

Dissolution rate enhancement of gliclazide by ordered mixing

VIKAS A. SAHARAN^{1*}
PRATIM K. CHOUDHURY²

¹ Institute of Pharmaceutical Sciences
and Drug Research, Seth G.L. Bihani
S.D. College of Technical Education
Sri Ganganagar, Rajasthan, India

² Department of Pharmaceutical
Sciences, M.L. Sukhadia University
Udaipur, Rajasthan, India

The poorly water soluble antidiabetic drug gliclazide was selected to study the effect of excipients on dissolution rate enhancement. Ordered mixtures of micronized gliclazide with lactose, mannitol, sorbitol, maltitol and sodium chloride were prepared by manual shaking of glass vials containing the drug and excipient(s). Different water soluble excipients, addition of surfactant and super-disintegrant, drug concentration and carrier particle size influenced the dissolution rate of the drug. Dissolution rate studies of the prepared ordered mixtures revealed an increase in drug dissolution with all water soluble excipients. The order of dissolution rate improvement for gliclazide was mannitol > lactose > maltitol > sorbitol > sodium chloride. Composite granules of the particle size range 355–710 μm were superior in increasing the drug dissolution rate from ordered mixtures. Reducing the carrier particle size decreased the dissolution rate of the drug as well as the increase in drug concentration. Kinetic modeling of drug release data fitted best the Hixson-Crowell model, which indicates that all the ordered mixture formulations followed the cube root law fairly well.

Keywords: gliclazide, excipient, dissolution, solubility, ordered mixture

Accepted June 7, 2011

Ordered mixtures consist of adhering fine particles of a hydrophobic drug to the surface of larger particles of a water soluble carrier substance (1). Carrier particles dissolve in the presence of water, whereby adherent particles of the pharmaceutical substance disperse throughout the liquid. This eliminates the inherent tendency of hydrophobic drug particles to collect into not-readily dissolvable and dispersible aggregate. Literature reveals that various water soluble excipients such as lactose, mannitol, sorbitol and sodium chloride have been extensively used in preparation of ordered mixtures (1–3).

Gliclazide is 1-(3,3a,4,5,6,6a-hexahydro-1H-cyclopenta[c]pyrrol-2-yl)-3-(4-methylphenyl)sulfonylurea with molecular mass of 323.41 (PubChem Database; <http://pubchem.ncbi.nlm.nih.gov>). Gliclazide is used for the treatment of type II non-insulin dependent

* Correspondence; e-mail: vikas.pharmaceutics@gmail.com

diabetes mellitus. Values for $\log P$ [calculated $\log P$] and $\log P$ [logarithm of partition coefficient between *n*-octanol and water, *i.e.* $\log (c_{\text{octanol}}/c_{\text{water}})$], for gliclazide are 1.09 and 1.97, respectively. $\log P$ classifies the drug as BCS (Biopharmaceutics Classification System) class IV and $\log P$ values as BCS class II (TSRL Inc. BCS Classification System; <http://69.20.123.154/services/bcs/search.cfm>). pK_a of gliclazide is 6.9 and intrinsic solubility ($\log S_o$, expressed as the average log molar concentration ± 1 standard deviation) is -4.07 ± 0.03 (4). The aqueous solubility of gliclazide at 37 °C is $55 \mu\text{g mL}^{-1}$ (5). It was of interest to improve its dissolution rate using the ordered mixing approach. Attempts have already been made to increase the solubility and dissolution rate of gliclazide with anionic and cationic surfactants (5), by preparing solid dispersions (6–8), *in situ* micronisation (9, 10), cogrinding (11) and complexation with cyclodextrins (12).

In the present work, water soluble excipients (lactose, mannitol, maltitol, sorbitol and sodium chloride), superdisintegrant (sodium starch glycolate, SSG) and surfactant (sodium lauryl sulphate, SLS) have been used to improve the dissolution rate of gliclazide in different formulations prepared by ordered mixing.

EXPERIMENTAL

Materials

Gliclazide was obtained as a gift sample from Ranbaxy Ltd., India. Lactose (Lactchem Fine Powder) was received as a gratis sample from Domo Holland, The Netherlands. Mannitol (Pearlitol 200 SD), maltitol (Maltisorb P90), sorbitol (Neosorb P60) and sodium starch glycolate (Glycolys LV) were obtained as gift samples from Roquette, India. Sodium chloride and sodium lauryl sulphate were procured from the Central Drug House, New Delhi, India.

Methods

Average particle size and size distribution of the drug. – Particle size and size distribution of gliclazide were determined by laser light diffraction. The equipment consisted of a Malvern Mastersizer 2000 (Malvern Instruments Ltd, UK) including a Scirocco 2000 module for dry measurement operating at 3×10^5 pascals air pressure for dispersion. It was established that sufficient dispersion of particles, but no milling, occurs at this level of air pressure. Evaluation of data was done by the Malvern software version 5.22 using the Fraunhofer approximation as the evaluation algorithm. Polystyrene latex particles were used as dispersion medium.

Preparation of composite carrier granules. – Lactose or mannitol or maltitol or sorbitol or sodium chloride, and/or sodium starch glycolate, and/or SLS were mixed in a blender (200 g working capacity, customized V blender, Shakti Engineering, Ahmedabad, India) for 30 minutes. Absolute ethanol was added to the powder mixture and the dough was screened through a sieve of aperture size $1000 \mu\text{m}$ to obtain composite carrier granules; this was followed by drying.

Mixing of composite carrier granules and gliclazide. – An ordered mixture of gliclazide (Table I) was prepared by placing the micronized drug between two layers of composite carrier granules in a borosilicate glass vial (10 mL) and shaking it vigorously by hand for 5 min. This method was found to produce consistently good quality ordered mixtures when observed by photomicrographs and concentration uniformity was assessed by homogeneity studies. The procedure had the advantage that it caused no size reduction of the carrier during mixing.

Homogeneity of gliclazide in ordered mixtures. – The accurately weighed ordered mixture (200 mg) was transferred to a volumetric flask (10 mL). The volume was made up to the mark with methanol and sonicated (Ultrasonicator 6.5L200H, PCI Analytics, India) for 30 minutes. Liquid samples were then centrifuged. Supernatant aliquot (500 μ L) was then diluted with distilled water to 10 mL and absorbance was measured at λ_{\max} 226 nm (Pharmaspec UV-1700, Shimadzu, Japan). The concentration was read off from the standard curve.

Table I. Gliclazide ordered mixture formulations, dissolution after 5 and 10 minutes

Formulation	Water soluble excipient	Superdisintegrant (8 %, <i>m/m</i>)	Surfactant (1 %, <i>m/m</i>)	Powder fraction (μ m)	Drug concentration (% , <i>m/m</i>)	Dissolution (%) ^a	
						5 min	10 min
GLF1	Lactose	–	–	125-710	5	73.6 \pm 1.3	85.4 \pm 1.4
GLF2	Lactose	SSG	–	125-710	5	85.1 \pm 0.9	92.5 \pm 1.6
GLF3	Lactose	–	SLS	125-710	5	71.8 \pm 1.1	85.3 \pm 1.5
GLF4	Lactose	SSG	SLS	125-710	5	88.3 \pm 1.3	96.8 \pm 0.9
GLF5	Lactose	SSG	SLS	355-710	5	82.4 \pm 1.1	88.3 \pm 1.4
GLF6	Lactose	SSG	SLS	250-355	5	77.8 \pm 1.3	84.9 \pm 0.9
GLF7	Lactose	SSG	SLS	180-250	5	73.5 \pm 1.5	80.7 \pm 1.1
GLF8	Lactose	SSG	SLS	150-180	5	72.7 \pm 1.5	80.2 \pm 1.1
GLF9	Lactose	SSG	SLS	125-710	1	83.8 \pm 1.4	95.5 \pm 1.2
GLF10	Lactose	SSG	SLS	125-710	7	83.6 \pm 1.8	94.4 \pm 1.4
GLF11	Lactose	SSG	SLS	125-710	10	61.9 \pm 1.0	79.2 \pm 1.0
GMF1	Mannitol	–	–	125-710	5	82.7 \pm 1.3	92.4 \pm 1.4
GMF2	Mannitol	SSG	–	125-710	5	87.4 \pm 1.0	94.4 \pm 1.6
GMF3	Mannitol	–	SLS	125-710	5	83.6 \pm 1.1	94.7 \pm 1.5
GMF4	Mannitol	SSG	SLS	125-710	5	88.8 \pm 1.0	96.0 \pm 0.8
GMF5	Mannitol	SSG	SLS	355-710	5	88.1 \pm 1.3	94.7 \pm 0.9
GMF6	Mannitol	SSG	SLS	250-355	5	80.5 \pm 1.6	88.3 \pm 1.3
GMF7	Mannitol	SSG	SLS	180-250	5	80.3 \pm 1.5	89.2 \pm 1.0
GMF8	Mannitol	SSG	SLS	150-180	5	77.5 \pm 1.0	87.1 \pm 0.8
GMF9	Mannitol	SSG	SLS	125-710	1	86.5 \pm 1.4	91.6 \pm 1.3

GMF10	Mannitol	SSG	SLS	125-710	7	83.9 ± 2.0	94.6 ± 1.5
GMF11	Mannitol	SSG	SLS	125-710	10	60.7 ± 1.0	78.3 ± 1.0
GSF1	Sorbitol	–	–	125-710	5	65.6 ± 1.4	77.5 ± 1.4
GSF2	Sorbitol	SSG	–	125-710	5	72.6 ± 1.4	83.1 ± 1.2
GSF3	Sorbitol	–	SLS	125-710	5	69.1 ± 0.9	80.8 ± 1.6
GSF4	Sorbitol	SSG	SLS	125-710	5	87.4 ± 1.0	94.3 ± 0.8
GSF5	Sorbitol	SSG	SLS	355-710	5	85.6 ± 1.5	92.8 ± 1.0
GSF6	Sorbitol	SSG	SLS	250-355	5	77.7 ± 1.4	87.7 ± 1.1
GSF7	Sorbitol	SSG	SLS	180-250	5	75.6 ± 1.5	84.9 ± 1.0
GSF8	Sorbitol	SSG	SLS	150-180	5	70.9 ± 1.3	79.9 ± 1.0
GSF9	Sorbitol	SSG	SLS	125-710	1	88.4 ± 1.4	98.3 ± 1.2
GSF10	Sorbitol	SSG	SLS	125-710	7	82.9 ± 1.8	94.0 ± 1.4
GSF11	Sorbitol	SSG	SLS	125-710	10	61.2 ± 1.0	78.8 ± 1.0
GMTF1	Maltitol	–	–	125-710	5	68.9 ± 1.3	80.8 ± 1.4
GMTF2	Maltitol	SSG	–	125-710	5	71.5 ± 1.2	85.2 ± 1.4
GMTF3	Maltitol	–	SLS	125-710	5	73.9 ± 1.1	85.8 ± 1.5
GMTF4	Maltitol	SSG	SLS	125-710	5	82.6 ± 1.1	92.7 ± 0.8
GMTF5	Maltitol	SSG	SLS	355-710	5	82.2 ± 1.3	91.4 ± 0.9
GMTF6	Maltitol	SSG	SLS	250-355	5	75.1 ± 1.6	85.0 ± 1.2
GMTF7	Maltitol	SSG	SLS	180-250	5	72.6 ± 1.5	83.5 ± 1.0
GMTF8	Maltitol	SSG	SLS	150-180	5	70.4 ± 0.5	81.9 ± 0.8
GMTF9	Maltitol	SSG	SLS	125-710	1	85.3 ± 1.4	91.0 ± 1.5
GMTF10	Maltitol	SSG	SLS	125-710	7	81.3 ± 4.0	92.5 ± 3.2
GMTF11	Maltitol	SSG	SLS	125-710	10	61.2 ± 1.0	78.5 ± 0.9
GSCF1	NaCl	–	–	125-710	5	29.9 ± 0.8	45.7 ± 0.8
GSCF2	NaCl	SSG	–	125-710	5	38.7 ± 2.1	55.0 ± 1.2
GSCF3	NaCl	–	SLS	125-710	5	32.4 ± 0.6	48.7 ± 0.9
GSCF4	NaCl	SSG	SLS	125-710	5	43.5 ± 1.5	66.7 ± 1.1
GSCF5	NaCl	SSG	SLS	355-710	5	42.6 ± 1.3	60.7 ± 0.9
GSCF6	NaCl	SSG	SLS	250-355	5	38.2 ± 0.9	61.5 ± 0.8
GSCF7	NaCl	SSG	SLS	180-250	5	23.9 ± 1.2	35.8 ± 0.9
GSCF8	NaCl	SSG	SLS	150-180	5	21.2 ± 1.5	30.7 ± 1.1
GSCF9	NaCl	SSG	SLS	125-710	1	48.9 ± 1.4	70.1 ± 1.2
GSCF10	NaCl	SSG	SLS	125-710	7	38.2 ± 1.8	54.0 ± 1.4
GSCF11	NaCl	SSG	SLS	125-710	10	30.0 ± 1.0	40.5 ± 1.0
Gliclazide	–	–	–	–	–	10.9 ± 1.4	12.8 ± 1.6
Gliclazide suspension	–	–	–	–	–	74.4 ± 0.8	76.5 ± 0.9

^a DP – cumulative percent drug release at a particular time, SLS – sodium lauryl sulphate, SSG – sodium starch glycolate

Scanning electron microscopy (SEM). – Scanning electron microscopy was used to determine the surface coverage of carrier particles by gliclazide particles. A perfectly dried sample of powder or ordered mixture was mounted onto the stubs using double-sided adhesive tape. The mounted sample was coated with gold palladium alloy (150–200 10^{-8} m) using a fine coat ion sputter (Fine coat ion sputter, JFC-1100, Jeol, Japan). The samples were subsequently analyzed under the scanning electron microscope (JSM 6100, Jeol, Japan) for external morphology.

Dissolution studies of ordered mixtures. – Dissolution studies of gliclazide from ordered mixture and powdered samples were performed using the USP XXIV (13) paddle method (TDT-08L, Electrolab, India) at a stirring speed of 100 rpm in distilled water. Samples of ordered mixture (200 mg) were sequentially added to 900 mL of distilled water, covered and maintained at 37 ± 0.5 °C. Aliquots of 5 mL were withdrawn and each time replaced with fresh medium. Obtained samples were analyzed for absorbance at 226 nm. The univariate ANOVA was applied to the dissolution data at each time point using DDSolver (China Pharmaceutical University, Nanjing, China), which is an add-in Microsoft Excel added in program for modeling and comparison of dissolution profiles, to determine significant time \times group interaction between formulations.

Dissolution studies of pure gliclazide and its suspension. – Pure gliclazide (aggregate form) and its suspension equivalent to the amount contained in ordered mixtures were also studied for drug release. Gliclazide suspension was prepared in distilled water containing 0.5 % sodium lauryl sulphate and stirred for 5 minutes using a propeller mixer. All the dissolution studies were performed in the same manner as given under dissolution studies of ordered mixtures.

Mathematical modeling of release kinetics. – The *in vitro* drug release data were fitted to various release kinetic models (14), viz. zero-order kinetic model $M_0 - M_t = k_0t$, first-order model $\ln(M_t/M_0) = k_1t$, Higuchi model $M_t = K\sqrt{t}$, Hixson-Crowell cube root model $(W_0)^{1/3} - (W_t)^{1/3} = k_{1/3}t$, where M_0 , M_t and M_∞ correspond to the drug amount taken at zero time, dissolved at a particular time (t) and at infinite (∞) time, respectively. The terms W_0 and W_t refer to the mass of the drug taken initially and at time t , respectively. Various other terms, viz. k_0 , k_1 , $k_{1/3}$ and K refer to the release kinetic constants obtained from the linear curves of zero-order, first-order, Higuchi model and Hixson-Crowell cube root law, respectively.

RESULTS AND DISCUSSION

Drug particle size, homogeneity of ordered mixtures, scanning electron micrographs

Particle size of the drug plays an important role in formulations of poorly soluble drugs. Gliclazide in micronized form is used for the preparation of various ordered mixtures. The surface weighted mean diameter and volume weighted mean diameter of drug particles were 2.446 and 3.686 μm , respectively. The specific surface area of gliclazide drug particles was 2.34 $\text{m}^2 \text{g}^{-1}$. The homogeneity of the prepared ordered mixtures was estimated as RSD (%) of their assay value, which were less than 3.5 for different formu-

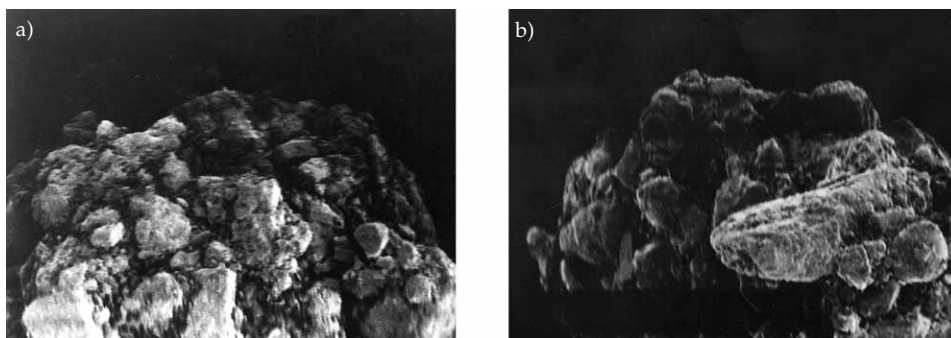


Fig. 1. Photomicrographs showing the surface of ordered mixtures of gliclazide with: (a) lactose, (b) mannitol.

lations (Table II). Scanning electron photomicrographs of gliclazide ordered mixtures with composite granules of lactose and mannitol are presented in Fig. 1. It seems rather difficult to identify drug particles lodged over the surface of composite granules. However, the presence of crevices and surface irregularities in photomicrographs are considered to be the potential sites where micronized gliclazide particles were lodged.

Table II. Homogeneity of gliclazide ordered mixtures

Formulation	Gliclazide (%) ^a
GLF4	101.1 ± 3.0
GMF4	100.8 ± 2.0
GMTF4	101.5 ± 3.0
GSF4	100.0 ± 2.1
GSCF4	101.1 ± 2.3

^a Mean ± SD, *n* = 6.

Variables affecting gliclazide release from ordered mixtures

Effect of formulation variables. – Gliclazide release from pure drug powder was 10.9 and 12.8 % after 5 and 10 minutes, respectively, while the drug release from suspension was 74.4 and 76.5 % after 5 and 10 minutes, respectively. All ordered mixture formulations increased the dissolution rate of gliclazide. The least increase in dissolution rate was observed with NaCl (Table I; GSCF1 to GSCF11). The order of the dissolution rate enhancement was mannitol > lactose > maltitol > sorbitol > sodium chloride (Table I). The dissolution rate of gliclazide from ordered mixtures containing sugar and sugars alcohols (Table I, GLF1-GLF11, GMF1-GMF11, GSF1-GSF11, GMTF1-GMTF11) was superior to gliclazide suspension at initial time points, *i.e.* 5 and 10 minutes.

Addition of superdisintegrant SSG in granules (Table I, GLF1, GLF2, GMF1, GMF2, GSF1, GSF2, GMTF1, GMTF2, GSCF1, GSCF2) further contributed to the increase in gliclazide dissolution from ordered mixtures. Maximum increase of 11.5 and 7.0 % after 5 and 10 min, respectively, was obtained in GLF2 compared to the GLF1. The minimum effect of superdisintegrant addition of only 1.9 % after 10 minutes was observed in GMF2. Superdisintegrant swells at a rapid rate and thereby disintegrates the granule so that carrier particles dissolve at a faster rate, which further increases the ability of the composite granule to release the individual, mutually discrete primary gliclazide particles. Surfactants in the range of 0.5–3 % by mass of the ordered mixture have been suggested to improve the dissolution of hydrophobic drugs (15). In our studies, a very slight increase of 0–5 % in dissolution rate was observed (Table I, GLF1, GLF3, GMF1, GMF3, GSF1, GSF3, GMTF1, GMTF3, GSCF1, GSCF3). When both superdisintegrant and surfactant were added to a composite granule, the synergistic effect of 6–17 % increase of dissolution rate after 10 minutes was observed (Table I, GLF1, GLF4, GMF1, GMF4, GSF1, GSF4, GMTF1, GMTF4, GSCF1, GSCF4). The synergistic increase in dissolution (GMF4 *vs.* GMF1) was minimum with mannitol, 6.2 and 3.6 % after 5 and 10 min, respectively. This was due to the very fast drug release with mannitol in the GMF1 formulation.

Effect of carrier particle size. – The coarsest granule fraction (average particle size 532.5 μm) was most effective in improving the dissolution of gliclazide with all the carriers (Table I, GLF6, GMF6, GSF6, GMTF6, GSCF6). The fine particle size of the composite carrier granule decreased the dissolution rate (Table I) with all the carriers. In sodium chloride ordered mixtures, the effect of particle size on the dissolution rate was comparatively higher (Table I, GSCF5–GSCF8). The fine ordered mixture (150–180 μm , GSCF8) released about 30.7 % drug while the coarser ordered mixture (355–710 μm , GSCF5) released 60.7 % drug in 15 minutes, which was a twofold increase. Coarser particles show a greater tendency to deviate from spherical size and possess cavities, capillaries and crevices, which increases the chances of adhesion of fine drug particles on the surface. This effect may affect the homogeneity of the formulation. Polydisperse carrier particles (125–710 μm , GLF4, GMF4, GSF4, GMTF4, GSCF4), mixtures of all size ranges of particles, were equally effective as the coarsest size composite particles in improving the dissolution rate (Table I). This is presumably due to the effect of fine particles present along with the coarse carrier particles.

Effect of drug concentration. – The ordered mixture with 1 and 5 % (*m/m*) gliclazide gave higher dissolution of gliclazide (Table I, GLF9, GLF4, GMF9, GMF4, GSF9, GSF4, GMTF9, GMTF4, GSCF9, GSCF4) than the formulations containing higher drug concentrations (7 and 10 % *m/m*) (Table I, GLF10, GLF11, GMF10, GMF11, GSF10, GSF11, GMTF10, GMTF11, GSCF10, GSCF11). When different ordered mixture formulations were compared for a change in the drug dissolution rate after 10 minutes with the increase of drug concentration from 1 to 10 % (*m/m*), it was found that the decrease was 16.4, 13.3, 20.1, 12.3 and 29.7 % with lactose, mannitol, sorbitol, maltitol and sodium chloride containing ordered mixtures respectively. At higher drug concentrations, 7 % (*m/m*) or more, uneven coatings and loadings above monolayer coverage of hydrophobic drug particles reduced the drug dissolution rates due to incomplete drug deagglomeration and carrier solubilization. Dissolution rate of ordered mixtures with gliclazide concentration of 1, 5 and 7 % (*m/m*) was faster than gliclazide suspension. Drug concentration of 10 % (*m/m*),

in ordered mixtures of sugar and sugar alcohols, decreased the dissolution rate, which approached the release rate of drug suspension. In case of ordered mixtures of gliclazide and sodium chloride, the dissolution rate of gliclazide was even lower than that of the drug suspension (Table I).

Mathematical modeling of release kinetics. – The regression parameters obtained after fitting various release kinetic models to the *in vitro* dissolution data are listed in Table III. After fitting these models to the dissolution data of formulations, the selection was based on comparison of higher determination coefficients. Drug release kinetics for ordered mixtures fitted best the Hixson-Crowell model. Ordered mixtures disintegrated rapidly, followed by quick dissolution of water soluble excipients (lactose, mannitol, sorbitol, maltitol and sodium chloride), thereby forming a drug suspension consisting of discrete primary drug particles. Wetting of hydrophobic drug particles was further aided by the presence of surfactant, which also reduced aggregation. Surface specific dissolution rate increased as the particle size of hydrophobic drugs decreased, especially for micronized drugs. The dissolution rate enhancement was anticipated due to the rapid decrease in thickness of the stagnant diffusion layer around micronized drug particles. Small diffusion boundary layer thickness resulted in faster transport of dissolved molecules from the particle surface. Therefore, it was anticipated that all the ordered mixture formulations followed the cube root law enunciated by Hixson-Crowell.

Table III. Regression parameters of selected formulations after fitting the drug release data to various release kinetics models

Formulation	R^2			
	Zero-order	First-order	Higuchi	Hixson-Crowell
GLF4	0.519	0.801	0.683	0.956
GMF4	0.608	0.915	0.768	0.972
GSF4	0.404	0.588	0.57	0.968
GMTF4	0.545	0.695	0.714	0.988
GSCF4	0.77	0.987	0.901	0.986

Comparison of dissolution data. – The dissolution rate of gliclazide from pure drug powder was extremely slow. Increase of 3.2 to 7.7 fold in cumulative percent drug release from ordered mixtures after 10 minutes (Table I) was observed. On the basis of cumulative percent dissolution and dissolution efficiency data (Table IV), the order of dissolution rate enhancement with various ordered mixtures was: mannitol (GMF4) > lactose (GLF4) > maltitol (GMTF4) > sorbitol (GSF4) > NaCl (GSCF4). The relative dissolution rate (RDr) of different formulations to gliclazide alone indicated that all sugar and sugar alcohols were equally effective in increasing the dissolution rate up to 30 minutes.

The results of univariate ANOVA (Table IV) showed that the cumulative percent drug dissolved was significantly different at each time point for different formulations, so time \times group interactions were found to be significant in all formulations ($p < 0.05$) com-

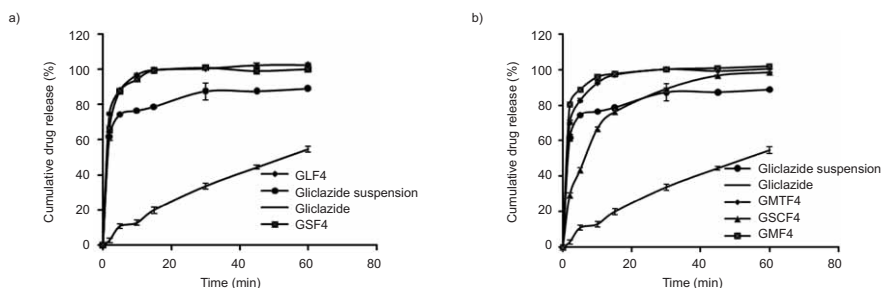


Fig. 2. Dissolution profiles of gliclazide alone and some selected ordered mixture formulations: a) GLF4, GSF4; b) GMF4, GSCF4, GMTF4. Mean \pm SD, $n = 3$.

pared to the gliclazide suspension, *i.e.*, dissolved was the dissolution profiles were not parallel and ordered mixtures had improved the dissolution rate of gliclazide.

When the ordered mixture formulations were compared to the GMF4 formulation ($p < 0.05$) by univariate ANOVA, the percent drug dissolved from GLF4 and GSF4 were found not significantly different after the second minute while that from GMTF4 was not significantly different after ten minutes. It was also observed that the percent drug dissolved for GSCF4 showed lower release than the other formulations. Differences between GSCF4 and the reference GMF4 were also significant ($p < 0.001$) at all time points (Fig. 2 and Table IV) which means that dissolution profiles were not parallel.

Table IV. Dissolution parameters of various ordered mixtures

Formulation	Dissolution parameter					
	$DP_{2 \text{ min}}$ (%)	$DP_{10 \text{ min}}$ (%)	$DP_{60 \text{ min}}$ (%)	$DE_{5 \text{ min}}$ (%)	$DE_{15 \text{ min}}$ (%)	$RDr_{30 \text{ min}}$ (%)
GMF4	80.54 ^b	96.02 ^b	102.02 ^b	85.38	96.73	2.96
GLF4	74.54 ^{a,b}	96.75 ^b	102.54 ^b	81.67	97.49	2.96
GSF4	66 ^{a,b}	94.31 ^b	100.08 ^b	78.8	98.57	2.98
GMTF4	70.15 ^{a,b}	92.69 ^{a,b}	100.75 ^b	78.05	96.03	2.96
GSCF4	29.38 ^{a,b}	66.71 ^{a,b}	98.52 ^{a,b}	37.74	73.6	2.64
Gliclazide suspension	61.69	76.52	88.86	70.49	79.59	2.58

DP – Cumulative percent drug release at a particular time.

DE (%): Dissolution efficiency at a particular time. Dissolution efficiency (%) up to 5 min ($DE_{5 \text{ min}}$) and 15

minutes ($DE_{15 \text{ min}}$) were calculated according to the following equation: $DE\% = \frac{\int_0^t y dt}{y_{100t}} \times 100$

$RDr_{30 \text{ min}}$ – Relative dissolution rate after 30 minutes, *i.e.*, ratio of cumulative percent drug release from formulation at 30 minute to cumulative percent drug released from pure drug.

^a Significant difference in cumulative percent drug release between the formulation and GMF4 formulation by univariate ANOVA, at the same time point; $p < 0.05$.

^b Significant difference in cumulative percent drug release between the formulation and gliclazide suspension by univariate ANOVA, at the same time point, $p < 0.05$.

Higher dissolution rate of gliclazide in ordered mixtures was therefore attributed to improved wetting of the drug owing to attachment of smaller size drug particles over the surface of water soluble excipients, *i.e.*, mannitol, lactose, *etc.* Mannitol and lactose thus physically separated drug particles, thereby preventing aggregation after introduction of ordered mixtures to the dissolution medium. Hydrophilic carriers are known to interact with drug molecules mainly by electrostatic forces and occasionally by other types of forces like hydrogen bonds but this phenomenon is drug- and excipient-specific. Mannitol and lactose thus incite a solubilizing effect. The difference in their ability of dissolution rate enhancement might be due to the difference in the solubilizing effect in the dissolution medium. Hydrophilic carriers attract the dissolution medium and increase its amount in the immediate vicinity of the gliclazide surface. Addition of surfactant, SLS, to the ordered mixture further aided the reduction of surface tension of the dissolution medium, thereby improving wetting and preventing aggregation of drug particles. Superdisintegrant, SSG, was helpful in disintegrating the granules and dispersing discrete drug particles in the entire dissolution medium, so that the system behaved like a well stirred aqueous dispersion.

CONCLUSIONS

Ordered mixtures of acceptable homogeneity can be prepared by simple manual mixing in a vial. Choice of carrier played an important role in improving gliclazide dissolution from prepared ordered mixtures. The order of dissolution rate enhancement of gliclazide from different ordered mixtures was: mannitol > lactose > maltitol > sorbitol > sodium chloride. Coarse granules of 355–710 μm were more effective than fine particles in improving the gliclazide dissolution. Dissolution rate from ordered mixtures of gliclazide concentration 1, 5 and 7 % (*m/m*) were higher than the dissolution from gliclazide suspension. Hixson Crowell model described the drug release from ordered mixtures which was presumably due to surface specific drug dissolution from discrete primary drug particles in the dissolution medium.

Acknowledgements. – Vikas A. Saharan acknowledges the administrative and motivational support of Prof. (Dr.) Vipin Kukkar, Director/Principal, and Mr. Mahesh Kumar Kataria, Assistant Professor, at Seth G.L. Bihani S.D. College of Technical Education, Sri Ganganagar, Rajasthan, India.

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S A Ž E T A K

Povećanje oslobađanja gliklazida iz smjesa dobivenih geometrijskim miješanjem

VIKAS A. SAHARAN i PRATIM K. CHOUDHURY

Teško topljivi antidijabetik gliklazid izabran je za proučavanje utjecaja pomoćnih tvari na povećanje oslobađanja. Homogene smjese mikroniziranog gliklazida s laktozom, manitolom, sorbitolom, maltitolom i natrijevim kloridom pripravljene su ručnim tresenjem staklenih bočica s lijekom i pomoćnom tvari/tvarima. Na oslobađanje lijeka utjecali su vrsta vodotopljivog ekscipijensa, dodatak surfaktanta i superdezintegratora, udio lijeka i veličina čestica punila. Sve vodotopljive pomoćne tvari povećavale su oslobađanje lje-kovite tvari i to sljedećim redom: manitol > laktoza > sorbitol > natrijev klorid. Najbolje oslobađanje lijeka bilo je iz kompozitnih granula veličine 355 do 710 μm. Iz smjesa s manjom veličinom čestica punila i većim udjelom lijeka oslobađanje lijeka bilo

je manje. Kinetičko modeliranje oslobađanja najbolje je odgovaralo Hixson-Crowellovom modelu, što ukazuje na to da sve formulacije prilično dobro slijede zakon trećeg korijena.

Ključne riječi: gliklazid, ekscipijens, oslobađanje, topljivost, smjese dobivene geometrijskim miješanjem

Institute of Pharmaceutical Sciences and Drug Research, Seth G.L. Bihani S.D. College of Technical Education, Sri Ganganagar, Rajasthan, India

Department of Pharmaceutical Sciences, M.L. Sukhadia University, Udaipur, Rajasthan, India