

DESIGN AND DEVELOPMENT OF SUSTAINED RELEASE SWELLING MATRIX TABLETS OF GLIPIZIDE FOR TYPE II DIABETES MELLITUS

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Abstract

The aim of the present study was to develop a sustained release monolithic system for the low soluble/low dose glipizide, for the treatment of type II diabetes mellitus.

The matrices were prepared by dry blending of polymers hydroxy propyl methyl cellulose (HPMC) or erodible Eudragit (ammonio methacrylate copolymers) and other excipients using direct compression method and were characterized using DSC (*differential scanning calorimetry*), FTIR (*Fourier transform infrared spectroscopy*), SEM (*scanning electron microscopy*), drug content, hardness, friability, *in vitro* dissolution and stability studies.

Hydrophilic matrix tablets exhibited swelling and erosion about 3 fold and 86.23 ± 1.5 % after 6 h. *In vitro* drug release data were analyzed for zero order, first order, Higuchi and Korsmeyer-Peppas models. A good linear relationship was observed in the case of release retarding polymer HPMC K100M. A comparison of the prepared and commercial product indicated that the drug release of the formulation GF6 was nearly similar to that of commercial product tested and found to be $98.03 \pm 2.51\%$ and $96.05 \pm 5.27\%$, respectively.

The GF6 was proven as the optimized swelling matrix tablet and showed non-Fickian diffusion release mechanism with optimum erosion. In conclusion, the rate controlling polymers HPMC K 100M at the 15 percent concentration showed the *in vitro* release of glipizide sustained for 16 h.

Rezumat

Scopul studiului prezentat a fost obținerea unui sistem monolitic cu eliberare controlată pentru glipizidă, agent hipoglicemiant cu solubilitate scăzută.

Matricile au fost obținute prin amestecarea pulberilor de hidroxipropilmetil celuloză (HPMC) sau Eudragit, și alți excipienți, utilizând metoda compresiei directe. Matricile au fost caracterizate utilizând tehnicile DSC (calorimetrie cu scanare diferențială), FTIR (spectroscopie în infraroșu cu transformată Fourier), SEM (microscopie electronică de baleiaj), conținutul în substanță activă, duritate, friabilitate, studii de stabilitate și dizolvare *in vitro*.

Keywords: Glipizide, sustained release, HPMC K100M, swelling matrix tablet.

Introduction

In last five to six decades, a large number of drug products, mainly in the form of tablet and capsule with controlled release characteristics, had been introduced. Sustained or controlled drug delivery systems can achieve predictable and reproducible release rates, extended duration of activity for short half life drugs, potential for cost saving and patentability, decreased toxicity and reduction of required dose, optimized therapy and better patient compliance [1-3].

Generally, primary objectives of sustained drug delivery systems are to ensure safety and to improve efficacy of drug and patient compliance, which could be achieved by better control of plasma drug levels and less frequent dosing [4]. For any sustained release dosage form it is very important to use the minimum number of excipients with minimum processing steps in order to reduce the tablet-to-tablet and batch-to-batch variations, using direct compression technique as suitable [5-8]. It has been shown that in aqueous medium the polymer undergoes a relaxation process resulting in slow direct erosion of the hydrated polymer. As these mechanisms can operate simultaneously, they will each contribute to the entire drug release rate. In particular, a careful balance between the diffusion and erosion mechanisms is required to optimize drug release toward zero-order kinetics [9, 10].

Among different technologies used in sustained drug delivery, hydrophilic matrix systems are the most popular because of the simplicity of formulation, ease of manufacturing, low cost, Food and Drug Administration (FDA) acceptance and applicability to drugs with wide range of solubility. For the development of sustained release dosage form, the solubility of drug is one of the limitations for availability of drug in gastrointestinal (GI) tract [11, 12].

Matrix systems appear to be a very attractive approach for economic process development and scale up point of view in sustained release systems. Hydrophilic polymer matrix is widely used for formulating a sustained release dosage form [13, 14]. It excludes complex production procedure such as coating and pelletization during manufacturing and drug release of the dosage form [15]. Drug release of these systems is the consequence of controlled matrix hydration, followed by gel formation, textural/ rheological behavior, matrix erosion, and/or drug dissolution and diffusion, the significance of which depends on drug solubility, concentration, and changes in matrix characteristics [16-20].

Diabetes mellitus is one of the major causes of death and disability in the world. Although the prevalence of both type-I and type-II diabetes is

increasing worldwide, the prevalence of type-II diabetes is expected to rise more rapidly in future because of sedentary lifestyle, increasing obesity and reduced activity levels. In United States of America (USA), about 90% of all diabetic patients have type-II diabetes [21].

Glipizide is a second-generation sulfonylurea and is one of the most widely used agents against type II diabetes. Glipizide is used for patients with type II diabetes who have failed diet and exercise therapy. Glipizide is a weak acid ($pK_a = 5.9$), practically insoluble in water and acidic environment, and highly permeable (Class II drugs in accordance to Biopharmaceutics Classification System, BCS). The oral absorption is uniform, rapid, and complete; its bioavailability is nearly 100% and its elimination half-life is 2–4 h. A rapidly absorbed drug having faster elimination rate with short half-life make it a suitable candidate to be formulated for the sustained delivery [22, 23].

To control and modulate the drug release properties of tablets, retarding polymers including hydrophilic polymers such as hydroxy propyl methyl cellulose (HPMC) and ammonio methacrylate copolymers Eudragit can be used. Among the swellable polymer used to prolong drug release, HPMC provoked considerable interest because most display good compression characteristics, including when directly compressed and have adequate swelling properties that allow rapid formation of external gel layer controlling drug release [24]. HPMC K100M forms transparent and flexible films from aqueous solution. The films dissolve completely in the GI tract at any biological pH and provide good bioavailability of the active ingredient. However, the use of hydrophilic matrix alone for extending drug release for water insoluble drugs is required [25-27].

In the present investigation, glipizide swelling matrix tablets were prepared by dry blending of excipients and direct compression method. Swelling matrix tablets were characterized by scanning electron microscopy (SEM), differential scanning calorimetry (DSC), Fourier transform infrared spectroscopy (FTIR), *in vitro* swelling, *in vitro* erosion, *in vitro* drug release and stability studies. The effects of hydrodynamic and pH on the release characteristics of the selected developed formulation were evaluated. The objective of the investigation was to develop a controlled release monolithic system for the low solubility/low dose drug glipizide, an oral anti-diabetic. The reference product used to compare dissolution profiles was the commercial product Glynase[®] sustained release tablet and these systems were not affected by either hydrodynamics or pH.

Materials and Methods

Materials

Glipizide[®] was supplied as a gift sample by Watson Pvt Ltd. Mumbai, India. Samples of Glynase[®] 10 (Glipizide 10 mg) sustained release tablet were obtained from a retail pharmacy and used as reference product. Hydroxypropyl methylcellulose (methocel) HPMC K 100 LV, K4M, K15M, K100M, K4M, K15M and Eudragit RLPO, RSPO were gift samples supplied by the Colorcon Asia Pacific, Mumbai, India. Spray dried lactose (Flowlac 100, Meggle, Germany) and magnesium stearate (Mallinckrodt, USA) used as a lubricant, were purchased from Central Drug House Pvt. Limited., Delhi, India.

Dose calculation in type II diabetes mellitus

The total dose of glipizide for once a day sustained-release formulation was calculated by the following equation (1) using reported pharmacokinetic data

$$D = d \times \left\{ 1 + 0.693 \left(\frac{T}{t} \right) \right\} \quad (1)$$

where, D indicates total dose of drug; d indicates dose of the immediate release part; T indicates time (hours) during which the sustained release is desired and t indicates the half-life of the drug.

Methods

Flow Properties of Formulation Blend

The formulation blends were evaluated for flow characteristics such as angle of repose, loose bulk density, tapped bulk density, Housners ratio and Carr's Index.

Preparation of sustained release swelling matrix tablets

Accurately weighed 10 g of drug, polymer and other excipients were physically mixed by geometric addition using a glass mortar and pestle for about 10 min and passed through the sieve number 30 (ASTM, 590 μ). Magnesium stearate was added as lubricant and passed through the sieve number 60 (ASTM, 250 μ) and blended with respective formulation for 2 min at 16 rpm (Multiplex, Apex Construction Ltd.). The homogeneous powder mixture of respective batch was fed into hopper of seventeen station automatic rotary tablet machine (Cadmach Ahmadabad, India) equipped with flat faced die-punch set of 8.5 mm diameter and compressed into 200 mg weight and an average hardness of 5-6 kg/cm² for all the tablets. The compositions of all the batches with their formulation code are shown in Table I.

Table I

Composition of the sustained release swelling matrix tablets

Composition in mg	GF 1	GF 2	GF 3	GF 4	GF 5	GF 6	GF 7	GF 8	GF 9	GF 10	GF 11	GF 12	GF 13
Glipizide	10	10	10	10	10	10	10	10	10	10	10	10	10
HPMC K 4M	20	30	-	-	-	-	-	-	-	-	-	-	-
HPMC K 15M	-	-	20	40	-	-	-	-	-	-	-	-	-
HPMC K 100M	-	-	-	-	20	25	30	-	-	-	-	-	-
Eudragit RLPO	-	-	-	-	-	-	-	20	60	100	-	-	-
Eudragit RSPO	-	-	-	-	-	-	-	-	-	-	10	30	60
Lactose SD	179	169	179	159	179	174	169	179	139	99	189	169	139
Mg Stearate	1	1	1	1	1	1	1	1	1	1	1	1	1
Total	200	200	200	200	200	200	200	200	200	200	200	200	200

Characterization of swelling matrix tablets

Differential scanning calorimetry (DSC)

The DSC Analysis was performed using a Mettler Toledo DSC 822c apparatus, Switzerland equipped with star “e” software. A 1:1 ratio of drug and excipient was weighed into crucible (sampling pan). The samples of pure drug, drug with HPMC K100M and formulation blend GF6 were analyzed by heating at a scanning rate of 20°C over a temperature range of 40-200°C at the 30mL/min flow rate of nitrogen.

Fourier transform infrared (FTIR)

Fourier transform infrared (FT-IR) spectral studies were conducted on a FTIR spectrophotometer (8400S Shimadzu, Japan) instrument using KBr pellets to investigate possible interactions between the respective polymers in the release media. All samples were crushed with potassium bromide. The weight ratio of a sample and potassium bromide was 2 mg to 300 mg. Crushed powders were compressed using hydraulic compactor at approximately 20,000 pounds under vacuum for 3 min. FT-IR measurements were performed under nitrogen atmosphere at a flow rate of 50 standard cubic feet per hour.

Scanning Electron Microscopy (SEM)

The surface morphology of the optimized batch before and after *in vitro* dissolution at different time intervals was analyzed by SEM. The tablet was mounted on brass stubs using carbon paste. SEM images were taken using a scanning electron microscope (JSM-5610LV; Jeol Ltd., Tokyo, Japan) at the required magnification at room temperature. A working distance of 39mm was maintained and the acceleration voltage used was 10 kV, with the secondary electron image (SEI) as the detector.

Post compression properties

Hardness

The hardness of ten tablets was measured using the Pfizer hardness tester (using Pfizer type hardness tester, Besto, Mumbai, India). The mean and standard deviation were computed, reported and expressed in kg/cm².

Friability

The friability of the tablets was determined using a Roche friabilator. It is expressed in percentage (%). Ten tablets were initially weighed and transferred into the friabilator. The friabilator was operated at 25 rpm for 4 min. After 4 min the tablets were weighed again. The friability was then calculated using the equation (2),

$$\% \text{ friable amount} = \frac{\text{Initial Weight} - \text{Final Weight}}{\text{Initial Weight}} \times 100 \quad (2)$$

Drug content

Ten tablets were weighed and average weight was calculated. All the 10 tablets were crushed in mortar. The powder equivalent to 50 mg of glipizide was dissolved in 100 mL of methanol and shaken for 20 min. Solution was filtered and 2.2mL of the filtrate was diluted to 100 mL using methanol. Absorbance of resultant solution was measured at 276 nm using methanol as a blank. The amount of drug present in one tablet was calculated. The drug content was measured for three determinations.

Hydration and erosion studies

The formulation capacity for hydration (buffer medium uptake) and their extent of erosion were evaluated gravimetrically. For each time point, two tablets of each formulation were weighed individually and exposed to 900 mL phosphate buffer (pH 7.5) medium under conditions similar to the dissolution test. At specific time points, tablets were removed from the medium, patted gently with a tissue paper, weighed, dried at 60 °C until constant weight was achieved, and then were discarded. Percent weight gain (hydration) and % mass loss (erosion) were calculated according to the following equations (3) and (4) using wet and dry weight values obtained from the testing.

$$\% \text{ Weight Gain} = \frac{\text{Wet Weight} - \text{Dry Weight}}{\text{Wet Weight}} \times 100 \quad (3)$$

$$\% \text{ Weight Loss} = \frac{\text{Original Weight} - \text{Remaining Weight}}{\text{Original Weight}} \times 100 \quad (4)$$

In vitro drug release

Dissolution of the tablets of each batch was carried out using USP type-II apparatus using paddle (TDT-08L plus, Electrolab, Mumbai). The

dissolution medium consisted of 900 mL of phosphate buffer (pH 7.5) for 16 h, maintained at $37 \pm 0.5^\circ\text{C}$. One tablet which was enclosed in ring mesh device was placed in each dissolution vessel and the paddle rotation speed was set at 50 rpm. 10 mL of the sample was withdrawn at the intervals of 1, 2, 4, 8, 16 hrs and the same volume of the fresh medium was replaced every time to maintain the sink condition. The samples were analyzed for drug content at a wavelength of 276 nm using double beam UV-Visible spectrophotometer (UV-1700, Shimadzu, Japan). The content of the drug was calculated using the equation generated from the standard curve. The percentage cumulative drug released was calculated [28].

Drug release kinetics

In order to propose the possible release mechanism, the release pattern was evaluated to check the best fit for zero-order release kinetic, Higuchi's square root of time equation, Korsmeyer–Peppas power law equation and Hixson–Crowell's cube root of time equation. The goodness of fit was evaluated by *r* (correlation coefficient) values [29-31].

The mean release profile (*n*=12) of the optimized batch was compared with that of the commercial formulation using the model independent pair-wise approach (5), the similarity factor (*F*₂).

$$F_2 = 50 \log \left\{ \left[1 + \frac{1}{n} \sum_{t=1}^n w_t (R_t - T_t)^2 \right]^{-0.5} \times 100 \right\} \cdot \cdot (5)$$

where, *F*₂ is similarity factor, *n* is the number of observations, *w_t* is optional weight, *R_t* is percentage drug dissolved from reference formulation (before stability studies) and *T_t* is percentage drug dissolved from test formulation at (after completion of 90 days in stability chamber). In general, *F*₂ values higher than 50 (50 – 100) show similarities of the dissolution profiles. The results were expressed as mean values of three determinations $\pm$ S.D.

Stability studies

The optimized glipizide formulation (GF6) were strip packed and subjected to accelerated stability studies as per ICH guidelines ($40^\circ\text{C} \pm 2^\circ\text{C} / 75\% \text{ RH} \pm 5\% \text{ RH}$) in the environmental stability chamber (using CHM-10S, Remi Instruments Ltd. Mumbai, India). The samples were withdrawn periodically (0, 15, 30, 60, 90, and 180 days) and evaluated for the different physicochemical parameters like appearance, weight variation, thickness, hardness, drug content, and in vitro release profile.

Results and Discussion

Flow Properties

The flow properties of formulation blend such as angle of repose, loose bulk density, tapped bulk density, Housners ratio and Carr's Index were shown in table II.

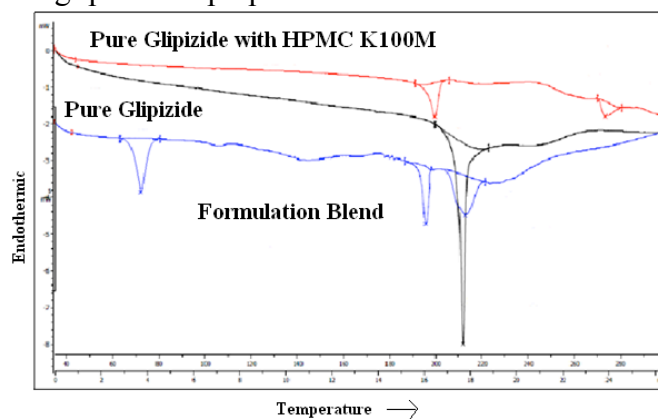
Table II

Flow properties of the various formulation blends of the respective batch of swelling matrix tablets

Formulation Code	Bulk density* (gm/cc) $\pm$ S.D.	Tapped density* (gm/cc) $\pm$ S.D.	Carr's index (%)	Hausner's ratio	Angle of repose* (degrees) $\pm$ S.D.
GF1	0.570 $\pm$ 0.006	0.65 $\pm$ 0.004	12.30	1.14	23 $\pm$ 1.537
GF2	0.56 $\pm$ 0.005	0.66 $\pm$ 0.014	15.15	1.17	25 $\pm$ 2.654
GF3	0.57 $\pm$ 0.01	0.67 $\pm$ 0.006	14.92	1.17	26 $\pm$ 0.546
GF4	0.550 $\pm$ 0.006	0.66 $\pm$ 0.003	16.66	1.2	29 $\pm$ 2.961
GF5	0.58 $\pm$ 0.005	0.66 $\pm$ 0.005	12.12	1.13	23 $\pm$ 1.852
GF6	0.56 $\pm$ 0.004	0.65 $\pm$ 0.011	13.84	1.16	25 $\pm$ 2.522
GF7	0.560 $\pm$ 0.006	0.66 $\pm$ 0.014	15.15	1.17	26 $\pm$ 2.196
GF8	0.56 $\pm$ 0.011	0.64 $\pm$ 0.015	12.5	1.14	26 $\pm$ 0.546
GF9	0.57 $\pm$ 0.007	0.65 $\pm$ 0.005	12.30	1.14	24 $\pm$ 2.961
GF10	0.57 $\pm$ 0.003	0.64 $\pm$ 0.013	10.93	1.12	23 $\pm$ 1.852
GF11	0.57 $\pm$ 0.008	0.66 $\pm$ 0.008	13.63	1.15	25 $\pm$ 2.522
GF12	0.550 $\pm$ 0.006	0.66 $\pm$ 0.005	16.66	1.2	28 $\pm$ 2.196
GF13	0.56 $\pm$ 0.004	0.67 $\pm$ 0.007	16.41	1.19	27 $\pm$ 1.176

Drug–excipients compatibility studies**Differential scanning calorimetry**

The DSC is carried out to understand the solid-state interaction in tablets. The DSC thermograms of pure drug, individual excipients, drug–excipient physical mixture (proportion same as the tablet composition) have shown in figure 1. To evaluate the internal structure modifications after compression of physical mixtures into tablet, tablet powder was also included in the study. Physical mixture showed simple superposition of their separated component DSC curves. According to the DSC findings of the matrix tablet powder, no major thermal event corresponding to chemical interaction was observed (and hence not shown) as well as no major change in melting point of glipizide. All these confirmed the suitability of all excipients with glipizide to prepare controlled-release matrices.

**Figure 1**

DSC thermograms of pure glipizide, glipizide with HPMC K100M and formulation blend GF6

Fourier Transform Infrared spectroscopy

The FT-IR studies were conducted to ensure interactions among glipizide and the excipients used in the formulation (Figure 2). The same peaks were also observed in the formulation indicating the stable nature of the drug. All the physical mixtures of glipizide and individual excipients show insignificant changes in actual peaks. Glipizide showed prominent peaks at 1651, 2943, 3354, 1529 and 1689 due to the presence of C = N aliphatic group, C-H₂ aliphatic, N-H stretching of NH₂, C-H aliphatic and C=O stretching. The same peaks with little difference were observed in the formulation indicating the stable nature of the drug.

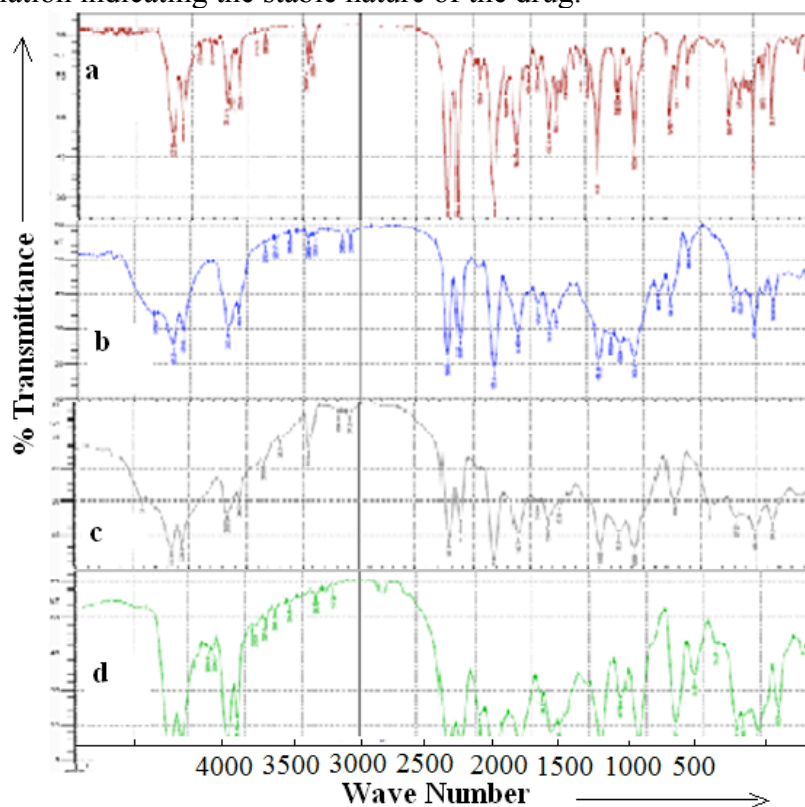


Figure 2

FT-IR spectra, a = FTIR spectra of pure Glipizide, b = FTIR spectra of Glipizide and HPMC K 100M (ratio 1:2.4), c = FTIR of spectra Glipizide and Lactose SD (ratio 1:3) and d = FTIR of spectra glipizide and magnesium stearate (1:0.5) and formulation blend GF6

Scanning Electron Microscopy

The surface morphology of optimized and remaining batches observed from the SEM studies (Figure 4). Scanning electron microscopy studies confirmed both diffusion and erosion mechanism from the optimized

batch of matrix tablet (formulation GF6) and shown in figure 3. The photograph of the matrix tablet taken at different time intervals after the dissolution experiment demonstrated. It reflects the matrix was intact and pores had formed throughout the matrix. On the other hand, SEM photomicrographs also be a sign of the surface of the fresh tablet did not illustrate any pores. These photomicrographs taken at the intervals also revealed formation of gelling structure and indicating the possibility of swelling of matrix tablets. Thus, the formation of both pores and gelling structure on the tablet indicates the involvement of both erosion and diffusion mechanism to be respectively formed sustaining the release of glipizide from matrix tablets.

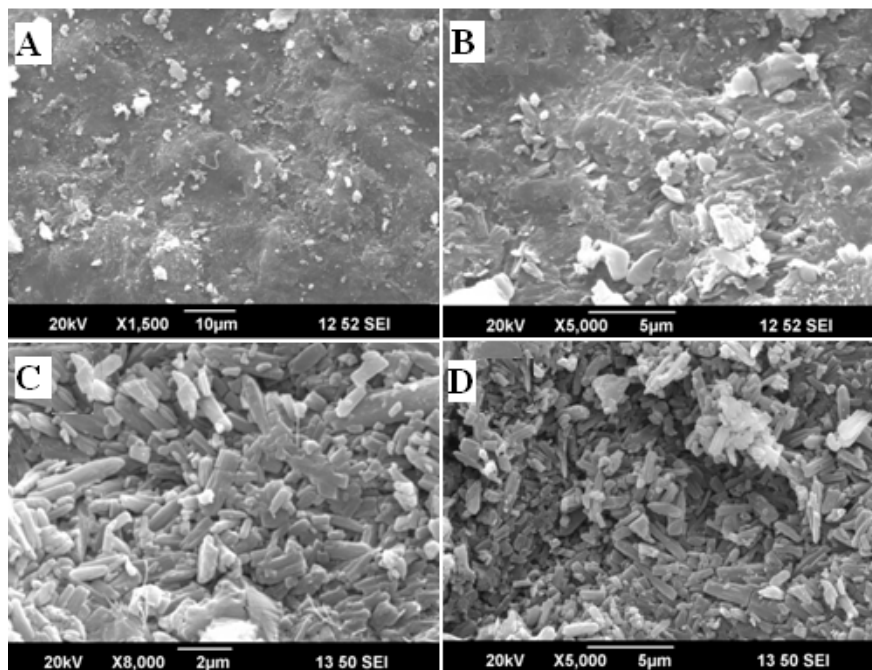


Figure 3

Scanning electron microscopy photographs of the swelling matrix tablets of GF6 taken at different time intervals after the dissolution. (A, B, C and D reveals the dissolution studies at the time of 0, 2, 8, 12 h, respectively)

Post Compression Properties

The results indicated that all the tablets prepared in these studies meet the USP 29 requirements for weight variation tolerance. Drug content of all tablet formulations were found in the range of 98.0 to 102.0% (Table III). Tablets of the same batch showed consistent dissolution behavior with little deviations in the subsequent dissolution studies.

Table III
Post compression parameters of swelling matrix tablets

Formulation Code	Thickness (mm) ± S.D.	Hardness (Kg/cm ²) ± S.D.	% Friability	% Drug content ± S.D.
GF1	3.0 ± 0.089	5.5 ± 0.540	0.094	98.43±0.35
GF2	3.0 ± 0.518	5.0 ± 0.550	0.223	98.56±0.45
GF3	3.0 ± 0.290	5.5 ± 0.789	0.197	99.78±0.62
GF4	3.0 ± 0.127	6.0 ± 0.681	0.064	98.22±0.71
GF5	3.0 ± 0.220	5.0 ± 0.337	0.061	99.77±0.23
GF6	3.0 ± 0.078	6.0 ± 0.896	0.063	98.99±0.32
GF7	3.0 ± 0.041	6.0 ± 0.725	0.065	98.34±0.83
GF8	3.0 ± 0.290	6.0 ± 0.789	0.197	98.20±0.66
GF9	3.0 ± 0.127	6.0 ± 0.681	0.064	99.90±0.64
GF10	3.0 ± 0.220	5.0 ± 0.337	0.061	99.44±0.83
GF11	3.0 ± 0.078	5.5 ± 0.896	0.063	98.88±0.95
GF12	3.0 ± 0.041	5.5 ± 0.681	0.065	99.12±0.32
GF13	3.0 ± 0.119	5.6 ± 0.540	0.011	99.32±0.25

Hydration and erosion studies

Investigation of matrix hydration and erosion directly by gravimetric analysis is a valuable exercise to better understand the mechanisms of release and the relative importance of participating parameters. Weight gain and mass loss proceeded throughout the entire course of the dissolution with matrix hydration showing a near zero order kinetics. The high capacity of HPMC matrix for water retention and the osmotic pressure generated by lactose are responsible for such behavior. The % swelling of optimized matrix tablets (GF6) at 1, 2, 4, 6, 8, 16 h were found to have 148.3 ± 1.2 , 203.8 ± 1.4 , 272.5 ± 2.0 , 305.1 ± 1.6 , 261.7 ± 1.1 , 14.6 ± 1.9 , respectively. As drug release by both mechanism diffusion as well as erosion, matrix tablet also studied for its erosion and it exhibited about $86.23\% \pm 1.5$ erosion (Mass loss) matrix tablet took place after 16 h.. Swelling matrix tablet (GF6) have shown the maximum swelling up to 3 fold at 6 h (Figure 4), which is slightly increased right from 1h, then decrease up to 16 h.



Figure 4

Swelling behavior of optimized matrix tablet at different time intervals (1, 2, 4, 6, 8, 12 and 16h)

***In vitro* drug release studies**

Formulation compositions affect drug release rates due to polymer–excipient interactions, drug–polymer interaction, as well as modulating matrix swelling and erosion rates. It might have cleared from the current studies that the rate of drug release from the matrix tablet depended on the polymer concentration and the type of polymer used. The glipizide formulation batch GF6 was found to have optimized batch which exhibits the drug release profile for 16 h (Figure 5 and 6). The rate of release at 75 rpm after first hour has increased to some extent, though not significantly, based on F2 calculation ($F_2 = 58.55$). This slight rate increase may be attributed to the high fluid flow intensity and enhancement of mass transport from the tablet periphery.

Effect of pH on release from Glynase SR and GF6 formulation was studied in pH 2, 4.4, and 7.5 at 75 rpm. As expected, dissolution rate was significantly lower in the acidic pH media for both systems tested, compared with release in pH 7.5 medium. This is attributed to low solubility of glipizide in acidic media. In addition, we noted that sink condition in the acidic pH is never met since saturation solubility of glipizide in pH 2 and 4.4 was extremely low, 1.0949 and 1.3183 mcg/ml, respectively.

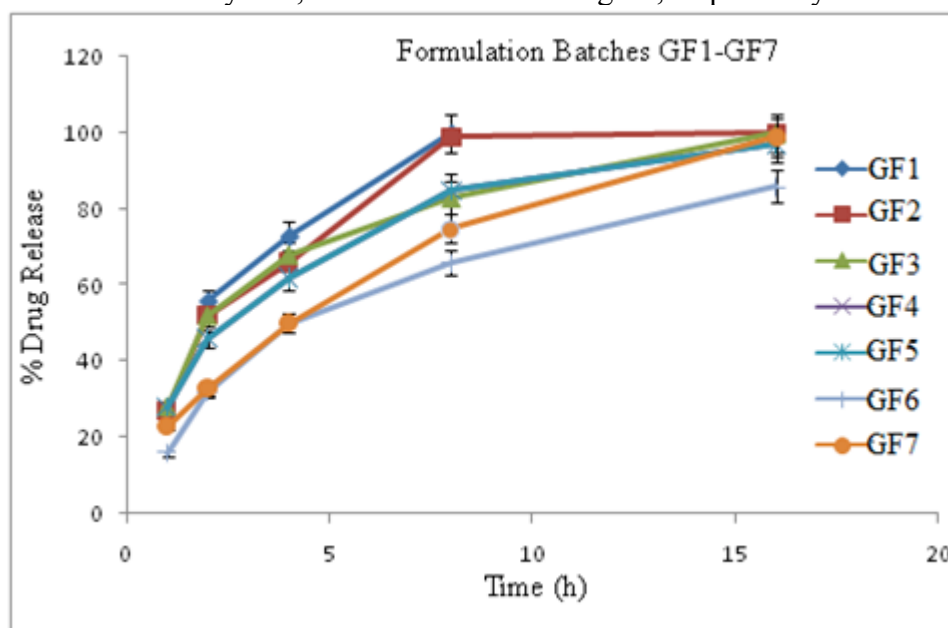


Figure 5

In vitro drug release profile of formulation batches of swelling matrix tablets (GF1 to GF7)

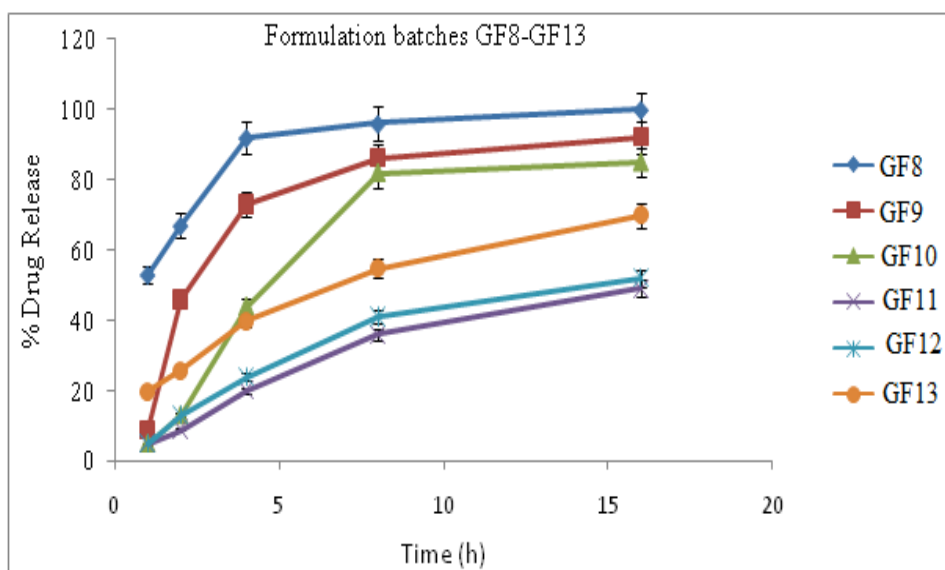


Figure 6

In vitro drug release profile of formulation batches of swelling matrix tablets (GF8 to GF13)

Effect of hydrophilic polymer on glipizide release

The release of drug decreased with increase in HPMC concentration and viscosity/molecular weight. Viscosity of HPMC solutions is the result of hydration of polymer chains, primarily through H-bonding of the oxygen atoms in the numerous ether linkages, causing them to extend and form relatively open random coils. A given hydrated random coil is further H-bonded to additional water molecules, entrapping water molecules within, and may be entangled with other random coils.

In case of K4M (GF1-GF2) we can't achieve desired drug release rates as drug is completely release within 4-6 hours, because of low viscosity. At lower HPMC grade, rapid swelling of matrices with less tight hydrogel structure resulted in higher initial drug release followed by complete release within short time period. Conversely at the higher HPMC content, the initial drug release was diminished and drug diffuses slowly continuously for more than 12 h. As the amount of HPMC in the matrix increased, there would be a greater degree of hydration with simultaneous swelling which results in a lengthening of the drug diffusion pathway and reduction in drug release rate. Hence K4M is unsuitable candidate for retarding drug release.

The complete replacement of HPMC K4M by HPMC K15M (F3-F4), the result is somewhat improved as compared to K4M that means K15M is able to sustained drug release, as viscosity of K15 is quiet greater

which helps to sustained drug release, but not up to the mark. It fails to sustained drug release upto 16 hours and complete release takes place upto 8 hours.

In case of HPMC K100M (GF5-GF7), it gives acceptable drug release rates if we compared with the marketed sustained release product Glynase SR. By reducing and selecting appropriate molecular weight of the polymer in the matrix, the rate of matrix hydration, and by implication, the rate of achieving disentanglement threshold can be controlled. Therefore, mechanism of drug release is based on the sum of diffusion and polymer relaxation. Rapid swelling and gel formation of the prepared matrix in this work minimized burst release of the glipizide which tends to be soluble in pH 7.5 buffer. The consistency of the dissolution results obtained from the GF6 tablets as observed by small standard deviations, suggests the precise control of the drug release by the matrix composition. GF6 was found to be optimized formulation as it able to match the dissolution profile with innovator (Glynase).

Effect of hydrophobic polymer on glipizide release

The *in-vitro* release from the GF12- GF17 matrix tablets showed much slower release rate because low water affinity for Eudragit (RLPO,RSPO). The release rate of tablets prepared with higher quantity of eudragit RLPO & RSPO reduces the permeation of water inside the matrix. The amounts of hydrophilic polymer in tablet formulation were reported to have a marked influence on disintegration time and dissolution of the tablet. As relative concentration of Eudragit is increased in the tablet, retards the penetration of dissolution medium in matrix by providing more hydrophobic environment and thus cause delay in the release of the drug from the tablet. GF12 to GF14 contains the RLPO grade for retarding the release rates. At lower concentration initial burst effect was observed, while at higher concentration much slower release rates takes place. The results of these hydrophobic polymers are similar to that RLPO with little difference in the rate of release.

Rational for use of ring-mesh device during dissolution studies

In the initial dissolution tests with HPMC formulations, It was noticed that tablets stuck to the bottom of the dissolution vessels for the greater part of the experiment. As a result, dissolution rates and extent were low and data variation was high. When studying the dissolution behavior of a drug delivery system, it is essential to simulate conditions of the gastrointestinal tract as much as possible in order to obtain a desired profile. Upon oral administration of a matrix tablet, all surfaces of the dosage form are in contact with the GI fluid, and at the same time the delivery system is

under considerable physical and hydrodynamic influence of GI motility and contractions. In order to provide full matrix exposure in the dissolution medium and fluid flow, in our study, a mesh was inserted below the paddle in the dissolution vessels and the tablets were placed on top of the mesh.

Statistical analysis of optimized formulation

The results of the release kinetic of all the formulations of swelling matrix tablets are shown in table IV. According to these results, the optimized formulation is GF6 that best fitted kinetic model korsemayers peppa's as R^2 value is 0.996 and n value is 0.539 which indicate that the drug release was followed by non fickinian diffusion (both due to diffusion as well as erosion).

Table IV

Coefficient of correlation values using various mathematical equations for swelling matrix tablets

Formulation Code	Zero order R^2	First order R^2	Higuchi R^2	Hixon Crowell R^2	Korsmayer's Peppas's	
					R^2	n
GF1	0.7013	0.7828	0.8387	0.7837	0.9018	0.412
GF2	0.7259	0.7793	0.8536	0.7819	0.9054	0.471
GF3	0.8251	0.9772	0.927	0.9826	0.9159	0.445
GF4	0.8874	0.9698	0.9681	0.9826	0.961	0.483
GF5	0.8653	0.9884	0.9568	0.9944	0.9684	0.455
GF6	0.9447	0.992	0.993	0.839	0.995	0.539
GF7	0.8909	0.9913	0.9709	0.9721	0.9539	0.589
GF8	0.6026	0.8985	0.75	0.9244	0.8663	0.234
GF9	0.6412	0.8948	0.777	0.8106	0.7476	0.761
GF10	0.7755	0.8412	0.885	0.8228	0.9175	0.108
GF11	0.9371	0.9721	0.9866	0.9618	0.9811	0.8585
GF12	0.9012	0.9496	0.974	0.9311	0.9532	0.841
GF13	0.927	0.9812	0.986	0.9668	0.9914	0.8585

Stability studies

Statistical analysis of optimized batch before and after the stability studies must be conducted, to assure the stability. The hardness and drug content of optimized batch GF6 were found to have 6.2 ± 0.05 and 99.52 ± 0.68 , respectively. The stability studies revealed that there was no significant change in appearance, hardness, friability, drug content and dissolution profiles of the formulation GF6.

In the present investigation, swelling matrix tablets of glipizide capable of providing controlled release was prepared using hydrophilic and

hydrophobic polymer. The DSC analysis of thermograms revealed no physical interaction between HPMC K100M and drug in the prepared swelling matrix tablets. The FTIR spectra have showed the representative peaks of pure glipizide and glipizide in formulation blend was not changed hence there was no any kind of compatibility issue in the formulations.

On the basis of desired swelling, erosion and release pattern (Figures 3, 4, 5 and 6) formulation batch code GF6 was selected as the optimized formulation for developing a swelling drug delivery system. Generally, an extended release tablet should release the required quantity of drug with predetermined kinetics in order to maintain an effective drug plasma concentration. To achieve this, the tablet should be formulated so that it releases the drug in a predetermined and reproducible manner. Visual observation of the tablets during dissolution testing revealed that swelling was dominant during the test procedure.

According to the theoretical release pattern, once daily glipizide SR formulation should release 2.5 mg in 1 h and 7.5 mg per hour up to 24 h. This approach involves the use of swelling polymers that could retain the delivery device in the stomach for the period of 16 h.

Swelling matrix tablet (GF6) have shown the maximum swelling up to 3 fold at 6 h, which is slightly increased right from 1h, then decrease up to 16 h. In the GF6 formulation, weight gain and mass loss proceeded throughout the entire course of the dissolution with matrix hydration showing a near zero order kinetics. The high capacity of HPMC matrix for water retention and the osmotic pressure generated by lactose are responsible for such behavior.

Researcher have reported that, drug release from HPMC matrices is sequent governed as follows at beginning, steep water concentration gradient are formed at the polymer/water interface resulting in water imbibition into the matrix, due to imbibitions of water, HPMC swells resulting in dramatic change in polymer and drug concentration and increasing dimension of system, upon contact with water drug dissolves and diffuses out of the matrix due to concentration gradients and with increasing water content, the diffusion coefficient of the drug increases substantially [32].

The increase in stirring rate can facilitate polymer chains detachment from the periphery of the matrix where polymer concentration has reached the disentanglement threshold, thus enhancing drug release especially when drug is insoluble. This effect can be more pronounced whenever erosion is the predominant part of release mechanism or when the gel structure is weak and likely to collapse under fluid flow shear stress at high agitation rates.

Hence, drug release from HPMC based swelling matrix tablet was followed by non fickinian diffusion (both due to diffusion as well as erosion). It is shown that GF6 formulation swells to a large extent, produces a firm gel, and releases drug predominantly via swelling/diffusion mechanism.

It is proposed that the pH and buffer species independent sustained release directly compressed tablet may exhibit the same release profile in the GI tract since a hydrogel is formed in acidic media similar to stomach fluid, and the resulting hydrogel would function to retard drug release in neutral and slightly alkaline media, irrespective of ionic strength. All of these factors contribute to larger effective size and increased frictional resistance to drug diffusion. The drug release rate decreased in the rank order HPMC K4M > K15M > K100M. Thus, HPMC was found to have dominating excipients controlling the release rate of glipizide in matrix tablets for 16 h. After complete swelling and drug release of system, percent erosion was increased. Due to increase in percent erosion and complete drug release the size of system was reduced to 6 to 9 mm or less and collapsed it. The optimized formulations (GF6) has shown the drug release up to 16 h hence these formulations revealed as sustained release dosage form. For further confirmation it requires the *in vivo* bioavailability studies in animals or healthy volunteers and *in vitro in vivo* correlation.

Conclusions

In the current work, a HPMC based swelling matrix tablet incorporating a low dose of poorly soluble glipizide is described. The HPMC with Lactose and Magnesium Stearate at particular proportions offered promising sustained-release formulations. The optimized formulations were characterized by the absence of an initial burst and satisfactory sustained-release properties. The stronger gel structure of HPMC K100M based formulation relative to that of eudragit (ammonio methacrylate copolymers) may provide superior quality *in vitro* performance in terms of matrix resistance to destructive forces within GIT. Hence, formulation (GF6) was found to have the best characteristics to accomplish the aim of this study. These tablets containing 15 percent HPMC K100M had good swelling, optimum erosion and sustained release of glipizide over a period of 16 h.

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