of drug dissolved from each formulation and that dissolved from the reference formulation (1a) at 5 min.

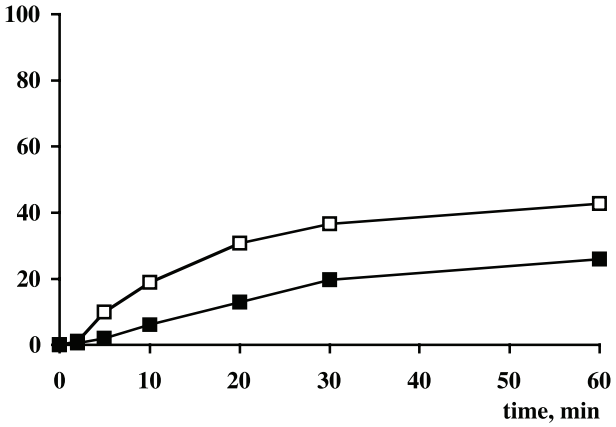

Figure 4. Effect of tablet production technique on glyburide dissolution behavior. Key: (□) direct compression; (■) wet granulation (mean of six simultaneous experiments, coefficient of variation < 1.5%).

solubilization effects associated with the carrier are considered the main ones responsible for their effect.[11]

The influence of varying the drug-to-carrier ratio in the solid dispersion was investigated by preparing tablets containing glyburide-PEG 6000 cofused products at different drug-polymer (w/w) ratios (1:5, 1:10, 1:20) (3a, 2a, 3b, Table 1). As expected, the drug dissolution rate increased with increasing the hydrophilic carrier content. However, this effect was significant only in the first phase of the dissolution process: after 5 min the percent dissolved from 1:20 (w/w) cofused was about 1.8- and 1.2-fold higher than from 1:5 and 1:10 ones. On the contrary, the DE values for 1:10 and 1:20 (w/w) drug-PEG cofused products were very similar (see Table 2). Therefore, the 1:10 (w/w) ratio was considered the optimal one.

Tablets containing 1:10 (w/w) drug-PEG cofused products prepared at two different hardness degrees (7–9 and 11–13 Kp) (2a, 4, Table 1) showed a marked decrease in drug dissolution rate with increasing tablet hardness (see Table 2). It is known that there is often a relationship between the compression force and drug dissolution rate from tablets, but it is ''a priori'' unpredictable and strongly dependent on both the drug and the excipients used in the formulation.[14,15] Evidently, in this case, the negative effect due to the higher mechanical firmness (and therefore lower porosity) that gave rise to longer disintegration time (from 1 to 3 min) and slower drug dissolution rate prevailed.

As for the effect of varying the PEG molecular weight, which is another possible and controversial influencing factor,[9,26,27] no important differences in drug dissolution profiles were observed in the present case when using PEG 4000 or 20000 (5, 6, Table 1) instead of 6000 in 1:10 (w/w) drug-carrier cofused products (see Table 2).

Finally, in order to study the effect of the solid dispersion particle size, tablets were prepared containing 1:10 (w/w) drug-PEG cofused or coevaporated products at four different granulometric sieve fractions (20–35, 35–45, 45–80 and >80 mesh) (7, 2a,8, 9, 10, 2b, 11, 12, Table 1). As shown in Fig. 6 for the series of tablets containing cofused products, it was unexpectedly found

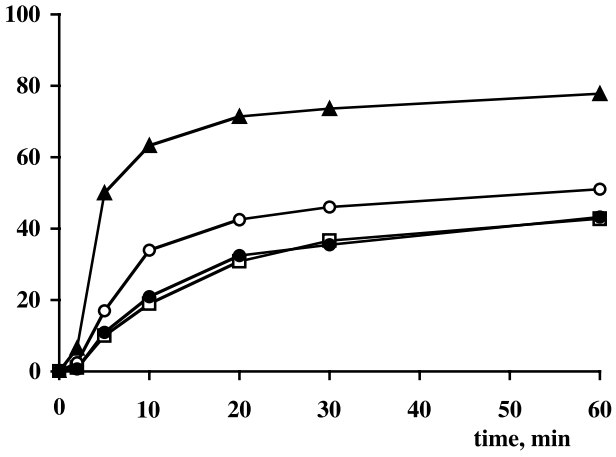

Figure 5. Dissolution curves of glyburide from the reference tablet (1a, Table 1) (□) and from tablets containing 1:10 (w/w) drug-PEG 6000 physical mixture (●), coevaporated (○) or cofused (▲) products (Mean of six simultaneous experiments, coefficient of variation < 1.5%).

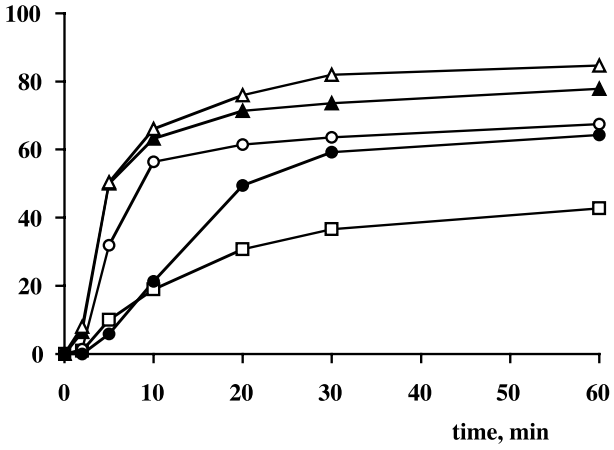

Figure 6. Effect of solid dispersion particle size on glyburide dissolution profile from tablets containing 1:10 (w/w) drug-PEG 6000 cofused products. Key: (□) reference tablet (1a, Table 1); (●) >80 mesh; (○) 45–80 mesh, (▲) 35–45 mesh; (△) 20–35 mesh (mean of six simultaneous experiments, coefficient of variation < 1.5%).

that glyburide dissolution rate increased with increasing the solid dispersion particle size. The same trend was obtained for the series of tablets containing coevaporated products (see Table 2). This result could be related to the soft and waxy nature of the carrier which, during compression, could plasticize, soften, and partially fill the pores within tablets, thus making their wettability properties worse.[18] Probably, the reduction of particle size, by increasing the contact area among particles, increased this natural tendency of PEG. This negative effect was confirmed by the longer disintegration times (6 and 13 min, respectively) shown by tablets containing cofused or coevaporated products at >80 mesh.

The tablet 7 formulation, with a 7–9 Kp hardness and a 20–35 mesh granulometric range of the incorporated 1:10 (w/w) drug-PEG 6000 cofused product, was the best of all the examined formulations. The dissolution profile of glyburide from this tablet was then compared to those from commercial tablets on the Italian market [Gliben (Gentili), Daonil (Hoescht), Euglucon (Boehringer Mannheim), and Gliboral (Guidotti)], all containing 5 mg of drug (Fig. 7). As is evident, none of the examined commercial dosage forms allowed a fast and complete drug dissolution. The drug release profile from the initial reference formulation (1a) was set within the range of dissolution curves shown by marketed products. On the contrary, the performance of the newly developed tablets (7, Table 1) was clearly better, showing increases in percent dissolved drug at 10 min and DE values of 2.4 and 1.7 times, respectively, in comparison with the best commercial product.

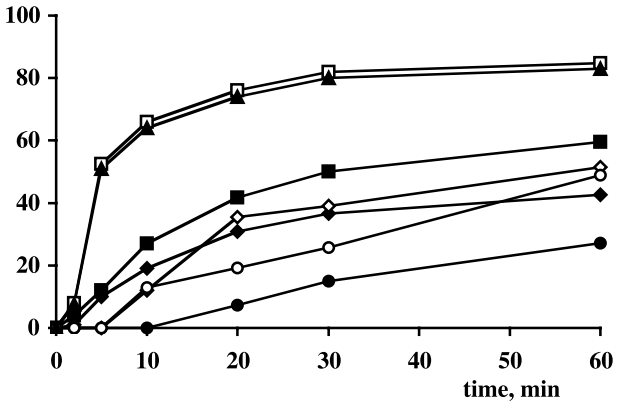

Figure 7. Dissolution curves of glyburide from Gliboral® (■), Gliben® (◇), Daonil® (○), Euglucon® (●) tablets, from the reference tablet (1a, Table 1) (◆) and from tablets with 1:10 (w/w) drug-PEG 6000 cofused products (7, Table 1) freshly prepared (□) or after 1 year of storage in closed glass containers at 25°C (▲), all containing 5 mg of drug (mean of six simultaneous experiments, coefficient of variation <1.5%).

It is well known that drugs formulated in solid dispersions in polymeric hydrophilic matrices can present a decrease in the dissolution properties upon aging.[18,27] Therefore, samples of tablets of the selected formulation, containing drug-PEG 6000 1:10 w/w cofused product, were checked for stability over time. Hardness and disintegration time of these tablets did not change appreciably after 3, 6, and 12 months (data not shown) and the drug dissolution profile after the storage period was practically superimposable on that obtained from fresh tablets (Fig. 7). These results confirmed the actual effectiveness and suitability of the selected tablet formulation.

CONCLUSION

The use of glyburide-PEG solid dispersions allowed preparation of tablets with good technological properties and satisfying and reproducible drug dissolution profiles, which are stable over time. In particular, tablets containing 1:10 (w/w) drug-PEG 6000 cofused product exhibited the best performance, giving a percent of drug dissolved after 10 min 3.5 times higher than that from the reference formulation containing micronized drug; furthermore, it enabled reaching 50% dissolved drug after less than 5 min, whereas more than 60 min were necessary for the reference formulation to reach the same result. Moreover, the drug dissolution rate and the dissolution efficiency from the developed tablets were markedly higher than those obtained from various commercial glyburide tablets, thus confirming the effectiveness of using solid dispersed drug in tablet formulation.

Finally, the importance of controlling and suitably selecting factors such as method of solid dispersion preparation, drug-to-carrier ratio, solid dispersion particle size, as well as tablet production technique and tablet hardness in order to maximize the drug dissolution rate improvement, has been pointed out. In particular, it was shown that the influence of some parameters on drug dissolution behavior, such as the solid dispersion particle size, can be different after solid dispersion incorporation in tablets, as a consequence of effects related to the tablet manufacturing process.

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