

Development of Discriminative Dissolution Media for Marketed Gliclazide Modified-Release Tablets

e-mail: vishnupriya.mukkala@gmail.com

M. Bala Vishnu Priya* and T. E. G. K. Murthy

Dept. of Pharmaceutics, Bapatla College of Pharmacy, Bapatla, Guntur, Andhra Pradesh, India

ABSTRACT

In vitro release studies were performed for three commercial, modified-release brands of the anti-diabetic drug gliclazide at 30-mg strength. Dissolution media such as 0.1 N HCl (pH 1.2), acetate buffer (pH 4.5), distilled water (pH 7.0), and phosphate buffer (pH 7.4) were evaluated to develop a dissolution method for better evaluation of gliclazide formulations, as there was no official method for gliclazide modified-release tablets. Drug release followed zero-order kinetics in all dissolution media except acetate buffer, where it followed first-order kinetics. The statistically treated data show a significant difference in release rates among the brands. The similarity factor and difference factor values also show the adjustment of differences in release profiles. The drug release studies carried out in 0.1 N HCl show that this medium is the most suitable for providing sink conditions and discriminating conditions.

INTRODUCTION

The release of active pharmaceutical ingredient from drug product, the dissolution of the drug under physiological conditions, and the permeability across the gastrointestinal tract determine drug absorption. Based on this, in vitro dissolution may be vital in assessing in vivo performance. Dissolution testing serves as a tool to distinguish between acceptable and unacceptable products. It is also used to assess the lot-to-lot quality of a drug product and can guide the development of new formulations. In the pharmaceutical industry, regulatory agencies often require discriminating dissolution methods. As product development continues at increasingly faster rates, dissolution method development must be able to keep pace with an increasing number of products. Dissolution scientists face great challenges in developing discriminating dissolution methods.

The development of a dissolution procedure involves selecting the dissolution medium, apparatus, and agitation rate appropriate to the product. The solubility of the active ingredient(s) is one of the key aspects in the screening of possible dissolution media. A slow stirring speed (50 rpm) may represent the most appropriate operating condition that allows maximum discriminatory power. However, use of a low rotation speed could result in a lack of robustness in the data due to poor hydrodynamics in the dissolution vessel and can more reflect system artifacts such as coning rather than true formulation changes. In most cases, a dissolution apparatus tends to become less discriminating when operated at higher stirring speeds (75 or 100 rpm) that result in flatter drug release profiles. In some cases, increased stirring speeds result in a method with a higher discriminating power by reducing the variability of the data and more accurately

reflect true formulation or manufacturing changes or processes. The final dissolution procedure selected should be robust and able to distinguish small changes in the product formulation (1).

Gliclazide is a second-generation hypoglycemic sulfonylurea used in the treatment of non-insulin-dependent diabetes mellitus (NIDDM). Gliclazide is classified as a Class 2 drug (poor solubility and high permeability) according to the Biopharmaceutics Classification System (BCS). The conventional formulation requires twice-daily administration. Once-daily, modified-release gliclazide (30–120 mg) was as effective as twice-daily gliclazide (80–320 mg) in reducing glycosylated hemoglobin (HbA1C) with fewer side effects and less risk of hypoglycemia (2–4).

In the present study, three marketed brands of gliclazide MR tablets (30 mg) were subjected to in vitro drug release studies over the physiological pH range (i.e., 1.2–7.4) with different basket stirring speeds to identify the sink and discriminative conditions.

EXPERIMENTAL

Materials and Methods

The marketed brands of gliclazide of 30-mg strength (Azukon, Nuzide, and Diamicon) were procured from the commercial market. Hydrochloric acid, sodium acetate, glacial acetic acid, potassium dihydrogen phosphate, and sodium hydroxide (Qualigens, Mumbai) were used. Distilled water was used throughout the study. USP dissolution Apparatus 1 (ELICO) and a UV-vis spectrophotometer (Shimadzu) were used.

Saturation Solubility Study

The saturation solubility studies of gliclazide were conducted as per BCS guidelines. A single-dose strength (30 mg) of gliclazide was added to 250 mL of each medium (0.1 N HCl pH 1.2, acetate buffer pH 4.5, distilled water pH 7.0, and phosphate buffer pH 7.4), placed in 500-mL conical flasks,

*Corresponding author.

Table 1. Solubility Studies and Sink Conditions of Gliclazide in Different Fluids

Buffer employed	Solubility (mg/mL)	Sink conditions (C _s /C _d)
0.1 N HCl pH 1.2	1.694	50.82
Acetate buffer pH 4.5	0.0335	1.005
Distilled water pH 7.0	0.3485	10.455
Phosphate buffer pH 7.4	1.8415	55.245

C_s: Saturation solubility of gliclazide in 900 mL of dissolution medium.
C_d: Dose of gliclazide in MR tablet formulation (30 mg).

and agitated continuously at room temperature for 48 h on a mechanical shaker. The saturated solutions were then filtered through Whatman filter paper (no. 41), suitably diluted, and analyzed spectrophotometrically at 235 nm.

In Vitro Drug Release Studies

Three different brands of 30-mg gliclazide MR tablets (i.e., Azukon, Nuzide, and Diamicon designated A, B, and C, respectively) were procured for comparative dissolution studies. The in vitro dissolution studies were performed on dissolution tester TDT-08L (THAI-MAHAL Advance Technology Co., Ltd.) using USP Apparatus 1 with 900 mL of medium at 37 ± 0.5 °C. Stirrer speeds were 50, 75, and 100 ± 2 rpm for phosphate buffer IP (pH 7.4) and 100 ± 2 rpm for 0.1 N HCl IP (pH 1.2), acetate buffer USP (pH 4.5), and distilled water (pH 7.0). These media were selected based on the FDA guidance for industry (5–7). Then at regular intervals (30 min), 5-mL samples were collected, and the same volume was replenished with fresh dissolution medium. The withdrawn samples were filtered through Whatman filter paper (no. 41), suitably diluted, and analyzed spectrophotometrically at a λ max of 235 nm.

Comparison of Dissolution Profiles by Model-Independent Method

A simple model-independent approach using a difference factor (f₁) and a similarity factor (f₂) to compare

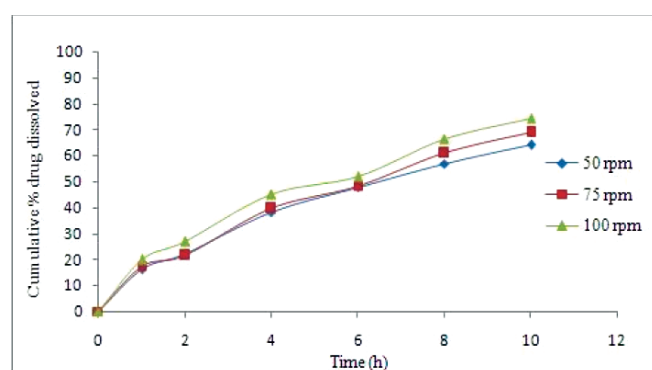


Figure 1. Comparative in vitro drug release profiles of Azukon at various agitation rates in pH 7.4 phosphate buffer.

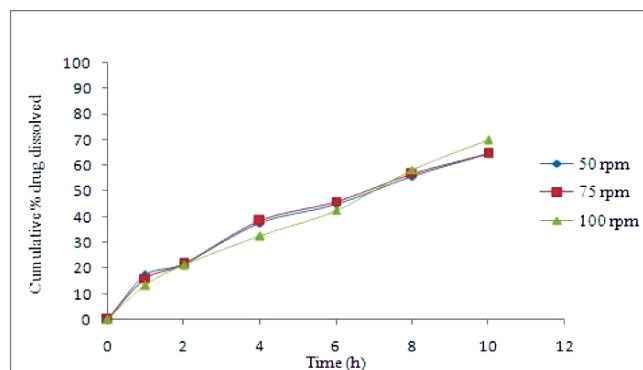


Figure 2. Comparative in vitro drug release profiles of Nuzide at various agitation rates in pH 7.4 phosphate buffer.

dissolution profiles was used (8, 9). The difference factor (f₁) calculates the percent difference between the two curves at each time point and is a measurement of the relative error between the two curves:

$$f_1 = \left\{ \left[\sum_{t=1}^n |R_t - T_t| \right] / \left[\sum_{t=1}^n R_t \right] \right\} \times 100$$

where *n* is the number of time points, *R_t* is the dissolution value of the reference (pre-change) batch at time *t*, and *T_t* is the dissolution value of the test (post-change) batch at time *t*.

The similarity factor is calculated from the dissolution data generated in different dissolution media and at various revolutions. The similarity factor is calculated by following equation:

$$f_2 = 50 \cdot \log \left\{ \left[1 + \frac{1}{n} \sum_{t=1}^n (R_t - T_t)^2 \right]^{-0.5} \times 100 \right\}$$

where *n* is the number of dissolution sampling times, and *R_t* and *T_t* are the individual or mean percent dissolved at each time point for the reference and test dissolution profiles, respectively.

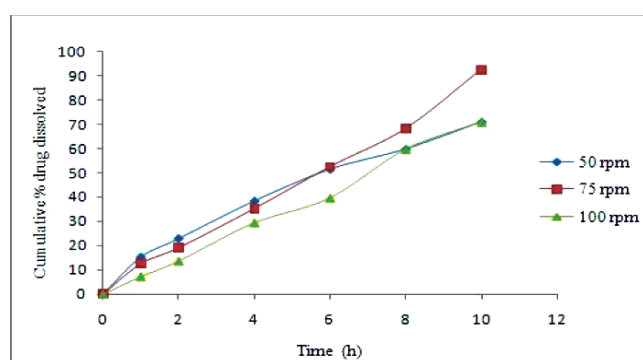


Figure 3. Comparative in vitro drug release profiles of Diamicon at various agitation rates in pH 7.4 phosphate buffer.

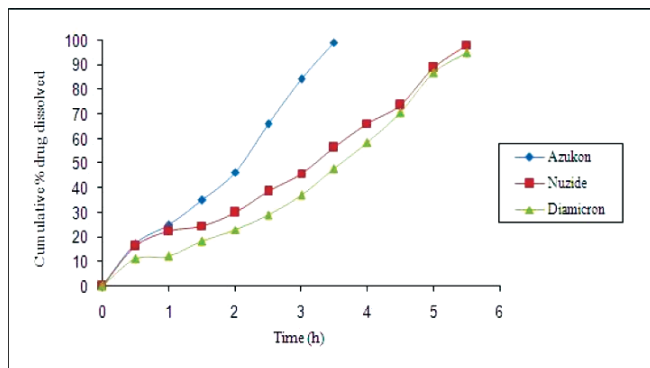


Figure 4. Comparative in vitro drug release profiles of various marketed brands of gliclazide MR tablets in HCl at 100 rpm.

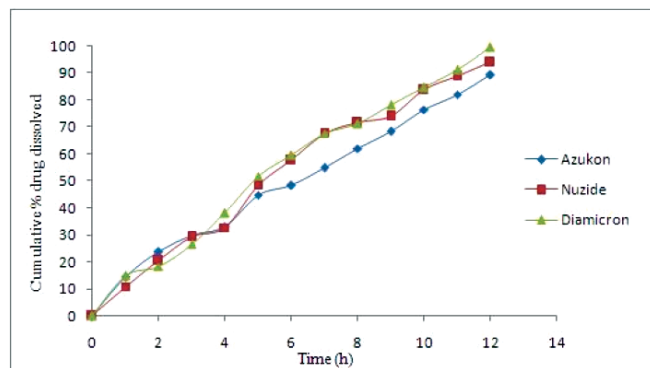


Figure 6. Comparative in vitro drug release profiles of various marketed brands of gliclazide MR tablets in water at 100 rpm.

Statistical Interpretation of Dissolution Data

The dissolution data were interpreted by statistical methods like analysis of variance (ANOVA) and *t*-test (10).

RESULTS AND DISCUSSION

The solubility data of gliclazide are shown in Table 1. The solubility of gliclazide was highest in pH 7.4 phosphate buffer (1.8415 mg/mL). According to the *USP*, the quantity of medium used should not be less than three times that required to form a saturated solution of the drug substance. The ratio of saturation solubility to the dose in 900 mL of dissolution medium (C_s/C_D) ≥ 3 for 0.1 N HCl (pH 1.2), distilled water (pH 7), and phosphate buffer (pH 7.4). Phosphate buffer (pH 7.4) was a more suitable medium for dissolution study, as a higher value was obtained compared with other dissolution media.

In vitro drug release studies of commercial brands of gliclazide MR tablets (i.e., Azukon, Nuzide, and Diamicon) were performed in four different dissolution media (0.1 N HCl, pH 4.5 acetate buffer, pH 7.4 phosphate buffer, and distilled water) at 100 rpm. The influence of stirring speed on drug release rate was studied in 900 mL of phosphate buffer (pH 7.4) employing three different agitation speeds (50, 75, 100 rpm). Comparisons of the dissolution profiles

of the three commercial brands of gliclazide in the four different media at three different agitation speeds are shown in Figures 1–7. The drug release from all formulations followed zero-order kinetics; however, for pH 4.5 acetate buffer medium, the drug release rate followed first-order kinetics. The corresponding correlation coefficient values are shown in Tables 2 and 3. In vitro dissolution parameters $T_{50\%}$ (time for dissolution of 50% of drug), $T_{90\%}$ (time for dissolution of 90% of drug), and release rate (mg/h) were calculated and are shown in Tables 2 and 3. Drug release was dependent on the composition of dissolution medium and agitation rate employed. Based on the drug release rate, the dissolution media can be ranked as 0.1 N HCl (pH 1.2) > distilled water (pH 7.0) > acetate buffer (pH 4.5) > phosphate buffer (pH 7.4). No correlation between the solubility and release rate of the drug in any of the buffers tested was observed. This may be due to the possible excipient effect on the solubility and dissolution rate of gliclazide. These experimental results suggest that 0.1 N HCl is more suitable than pH 7.4 phosphate buffer for dissolution studies of gliclazide modified-release formulations. It may be necessary to conduct further dissolution studies in 0.1 N HCl to confirm the absence of dose dumping. The mechanism of drug

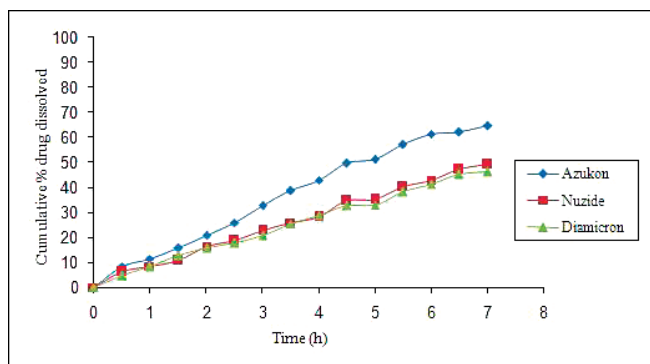


Figure 5. Comparative in vitro drug release profiles of various marketed brands of gliclazide MR tablets in pH 4.5 acetate buffer at 100 rpm.

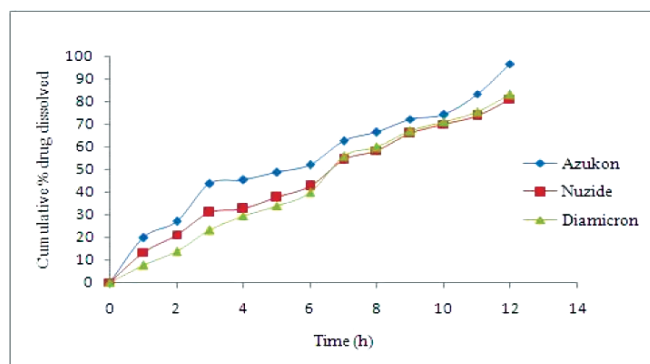


Figure 7. Comparative in vitro drug release profiles of various marketed brands of gliclazide MR tablets in pH 7.4 phosphate buffer at 100 rpm.

Table 2. In Vitro Dissolution Parameters of Gliclazide MR Marketed Tablets at Various Agitation Rates in pH 7.4 Phosphate Buffer

Agitation Rate (rpm)	Brand	Correlation coefficient (R^2)		Release rate (mg/h)	$T_{50\%}$ (h)	$T_{90\%}$ (h)	Parameter for Korsmeyer–Peppas equation (n)	Similarity factor (f_2)			Difference factor (f_1)		
		Zero order	First order					AB	BC	CA	AB	BC	CA
50	Azukon	0.9483	0.6072	2.1825	6.9	12.4	0.6201	55.78	52.00	58.21	7.002	14.03	10.27
	Nuzide	0.9187	0.9875	3.168	6.6	21.8	0.5420						
	Diamicron	0.9771	0.8081	2.3714	6.3	11.4	0.6758						
75	Azukon	0.9688	0.9351	2.2393	6.7	12.1	0.6663	71.58	45.72	49.95	6.42	17.16	14.10
	Nuzide	0.9613	0.8831	2.0085	7.5	13.4	0.6183						
	Diamicron	0.9947	0.8355	2.6148	5.7	10.3	0.8015						
100	Azukon	0.9368	0.6915	2.4598	6.1	11.0	0.5535	50.68	65.70	50.93	15.58	8.27	17.36
	Nuzide	0.9774	0.9662	2.0717	7.2	13.0	0.6953						
	Diamicron	0.9962	0.9445	2.1129	7.1	12.8	0.9413						

A: Azukon; B: Nuzide; C: Diamicron

release from the marketed formulations was non-Fickian diffusion, as the exponential coefficient of Korsmeyer–Peppas equation was between 0.5 and 1.0.

To compare the release profiles of the marketed formulations, difference factors (f_1) and similarity factors (f_2) were calculated (Tables 2 and 3). Two dissolution profiles are considered similar when the f_1 value is closer to zero (i.e., 0–15) and the f_2 value is greater than 50. The f_2 values were greater than 50 at 100 rpm in pH 7.4 phosphate buffer and water (Table 2). More discrimination among the commercial brands was noticed when dissolution studies were conducted in 0.1 N HCl. The release rates observed from different commercial brands of gliclazide were treated statistically, and the data are

depicted in Table 4. The release rate constant observed from different brands in various dissolution media was treated statistically with one-way ANOVA. A significant difference in release rate was noticed from these brands. To detect significant differences between two brands, the data were further analyzed with the Bonferroni multiple comparison test. The statistical results demonstrate that the differences in dissolution rate between each pair of brands are significant.

CONCLUSION

The rate of dissolution was dependent on stirring speed and composition of the dissolution medium. The dissolution medium pH 7.4 phosphate buffer satisfied sink

Table 3. In Vitro Dissolution Parameters of Gliclazide MR Marketed Tablets in Different Dissolution Media at 100 rpm.

Dissolution medium	Brand	Correlation coefficient (R^2)		Release rate (mg/h)	$T_{50\%}$ (h)	$T_{90\%}$ (h)	Parameter for Korsmeyer–Peppas equation (n)	Similarity factor (f_2)			Difference factor (f_1)		
		Zero order	First order					AB	BC	CA	AB	BC	CA
0.1 N HCl pH 1.2	Azukon	0.9913	0.7740	8.0971	1.9	3.3	0.9121	30.55	58.21	25.38	37.98	12.75	52.67
	Nuzide	0.9901	0.8041	5.078	3.0	5.3	0.7760						
	Diamicron	0.9747	0.8274	4.6287	3.2	5.8	0.9713						
Acetate buffer pH 4.5	Azukon	0.9918	0.9933	4.431	4.7	15.6	0.8571	45.86	77.54	43.50	28.88	6.86	32.06
	Nuzide	0.9974	0.9890	2.1831	6.9	12.4	0.8552						
	Diamicron	0.9919	0.9970	2.580	8.1	26.8	0.8667						
Distilled water pH 7.0	Azukon	0.9877	0.8050	2.2979	6.5	11.7	0.7096	61.13	79.51	55.64	13.07	6.24	17.44
	Nuzide	0.9871	0.9157	2.5248	5.9	10.7	0.8423						
	Diamicron	0.9883	0.8268	2.6444	5.7	10.2	0.8287						
Phosphate buffer pH 7.4	Azukon	0.9368	0.6915	2.4598	6.1	11.0	0.5535	52.26	65.70	50.93	15.58	8.27	17.36
	Nuzide	0.9774	0.9662	2.0717	7.2	13.0	0.6953						
	Diamicron	0.9962	0.9445	2.1129	7.1	12.8	0.9413						

Table 4. Statistical Treatment of Release Rates of Gliclazide from Commercial Brands

Dissolution Medium	Release Rate in Different Brands			ANOVA at df (2, 6)		t-Test Summary		
	Azukon (A)	Nuzide (B)	Diamicon (C)	Calculated value	P value	Bonferroni Multiple Comparison Test		
						A & B	B & C	A & C
0.1 N HCl pH 1.2	8.0971	5.078	4.6287	11440	$P < 0.0001$	121.7 ($P < 0.001$)	16.97 ($P < 0.001$)	138.7 ($P < 0.001$)
Acetate buffer pH 4.5	4.431	2.1831	2.580	826.3	$P < 0.0001$	31.90 ($P < 0.001$)	5.880 ($P < 0.01$)	37.78 ($P < 0.001$)
Distilled water pH 7.0	2.2979	2.5248	2.6444	111.7	$P < 0.0001$	9.813 ($P < 0.001$)	4.861 ($P < 0.01$)	14.67 ($P < 0.001$)
Phosphate buffer pH 7.4	2.4598	2.0717	2.1129	227.1	$P < 0.0001$	16.40 ($P < 0.001$)	3.583 ($P < 0.05$)	19.99 ($P < 0.001$)

conditions because the drug is highly soluble in it. More discrimination in dissolution profiles of gliclazide was observed from the dissolution studies conducted in 0.1 N HCl.

REFERENCES

1. Gray, V. A.; Brown, C. K.; Dressman, J. B.; Leeson, J. A New General Information Chapter on Dissolution. *Pharm. Forum* **2001**, 27 (6), 3432–3439.
2. Sweetman, S. C., Ed. *Martindale, the Complete Drug Reference*, 36th ed.; Pharmaceutical Press: London, 2009; p 322.
3. Scherthaner, G.; Grimaldi, A.; Di Mario, U.; Drzewoski, J.; Kempler, P.; Kvapil, M.; Novials, A.; Rottiers, R.; Rutten, G. E.; Shaw, K. M. GUIDE study: double-blind comparison of once-daily gliclazide MR and glimepiride in type 2 diabetic patients. *Eur. J. Clin. Invest.* **2004**, 34 (8), 535–542.
4. Wangnoo, S. K. Treatment of Type 2 diabetes with Gliclazide Modified Release 60 mg in the Primary Care Setting of India. *Int. J. Diabetes Dev. C.* **2005**, 25, 50–54.
5. Wit, J. B. M.; Doshi, H. A. Sustained-release formulation of gliclazide. Eur. Pat. Appl. 2181705, 2010.
6. *Indian Pharmacopoeia*; Government of India, Ministry of Health and Family Welfare, The Indian Pharmacopoeia Commission: Ghaziabad, India, 2007; Vol. 2.
7. *The United States Pharmacopoeia and National Formulary USP 25–NF 20*; The United States Pharmacopoeial Convention, Inc.: Rockville, MD, 2002.
8. *Dissolution Testing of Immediate Release Solid Oral Dosage Forms*; Guidance for Industry; U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), U.S. Government Printing Office: Washington, DC, 1997.
9. Moore, J. W.; Flanner, H. H. Mathematical comparison of curves with an emphasis on in vitro dissolution profiles. *Pharm. Technol.* **1996**, 20 (6), 64–74.
10. Soni, T.; Nagda, C.; Gandhi, T.; Chotai, N. P. Development of Discriminating Method for Dissolution of Aceclofenac Marketed Formulations. *Dissolution Technol.* **2008**, 15 (2), 31–35.