Effect of Granulation Technique and Drug-Polymer Ratio on Release Kinetics of Gliclazide from Methocel K4M Matrix Tablet

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Abstract

The effect of different percentages of a hydrophilic polymer and impact of granulation technique on the release profile of gliclazide from matrix system was investigated. Matrix tablets of Gliclazide were prepared by both direct compression and wet granulation process using METHOCEL K4M CR. The release mechanism was explored and explained with zero order and Higuchi equation. Release kinetics of Gliclazide matrix tablets were determined using USP paddle method at Phosphate buffer (pH 7.4) and conducting for 10 hours. Statistically significant differences were found among the drug release profile from different polymeric concentration and granulation process. Higher polymer content (35%) in the matrix decreased the rate of the drug due to increased tortuosity and decreased porosity. At lower polymeric level (15%) the rate of drug release was elevated. In this study effect of granulation process on drug release also examined and found that tablets prepared by wet granulation technique possessed more sustained release property than those of direct compression.

Keywords: Matrix tablet, Gliclazide, Direct compression, Wet granulation.

Introduction

Matrix systems appear to be a very attractive approach from the economic as well as from the process development and scale-up points of view in modified-release system (Rekhi *et al*., 1995). Methocel (HPMC) is used frequently as a rate-controlling polymer in matrix tablets. Methocel offers the advantages of being non-toxic and relatively inexpensive; it can be compressed directly into matrix and is available in different chemical substitution, hydration rates and viscosity grades (Perez-Marcos *et al*., 1994).

When hydrophilic matrices interact with aqueous media (water, buffers, physiological fluids, etc.), both the polymer hydration (glassy/rubbery transition) and the dissolving of soluble components take place. Dissolution of the drug at the tablet surface causes a burst effect in the release profile of the system. This is more or less pronounced depending on the drug solubility and the polymer hydration rate (Huang & Brazel, 2001).The release kinetics working after the initial which inurn depends on the relative position of the eroding front (separating the release environment from the gel and generally moving outwards) and the swelling front (separating the dry glassy tablet core from the gel layer and moving inwards). Additionally, in the case of sparingly soluble drugs, a third front, the diffusion front can appear between the outer portion of the gel layer, where the drug is completely dissolved and the inner one, where undissolved drug particles still exist (Lee & Kim,1991). Delivery of drug from hydrophilic matrices is known to be affected by many factors such as the polymer swelling and erosion behavior, the drug dissolution characteristics, the drug/polymer ratio, the granulation technique and the tablet shape (Colombo *et al*., 1999b).

The purpose of the present study is to develop a reproducible extended release dosage form of Gliclazide using water swellable pH independent hydrophilic matrix to evaluate in-vitro release characteristics of Gliclazide from formulated

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tablets. The particular emphasis has been given on METHOCEL K4M– a hydrophilic matrix system on the release profile of drug. The sustaining behavior of this polymer has been assessed by varying the polymer percentage in the formulation. Effect of granulation process on drug release was also studied in present study.

In this study, Gliclazide has been a drug of choice. It is a member of second generation sulphonylurea oral hypoglycemic agent used in the treatment of non-insulin-dependent diabetes mellitus (NIDDM). It improves defective insulin secretion and may reverse insulin resistance observed in patients with NIDDM.

Currently, both conventional and modified release preparation are available. But most of them are failed to give reproducible and desirable drug release profile. So, a lot of researches are carried out to prepare modified release gliclazide tablets with pharmacokinetic characteristics suited to the circadian glycemic profile of type two diabetes. This approach will minimize the complications associated with diabetes mellitus.The development of a generic version of gliclazide will reduce the total requirement of API and reduce the price of drug and make the drug more affordable to the patients. To achieve this objective, the present study will be effective to formulate an appropriate modified release oral dosage form of gliclazide.

Materials and Methods

Materials

Gliclazide used in this experiment was received from Zhejiang jiuzhou Pharmaceuticals Ltd, China. Methocel K4M (Colorcon Asia Pvt. Ltd, USA), lactose monohydrate (Lactose company, Newzeland), spray dried lactose (Sunny Pharmaceutical Ltd, China), magnesium stearate (Peter greven, Netherland) were received from the respective sources. All other chemicals used were of analytical grade.

Preparation of Gliclazide Matrix Tablet

Direct Compression

Individual ingredient was taken according to table 1 and was sieved through 30 mesh sieve. At first, Gliclazide and Methocel K4M were mixed uniformly. Latter lactose was added with this mixture and finally magnesium stearate was added with it. Tablets were made by a compression machine (Erweka, TR 16, Germany) using a 5X10 mm caplet shaped punch and die set.

Table 1: Formulation of Gliclazide matrix tablet by direct compression

Formulation	Gliclazide (mg)	Methocel K4M (mg/Tab)	Lactose/ (mg/Tab)	Mg stearet (mg/Tab)	Total weight
DM15	30	18	131.1	0.9	180
DM20	30	27	122.1	0.9	180
DM25	30	36	113.1	0.9	180
DM30	30	45	104.1	0.9	180
DM35	30	54	95.1	0.9	180

Wet Granulation

Individual ingredient was taken according to table 2 and was sieved through 30 mesh sieve. At first, Gliclazide and Methocel K4M were mixed uniformly and latter lactose was added with this mixture. About 30% (w/w) purified water was then added with the mixture drop wise with continuous rubbing to get desirable soft granules. This mixture was passed through 1mm sieve to reduce the partical size and dried at tray dryer at 75°C to reduce the LOD below 15%. The granules were again passed through wet miller and dried at tray dryer to reduce the LOD below 2%. Finally, magnesium stearate was added to it for lubrication. Prepared granules were then compressed following the same procedure as for direct compression.

Table 2: Formulation of Gliclazide matrix tablet by wet granulation

Formulation	Gliclazide (mg)	Methocel K4M (mg/Tab)	Lactose/ (mg/Tab)	Mg stearet (mg/Tab)	Total weight
WM15	30	18	131.1	0.9	180
WM20	30	27	122.1	0.9	180
WM25	30	36	113.1	0.9	180
WM30	30	45	104.1	0.9	180
WM35	30	54	95.1	0.9	180

Physical property analysis of the formulated tablets

The weight variation was determined by taking 10 tablets using an electronic balance (AY120,

Shimadzu, Japan). Friability was determined by testing 10 tablets in a friability tester (FTA-20,Campbell Electronics) for 4 minutes at 25rpm. Tablet thickness, diameter and hardness were determined for 6 tablets using a DR. SCHLEUNIGER PHARMATRON Tablet Tester 8M (UK).

In vitro dissolution study of Gliclazide tablet

In vitro dissolution study was carried out for 10 hours in a USP XXII dissolution apparatus (Erweka DT700, Germany) using paddle method. Rotation of the paddle was set at 100rpm and dissolution media was 900ml phosphate buffer of pH 7.4 maintaining the temperature at 37±0.5°C. Dissolution samples were withdrawn at predetermined intervals and were filtered through syringe filter. The samples were directly or after appropriate dilution were analyzed by a spectrophotometer (Shimadzu UV 1800, Japan) to determine the absorbance at the wavelength of maximum 226nm and 290nm using 1cm cell and then the difference between these two absorbance's were calculated.

Results and Discussion

Physical properties of the formulated tablets

The physical appearance, tablet thickness, diameter, hardness, friability and weight variation of all tablets were found to be satisfactory and reproducible as observed from the table 3. Thickness was within the range of 3.20 to 3.50, diameter within the range of 9.99 to 10.02, hardness was within the range of 8.1 to 11.3. Friability value for all the tablets was less than 0.5. Weight variation of the tablets was also within acceptable range.

Table 3: Physical properties of the designed Gliclazide tablets

Formulation	Hardness (Kg)	Thickness (mm)	Diameter (mm)	Friability (%)	Weight Variation
DM15	9.8±0.5	3.31	10.02	0.35	± 1.8
DM20	11.1±0.08	3.23	10.01	0.37	± 1.4
DM25	9.3±1.2	3.30	10.00	0.34	± 1.6
DM30	8.1±0.5	3.30	10.00	0.46	± 1.6
DM35	9.7±0.08	3.32	10.01	0.31	± 1.7
WM15	10.3±0.5	3.26	10.00	0.38	± 1.4
WM20	9.2±0.01	3.21	9.99	0.42	± 2.0
WM25	11.2±0.05	3.32	10.02	0.38	± 2.2
WM30	10.5±0.1	3.50	10.00	0.35	± 2.1
WM35	11.3±0.03	3.20	10.05	0.31	± 1.7

Release Study of Gliclazide

Figure 1A shows the release of gliclazide from matrix tablets prepared by direct compression. In case of 15% methocel K4M, 96.52% gliclazide was released after 10 hours. When the amount of methocel K4M was increased in the formulations, release of gliclazide became slower gradually. Gliclazide release were 73.076%, 69.259%, 65.45% and 57.253% when respectively 20%, 25%, 30% and 35% methocel K4M was used in the tablet formulations. But in case of higher content of methocel K4M, a significant change in the release pattern was observed. With the increment of this polymer in the tablet matrix, burst release of the drug was also reduced along with the final total amount of the drug. This might be due to the release retarding capacity of the polymer. Methocel K4M is a cellulosic polymer which is actually hydroxypropyl methyl cellulose. It is a kind of pH-independent polymer and has been widely used as matrices for oral controlled-release drug delivery system. However, after salvation of the polymer chains, the dimensions of the polymer molecule increase due to the polymer relaxation by stress of the penetrated solvent. This phenomenon is defined as swelling and it is characterized by the formation of a gel-like network surrounding the tablets (Alderman, 1987).

This swelling and hydration property of HPMC causes an immediate formation of a surface barrier around the matrix tablet. The thickness of the barrier increases with time which governs the rate of drug release in swelling controlled pattern. The mechanical property of the surface hydrated gelatinous barrier play an important role in overall drug release rate (Talukder *et al.* 1996). Due to these release retarding properties, gliclazide was released in a controlled fashion from the designed matrix tablets. On the contrary, figure 1B shows the release of gliclazide from the designed tablets where the tablets were prepared by wet granulation technique. Gliclazide was also released in a controlled way from the formulated tablets but release was more controlled in case of wet granulated tablets. While 15% methocel K4M was used in the formulation, 79.42% gliclazide was released after 10 hours. In case of other formulations, gliclazide release was 70.25%, 65.124%, 59.87% and 55.47% when respectively 20%, 25%, 30% and 35% of methocel K4M was used.

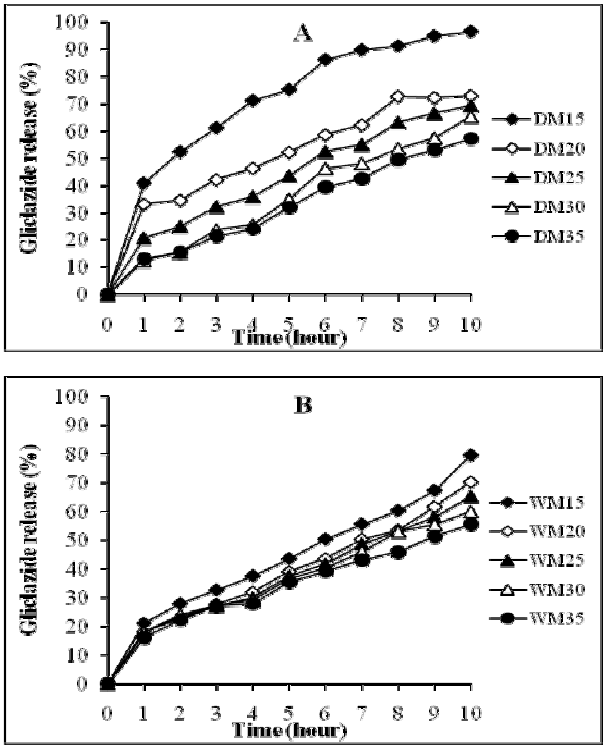

Figure 1: Zero order release curve of gliclazide from (A) direct compression and (B) wet granulated tablet formulated with Methocel K4M.

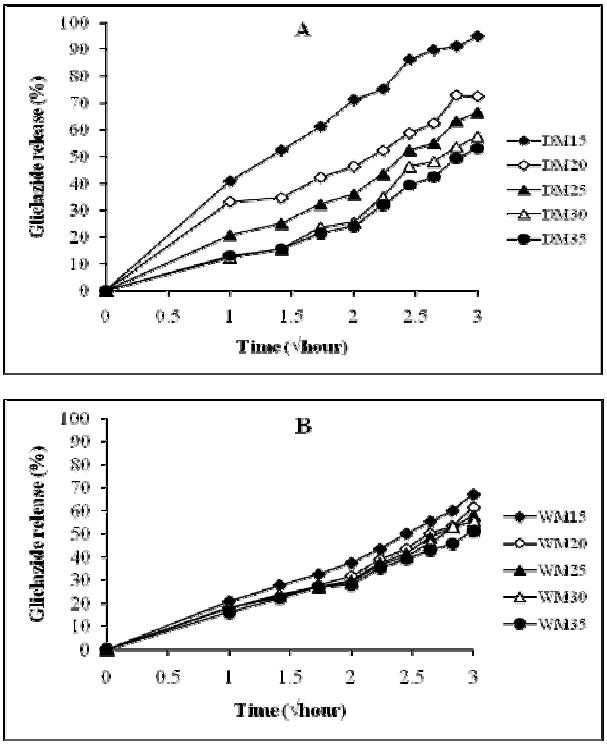

Figure 2: Higuchi release of gliclazide from (A) direct compression and (B) wet granulated tablet formulated with Methocel K4M

Figure 3 shows the comparative release rate study between the direct compressing and wet granulated tablets. In the figure ash boxes represent the release rate from direct compression tablets whereas black boxes represent release rate from wet granulated tablets. Gliclazide release was 96.52% in case of direct compression while 15% polymer was used whereas release was 79.42% in case of wet granulation. Higher drug release was obtained for all other direct compression formulation. Water activates methocel K4M and produce better agglomeration in wet granulation method. Thus drug release from wet granulated matrix tablet was lower comparing to direct compression. This clearly indicates that tablets prepared by wet granulation technique possessed more sustained release property than those of direct compression. To establish the release data, release rate from higuchi plots was also considered. With the increase in the polymer content from 15% to 35%, gliclazide release became slower gradually for both cases. But comparatively shorter black boxes in the figure-3 indicate smaller release rate values of gliclazide.

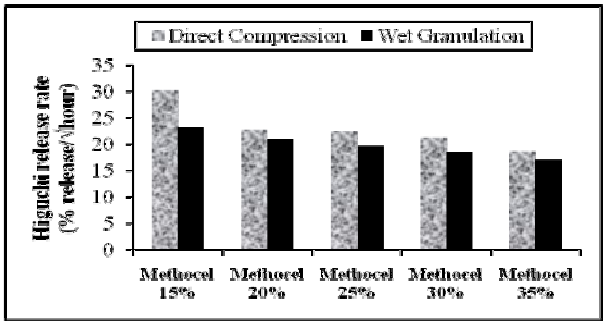

Figure 3: Comparative release rate study between the direct compressed and wet granulated tablets.

The release mechanism was explored and explained with zero order, and Higuchi equation. Table -4 shows the r^2 values of of the release curve for both zero order and Higuchi model. It's found that at lower concentration of polymer (15%) most of the formulation tends to Higuchi release kinetics and at higher concentration (35%) best fit with Zero order release kinetics. The result generated in this study showed that the profile and kinetics of drug release were functions of polymeric content and granulation process.

Table 4: Release kinetics of Gliclazide from METHOCEL K4M CR matrix tablets

Formulation	Zero order		Higuchi	
	r^2	K_0	r^2	K_H
DM15	0.833	8.062	0.980	30.38
DM20	0.885	6.266	0.978	22.89
DM25	0.961	6.414	0.979	22.50
DM30	0.985	6.287	0.936	21.31
DM35	0.986	5.507	0.945	18.73
WM15	0.833	8.062	0.980	30.38
WM20	0.885	6.266	0.978	22.89
WM25	0.961	6.414	0.979	22.50
WM30	0.985	6.287	0.936	21.31
WM35	0.986	5.507	0.945	18.73

Conclusion

From the investigation it was found that tablets prepared by direct compression offered maximum drug release in all polymeric contents than those were prepared by wet granulation technique. It was also observed that Higher polymer content in the matrix decreased the rate of the drug due to increased tortuosity and decreased porosity and at lower polymeric level the rate of drug release was elevated. The tablets showed good tabletting properties which may also be taken in account to evaluate the polymeric content and granulation process. Thus a controlled plasma level profile of drug can be obtained by judicious selection of polymeric content and granulation process in matrix system.

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