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Research Article

In-Vitro Study of low viscosity, and high viscosity direct compression and conventional grade hypromellose for modified release gliclazide tablets

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Abstract

Six different low to high viscosity hypromellose were used with lower soluble Gliclazide, alone to investigate the dissolution study and flow property. Dissolution behavior of formulated tablets was tested to identify the better efficacy. Dose dumping, pH dependency also was examined. Anti-diabetic Gliclazide tablets were prepared by direct compression method and the results of dissolution was found good in Methocel K100M DC for 73.25%. Tablets showed uniform weight, thickness, and lower percent (<0.5%) friability. Result of Carr's index and Hausner ratio indicated good flow properties of powder granules. The percent release of the Gliclazide was analyzed by kinetic models. Release of the drug was higher using the higher viscosity grade. Gliclazide tablets were determined with the goodness of fit test of kinetic models. The release showed linearity in Higuchi Model with correlation coefficient value of R^2= 0.973. In-vitro study demonstrated improved release profile using DC grade than CR grade alone.

1. Introduction

Gliclazide is an oral hypoglycemic agent and classified as a sulfonylurea of 1-(3-azabicyclo[3.3.0]oct-3-yl)-3-*p*-tolylsulphonylurea. It acts as both a first-generation[1] and second-generation[2] sulfonylurea to reduce blood sugar levels. This drug is prescribed 2 to 4 times daily depending upon the severity of the diabetes.Sustained release tablet can give the multiple therapeutic doses by a single administration.

Methocel cellulose ethers are two types, methylcellulose (MC) and Hypromellose (HPMC). Various grades of hypromellose is commonly used for the design of modified release tablets.

The grades are ranging from 3 to 200,000 mPa's. Viscosity of the solution depends on the concentration of Methocel that allows the desired level of performance for dissolution, floe properties. Hypromellose (HPMC) found as various branded like Methocel E, methocel F, Methocel J, and Methocel K. Premium grades of these Methocel products meet the specification for pharmaceutical modified release drugs.

Various types of HPMC are used in many researches to design and development of sustained release Gliclazide tablet. Researchers used compatible excipients such as mannitol, calcium hydrogen phosphate dehydrate, and change of ratio of the polymer to design the formulation. The type and concentration of HPMC influenced the rate and release of drug discussed by Williams *et al*[3]. Another study by Samani *et al*[4] proved that the drug release depended on the type and proportion of polymer. HPMC K100M and HPMC K100 LV which is special lower grade viscosity was found better matrix

former for Gliclazide sustained release tablet in many research studies.

Gliclazide has low has low solubility and high permeability for the variability in absorption due to the physicochemical properties of gliclazide, which belongs to Class II of the biopharmaceutical classification system. For that reason the dissolution is the rate controlling step during drug absorption. The dissolution rate of gliclazide depends on the gastric emptying time and the dissolution rate in the small intestine, where the compound is soluble.

This study employed for desired improvement in powder flow compared to conventional HPMC and in dissolution study with newly introduced DC grade HPMC.

2. Experimental

2.1 Materials: Gliclazide BP was obtained from Zhejiang Huayi Pharmaceutical Co. Ltd, China. Low viscosity, DC grade hypromellose (Premium Methocel K 100 LV CR, Methocel K 100 LV DC) and high viscosity Methocel K4M CR, Methocel K4M DC, Methocel K 100 M CR, Methocel K 100 M DC were obtained from Dow Chemical Company (Midland, MI USA). Methocel K 100 LV CR is conventional grade and Methocel K 100 LV DC, K4M DC, K 100 M DC is newly introduced for direct compression method which influences the flow property and dissolution rate than previous HPMC. All other chemicals used were of analytical grade (Merck, Germany).

K100LV DC is a lower viscosity of 100 mPa·s and Table shows the grade of other HPMC.

Table 1: Typical properties of CR and DC grade METHOCEL™

Properties	Methocel K 100 LV Premium CR	Methocel K 100 LV Premium DC	Methocel K4M Premium CR	Methocel K4M Premium DC	Methocel K 100 M Premium CR	Methocel K 100 M Premium DC
Viscosity (mPa·s)	80–120	80–120	2663–4970	2663–4970	72,750-135,800	72,750-135,800
Bulk densitya (g/cm3)	0.25–0.35	0.25–0.35	0.12–0.15	0.12–0.15	0.12–0.15	0.12–0.15
Moisturea (%)	5% max	5% max	5% max	5% max	5% max	5% max

Low viscosity ⟶ *High Viscosity*

K100 LV CR à K100 LV DC à K4M CR à K4M DC à K100 M CR à K100 M DC

2.2 Method: The flow properties of powder were determined by examining of Carr's Index and Hausner's ratio. The bulk density of the powder was determined by weight of the powder divided by the volume it occupies, normally expressed as g/mL. Tap density was determined by subjecting the powder in a graduated cylinder to 500 taps by a standardized tapping procedure of USP –II method (using VTAP MATIC-II) by following equation:

$$\text{Tapped density} = \frac{Mass of powder}{tapped volume}$$

The Hausner's ratio was determined as the ratio of the initial bulk volume to the tapped volume. The Carr's index was calculated using bulk and tapped densities data by following equation:

$$\text{Carr's index} = \frac{tapped\ density - bulk\ density}{tapped\ density} \times 100\%$$

The formulations were blended with the proper amounts of ingredients in a Laboratory scale V-blender (Patterson-Kelley, East Stroudsburg, PA USA) for the preparation of tablet. The hypromellose (HPMC)(amount described in table 2), Gliclazide (table 2), 98 mg of Avicel PH 102, 1 mg of Aerosil 200 were blended for 10 min. The magnesium stearate was then added and blended for 1 additional minute. Tablets were produced using a Manesty 16-station Betapress (Oystar Manesty, Merseyside, England). Flat-face, 3/32-inch tooling was used at 5000 lb compression force. The press was operated at 18 rpm. Target tablet weight was 205 mg.

Table 2: Amounts of METHOCEL™ in Gliclazide Tablets

Tablet formulation	Methocel K4M Premium CR	Methocel K4M Premium DC	Methocel K100M Premium CR	Methocel K100M Premium DC	Methocel K 100 LV Premium CR	Methocel K100 LV Premium DC
F-1	70	---	---	---	---	---
F-2	---	70	---	---	---	---
F-3	---	---	70	---	---	---
F-4	---	---	---	70	---	---
F-5	---	---	---	---	70	---
F-6	---	---	---	---	---	70

Thickness and diameter of the tablets were measured by digital Vernier calipers. The crushing strength of the tablets determined at room temperature by diametric compression using a hardness tester (Veego Scientific devices, Mumbai, India). The percentage friability of the tablets was determined using the tablet friability apparatus (Veego Scientific devices, Mumbai, India) operated at 25 rpm for 4 minutes. Tablets were weighed accurately placed in the chamber and rotated for 4 minutes (100 rotations). At the end of the run, the dusts on the tablet cleaned carefully, weighed accurately again and the percent friability (f) computed from the weight of the tablets before and after the test according to the below equation:

$$f = \left(1 - \frac{W}{Wo}\right) \times 100$$

where, W_o and W are the weights of tablets before and after the test respectively.

Hardness of the tablets was determined by Monsanto hardness tester and should be found within the range of 3-7 kg/cm^2.

The swelling properties of the compacts in 900 mL of Phosphate buffer pH 7.4 were determined using a modified version of the method. The HPMC compacts was dissolved in the medium for certain time periods (15, 30, 60, 120 minutes) before they were removed into a pre-weighted plastic container. The excess dissolution medium was sapped and blotted from around the disc without touching it. The compact and the container were weighted and then the wet weight of the compact was established. The wet weight at each time point was determined in triplicate, and the averages and standard deviations were calculated.

The relative swelling of the compacts, calculated as the ratio of the wet weight (Ww) to the initial weight (Wi) was determined, as an indication of the extent of matrix swelling using a similar index to Panomsuk *et al*. [5].

Relative swelling = *Ww / Wi*

Dissolution tests were performed in a VEEGO-BDA-8DR-USP Standards dissolution bath using USP Apparatus II (paddles) in 900 mL of Phosphate buffer pH 7.4 at 100 rpm. Tablets were

subjected to the hydro-alcoholic media for duration of either 24 hours or 1 hour followed by 23-hour dissolution in water. Absorbance was measured using a dual-beam UV/Vis spectrophotometer (PerkinElmer) using 5 mm quartz cells at 228 nm for gliclazide. Cumulative percent release of the drug calculated for the comparative analysis of all formulations and In-Vitro drug release performance using MS-Excel software.

Cumulative percent release was fitted to following power model in order to study the dissolution behavior and mechanism of drug release from matrix tablets. $\mathbf{Q = K_H . t^{1/2}}$

where, Q = Per cent Drug released at time, t, K_H = Higuchi rate constant, t = Time

If the release of the drug does not depend on the concentration of the drug in the depot, then it follows the zero order model and the equation derived as $\mathbf{M = M_0 - K_0 . t}$

Here, M_0 = Per cent drug remaining at time, t = 0. M = Per cent drug remaining at time, t = t. K = Zero order rate constant. t = Time.

In the first order model, the release of the drug depends on the concentration of the drug in the depot which is expressed as

$$\mathbf{lnC = lnC_0 - K_1 . t}$$

Here, $\mathbf{C_0}$ = Per cent drug remaining at time, t = 0. (100% drug remains), **C** = Per cent drug remaining at time, t = t, K_1 = First order rate constant. t = Time.

3. Results

3.1 Evaluation of physical properties of matrix tablets: The weight, hardness, and thickness were in the range of 206.63 mg to 203.25 mg, 4.121 kg/cm^2 to 4.222 kg/cm^2 and 3.78 mm to 3.58 mm, respectively. The percent friability was less than 0.5%. The data obtained were showed in the following table 2:

Table 3: Physical characteristics of Gliclazide Tablet

Formula	Avg. Wt. (mg.)	Avg. hardness (kg/cm2)	Avg. thickness (mm.)	Friability (%)
F-1	205.26 ± 4.3477	4.136 ± 0.3886	3.78 ± 0.0716	0.2554
F-2	203.76 ± 3.7427	4.121 ± 0.5801	3.58 ± 0.0716	0.1345
F-3	203.87 ± 5.3320	4.222 ± 0.6620	3.64 ± 1.3886	0.1541
F-4	206.63 ± 4.6378	4.132 ± 0.6531	3.72 ± 1.5801	0.1247
F-5	205.55 ± 4.3325	4.131 ± 0.6602	3.76 ± 1.6621	0.4512

Carr's index, Hausner's ratio of the powder was within the range indicating good flowability and results were showed in the table 3:

Table 4: Flow properties of powder

Tablet formulation	Compressibility index (in per cent)	Hausner ratio
F1	10.142	1.291
F2	9.320	1.019
F3	10.255	1.220
F4	8.253	1.003
F5	10.050	1.279
F6	9.101	1.025

Compact relative swelling was <4 in Phosphate buffer pH 7.4 media (table 5). Higher relative swelling was recorded for K100 LV Premium CR and lower relative swelling for K100 LV Premium DC. No significant difference in compact swelling was observed for METHOCEL™. Any differences in drug release profiles can be explained from this solubility.

Table 5: Effect of Media on Relative Swelling (Ww/Wi) of Methocel Product

Tablet Formulation	Methocel	Relative Swelling (Ww/Wi) in Phosphate Buffer pH 7.4			
		15min	30min	60min	120min
F-1	K4M Premium CR	1.96	2.13	2.27	2.33
F-2	K4M Premium DC	2.00	2.12	2.29	2.73
F-3	K100 M Premium CR	2.15	2.38	2.51	2.63
F-4	K100 M Premium DC	1.44	1.47	1.48	1.50
F-5	K100 LV Premium CR	2.19	2.55	2.87	3.01
F-6	K100 LV Premium DC	1.49	1.52	1.53	1.56

3.2 Dissolution pattern: Dissolution test was performed for 24 hours. F1 – F6 tablets were constituted with only alone Methocel K100 LV CR, K100 LV DC, K4M CR, K4M DC, K100 M CR, K100 M DC. The drug release showed 100% release from all grade Methocel except K100 M DC of 73.25% for 24 hours. Total percent release of F1 was 99% for 18 h, and F2 99% for 22 h, F3 100% for 19 h, F4 73.25% for 24 h, F5 100% for 19 h, F6 100% for 19 h.

The API Gliclazide was released 20 to 30% in early time point according to European Medicines Agency (EMEA). This simple formulation did not show the dose dumping problem from HPMC polymer mechanism.

Dissolution rate was analyzed with Zero order, First order and Higuchi release kinetic model but the best fitted model was Higuchi model (R value: 0.973) and partially fitted with zero order model (R value: 0.980) for all formulations except F5. First order model was not fitted for F2 to F6 except F1(R value: 0.988).

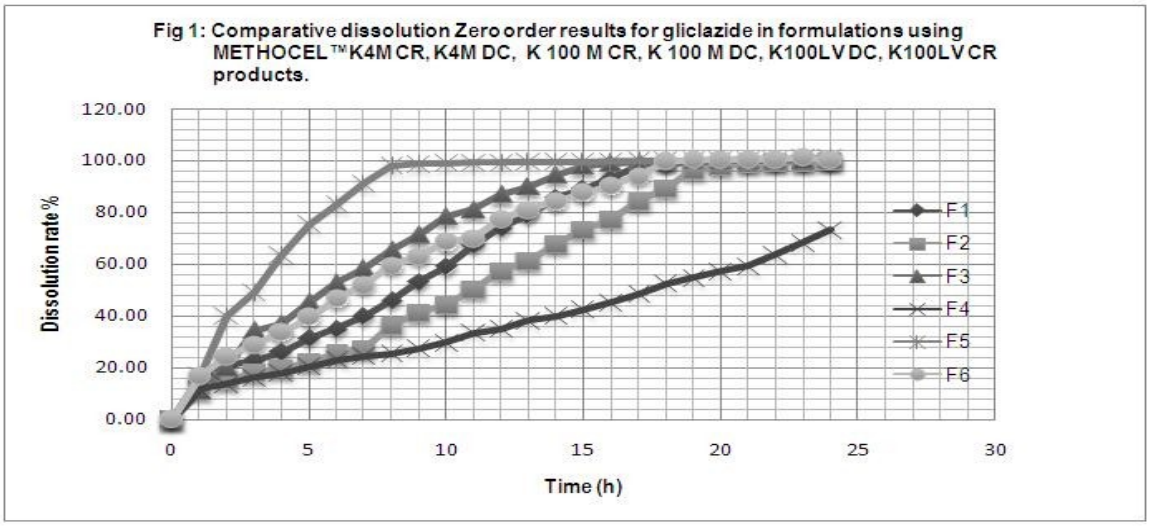
Table 4: Mathematical modeling of Gliclazide tablets.

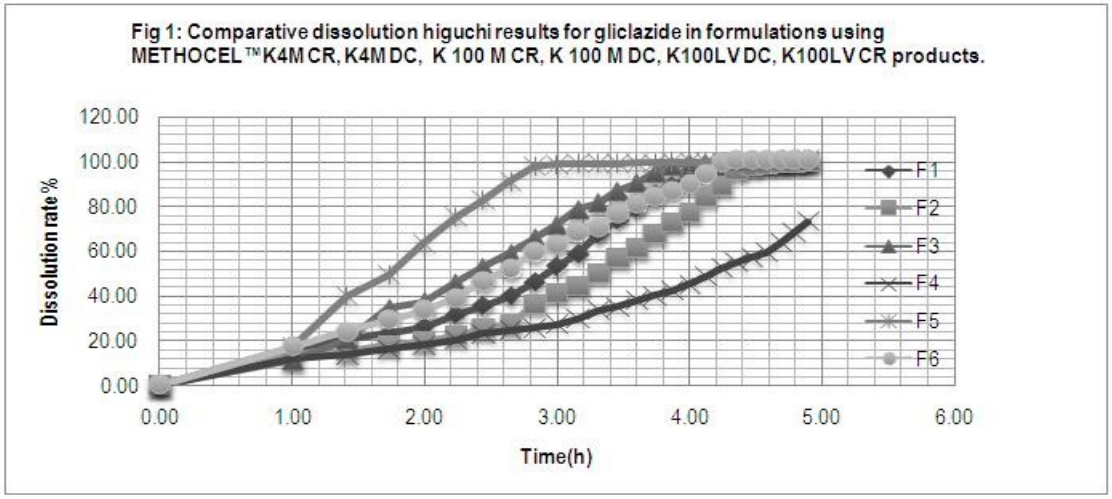
Formulation	Zero-order	Higuchi
F1	0.897	0.918
F2	0.980	0.852
F3	0.685	0.951
F4	0.961	0.890
F5	-0.253	0.712
F6	0.811	0.973

4. Discussion

Gliclazide tablets were prepared using Direct Compression (DC) and conventional grade (CR) HPMC in order to control the release of water insoluble Gliclazide for the detailed investigation on dissolution behavior, swelling and flow property.

All the prepared Gliclazide matrix tablets showed an optimum weight variation range from 203.25 to 206.63 with standard deviation <5%. Tablet weight depends on the compression and blending technology and influences the hardness for proper drug release in the dissolution media. Flow properties of the granules have impact on tablet weight and drug release. Hardness variation range of these tablets was very minor and good for optimum dissolution at a controlled rate. The prepared tablets showed a uniformity of thickness. The values of tablet thickness were in range of 3.58 – 3.78 mm. The concentration of drug in the tablets was not <97% and found under labeled potency with standard deviation 2%. This obtained data complied with the Pharmacopoeial limits for content uniformity[6].





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F-4	K100 M Premium DC	1.44	1.47	1.48	1.50
F-5	K100 LV Premium CR	2.19	2.55	2.87	3.01
F-6	K100 LV Premium DC	1.49	1.52	1.53	1.56

The In-Vitro study of Gliclazide tablets formulas F1, F2, F3, F5, F6 showed that the extent of drug release was 74.32%, 57.15%, 86.91%, 35.12%, 99.31%, 77.39% respectively for 12 h(Figure 1, Figure 2). F1, F2 released 99% gliclazide at 18 h and 22 h respectively. F3 released 100% gliclazide at 19 h and F4 73.25% at 24 hour only. Both F5, F6 released 100% drug at 19 h.

It was depicted that Direct Compression (DC) grade Methocel can extend the release rate more than conventional release grade Methocel. It seemed that both F5, F6 released 100% gliclazide but the precise value depicted that DC grade is better. Also, DC grade allowed the better floe properties than CR grade for this custom release.

Higher viscosity grade Methocel K100M Premium DC (72,750–135,800 mPa·s) capable to release gliclazide for more than 12 hours and it was 73.25 for 24 h. It was described that this ability of release rate was better than same conventional CR grade Methocel and lower viscosity grade K100LV CR and K100LV DC. But the precisely K100LV DC was better than CR grade.

This experiment showed more extended release was passable to design using higher grade DC Methocel alone. But it is predicted that combined grade of Methocel in the formulation can exted the rate of release more suitably.

The zero order released extended Gliclazide tablets showed slow release for 24 hour which was controlled and followed zero order kinetics and Higuchi kinetics. The percent of drug release was not depended on the concentration of drug in the depot. It is indicated a dependent release mechanism on the viscosity grade and concentration of the HPMC. The

drug release was poor and controlled for surface erosion or initial disaggregation of matrix tablets prior to gel layer formation around the tablet core.

Dissolution behavior of the prepared matrix tablets was significantly different according to viscosity grades of the Methocel at 12 h. In-Vitro release of Gliclazide was extended with the viscosity grade of the polymer. The more extended release was found 73.25% for 24 h using Methocel K100M DC.

Lower viscosity grade (K100LV CR) showed 100% release for 24 h. The release of the drug was directly proportionate to the viscosity grade of the matrix tablets containing Methocel. In-Vitro drug release data showed dependent dissolution mechanism on the viscosity grade of the polymer.

F2, F4 was better in terms of release profile. The reason may be for the surface erosion and diffusion of the matrix tablet to gel layer formation. The release may be extended for 24 h at a controlled manner and slower diffusion and erosion of the surface prior to gel layer formation[7] was the cause of this slower release which could be extended at the desired release rate by determining the amount of polymer level with high or low basis. From this point of view F2, F4 tablets showed good formulation as the half-life of Gliclazide is 10-12 hours. The cause of this release pattern may be for the Higher viscosity reduced greater chain entanglement to form thicker gel barrier. This viscosity of the polymer is related to the molecular weight[8] Previously published study of Rahman *et al*[9]showed inverse relationship between the viscosity grades of the polymer and drug release, but Gliclazide formulated polymeric tablets showed direct relationship. The reason for this may be drug-excipients interaction, diffusion mechanism and pH of the buffer 7.4.

The release data were subjected to kinetic analysis using linear regression with Higuchi Kinetic Model (R value: 0.973). The drug release from all formulas was found followed Higuchi model and zero order model but F5 did not fitted with zero order model. All tablet formulations showed a significant differences ($p<0.05$) in the release profiles for 12 h. The release followed non-Fickian diffusion[9]. It was observed that both diffusion of drug and relaxation of polymer controlled the release rate from the matrix system.

5. Conclusion

In this experiment the dose was not dumped and widely acceptable pH range. The method was simple and cost effective. Methocel K100M DC grade either provide the desired flow property and dissolution rate than previously available CR grade. Also, Methocel K100LV DC grade is counterpart. DC grade can be used alone as per this experiment or suggested in combination with other DC grades for further investigation on custom dissolution profile. Viscosity grades of the HPMC determined the rate of release at the desired level for 30 mg of Gliclazide modified release dosage form for promising technique for oral delivery of Gliclazide.

References

1. Ballagi-Pordany G, Koszeghy A, Koltai MZ, Aranyi Z, Pogatsa G. Divergent cardiac effects of the first and second generation hypoglycemic sulfonylurea compounds. Diabetes Res ClinPract, 1990; 8(2): 109-114.
2. Shimoyama T, Yamaguchi S, Takahashi K, Katsuta H, Ito E, Seki H, Ushikawa K, Katahira H, Yoshimoto K, Ohno H, Nagamatsu S, Ishida H. Gliclazide protects 3T3L1 adipocytes against insulin resistance induced by hydrogen peroxide with restoration of GLUT4 translocation. Metabolism, 2006; 55(6):722-730.
3. R.O. Williams III, T.D. Reynolds, T.D. Cabelka, M.A. Sykora, V. Mahaguna. Investigation of excipient type and level on drug release from controlled release tablets containing HPMC.Pharm. Dev. Tech., 2002; 7(2): 181–193.
4. Samani S.M., Montaseri H., Kazemi A. The effect of polymer blends on release profiles of Diclofenac from matrices.Eur. J. Pharm. Biopharm., 2003; 55: 351- 355.
5. Panomsuk S.P., Hatanaka T, Aiba T, Katayama K, Koizumi T, A study of the hydrophilic cellulose matrix: effect of drugs on swelling properties. Chem. Pharm. Bull. 1996; 44: 1039-1042.
6. The Pharmacopoeia of the United States of America 27, The National Formulary 22, Asian Edition. Rockville, MD: Pharmacopoeial Convention, Inc., 2004; 454–8.
7. Ebube NK HA, Wyandt CM, Beer DC, Miller LG, Jones AB. Sustained release of acetaminophen from heterogeneous matrix tablets, influence of polymer ratio, polymer loading and coactive on drug release. Pharm Dev Technol. 1997; 2: 161-170.
8. Lee. Prediction of polymer dissolution in swellable controlled release systems. J Control Release, 1987; 6: 207–215.
9. Md. Mofizur Rahman MKJ, Md. Qamrul Ahsan, Taslima Begum. Effect of various grades of hydroxypropylmethylcellulose matrix systems as oral sustained release drug delivery systems for ranolazine. IJPI's Journal of Pharmaceutics and Cosmetology, 2011 ; 1(2): 81-92.
10. Higuchi T. Mechanism of Sustained-Action Medication. Theoretical Analysis of Rate of Release of Solid Drugs Dispersed in Solid Matrices. J Pharm Sci, 1963; 52: 1145-1149.