Controlled release matrix tablets of glipizide: Influence of different grades of ethocel and Co-excipient on drug release

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Abstract: The aim of the current study was to formulate and evaluate glipizide controlled release matrix tablets by means of different grades of polymer Ethoceland different co-excipients 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 using different grades of ethyl cellulose polymer with a drug-polymer ratio of 1:3by the direct compression method. The effect on drug release of partial replacement of lactose by different co-excipients, HPMC K100M, starch and CMC, were also studied. Diameter, thickness, hardness, friability, weight variations, drug contents of formulations were tested, these properties were within prescribed limits. Co-excipients and polymer containing formulations were compared to the without co-excipients and polymer containing formulations with respect to their release profile. After a 24-hour release study, ethyl cellulose polymer containing formulation exhibited prolonged release for 5-16 hours; however the polymer Ethocel® standard FP 7 Premium without co-excipient containing formulation exhibited controlled release for 24 hours. Incompatibility was investigated between drugs, co-excipient DSC and polymer study was performed and any type of interaction was not found. Different kinetic models were used to study the release mechanism. An enhanced release rate was observed in case of excipients containing formulations.

Keywords: Glipizide, Ethocel, HPMC, CMC, Starch, zero order equation, Higuachi equation, Korsmeyer and Peppas, Hixon Crowel's equation.

INTRODUCTION

Diabetes mellitus is a metabolic disorder and is responsible for early death and prolonged mortality (Arunachalam and Gunasekaran, 2002). 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). Glipizide is anantihyperglycemic agent and is ten times more active than tolbutamide in stimulating the insulin secretion from pancreas (Gerich, 1989; Marchetti and Navalesi, 1989). 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). 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).

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, for this purpose different grades of hydrophobic ethyl cellulose polymer were used because ethyl cellulose polymer shows controlled release properties when the tablets are formulated by the direct compression method (Brabander *et al,* 2003) and for extended release formulations, it is mostly used as a controlling agent. The starch, hydroxypropyl methyl cellulose (HPMC) and sodium carboxy methyl cellulose (CMC) and hydrophilic polymer (Ethocel) were used as co-excipients to show the effect on drug release from hydrophobic matrices.

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MATERIAL AND METHODS

Chemicals

Glipizide (Donated by Pfizer International, Karachi, Pakistan), lactose and magnesium stearate (BDH chemical limited, England), mono basic potassium phosphate, Ethocel Standard 7, 10, 100, Ethocel FP Premium 7, 10, 100 (Dow Chemical Company, Germany), Sodium hydroxide (Merck, Germany), HPMC K100M (Dow Chemical Company), Na- CMC, Starch. All the chemicals were of analytical grade and were used without any further purification.

Instruments

UV-Visible spectrophotometer (UVIDEC-1601 Shimadzu, Japan), DSC instrument (Mettler Toledo DSC 822e, Greifensee, Switzerland), micropipette, pH-meter (Denver, USA), Analytical balance (AX-200, Shimadzu, Japan), Vernier calipers (Germany), test tubes (Pyrex, Japan), beakers, volumetric flasks, syringes (Otsuka, Pakistan), Hardness Tester (Erweka Apparatus TB24, Germany), Friability Tester (Erweka TA3R, Germany), Single Punch tablet machine (Erweka AR 400, Germany) and Pharma Test Dissolution Apparatus (D-63512, Hainburg, Germany).

Differential scanning calorimetry (DSC) studies

The differential scanning calorimetry (DSC) study was performed using DSC instrument (Mettler Toledo DSC 822e, Greifensee, Switzerland) for the determination of drug interactions with polymers equipped with the Stare computer program. Aluminum crucible was used to weigh the 5mg of sample and then punched lid was used for sealing. The temperature range was 40-300^{o}C, with a heating rate of 10^{o}C/min under nitrogen gas flow.

Preparation of Glipizide tablets with different grade of Ethocel and co-excipient

Glipizide tablets were prepared using Ethocel standard premium 7, 10, 100 and Ethocel standard FP premium 7, 10, 100 polymers; HPMC K100 M, Na-CMC and starch were used as co-excipients to determine their influence on the release mechanism of glipizide from polymers and magnesium stearate was used as a lubricant and lactose as filler. The direct compression method was used to prepare the matrix tablets. All ingredients except magnesium stearate were mixed according to the dilution principle of powders and then a polybag was used for further mixing. After this for thorough mixing the powder mixture was passed through a No 30-mesh size screen and then the required amount of magnesium stearate 0.5% was added as lubricant and mixed well and same mesh screen was used to pass each resultant mixture through it and then single punch machine was used to directly compress the each mixture (Erweka, Germany) equipped with an 8 mm punch and die set. The composition of the different formulations is given in table 1.

Physico-chemical evaluation of powder and tablets

Hardness tester (Erweka Apparatus TB24, Germany) was used to test the hardness of the tablets and vernier caliper was used for dimensional tests. Friability tester (Erweka TA3R, Germany) was used to test the friability of the tablets. For uniformity of drug content (Deepak *et al.,* 2011). tablets were crushed and 100mL methanol was added to this fine powder and glipizide was extracted. UV –visible spectrophotometer was used for Glipizideassay (Shimadzu, Japan) at 223nm. Carr's compressibility index was used for determination of compressibility index of the granules (Equation 1).

$$\text{Carr's Index } (\%) = (TD - BD) \times 100 / TD \quad \ldots\ldots\ldots 1$$

The funnel method was used for the determination of angle of repose of granules. The granules were allowed to flow through the funnel freely onto the surface. Powder cone was measured for its diameter and calculation of angle of repose was done with the help of this equation (Chowdary and Rao, 2003).

$$\text{Tan?} = h/r \quad \ldots\ldots\ldots 2$$

'h' represents height and 'r' is for radius of the powder cone. Tapped density (TD) and Both Bulk density (BD) were measured. A measuring cylinder was taken and 2 gram of powder of each formulation were put in it and tapped until no further variations were observed in their volume. Following formula was used for calculation of BD and TD.

$$BD = \text{Weight of the powder/ Volume of the packing} \quad \ldots\ldots 3$$

$$TD = \text{Weight of the powder/ Tapped Volume of the packing} \quad \ldots. 4$$

In vitro evaluation and drug release kinetics

A six station Pharma Test Dissolution Apparatus (D-63512, Hainburg (Germany) was used for *in vitro* dissolution studies containing 900mL dissolution medium (phosphate buffer pH 7.4) maintained at 37°C±0.1. The optimized tablets were placed in dissolution medium and stirred at 100rpm according to USP method-I. The total concentration of glipizide released after specific time intervals (0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 20 and 24h) was determined using UV-Visible spectrophotometer at 223 nm.

In vitro drug release mechanism

In order to determine the rate and drug transport mechanism of Glipizide from controlled release tablets, the dissolution profiles were fitted in various kinetic/mathematical models given as under Zero order Kinetics.

($W = K_1 t$), (Hsieh *et al.,* 1983).

First order kinetics [$ln\,(100 - W) = In100 - K_2 t$], (Baker and Weng, 1992).

Higuchi Kinetics ($W = K_4\, t^{1/2}$), (Siepmann and Peppas, 2011).

Hixson Crowell kinetics ($100 - W)^{1/3} = 100^{1/3} - K_3 t$), (Soni and Chotai, 2010).

And Korsmeyer Peppas kinetics ($M_t / M_\infty = K_5 t^n$). (Dash *et al.,* 2010).

Table 1: Composition of controlled release matrix tablets of glipizide

F. Code	Drug	Polymer	Polymer	Lactose	Co-excipient
GLP-1	5mg	----	---	94mg	----
GLP-2	5mg	Ethocel Standard 7P Premium	15mg	79mg	----
GLP-3	5mg	Ethocel Standard 7FP Premium	15mg	79mg	----
GLP-4	5mg	Ethocel Standard 10P Premium	15mg	79mg	----
GLP-5	5mg	Ethocel Standard 10FP Premium	15mg	79mg	----
GLP-6	5mg	Ethocel Standard 100P Premium	15mg	79mg	----
GLP-7	5mg	Ethocel Standard 100FP Premium	15mg	79mg	----
HPMC					
GLP-8	5mg	Ethocel Standard 7P Premium	15mg	59mg	20mg
GLP-9	5mg	Ethocel Standard 7FP Premium	15mg	59mg	20mg
GLP-10	5mg	Ethocel Standard 10P Premium	15mg	59mg	20mg
GLP-11	5mg	Ethocel Standard 10FP Premium	15mg	59mg	20mg
GLP-12	5mg	Ethocel Standard 7P Premium	15mg	59mg	20mg
GLP-13	5mg	Ethocel Standard 7FP Premium	15mg	59mg	20mg
Starch					
GLP-14	5mg	Ethocel Standard 7P Premium	15mg	59mg	20mg
GLP-15	5mg	Ethocel Standard 7FP Premium	15mg	59mg	20mg
GLP-16	5mg	Ethocel Standard 10P Premium	15mg	59mg	20mg
GLP-17	5mg	Ethocel Standard 10FP Premium	15mg	59mg	20mg
GLP-18	5mg	Ethocel Standard 7P Premium	15mg	59mg	20mg
GLP-19	5mg	Ethocel Standard 7FP Premium	15mg	59mg	20mg
CMC					
GLP-20	5mg	Ethocel Standard 7P Premium	15mg	59mg	20mg
GLP-21	5mg	Ethocel Standard 7FP Premium	15mg	59mg	20mg
GLP-22	5mg	Ethocel Standard 10P Premium	15mg	59mg	20mg
GLP-23	5mg	Ethocel Standard 10FP Premium	15mg	59mg	20mg
GLP-24	5mg	Ethocel Standard 7P Premium	15mg	59mg	20mg
GLP-25	5mg	Ethocel Standard 7FP Premium	15mg	59mg	20mg

Each formulation contain 1mg of magnesium stearate

In Korsmeyer's Peppas kinetic model an (n) value, which is a diffusional exponent defines the mechanism of drug transport from matrix tablets. When n=0.5 then drug diffuses with a quasi-Fickian diffusion mechanism from a matrix tablet. When the value of n >0.5 then anomalous or non-Fickian diffusion mechanism of drug occurs and when n=1 then non-Fickian, Zero order or case-II release kinetics occurs (Malaterre *et al.,* 2009; Kuksal *et al* 2006; Mehrgan and Mortazavi, 2005).

Stability study

Three different batches of selected formulations from the test were prepared at three different periods for stability study. Air tight closed high-density polyethylene jars were used to pack the tablets and a proper accelerated storage conditions was maintained i.e. 40±2°C/75±5 %relative humidity (RH) using a stability chamber (Ti-Sc-THH-07-0400 Faisalabad, Pakistan) for 6 months as per international commission for harmonization guidelines (Dixon, 1998; Yogeshwar and Vandana, 2009). After 6 months, storage tablets were evaluated for drug content, friability, hardness and appearance at pre-storage (0 time) and after storage for30, 60, 120, and 180 days.

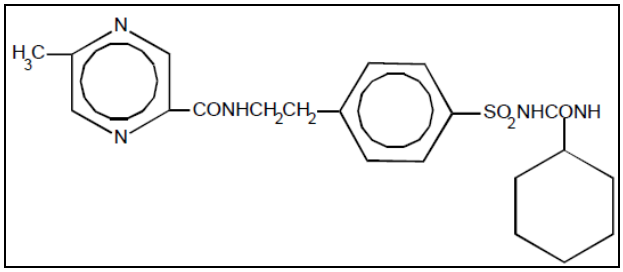

Fig. 1: Chemical Structure of Glipizide

STATISTICAL ANALYSIS

Different formulations were compared for their release rate by using one-way ANOVA One-way For this purpose; the statistical Package for Social Sciences SPSS was used.

RESULTS

Differential scanning calorimetry (DSC) studies

Differential scanning calorimetry studies were performed to investigate possible drug-polymer and excipient

interactions. The DSC thermogram of pure drug, with physical mixture of ethylecellulose polymer and different excipients such as lactose, hydroxypropylmethylcellulose (HPMC), magnesium sterate, carboxymethylcellulose (CMC) and starch are shown in fig. 2 (A, B, C, D). A single endothermic peak was at 209^{o}C that is represented by thermal curve of pure drug (fig. 2, A) that is related to Glipizide melting point as shown in fig 2,

Physico-chemical evaluation of powder and tablets

Compressibility index, tapped density, bulk density, drug content and angle of response of granules of different formulations were evaluated (table 2). The mixed powder of all the formulations showed good flow properties and compressibility as shown in table 2. Compressibility index is 12.82±0.01 to 13.11±0.03 and angle of repose is 25.06±0.2 to 28.86±0.6.Flow properties of granules are good due to angle of repose that is <30. Lower compressibility values further support these flow properties (table 2). Commonly, flow properties are excellent on 15% values of compressibility index. The results of BD and TD ranged from 0.36±0.03to 0.45±0.01and 0.48±0.01 to 0.55±0.01, respectively. Uniformity was found in the drug content of granules in grades of formulations.

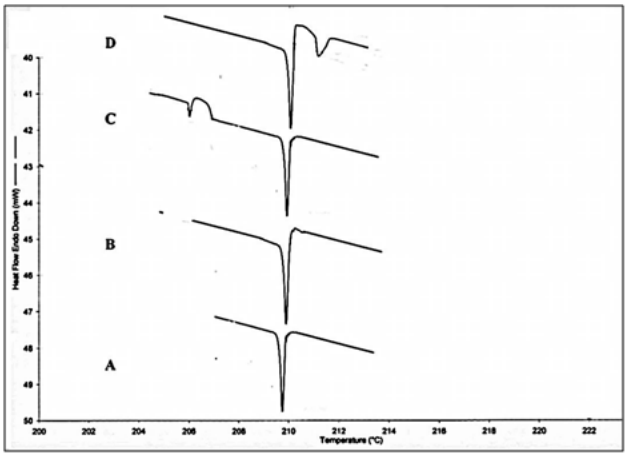

Fig 2: DSC Thermo gram of (A) pure drug, (B) physical mixture of glipizide with ethyl cellulose polymer, magnesium stearate, lactose and HPMC, (C) physical mixture of glipizide with ethyl cellulose polymer, magnesium stearate, lactose and starch, (D) physical mixture of glipizide with ethyl cellulose polymer, magnesium stearate, lactose and CMC.

Friability, hardness, uniformity of drug content, diameter and thickness of tablets of different formulations was evaluated table 3. Uniform thickness (C.V<0.5%) was observed in all formulations, uniform weight was observed in all formulation with little significance difference (p>0.1). Averages deviation of formulation were within normal limits and were according to official limits. All batches of formulation were uniform in drug content (n=20) and ranged from 97.93±1.05 to 100.23±2.22. The hardness and thickness of the tablets (n=20) ranged from 6.372±0.013 to 7.431±0.025kg/cm^2 and 3.427±0.024 to 3.649±0.031mm, respectively. The percentage friability of the tablets (n=20) ranged from 0.16±0.007 to 0.24±0.003%. All the formulations have less than 1% friability that is within normal limits (Sanchez *et al*., 2002; Saravanan *et al,* 2003). Acceptable pharmacopoeial characteristics were found in all types of formulation with respect to their friability, hardness, thickness, drug content and weight variations.

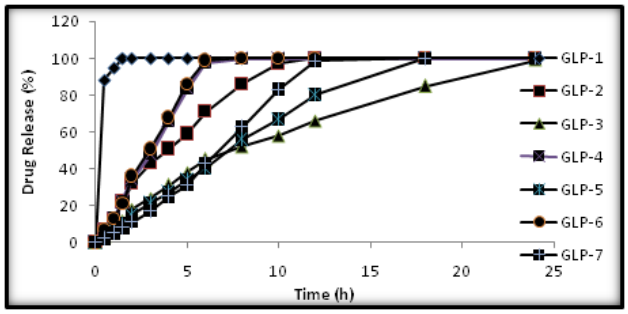

Fig. 3: Release profile of Glipizide from different grades of ethyl cellulose.

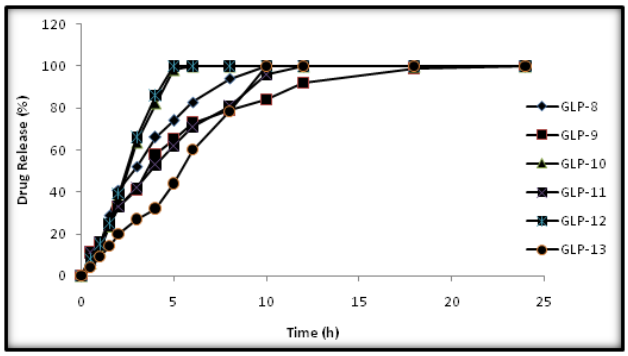

Fig. 4: Release profile of Glipizide from different grades of ethyl cellulose polymer in the presence of HPMC as co-excipient.

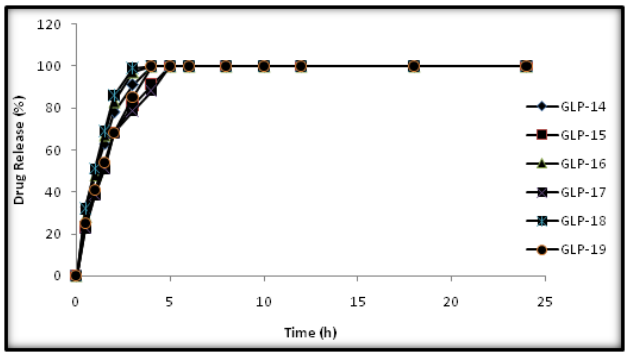

Fig. 5: Release profile of Glipizide from different grades of ethyl cellulose polymer in the presence of Starch as co-excipient.

In vitro release analysis of Glipizide from matrices

Figs. 3, 4, 5 and 6 show *invitro* glipizide release from matrix tablets containing different grades of ethyl cellulose polymer and co-excipients. As shown in fig. 3,

Table 2: Flow properties of pureGlipizide formulation blends ±SD.

F. Code	Angle of repose (°)	Bulk density (g/ml)	Tap density (g/ml)	Carr's index (%)
GLP-1	28.16±1.2	0.44±0.02	0.51±0.01	12.99±0.03
GLP-2	27.19±0.2	0.42±0.001	0.50±0.02	12.97±0.01
GLP-3	26.33±0.8	0.38±0.004	0.53±0.01	13.07±0.01
GLP-4	25.11±1.3	0.41±0.01	0.49±0.02	13.01±0.03
GLP-5	28.31±0.7	0.37±0.002	0.55±0.01	13.02±0.04
GLP-6	27.23±1.4	0.39±0.03	0.52±0.01	12.89±0.01
GLP-7	25.06±0.2	0.45±0.01	0.51±0.02	12.96±0.03
GLP-8	25.21±2.2	0.44±0.02	0.51±0.01	12.93±0.01
GLP-9	26.46±0.8	0.42±0.001	0.50±0.02	12.97±0.02
GLP-10	25.61±1.3	0.38±0.004	0.53±0.02	13.07±0.01
GLP-11	28.86±0.6	0.40±0.01	0.49±0.01	13.07±0.03
GLP-12	27.46±0.4	0.38±0.001	0.55±0.03	13.05±0.04
GLP-13	26.55±0.5	0.39±0.05	0.52±0.01	12.82±0.01
GLP-14	27.45±0.2	0.42±0.01	0.50±0.02	12.91±0.02
GLP-15	28.07±0.1	0.41±0.02	0.55±0.01	12.92±0.01
GLP-16	27.66±1.1	0.42±0.001	0.51±0.02	12.87±0.03
GLP-17	27.06±1.3	0.39±0.007	0.48±0.01	13.11±0.01
GLP-18	28.47±1.2	0.39±0.02	0.49±0.02	13.03±0.03
GLP-19	26.31±0.4	0.41±0.004	0.53±0.01	13.06±0.04
GLP-20	28.63±0.8	0.36±0.03	0.49±0.01	12.83±0.01
GLP-21	26.41±0.9	0.41±0.01	0.50±0.02	12.90±0.02
GLP-22	27.09±0.6	0.44±0.006	0.52±0.01	12.93±0.02
GLP-23	28.16±0.5	0.42±0.006	0.48±0.02	12.92±0.03
GLP-24	28.34±0.3	0.39±0.001	0.53±0.01	13.04±0.02
GLP-25	25.28±0.5	0.41±0.03	0.49±0.02	13.05±0.01

formulation GLP-1 containing glipizide and lactose without polymer and co-excipient released all of the drug after 1.0h because no polymer was used to retard the release of the drug but, as shown in the same fig. show release of glipizide was observed from formulations such as GLP-2, GLP-3, GLP-4, GLP-5, GLP-6 and GLP-7, containing different grades of ethyl cellulose polymer. The fig. shows that release profile of tablets containing the granular grade of Ethocel is different from the tablets containing the Ethocel® fine particle (FP) grade. As shown, all the drugs was released from GLP-2, GLP-4, GLP-5, GLP-6 and GLP-7 after 24 hours but release from formulation GLP-3 was only 97.3% even after 24h because in this formulation Ethocel® standard FP 7 Premium polymer was used.

Influence of different co-excipients on drug release

Figs. 4, 5 and 6 show the release of glipizide from different grades of ethyl cellulose polymer in the presence of co-excipients such as HPMC, starch and CMC, respectively. The release of drug from the formulation containing HPMC K100Mwas extended compared with formulations containing starch and CMC, because 90% of the drug was released in 5-12 hours from formulation GLP-8 to GLP-13, but, compared with the release from formulation GLP-3 containing Ethocel® standard FP 7 Premium without co-excipient, the release from these formulations was fast, and the more extended release as compared with starch and CMC.

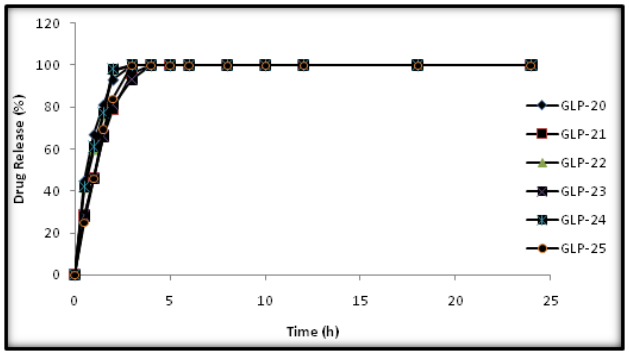

Fig. 6: Release profile of Glipizide from different grades of ethyl cellulose polymer in the presence of CMC as co-excipient.

Drug release kinetics

Data of different formulations for their kinetic release is given in table 4. Table shows the rate constant, r^2 for zero order, first order, Higuichi, Hixon Crowell and Korsmeyer and "n" values for power law of the formulated matrix tablets. Considering the r^2 values derived from different kinetic equations, glipizide release from most of the formulations, such as GLP-2, GLP-3, GLP-F4, GLP-5, GLP-6, GLP-7, GLP-8, GLP-9, GLP-10, GLP-12 and

Table 3: Physicochemical characteristics of Glipizide controlled release tablets (Mean ± SEM, *n*= 6).

F. Code	Friability (%)	Hardness (Kg/cm^2)	Drug content (%)	Weightin gram %	Thickness (mm)
GLP-1	0.19±0.003	7.171±0.061	98.87±2.72	100.01±0.501	3.435±0.021
GLP-2	0.19±0.004	6.983±0.037	99.92±3.15	99.01±0.602	3.796±0.035
GLP-3	0.21±0.001	7.092±0.028	97.93±1.05	100.03±0.301	3.501±0.023
GLP-4	0.23±0.005	7.415±0.027	99.71±3.14	100.01±0.101	3.487±0.027
GLP-5	0.24±0.003	7.431±0.025	98.86±4.07	99.9±0.308	3.513±0.042
GLP-6	0.22±0.01	6.945±0.021	99.96±3.03	100.05±0.605	3.427±0.024
GLP-7	0.17±0.004	6.372±0.013	97.97±2.47	100.05±0.394	3.481±0.033
GLP-8	0.21±0.003	6.799±0.038	99.53±2.88	100.15±0.587	3.506±0.035
GLP-9	0.23±0.007	7.102±0.033	99.27±2.234	100.05±051	3.443±0.031
GLP-10	0.17±0.009	7.311±0.013	100.23±2.22	99.95±0.394	3.465±0.026
GLP-11	0.24±0.001	6.819±0.085	100.03±3.14	99.85±0.489	3.516±0.026
GLP-12	0.18±0.0.4	6.514±0.071	99.34±2.37	100.1±0.447	3.448±0.026
GLP-13	0.24±0.002	6.697±0.038	99.71±2.37	100.01±0.501	3.479±0.022
GLP-14	0.17±0.006	7.171±0.088	98.69±2.83	99.01±0.602	3.503±0.031
GLP-15	0.21±0.004	6.497±0.029	97.94±2.12	100.03±0.301	3.649±0.031
GLP-16	0.16±0.007	6.602±0.052	99.44±2.82	100.01±0.101	3.511±0.041
GLP-17	0.21±0.05	6.798±0.045	98.13±2.67	99.9±0.308	3.496±0.035
GLP-18	0.17±0.001	6.899±0.021	99.04±2.66	100.05±0.605	3.473±0.051
GLP-19	0.22±0.006	6.595±0.028	99.78±2.97	100.05±0.394	3.491±0.035
GLP-20	0.16±0.004	6.489±0.051	98.39±2.53	100.15±0.587	3.649±0.024
GLP-21	0.2±0.001	6.495±0.032	98.54±2.12	100.05±051	3.507±0.066
GLP-22	0.22±0.004	6.195±0.025	98.83±2.22	99.95±0.394	3.458±0.0221
GLP-23	0.23±0.003	7.269±0.035	100.03±3.74	99.85±0.489	3.512±0.022
GLP-24	0.21±0.004	7.185±0.034	99.54±2.67	101.1±0.447	3.469±0.032
GLP-25	0.18±0.007	7.259±0.038	99.51±2.87	101.4±0.501	3.445±0.031

GLP-13, was found to follow the first order equation, zero order equation, Higuichi equation, Hixon Crowel's equation and power law. Results shows that majority of the formulations have "n" value between 0.596 and 0.784.

Stability studies

There was no significant change in physical appearance, drug content, friability and hardness at accelerated storage conditions (40°C±2 &75±5% RH) after storage for 30, 60, 120 and 180 days (table 5).

DISCUSSION

The DSC study shows that a single endothermic peak was at 209^{o}C that is represented by thermal curve of pure drug (fig. 2, A) that is related to Glipizide melting point as shown in fig 2, B-D the endothermic peaks of Glipizide in the physical mixture of ethyl cellulose polymer and excipient were found at the same temperatures as with pure glipizide, indicating that no possible chemical interaction was found between glipizide, polymer and different co-excipient.

Ethocel control the release of glipizide. This extended release effect with Ethocel® standard FP 7 Premium polymer is because of small size of polymer as compared with other grades of ethyl cellulose such as Ethocel® standard FP 10 Premium, Ethocel® standard FP 100 Premium, Ethocel® standard 7 Premium, Ethocel® standard 10 Premium and Ethocel® standard 100 Premium because all these grades have a larger particle size as compared with Ethocel® standard FP 7 Premium. It can thus be concluded that the capacity to sustain drug release is inversely proportional to particle size of the rate-modifying polymer. The same findings were observed by Khan and Meidan (Khan and Median, 2007) so, these results confirm their findings.

The drug release from the formulation containing HPMC K100 as co-excipient was extended as compared to the other formulation may be due to the lower hydration capacity of HPMC K100M (Luana *at al,* 2004). While the higher release compared with the formulation containing Ethocel® standard FP 7 Premium without co-excipient may be due to the development of osmotic pressure because HPMC creates osmotic forces following penetration of water within the matrices. These results confirm the findings of (Ford *et al,* 1987; Khan and Zhu 1998; Gohal *et al,* 2003) that HPMC in small quantities may act as a channeling agent and can increase the release rate, but note the results shown in fig. 5 for the release of glipizide from formulations containing starch as co-excipient. The drug is released more than 95% within 2-3 hr as shown in fig. 5. This is because starch is insoluble in

Table 4: Different kinetic models applied to determine release profile of Glipizide

F. Code	Zero-order		First-order		Higuchi		Hixon Crowell		Korsmeyer		N
	k_1±SD	r_1	k_2±SD	r_2	k_3±SD	r_3	k_4±SD	r_4	k_5±SD	r_5	
GLP-1	1.582± 5.32	0.0256	1.571±0.98	0.257	1.187±0.87	0.159	1.027±2.82	0.251	0.000±0.000	0.407	0.000
GLP-2	7.891± 6.321	0.791	0.187±1.92	0.724	0.162±0.08	0.862	4.962±1.28	0.882	0.087±0.033	0.978	0.674
GLP-3	4.831±1.62	0.9951	0.065±0.09	0.931	0.133±0.17	0.971	6.238±2.13	0.991	0.176±0.12	0.991	0.791
GLP-4	7.841±7.671	0.837	0.176±0.05	0.722	0.172±0.19	0.865	8.271±3.12	0.872	0.037±0.11	0.971	0.651
GLP-5	5.762±2.78	0.961	0.218±0.65	0.765	0.377±0.17	0.737	6.307±4.17	0.965	0.103±0.043	0.956	0.759
GLP-6	7.482±3.19	0.871	0.354±1.88	0.771	0.144±0.38	0.866	8.149±2.03	0.879	0.056±0.054	0.949	0.634
GLP-7	5.991±4.76	0.931	0.182±0.87	0.755	0.359±0.47	0.769	6.151±3.08	0.948	0.089±0.022	0.972	0.756
GLP-8	5.99±3.29	0.941	0.254±0.09	0.715	0.201±0.09	0.843	6.201±4.11	0.866	0.031±0.041	0.977	0.726
GLP-9	6.879±5.44	0.961	0.186±0.18	0.799	0.229±0.08	0.799	7.254±2.12	0.748	0.018±0.039	0.981	0.751
GLP-10	7.651±3.81	0.963	0.211±1.92	0.826	0.181±0.06	0.832	6.199±4.17	0.829	0.011±0.016	0.972	0.694
GLP-11	8.351±4.61	0.789	0.265±1.97	0.833	0.289±0.11	0.851	8.222±2.34	0.809	0.023±0.011	0.929	0.634
GLP-12	8.875±3.871	0.849	0.358±1.99	0.811	0.328±0.17	0.854	8.319±3.44	0.765	0.019±0.015	0.919	0.619
GLP-13	9.323±5.32	0.955	0.217±0.17	0.677	0.285±0.13	0.786	6.280±2.31	0.711	0.012±0.022	0.981	0.689
GLP-14	3.461±2.022	0.371	1.872±0.87	0.533	1.762±0.18	0.245	3.777±3.22	0.232	0.073±0.012	0.951	0.065
GLP-15	3.674±4.110	0.232	1.22±0.64	0.187	1.181±0.87	0.087	2.138±2.29	0.199	0.000±0.000	0.876	0.046
GLP-16	3.641±3.18	0.187	1.134±0.83	0.266	1.083±0.76	0.088	3.071±4.49	0.181	0.000±0.000	0.789	0.041
GLP-17	3.733±3.47	0.201	1.183±0.77	0.065	1.095±0.77	0.007	2.091±4.32	0.176	0.000±0.000	0.675	0.022
GLP-18	1.344±3.07	0.135	1.284±1.09	0.044	1.176±0.64	0.045	2.151±3.33	0.099	0.000±0.000	0.865	0.008
GLP-19	3.441±5.130	0.156	1.231±1.02	0.076	1.136±1.09	0.007	2.106±3.16	0.156	0.000±0.000	0.737	0.041
GLP-20	3.068±3.18	0.0765	1.378±0.92	0.034	1.209±1.01	0.016	1.169±2.21	0.288	0.000±0.000	0.729	0.023
GLP-21	3.065±4.255	0.0822	1.177±0.88	0.039	1.181±1.03	0.005	1.146±2.66	0.087	0.000±0.000	0.689	0.022
GLP-22	2.687±2.112	0.0684	1.318±0.98	0.018	1.133±0.99	0.077	1.193±4.23	0.092	0.000±0.000	0.722	0.018
GLP-23	2.231±1.43	0.0159	1.09±0.66	0.016	1.187±1.08	0.081	1.107±2.11	0.029	0.000±0.000	0.696	0.016
GLP-24	2.098±1.87	0.0346	1.211±1.18	0.042	1.165±1.03	0.006	1.235±3.03	0.043	0.000±0.000	0.688	0.012
GLP-25	2.214±2.481	0.0142	1.418±1.91	0.038	1.155±1.05	0.019	1.159±3.01	0.076	0.000±0.000	0.692	0.003

Table 5: Stability parameters of Glipizide tablets formulation GLP-3 (Mean ± SEM, n=3).

Periods of sampling	Drug content (%)	Friability (%)	Hardness (kg)	Appearance (Color)
Pre-storage (0 time)	101.54± 1.78	0.22±0.09	6.7±0.15	White
After 30 days	100.05±1.33	0.20±0.12	6.8±0.13	White
After 60 days	99.87±1.98	0.19± 0.15	7.0±0.17	White
After 120 days	99.06±2.01	0.19±0.33	7.1±0.54	White
After 180 days	98.76±1.77	0.18±0.21	7.2±0.76	White

water and due to the insoluble nature of starch it may cause non-uniformity of the polymeric material around the drug and due mostly to this property imperfections in the membranes occur, which causes the quick release of the drug from tablets and it may be due to the swellable nature of starch in water that the same findings were observed by Khan and Zhu, 1998 for the enhancement of drug release from formulations containing starch. This is attributed to the water-swellable properties of starch because due to this property it might cause the polymeric membrane to be ruptured, causing the enhancement of the drug release rate. The same findings were observed when CMC was used as co-excipient as shown in fig. 6 because all the drugs was released from the formulations containing CMC within 2hr. Lower viscosity of CMC attributes these results that is responsible for rapid dilution and low swell ability (Hamdy *et al,* 2007). The disintegrating properties of CMC might also contribute to this effect (Khan and Rhodes, 1975). Furthermore, this rapid release may be due to the solubility of CMC in water, because it has also been observed by Khan and Zhu, 1998 that a water-soluble co-excipient may break up the polymeric membrane due to the creation of osmotic forces within matrices, causing a higher drug release rate.

In this study majority of the formulations (GLP-2, GLP-3, GLP-F4, GLP-5, GLP-6, GLP-7, GLP-8, GLP-9, GLP-10, GLP-12 and GLP-13) have a diffusional exponent value "n" between 0.596 and 0.784, indicating that these formulations follow a non-Fickian anomalous release mechanism (n value between 0.45 and 0.89); this indicates coupling of the diffusion and erosion mechanism may show that more than one process can be used to control the release of drug, while the remaining formulations showed n value less than 0.45. Ethocel® standard FP 7 Premium (GLP-3) containing formulation exhibited good release kinetics as compared to other formulation having various grades of ethyl cellulose polymer and formulations containing co-excipients as shown in table 4

CONCLUSION

Thus, the results of the current investigation indicate that the formulations containing different grades of ethyl

cellulose polymer showed prolonged releaseupto 12 hrs compared with the formulation without polymer, but drug release from the formulation containing Ethocel® standard 7 Premium polymers was prolonged and controlled over24 hrs. All the co-excipients used in this study, such as HPMCK100 M, starch and CMC, produced an enhancement in the drug release rate. However, HPMC K100M showed a slower drug release rate compared with starch and CMC. No possible interactions of the drug with different grades of ethyl cellulose polymer and excipients were observed in this investigation, as confirmed by the DSC studies. It is concluded that good controlled release formulation of glipizide can be prepared without risk of possible interactions using Ethocel® standard FP 7Premium polymer to avoid the side effects of glipizideand improve patient compliance due to reduced dosage frequency.

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