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# UV-spectrophotometric approach in comparative studies of Gliclazide modified-release tablets

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The aim of the present work was to study the applicability of the UV-spectrophotometric method for routine determination of the content and release kinetics of Gliclazide from different pharmaceutical modified-release drug products. *In vitro* release behavior in a phosphate buffer with pH 7.4 was investigated for all tested products and the obtained data were evaluated using various kinetic models - zero and first order, Higuchi and Korsmeyer-Peppas models. The most appropriate model was defined by means of a correlation coefficient.

The results from the drug release study conducted in a phosphate buffer with pH 7.4 evidenced a comparable behavior between the original and the generic drug products. The fact was confirmed by the calculated difference factor - $f_1$. Value below 15 was achieved for all generic products. The release of Gliclazide from the original and from two of the generic products followed first-order kinetics while for the other generic products the release was described by zero-order kinetics. A Non-Fickian, super case II transport mechanism was specific for all tested products.

**Keywords:** Gliclazide, modified-release tablets, drug release, kinetic models

## INTRODUCTION

Gliclazide is an oral hypoglycaemic agent which possesses good tolerability, rarely causing hypoglycaemia [1]. Gliclazide controls not only the glycemic level, but also inhibits key mechanisms in diabetic angiopathy [2].

The slow release of the active substance (Gliclazide) from Diamicron MR modified-release tablets is due to the utilized polymer, namely: hydroxypropyl methylcellulose (hypromellose). Hypromellose is cellulose, in part being O-methylated and O-(2-hydroxypropylated). It is applied in tablet formulations as a binder, a polymer in the film-coating suspension and as a matrix which provides the extended-release of a drug [3].

Mechanisms such as dissolution, diffusion and erosion characterize the drug release from hydrophilic matrices [4]. When the matrix comes into contact with the dissolution medium two fronts are formed around it – penetration front (a front between the non-relaxed polymer and the gel) and dissolution front (a front between the gel and the dissolution medium). Observed at the first front are processes of hydration and swelling, while dissolution of the hydrated matrix takes place at the second front [5]. Factors which affect the release of the drug are the molecular size and drug water solubility, as well as the amount of drug in a tablet [6]. Concentration of the utilized polymer is another significant factor which affects the drug release [7]. Water-soluble drugs are released through the hydrophilic matrices by diffusion, while with drugs of low water-solubility diffusion and erosion take place [8].

The kinetics of drug release could be evaluated by using different kinetic models.

The zero order describes systems where drug release rate is independent of its concentration, while the first order describes concentration-dependent drug release [9]. The Higuchi model describes drug release from a matrix system. The amount of released drug is in proportion to the square root of time [10]. The power law describes drug release from polymeric systems. It is applied in cases when the release mechanism is unknown or when the drug release is carried out by more than one phenomenon. According to the value of the exponent of release *n*, the mechanism of transport could be Fickian or Non-Fickian [11]. When *n* is *0.5* drug release is carried out by diffusion, *n=1* indicates release by swelling, $0.5 < n < 1.0$ is an indicator of both diffusion and swelling. These values are only valid for the release of active substance from a matrix of planar geometry. Values are different for matrices of cylindrical or spherical geometry [12,13].

The aim of the present work was to study the applicability of the UV-spectrophotometric method for routine determination of the content and release kinetics of Gliclazide from different pharmaceutical modified-release drug products.

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## MATERIALS AND METHODS

### *Materials*

Gliclazide, potassium phosphate (Merck, Germany), sodium hydroxide (Merck, Germany) and purified water were used in the preparation of a phosphate buffer with pH 7.4. The original product Diaprel MR 60 mg modified-release tablets, batch № 601062, (Les Laboratoires Servier) and the three generic products (Normodiab MR 60 mg modified-release tablets, batch № 248216, (Actavis Group PTC ehf.), Gliclazide Zentiva 60 mg modified-release tablets, batch № 5151700, (Zentiva), Madras MR 60 mg modified-release tablets, batch № 5151952, (Stada Arzneimittel AG)), each of them containing 60 mg of Gliclazide, were purchased from pharmacies in Sofia, Bulgaria. All products were within their shelf life at the time of the conducted study. The products were denoted with the first letter of their trade name, respectively D, N, G and M.

### *Methods*

*Preparation of standard calibration curve in a phosphate buffer with pH 7.4.* Accurately weighed 6.7; 5.5; 4.4; 3.3 and 1.7 mg of Gliclazide were separately put in volumetric flasks of 100 ml. Added in each flask were 3 ml methanol in order to dissolve the active substance. The volume was adjusted up to the mark with a phosphate buffer with pH 7.4. Pipetted out was 1 ml of each solution which was transferred to a series of 5 ml-volumetric flasks and the volume was topped up with the phosphate buffer of pH 7.4. Concentrations of 0.0134, 0.011, 0.0088, 0.0066, and 0.0034 mg/ml were obtained.

*In vitro drug release studies.* A test was carried out by using the RC-8D Dissolution tester apparatus, Minhua Pharmaceutical Machinery Co., Limited, China. Use was made of an apparatus 2 (paddle method). The dissolution medium used was a phosphate buffer with pH 7.4. The test was conducted at a rotation speed of 75 ± 2 rpm, in a 900 ml volume and set temperature of 37 ± 0.5 ºC. Tablets of each product were investigated in the dissolution apparatus. 10 ml samples were withdrawn every hour and the quantity withdrawn was replaced by 10 ml of dissolution medium. Each sample was filtered through a membrane filter and the amount of released drug was determined using a spectrophotometric method. A Rayleigh-UV-9200, Beijing Beifen-Ruili Analytical Instrument Co., Ltd., China, spectrophotometer was used. The amount of released drug was determined at 226 ± 2 nm wavelength. The percentage of released Gliclazide was calculated by employing a standard calibration curve obtained in advance.

*Determining the drug release kinetics*. Use was made of the following kinetic models:

Zero-order kinetics: $C_t = k_0 t$ (1)

First-order kinetics:

$C_t = C_0 . e^{-k_1 t}$ (2)

Higuchi model [10]: $C_t = k_2 \sqrt{t}$ (3)

Korsmeyer-Peppas model [11]:

$C_t / C_\infty = kt^n$ (4)

where, $C_o$ is the initial amount of drug in the dosage form, $C_t$ is the amount of drug released at time *t*, $c_t / C_\infty$ is the fraction of drug released at time *t*, $k_o$, $k_1$, $k_2$ are release constants, *k* is a constant which incorporates the structural and geometrical characteristics of the dosage form, n is the release exponent.

*Determining the difference factor ($f_1$).* The difference factor ($f_1$) was defined as follows:

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

where *n* is the number of time points, $R_t$ is the average percentage of original drug dissolved at time *t*, $T_t$ is the average percentage of generic drug dissolved at time *t*. The dissolution profiles are similar when the values for $f_1$ are between 0 and 15 [14].

## RESULTS AND DISCUSSION

### *Validation of the UV-spectrophotometric method*

The UV-spectrophotometric method used for assay of Gliclazide was validated in terms of selectivity and linearity.

### *Selectivity*

Selectivity of the method used was proved by analyzing a standard solution, a sample solution and placebo (placebo contained the used excipients without the active substance). The standard and the sample solutions had similar absorbance maxima at 226 nm wavelength. The placebo solution showed zero absorbance at the same wavelength which proved the selectivity of the method in use.

### *Linearity*

The absorbance of each concentration at λ = 226 nm was measured and the obtained results are summarized in table 1.

**Table 1**. Linearity of Gliclazide at 226 nm wavelength

| Concentration, mg/ml | Absorbance, AU |
|---|---|
| 0.0134 | 0.443 |
| 0.011 | 0.376 |
| 0.0088 | 0.302 |
| 0.0066 | 0.246 |
| 0.0034 | 0.146 |

Linear regression analysis was performed. A linearity curve was plotted for absorbance against concentration in a phosphate buffer with pH 7.4 (Fig.1).

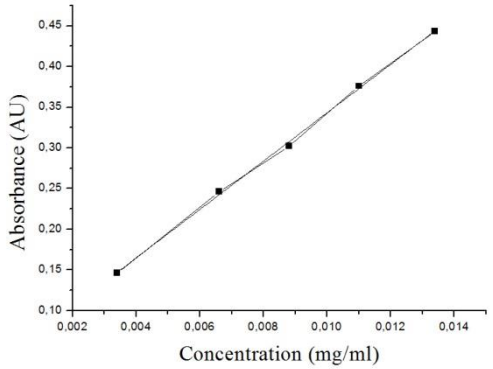


**Fig. 1.** Linear relationship of Gliclazide concentration against the absorbance in a phosphate buffer of pH 7.4.

The regression equation which described the linear relationship was as follows: y = 0.0461+29.688 x. The correlation coefficient ($R^2$) was found to be 0.99946 for concentrations ranging from 0.0034 to 0.0134 mg/ml. The slope is 29.688 and the intercept is 0.0461.

*In vitro drug release studies*

*In vitro* drug release of Gliclazide from the original drug product (Diaprel MR 60 mg modified-release tablets) and three generic products (Normodiab MR 60 mg, Gliclazide Zentiva 60 mg and Madras MR 60 mg modified-release tablets) was investigated in a phosphate buffer with pH 7.4. The obtained results are presented graphically (Fig. 2) as % of drug released against time.

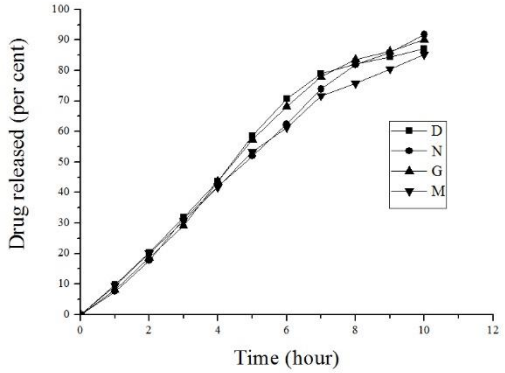


**Fig. 2.** Phosphate buffer with pH 7.4.

The percentage of drug released after 2 h was between 17 and 21 %, after 4 h between 41-44% and after 9 h - more than 80%.

*Determination of drug release kinetics*

Data from the *in vitro* release were fitted into different kinetic models (zero and first order, Higuchi and Korsmeyer-Peppas models) in order to determine the mechanism of drug release. A criterion for determining the most appropriate model was the value of the correlation coefficient (R). The obtained results are presented in table 2.

**Table 2.** Kinetic parameters of drug release - correlation coefficient and release exponent

| Drug product | Phosphate buffer pH 7.4 | | | | |
|---|---|---|---|---|---|
| | Zero order (R) | First order (R) | Higuchi (R) | Korsmeyer-Peppas | |
| | | | | R | n |
| D | 0.979 | 0.990 | 0.967 | 0.991 | 0.987 |
| N | 0.994 | 0.976 | 0.965 | 0.995 | 1.093 |
| G | 0.986 | 0.988 | 0.964 | 0.992 | 1.080 |
| M | 0.990 | 0.993 | 0.973 | 0.995 | 0.969 |

Figs. 3-6 are graphic presentations of the various kinetic models – zero- and first-order, Higuchi and Korsmeyer-Peppas models.

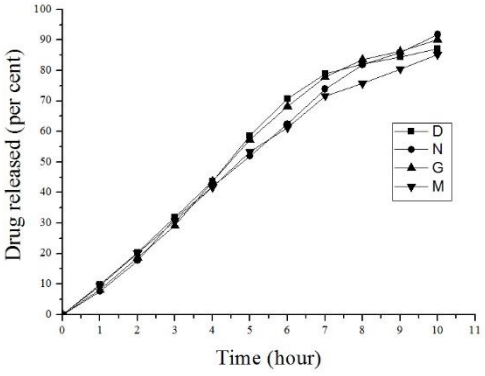


**Fig. 3.** Zero order.

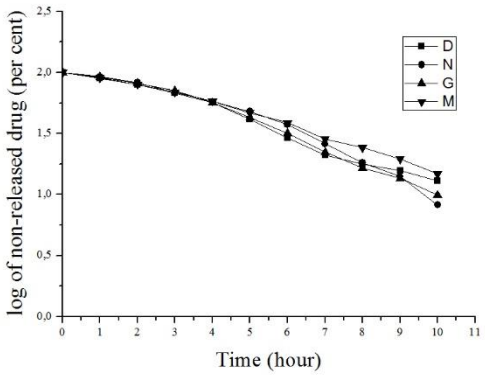


**Fig. 4.** First order.

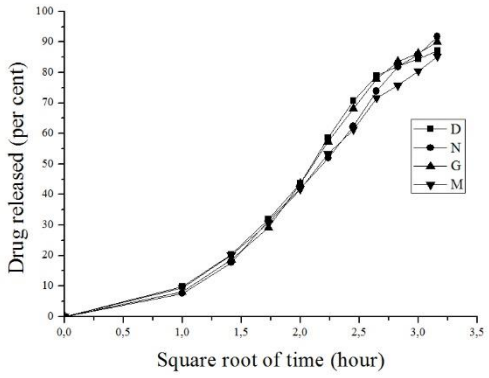


**Fig. 5.** Higuchi model.

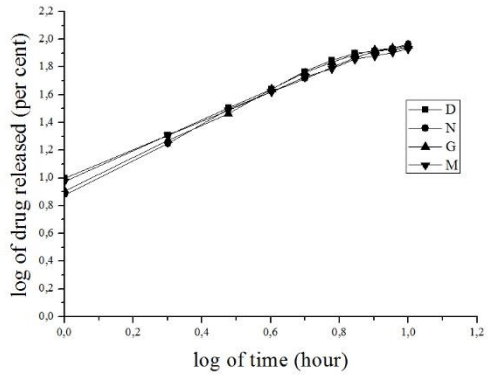


**Fig. 6.** Korsmeyer-Peppas model.

Three of the products (D, G and M) demonstrated the best linearity in the phosphate buffer of pH 7.4 when the data were fitted to first order. The correlation coefficient was 0.990, 0.988 and 0.993, respectively. The values of the correlation coefficient for generic products G and M were at the limits of zero and first order. The difference in the values was ± 0.002 for G and ± 0.003 for M. Generic product N released the active substance according to zero order (R=0.994).

According to Korsmeyer-Peppas model, the value of the release exponent is used to characterize the type of release mechanism. Values above 0.89, valid for polymeric matrices with geometry of a cylinder, define super case II transport mechanism [11]. For all tested drug products the values obtained for the release exponent were above 0.89, namely, from 0.969 to 1.093. Therefore, the Non-Fickian release mechanism was determined and more precisely the release from the tablets followed super case II transport.

*Determining the difference factor ($f_1$)*

The dissolution profiles of the original and the three generic products were compared by calculating the difference factor. The obtained results are presented in table 3.

The values obtained for the difference factor were less than 15. Therefore the requirement for $f_1$ was achieved for all generic products and is a proof that the dissolution profiles of the tested generic products are similar to the dissolution profile of the original drug product.

**Table 3.** Difference factor

| | D, batch № 601062 |
|---|---|
| Generic products | pH 7.4 |
| N, batch № 248216 | 6.04 |
| G, batch № 5151700 | 3.03 |
| M, batch № 5151952 | 6.65 |

## CONCLUSIONS

The dissolution behavior of generic products was comparable to that of the original product in the phosphate buffer with pH 7.4, which was confirmed by the values obtained for the difference factor. The release of Gliclazide from the original and two of the generic products followed first order, while for the other generic product the release was better described by zero-order kinetics. Non – Fickian, super case II transport mechanism was specific for all tested products.

## REFERENCES

1. K.J. Palmer, R.N. Brogden, *Drugs*, **46**, 92 (1993).
2. G. Schernthaner, *Metab., Clin. Exp.*, **52**, 29 (2003).
3. T.L. Rogers, in: Handbook of Pharmaceutical Excipients, R.C. Rowe, P.J. Sheskey, M.E. Quinn (eds.), 6th edn., Pharmaceutical Press, London, 2009, p. 326.
4. M.H. Shoaib, J. Tazeen, H.A. Merchant, R.I. Yousuf, *Pak. J. Pharm. Sci.*, **19**, 119 (2006).
5. K.C.Sung, P.R. Nixon, J.W. Skoug, T. Robert Ju, P. Gao, E.M. Topp, M.V. Patel, *Int. J. Pharm.*, **142**, 53 (1996).
6. K. Tahara, K. Yamamoto, T. Nishihata, *J. Controlled Release*, **35**, 59 (1995).
7. M.U. Ghori, B.R. Conway, *Am. J. Pharmacol. Sci.*, **3**, 103 (2015).
8. M. Rane, J. Parmar, A. Rajabi-Siahboomi, *Pharma Times*, **42**, 41 (2010).
9. S.A. Chime, G.C. Onunkwo, I.I Onyishi, *Res. J. Pharm., Biol. Chem. Sci.*, **4**, 97 (2013).
10. T. Higuchi, J. Pharm. Sci., **52**, 1145 (1963).
11. M. L. Bruschi, in: Strategies to modify the Drug Release from Pharmaceutical Systems, Woodhead Publishing Limited, UK, 2015, p. 63.
12. J. Siepmann, N.A. Peppas, *Adv. Drug Delivery Rev.*, **48**, 139 (2001).
13. P. Costa, J.M.S. Lobo, *Eur. J. Pharm. Sci.*, **13**, 123 (2001).
14. Food and Drug Administration, Center for Drug Evaluation and Research, U.S. Department of Health and Human Services, Guidance for Industry. Dissolution Testing of Immediate Release Solid Oral Dosage Forms, 1997.