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FORMULATION AND INVITRO EVALUATION OF CONTROLLED RELEASE TABLETS OF GLIPIZIDE

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Abstract:
The aim of the current study was to formulate and evaluate glipizide controlled release tablets by means of different polymers in order to evaluate their effect on drug release profiles during in vitro dissolution studies. Type II diabetes mellitus is usually treated with Glipizide. Glipizide belongs to sulfonylurea group. Gastric disturbance and severe hypoglycemia has been observed after taking glipizide orally. To overcome these problems, controlled release matrices were developed by the direct compression method usingthe polymers like HPMC, Guar Gum, Xanthum Gum and Sodium Alginate. The prepared tablets were evaluated for Diameter, thickness, hardness, friability, weight variation, drug contents of formulations were tested, these properties were within prescribed limits.After the invitrodissolution studies the data was fitted in various kinetic dissolution models, Higuchi model indicated good fit suggesting that diffusion is the predominant mechanism limiting drug release.

Keywords: Glipizide, HPMC, XanthumGgum, Guar Gum, Release Kinetics

INTRODUCTION:

Diabetes mellitus is a metabolic disorder and is responsible for early death and prolonged mortality[1]. Diabetes mellitus is characterized by hyperglycemia and glycosuria that occurs due to absolute or relative deficiency of insulin (Davis and Granner, 1996; Nolte and Karam, 2003)[2]. Glipizide is an antihyperglycemic agent and is ten times more active than tolbutamide in stimulating the insulin secretion from pancreas (Gerich, 1989; Marchetti and Navalesi, 1989)[3]. Control release of glipizide helps in controlling the blood glucose level within normal limits and side effects of glipizide can be minimized. There are few control release formulations of Glipizide commercially available. Glipizide is used for the treatment of type II diabetes (Brogden*et al,* 1979, Dhawan*et al,* 2006)[4]. Glipizide belongs to sulfonylurea group and is taken orally. Glipizide exerts side effects such as severe hypoglycemia and gastric trouble. To overcome these problems, controlled release formulations as sustained release and controlled release tablets are available. Glipizide overdose symptoms include low blood sugar. Better efficacy of Glipizide has been observed in controlled release preparation as compared to immediate release (Berelowitz*et al,* 1994; Blonde *et al,*1996)[5]. Patient compliance is increased by such dosage form design. Side effects are also reduced. The main objectives of the current investigation was to evaluate glipizide controlled release tablets. The tablets wereprepared by direct compression method (Brabander*et al,* 2003)[6]. Using different polymers likeHPMC, Guar Gum, Xanthum Gum, Sodium Alginate.

MATERIALS AND METHODS: Glipizide was procured from Alkem Pvt, Mumbai, HPMC K100M, Guargum, Xanthum Gum, SodiumAlginate, PVP K -30, Iso propyl alcohol, MCC, Magnesium stearate, Talc are of analytical grade.

Ultraviolet Visible (UV-visible) spectroscopy:

Construction of Calibration Curve:

Preparation of Stock Solution:100 mg of Glipizide was taken in a 100 ml volumetric flask. To that 5 ml of methanol was added and shaken well to dissolve the drug. The solution was made up to the mark with 0.1N HCl.From the above solution 1 ml was diluted to 10 ml with, 0.1N HCl solution to give 100 µg /ml concentration. From the above solution 1 ml was diluted to 10 ml with, 0.1N HCl solution to give 10 µg /ml concentration. The prepared solution i.e., 10 µg/ml concentration was scanned for λ_{max} from 200-400 nm in UV/Visible spectrophotometer.

Evaluation of blend:[7]

Angle of Repose: The flow property was determined by measuring the Angle of Repose. In order to determine the flow property, the Angle of Repose was determined. It is the maximum angle that can be

obtained between the free standing surface of a powder heap and the horizontal.

Angle of repose= $\tan^{-1}$ (h/r)

Where, h = height r = radius

Procedure: 20gms of the sample was weighed and passed through the funnel slowly to form a heap. The height of the powder heap formed was measured. The circumference formed was drawn with a pencil on the graph paper. The radius was measured and the angle of repose was determined. This was repeated three times for a sample.

Bulk density: Bulk density is ratio of given mass of powder and its bulk volume. Bulk density was determined by measuring the volume of known mass of powder sample that has been passed through the screen in to graduated cylinder or through volume measuring apparatus in to cup. This was repeated three times for a sample.

Bulk density = M / V_0

Where M= mass of the powder; V_0=bulk volume of the powder.

Tapped density: A known quantity of powder was transferred to a graduated cylinder and volume V_0 was noted. The cylinder fixed to a density determination apparatus, tapped for 200 times then reading was observed. The density is achieved by mechanically tapped by a measuring cylinder containing the powder sample. After observing the initial volume the cylinder is mechanically tapped and volume reading were taken until little further volume changes is observed. This was repeated three times for a sample.

Tap density = M / V_r

Where M = mass of the powder, V_r = final tapping volume of the powder.

Compressibility index and Hausner ratio: The method involves measuring the unsettled apparent volume(V_O), and the final tapped volume, (V_f), of the powder after tapping the material until no further volume changes occur. This was repeated three times for a sample. The compressibility index and the Hausner ratio are calculated as follows:

Compressibility index = $100 \times Vo\text{-}V_f/Vo$

Hausner ratio = Vo/V_f

Where, V_o = apparent volume, V_f= final tapped volume.

Preparation: Drug and polymer (HPMC100 M, guargum, xanthan gum and Sodium alginate) were passed through #22 mesh separately and then transferred into a poly bag and mixed for 3 minutes. PVPK-30 dissolved in isopropyl alcohol was used as a granulating agent.Above drug-polymer blend was granulated using binder solution.Rest of the ingredients were incorporated into the prepared blend. Later Magnesium Stearate and Talc were added and mixed for 2 minutes.Finally prepared blend was compressed by using 5.5 mm round punches.

Evaluation of tablets:prepared tablets were evaluated for the hardness, thickness, weigh variation and content uniformity.

Hardness: Tablet requires a certain amount of strength or hardness and resistance to friability to withstand mechanical shakes of handling in manufacture, packaging and shipping. Hardness generally measures the tablet crushing strength. For each formulation, the hardness of six tablets was measured using the Monsanto hardness tester and mean value and standard deviation was calculated. Generally 4-6kg/$cm^2$is the optimum hardness**.**

Weight variation test: This is an in process quality control test to ensure that the manufacturers control the variation in the weight of the compressed tablets, different pharmacopoeia specify these weight variation tests.. These tests are primarily based on the comparison of the weight of the individual tablets (xi) of a sample of tablets with an upper and lower percentage limit of the observed sample average (x-mean). The USP has provided limits for the average weight of uncoated compressed tablets. These are applicable when the tablet contains 50mg or more of the drug substance or when the latter comprises 50% or more, by weight of the dosage form.

Method: Twenty tablets were weighed individually and the average weight was calculated. The individual tablet weights are then compared to the average weight. Not more than two tablets should differ in their average weight by more than percentages stated in USP. No tablet must differ by more than double the relevant percentage.

Content Uniformity: The drug content of the matrix tablets was determined by standards and it meets the requirements if the amount of the active ingredient in

each of 10 tested tablets lies within the range of 90% to 110% of the standard amount.

Method: Ten tablets were weighed and taken into a mortar and crushed into fine powder. An accurately weighed portion of the powder equivalent to about 10mg of Glipizide was transferred to 100ml volumetric flask containing 70ml of 6.8 pH phosphate buffer. It was shaken by mechanical means for 1hr then it was filtered through Watsmann filter paper (no.1) and diluted to 100ml with 6.8 pH phosphate buffer. From this resulted solution 1ml was taken, diluted to 50ml with 6.8 pH phosphate buffer and absorbance was measured against blank at 229 nm.

Friability: Friction and shock are the forces that most often cause tablets to chip, cap or break. The friability test is closely related to tablet hardness and designed to evaluate the ability of the tablet to withstand abrasion in packaging, handling and shipping. It is usually measured by the use of the Roche friabilator.

Method: A number of tablets are weighed and placed in the apparatus where they are exposed to rolling and repeated shocks as they fall 6 inches in each turn within the apparatus. After four minutes of this treatment or 100 revolutions, the tablets are weighed and the weight compared with the initial weight. The loss due to abrasion is a measure of the tablet friability. The value is expressed as a percentage. A maximum weight loss

FORMULATION DEVELOPMENT

Table1: COMPOSITION OF GLIPIZIDE CONTROLLED RELEASE TABLETS

S.NO.	INGREDIENTS	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)	F8 (mg)	F9 (mg)	F10 (mg)	F11 (mg)
1	Glipizide	10	10	10	10	10	10	10	10	10	10	10
2	HPMC K100M	10	20	---	---	---	---	---	---	10	10	10
3	Guar gum	---	---	10	20	---	---	---	---	10	---	---
4	Xanthan gum	---	---	---	---	10	20	---	---	---	10	
5	Sodium alginate	---	---	---	---	---	---	10	20	---	---	10
6	Microcrystalline Cellulose	90	80	90	80	90	80	90	80	80	80	80
7	PVP K-30	5	5	5	5	5	5	5	5	5	5	5
8	Magnesium stearate	3	3	3	3	3	3	3	3	3	3	3
9	Talc	2	2	2	2	2	2	2	2	2	2	2
10	IPA	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
	Total wt	120	120	120	120	120	120	120	120	120	120	120

Table 2: Standard graph of Glipizide in 0.1 N HCL 1.2 pH buffer at λ_{max}= 275 nm

S. no.	CONCENTRATION(µg/ml)	ABSORBANCE
1	0	0
2	2	0.105
3	4	0.235
4	6	0.346
5	8	0.463
6	10	0.564

Figure 1: Standard graph of Glipizide in 0.1N HCl (1.2 pH)

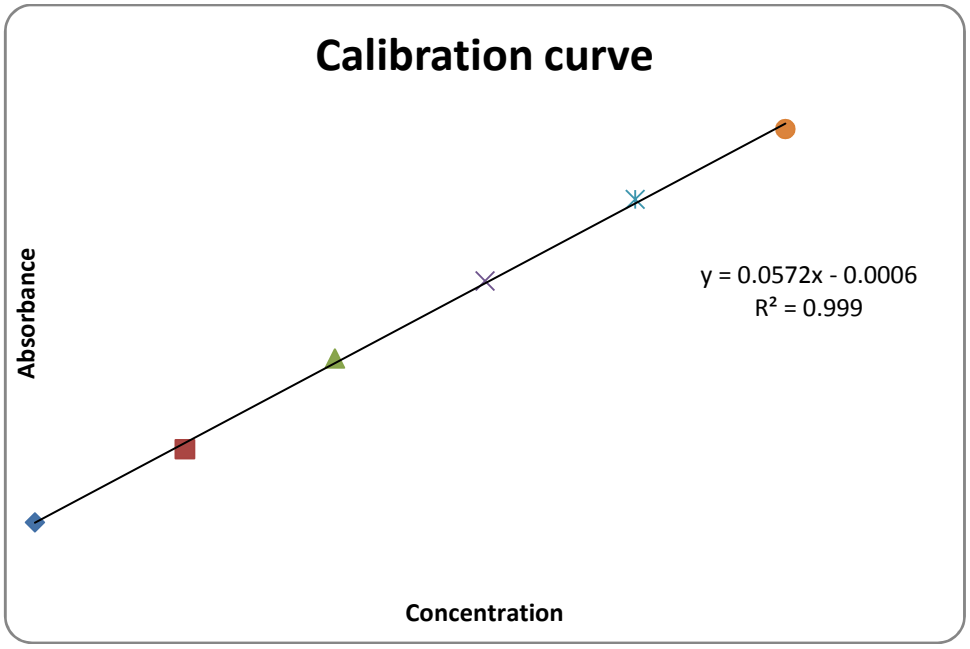

Table 3: Standard graph of Glipizide in 6.8 pH Phosphate buffer at λ_{max}= 275 nm

S. no.	CONCENTRATION(µg/ml)	ABSORBANCE
1	0	0
2	2	0.125
3	4	0.244
4	6	0.362
5	8	0.478
6	10	0.589

Figure 2: Standard graph of Glipizide in 6.8 pH Phosphate buffer

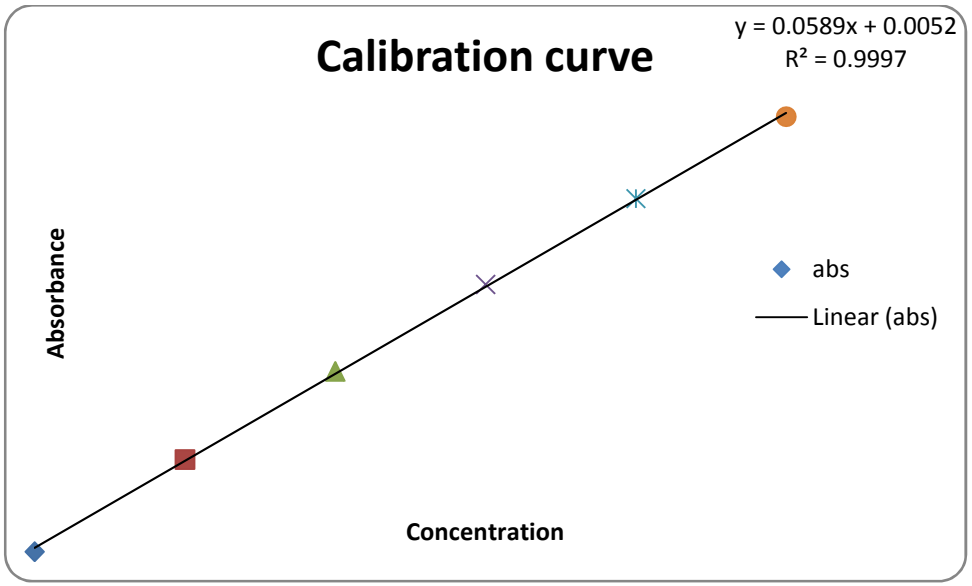

Table 4: Flow properties and corresponding Angle of repose, Compressibility index and Hausner ratio:

Parameter	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
Angleof repose	$25^0$43' ±0.1	$26^0$46' ±0.2	$23^0$31' ±0.1	$26^0$89' ±0.17	$29^0$14' ±0.1	$28^0$14' ±0.2	$29^0$12' ±0.1	$24^0$21' ±0.1	$27^0$14' ±0.4	$25^0$13' ±0.4	$23^0$13' ±0.4
Bulk density	1.041 ±0.3	1.02 ±0.4	1.01 ±0.2	1.02 ±0.28	0.96 ±0.24	0.95 ±0.24	0.94 ±0.2	0.96 ±0.2	1.041 ±0.3	1.02 ±0.4	1.01 ±0.4
Tapped density	1.16 ±0.1	1.12 ±0.2	1.11± 0.1	1.11 ±0.21	1.03 ±0.27	1.03 ±0.27	1.03 ±0.2	1.04 ±0.2	1.16 ±0.1	1.12 ±0.2	1.11 ±0.2
%Compressibility	11.4	9	9	8	7	9.5	9	8	11.4	9	9
Hausner's ratio	1.114	1.09	1.09	1.08	1.07	1.095	1.095	1.08	1.114	1.09	1.09

Table 5: Post compresson evaluation parameters:

S.NO	Formulation Code	Thickness	Hardness	Weight variation	Drug Content
1	F1	2.01±0.06	8.9±1.4	120±0.4	95.01%±0.2
2	F2	2.04±0.01	7.4±1.2	119±0.4	96.4%±0.4
3	F3	2.06±0.04	8.2±1.2	119±0.7	98.7%±0.3
4	F4	2.03±0.01	6.9±0.9	120±0.1	98.8%±0.2
5	F5	2.01±0.02	8.4±1.9	119±0.3	99.8%±0.3
6	F6	2.05±0.03	8.1±1.7	120±0.2	99.19%±0.2
7	F7	2.01±0.02	8.2±1.5	119±0.9	99.18%±0.2
8	F8	2.05±0.05	8.3±1.6	120±0.8	99.88%±0.2
9	F9	2.05±0.02	8.2±1.4	120±0.1	99.18%±0.2
10	F10	2.05±0.02	8.2±1.5	120±0.3	99.58%±0.2
11	F11	2.03±0.01	7.8±1.5	120±0.2	99.92%±0.3

Table 6: Results of Dissolution profile for all the formulations:

TIME	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11

0	0	0	0	0	0	0	0	0	0	0	0
1	38.91	34.92	58.91	55.83	58.44	56.29	32.37	28.35	53.83	47.92	26.94
2	56.24	48.92	67.24	64.26	66.83	63.21	42.47	39.81	61.26	58.92	32.59
4	62.84	59.21	78.84	73.87	76.47	75.38	59.28	50.47	70.87	68.21	46.86
6	80.78	74.93	89.78	86.38	88.74	87.78	74.41	64.87	84.38	79.92	58.48
8	92.72	89.72	97.72	93.71	96.82	95.36	88.26	79.38	92.71	89.72	69.83
10	98.38	97.92	100	100	100	100	92.49	88.61	100	97.92	87.57
12	100	100					98.85	97.76		100	96.29

F1, F2: Glipizide + HPMC K100m F3, F4: Glipizide+Guar Gum F5, F6: Glipizide+Xanthangum
F7, F8: Glipizide+Sodium Alginate F9, F10, F11: Glipizide+Combination Polymers

Table 7: Release Kinetics of the optimized formulation:

S.NO	time	log T	Square root of Time	%CR	%Drug remaining	log %CR	log% drug retained	cube root of %drug remaining
1	0	0	0	0	100	0	2	4.641589
2	1	0	1	26.94	73.06	1.430398	1.86368	4.180484
3	2	0.30103	1.414214	32.59	67.41	1.513084	1.828724	4.069816
4	4	0.60206	2	46.86	53.14	1.670802	1.725422	3.75959
5	6	0.778151	2.44949	58.48	41.52	1.767007	1.618257	3.462734
6	8	0.90309	2.827527	69.83	30.17	1.844042	1.479575	3.113091
7	10	1	3.162278	87.57	12.43	1.942355	1.094471	2.316454
8	12	1.079181	3.464102	96.29	3.71	1.983581	0.569374	1.548073

of not more than 1% of the weight of the tablets being tested during the friability test is considered generally acceptable and any broken or smashed tablets are not picked.

The percentage friability was determined by the formula:

$$\% \text{ friability} = (W_1 - W_2) / W_1 \times 100$$

W_1 = Weight of tablets before test

W_2 = Weight of tablets after test

***In vitro* drug release study:**

In vitro drug release was studied using USP II apparatus, with 900 ml of dissolution medium maintained at 37±1°C for 12 h, at 50 rpm. 0.1 N HCl (pH 1.2) was used as a dissolution medium for the first 2 h, followed by pH 6.8 phosphate buffers for further 10 h. 5ml of sample was withdrawn in different time intervals, and was replaced by an equal volume of fresh dissolution medium of same pH. Collected samples were analyzed spectrophotometrically at 229 nm, and cumulative percent drug release was calculated. The study was performed in triplicate.

Kinetic-models: In order to describe the DS release kinetics from individual tablet formulations, the corresponding dissolution data were fitted in various kinetic dissolution models:

Zero order, first order, and Higuchi respectively.

$$Qt = Q0 + K0\ t$$

where, Qt is the amount of drug released at time t; Q0 the amount of drug in the solution at t = 0, (usually, Q0 = 0) and K0 the zero order release constant.

$$\log Qt = \log Q\alpha + (K1 / 2.303)\ t$$

Qα being the total amount of drug in the matrix and K1 the first order kinetic constant.

$$Qt = KH.\ t^{1/2}$$

where, KH is the Higuchi rate constant.

Further, to better characterise the mechanism of drug release from matrices, dissolution data were analyzed using the equation proposed by Korsmeyer and Peppas.

$$Q\ (t-l)\ /Q\alpha = KK\ (t-l)n$$

where, Qt corresponds to the amount of drug released in time t, *l* is the lag time (*l* = 2 hours), Qα is the total amount of drug that must be released at infinite time, KK a constant comprising the structural and geometric characteristics of the tablet, and n is the release

exponent indicating the type of drug release mechanism. To the determination of the exponent n, the points in the release curves where Q (t-*l*)/Qα>0.6, were only used. If n approaches to 0.5, the release mechanism can be Fickian. If n approaches to 1, the release mechanism can be zero order and on the other hand if 0.5<n<1, non-Fickian (anomalous) transport could be obtained. Anomalous (non-Fickian) transport generally refers to the drug release by the summation of both diffusion and erosion of the polymeric matrix. The criteria employed to select the ‘‘best model’’ was the one with the highest coefficient of determination (r^2).

RESULTS AND DISCUSSION:

The λmax of Glipizide was found to be at 229 nm in 0.1N HCL and 6.8 Phosphate buffer. Standard graph of Glipizide in 0.1N HCl and Phosphate Buffer (pH 6.8). Good linearity was observed with the plot.

Pre compression Studies of blend

The method employed for tableting- in this study was wet granulation for which the drug or the mixture of drug and polymer should possess good flow properties. Granules ready for compression containing drug and various excipients were subjected for pre-compression parameters (Micromeritic properties) to study the flow properties of powder blend, to achieve constant uniformity of tablet weight.

Angle of repose (θ):

The data obtained for angle of repose for all the formulations were tabulated in the table no 4. The values were found to be in the range of $23^0$13’ and $29^0$14’. All the formulations showed the angle of repose less than 30^0, which reveals the good flow property.

Bulk density:

Loose bulk density (LBD) and tapped bulk density (TBD) for the blend is shown in table no.4 The Loose bulk density and tapped bulk density for the entire formulation blend varied from 0.94 to 1.041 and 1.03 to 1.16 respectively.

Carr’s consolidation index:

The results of Carr’s consolidation index or compressibility index (%) for the entire formulation blend ranged from 7 to 11.4 %. the powder blend showed excellent compressibility index values up to 15% result in good to excellent flow properties.

Post compression Evaluation studies of Glipizide Controlled release tablet

All the formulations of Glipizide Controlled Release Matrix Tablet has shown uniform thickness. In a weight variation test, the average percentage deviation of all the tablet formulations was found to be within the above limit, and hence all the formulations passed the test for uniformity of weight as per the official requirements. Good uniformity in drug content was found among different batches of tablets, and percentage of drug content was more than 95%.All the formulationshave shown required hardness because of sufficient binder concentration. In the present study the percentage friability for all the formulations was below 1% indicating that the friability is within the prescribed limits. All the tablet formulations showed acceptable properties and complied with the in-house specifications for weight variation Postcompressional parameters i.e. hardness, friability, thickness, weight variation, and drug content were within acceptable official IP limits and the results are tabulated as follows:

In vitro Dissolution studies: *In vitro* drug release studies were carried out on dissolution test apparatus USP XXIII with paddles in 900ml of 0.1N HCl for 2 hours and phosphate buffer 6.8 pH for the next remaining hours. The release rate of the drug from the matrix tablets decreased with an increase in polymer proportion and also depends on type of polymer used because of increase in gel strength as well as the formation of a gel layer with a longer diffusional path. The drug release was slower from the tablets containing HPMCK100M and sodium alginate in equal concentrations has compared with that of other formulations. The dissolution data were examined for best drug release formulation. It can be fitting for the models of zero order, first order, Higuchi, and KorsemeyerPeppas model shown in the following table. Study indicated good fit of Higuchi model suggesting that diffusion is the predominant mechanism limiting drug release.

Release kinetics: The dissolution data was examined for best drug release formulation. It can be fitting for the models of zero order, first order, Higuchi, and KorsemeyerPeppasmodel.Study indicated good fit of Higuchi model suggesting that diffusion is the predominant mechanism limiting drug release.

Conclusion:

Controlled release tablets of Glipizide were prepared by direct compression using 5.5 mm round punches. Various formulations were designed using different polymers like HPMC, Xanthum Gum, Guar Gum, sodium alginate and all polymers in combination.The evaluation parameters like weight variation, uniformity in drug content, invitro drug release studies were done. After the invitrodissolution studies the data was fitted in various kinetic dissolution models, Higuchi model indicated good fit suggesting that diffusion is the predominant mechanism limiting drug release.The results of the current investigation indicate that the formulationF11 containing combination of polymers has shown controlled release up to 12 hours. It is concluded that good controlled release formulation of glipizide can be prepared using combination of polymers HPMC and Sodium Alginateto avoid the side effects of glipizide and improve patient compliance due to reduced dosage frequency.

References:

1. Arunachalam S and Gunasekaran S (2002). Diabetic research in India and China today: From literature based mapping to health-care policy. Curr. Sci., 82:1086-1097.
2. Davis S and Granner D (1996). Insulin, oral hypoglycemic agents and the pharmacotherapy of the endocrine pancreas.Pharmacol.Basis. Therap., 9: 1487-1517.
3.Gerich J (1989). Oral hypoglycemic agents.N. Engl. J. Med., 321: 1231-1245.
4. Brogden R, Heel R, Pakes G, Speight T and Avery G (1979). Glipizide: A review of its pharmacological
properties and therapeutic use. Drugs, 18: 329-353.
5. Berelowitz M, Fischette C, Cefalu W, Schade D, SutfinTandKourides I (1994). Comparative efficacy of once daily controlled-release formulation of glipizide and immediate-release glipizide in patients with NIDDM.Diabetes Care, 17: 1460-1464.
6. Brabander D, Veraet C and Remon J (2003). Development and evaluation of sustained release mini matrices prepared via hot melt extrusion. J. Control Release, 89: 235-247.
7. Cooper J, Gun C, Carter SJ.1986; Powder Flow and Compaction. Tutorial pharmacy. New Delhi; CBS Publishers;211-233.