
Design and Evaluation of Mucoadhesive Controlled Release Oral Tablets of Glipizide

K. P. R. CHOWDARY* AND G. BALATRIPURA SUNDARI

Department of Pharmaceutical Sciences, Andhra University, Visakhapatnam-530 003.

Matrix tablets of glipizide were formulated using two mucoadhesive polymers namely sodium carboxymethylcellulose and hydroxypropylmethylcellulose and with and without ethylcellulose and the tablets were evaluated. Tablets formulated employing sodium carboxymethylcellulose or hydroxypropylmethylcellulose and with ethylcellulose provided slow release of glipizide over a period of 12 h and were found suitable for maintenance portion of oral controlled release tablets. Glipizide release from these tablets was diffusion controlled and followed zero order kinetics after a lag time of 1 h and up to 90 per cent release. The matrix tablets exhibited good mucoadhesion in the small intestine for 10 h as evaluated by X-ray studies. Two layered tablet formulations, designed with an immediately releasing layer consisting of glipizide and a super disintegrant (Ac-Di-Sol) and a slow releasing matrix consisting of glipizide in sodium carboxymethylcellulose or hydroxypropylmethylcellulose and ethylcellulose as second layer, gave release close to the theoretical sustained release needed for glipizide based on its pharmacokinetic parameters.

Glipizide is widely used in the treatment of type II diabetes. It has a short biological half-life of 3.4 ± 0.7 h¹. Because of its short biological half-life and problems associated with gastrointestinal disturbances, attempts have been made to develop sustained release products with prolonged clinical efficacy, reduced side-effects and dosing frequency. There are a few reports on the formulation of oral controlled release products of glipizide by encapsulation² and marumerizer³ techniques. A few sustained release formulations of glipizide (10 mg) are also available commercially. In the present investigation mucoadhesive oral controlled release tablets of glipizide were formulated employing sodium carboxymethylcellulose (CMC) and hydroxypropylmethylcellulose (HPMC). These materials are reported to have good mucoadhesive properties⁴. Mucoadhesive polymers prolong the residence time of the dosage form in the gastrointestinal tract and hence are more suitable as matrix materials for oral controlled release. The tablets were evaluated for controlled release kinetics, mechanisms and *in vivo* mucoadhesive property. The *in vitro* drug

release rates of the tablets were compared with the theoretical sustained release rate needed for glipizide based on its pharmacokinetics.

MATERIALS AND METHODS

Glipizide was a gift sample from M/s Micro Labs Ltd., Pondichery. Hydroxypropylmethylcellulose (HPMC with a viscosity of 50 cps in 2% by weight aqueous solution at 20^o) and croscarmellose sodium (Ac-Di-Sol) were gift samples from M/s Natco Pharma Pvt. Ltd., Hyderabad. Sodium CMC (with a viscosity of 1500-3000 cps in a 1% w/v aqueous solution at 25^o), ethylcellulose (with an ethoxyl content of 47.5% by weight and viscosity of 22 cps in 5% w/w in 80 : 20 toluene - ethanol solution at 25^o), methanol GR, talc IP and magnesium stearate IP were procured from M/s Loba Chemie, Mumbai.

Preparation of mucoadhesive tablets:

Mucoadhesive matrix tablets each containing 10 mg of glipizide were prepared by conventional wet granulation method employing CMC, HPMC and ethyl cellulose as matrix materials as per the formulae given in Table 1. A blend of all ingredients was granulated with a solvent blend of water

*For correspondence

E-mail: profkprc@rediffmail.com

TABLE 1: FORMULAE OF GLIPIZIDE MUCOADHESIVE TABLETS PREPARED.

Ingredient (mg/tablet)	Formulation					
	F1	F2	F3	F4	F5	F6
Glipizide	10	10	10	10	10	10
Sodium CMC	134		126.5	119	-	-
HPMC	-	134	-	-	126.5	119
Ethylcellulose	-	-	7.5	15	7.5	15
Talc	3	3	3	3	3	3
Magnesium stearate	3	3	3	3	3	3

and alcohol (1:1 v/v). The wet masses were passed through 12 mesh sieve and the resulting granules were dried at 60° for 4 h. The dried granules were passed through 16 mesh. After blending with talc and magnesium stearate in a laboratory cube blender for 5 min, they were compressed into 150 mg tablets to a hardness of 7-8 kg/cm² on a Cadmach single punch tablet machine (M/s Cadmach Machinery Co., Pvt. Ltd. Ahmedabad) using 9 mm flat surface punches. All the prepared tablets were evaluated for hardness, friability and disintegration time. Disintegration times were determined using water, 0.1 N HCl and phosphate buffer of pH 7.4 as the test fluids.

Preparation of two layered tablets:

Oral controlled release tablets each containing 10 mg of glipizide were designed as two layered tablets with an immediately releasing layer consisting of glipizide (3 mg), Ac-Di-Sol (7.0 mg), lactose (10 mg) and PVP (0.01 mg) and a matrix consisting of glipizide (7 mg) in sodium CMC (OCR1) or HPMC (OCR2) with 5% ethylcellulose as second layer.

Estimation of glipizide:

An ultraviolet (UV) spectrophotometric method⁵ based on the measurement of absorbance at 223 nm in phosphate buffer of pH 7.4 was used for the estimation of glipizide. The method obeyed Beer-Lambert's law in the concentration range of 0-20 µg/ml. When a standard drug solution was assayed repeatedly (n=6) the relative error (accuracy) and relative standard deviation (precision) were found to be 0.9 % and 1.2 %, respectively. No interference from the excipients used was observed.

Drug release study:

Release of glipizide from the matrix tablets was studied in phosphate buffer of pH 7.4 (900 ml) as prescribed in the dissolution rate test of glipizide tablets in USP XXIV employing apparatus 2. One tablet containing 10 mg of glipizide, a speed of 50 rpm and a temperature of 37±0.5° were employed in each test. Samples were withdrawn through a filter (0.45 µm) at different time intervals, suitably diluted and assayed for glipizide at 223 nm. Drug release experiments were conducted in triplicate.

In vivo mucoadhesion testing:

The *in vivo* evaluation of the mucoadhesive property of the tablets formulated was performed in human subjects by X-ray studies. The Institutional Ethics Committee has approved the protocols and given permission to conduct the *in vivo* study using healthy human volunteers. Informed consent was taken from all the study participants. For conducting the *in vivo* study, tablets containing barium sulphate (instead of glipizide) were prepared employing CMC and HPMC as matrix materials. These tablets were administered to healthy human subjects along with a glassful of water after overnight fasting. X-ray photographs were taken at different time intervals (0, 2, 4, 6, 8, 10 and 12 h) to observe for the position of the tablets.

RESULTS AND DISCUSSION

The prepared mucoadhesive matrix tablets were found to be non-disintegrating in water, 0.1 N HCl and phosphate buffer of pH 7.4. Hardness of the tablets was in the range 7-8 kg/cm². Percentage weight loss in the friability test was less than 0.2 % in all the batches. The tablets in all the batches contained glipizide within 100±5 % of the labeled content. Overall all the prepared tablet batches were of good quality with regard to hardness, friability and drug content.

Release of glipizide from the tablets was slow and extended over a period of 16 h. The release profiles are shown in Table 2. Glipizide tablets were formulated employing mucoadhesive polymers alone and incorporating ethylcellulose, a water insoluble polymer to evaluate its influence on drug release from the mucoadhesive tablets.

Tablets containing CMC and HPMC alone gave slow release over a period of 10 h. Application of difference factor^{6,7} (f₁) and similarity factor^{6,7} (f₂) to the drug release data indicated that the drug release profiles of tablets containing sodium CMC and HPMC were similar. Incorporation of ethyl cellulose along with the mucoadhesive polymers reduced

TABLE 2: RELEASE PROFILES OF MUCOADHESIVE TABLETS OF GLIPIZIDE.

Formulation	Mean per cent glipizide released at time (h)					
	1.0	2.0	4.0	8.0	10.0	12.0
F1	12.7 (1.7)*	19.3 (1.0)	45.9 (3.9)	88.3 (2.5)	99.2 (1.2)	-
F2	13.9 (0.5)	23.9 (1.0)	46.0 (5.6)	86.8 (2.1)	99.6 (0.8)	-
F3	12.3 (0.30)	14.69 (0.70)	34.9 (0.8)	74.0 (0.10)	90.9 (1.5)	97.3 (0.9)
F4	9.3 (0.30)	13.6 (0.6)	27.5 (0.3)	47.3 (1.1)	58.3 (0.8)	69.7 (0.70)
F5	10.2 (0.30)	14.3 (0.70)	30.8 (0.50)	72.1 (1.00)	86.5 (0.8)	95.2 (1.1)
F6	9.5 (1.5)	12.3 (0.00)	28.5 (1.3)	56.4 (0.3)	70.6 (0.6)	80.2 (0.7)
OCR 1	27.2 (1.9)	33.7 (0.8)	50.65 (0.7)	71.4 (1.4)	81.0 (0.4)	92.2 (0.7)
OCR 2	28.6 (0.40)	34.52 (1.3)	48.8 (0.5)	71.9 (0.8)	80.6 (0.5)	90.2 (0.5)
Theoretical SR release profile needed	30.0	36.0	48.0	72.0	84.0	96.0

F1 to F6 are mucoadhesive matrix tablets prepared; OCR 1 and OCR 2 are two-layered oral controlled release tablets designed. * Figures in parentheses are standard deviation (s.d.) values.

the drug release and the release was spread over a period of 14-16 h. Overall glipizide release from the prepared matrix tablets followed zero order kinetics after a lag time of 1.0 h and up to 90% release ($r > 0.95$). Plots of amount released versus square root of time (fig. 1) were linear suggesting diffusion controlled release of glipizide from the prepared matrix tablets.

X-ray studies showed that matrix tablets of barium sulphate formulated employing sodium CMC and HPMC with 5% ethyl cellulose (similar in composition to formulations F3 and F5) were intact and remained in the small intestinal region even after 10 h of administration (fig. 2) indicating good mucoadhesion of the tablets in this intestinal region from where the glipizide absorbs.

The matrix tablets containing CMC or HPMC and 5% ethylcellulose (F3 and F5) were found suitable for maintenance portion of oral controlled release tablets. As the initial release from these tablets was very low (small burst effect), an immediately releasing loading dose was applied as a layer on the matrix tablets.

The desired sustained release rate (K_0), initial, maintenance, and total doses needed for glipizide SR tablets for b.i.d. administration were calculated based on its pharmacokinetics as suggested by Wagner⁸. An oral controlled release formulation of glipizide should contain a total dose of

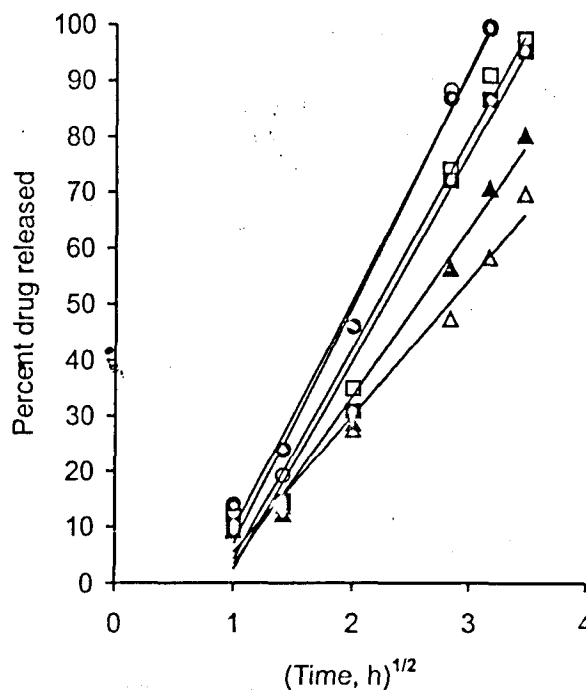


Fig. 1: Release profiles of glipizide mucoadhesive tablets prepared.

Percent drug released Vs square root of time plots of formulation, F1 (-○-), F2 (-●-), F3 (-□-), F4 (-△-), F5 (-■-), F6 (-▲-).

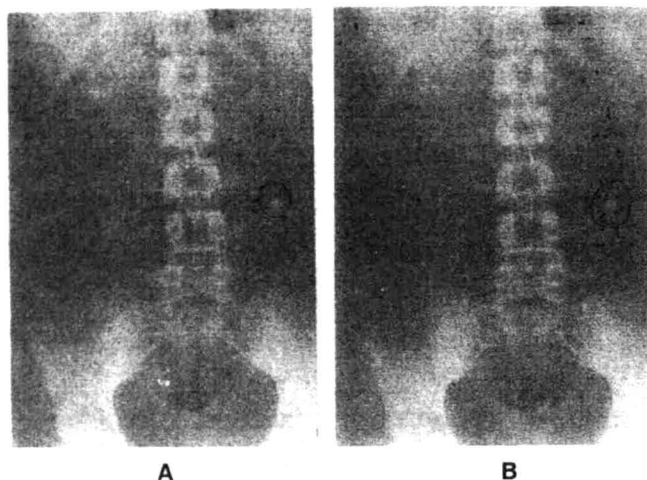


Fig. 2: X-ray photographs.

X-ray photographs taken at 10 h after oral administration of matrix tablets of barium sulphate formulated employing CMC (A) and HPMC (B) similar in composition to formulation F3 and F5 respectively.

10 mg (initial-3.0 mg, maintenance-7.0 mg) and the drug should be released at a rate (K_0) of 0.61 mg/h. Based on these doses and release rate (K_0) an oral controlled release tablet should provide a release of 30% in 1h, 36% in 2 h, 48% in 4 h, 72% in 8 h and 100% in 12 h.

The release profiles of the two layered tablets along with the theoretical SR profile of glipizide are shown in fig. 3. Both the two layered tablet formulations designed (OCR1 and OCR2) gave glipizide release close to the theoretical SR needed for glipizide. The values of f_1 and f_2 were 4.6 and 76.4 for the comparison of release profiles of OCR1 and the theoretical SR needed and 3.2 and 76.4 for the comparison of release profiles of OCR2 and the theoretical SR needed for glipizide respectively. These values indicated that the release profiles of the two layered tablets designed were similar to the theoretical SR needed for glipizide.

Thus slow, controlled and complete release of glipizide over a period of 12 h was obtained from matrix tablets formulated employing CMC or HPMC with 5% ethylcellulose and these matrix tablets were found suitable for maintenance portion of oral controlled release tablets. These tablets exhibited good mucoadhesion in the small intestine for over 10 h. Glipizide release from the mucoadhesive matrix tablets was diffusion controlled and followed zero order kinet-

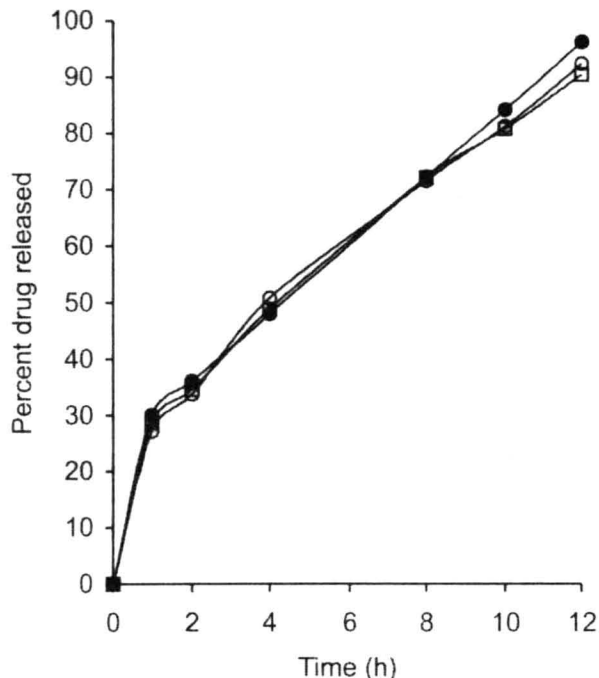


Fig. 3: Release profiles of two-layered oral controlled release tablets of glipizide designed.

Release profiles of OCR 1 (-○-), OCR 2 (-□-) and theoretical SR needed for glipizide (-●-).

ics after a lag time of 1 h and up to 90% release. Good oral controlled release two layered tablets of glipizide could be developed with these mucoadhesive matrix tablets.

REFERENCES

- Insel, P.A., In; Hardman, J.G., Limbard, L.E., Molinoff, P.B., Rudden, R.W. and Gilman, A.G., Eds., Goodman and Gilman's The Pharmacological Basis of Therapeutics, 8th Edn., McGraw-Hill, New York, 1991, 1484.
- Thombre, A.G., Denoto, A.R. and Gibbes, D.C., *J. Control. Release*, 1999, 60, 333.
- Garcia, J., Ghaly, E.S., *Pharm. Develop. Tech.*, 2001, 6, 407.
- Chowdary, K.P.R., Kamalakar Reddy, G. and Bhaskar, P., *Int. J. Pharm. Excip.*, 2001, 2, 33.
- The United States Pharmacopoeia, XXIV, The United States Pharmacopoeial Convention Inc., Rockville, MD, 1999, 773.
- Polli, J.E., Rekhi, G.S., Augsburger, L.L. and Shah, V.P., *J. Pharm. Sci.*, 1997, 86, 690.
- Fassihi, R. and Pillay, V., *J. Control. Release*, 1998, 55, 45.
- Wagner, J.G., In; Biopharmaceutics and Relevant Pharmacokinetics, 1st Edn., Drug Intelligence Publications, Chicago, 1971, 150.