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Research Article

Formulation development of Glipizide matrix tablet using different proportion of natural and semi synthetic polymers

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ABSTRACT

Increased complications and costs of marketing of innovative drugs focused greater attention to the development of sustained release (SR) or controlled release (CR) drug delivery systems. Delivery systems extended release or controlled release rate can achieve predictable and reproducible, the extended duration of activity for the short time of life - drugs, reduced toxicity, and dose reduction request, the optimized therapy and better patient compliance. It is controlled primarily by the type and the proportion of the polymers used in the preparation. The overall objective of this work was to develop a tablet glipizide oral sustained release (SR) prepared by the method of direct compression, using hydroxy propyl methyl cellulose (HPMC) and guar gum polymer alone and in combination at various concentrations. Glipizide hydrochloride (HCl), a biguanide, has a relatively short plasma half-life and low absolute bioavailability. All lots were evaluated for the thickness, weight variation, hardness and drug content uniformity and drug release *in vitro*. Dissolution time average is used to indicate the speed of release of the drug from a dosage form, and indicates the drug release retardant efficiency of the polymer. The hydrophilic matrix of HPMC alone cannot control the release Glipizide effective for 12 h while when combined with guar gum, may slow down the release of the drug and, therefore, can be successfully employed for the formulation of matrix tablets SR.

Key words: Glipizide, Matrix, Biguanides, Hypoglycemic, Polymers, Retardant.

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INTRODUCTION

Sustained release dosage forms are the formulations which release the therapeutically active agents for longer period of time at expected rate after its single dose administration.[1] When highly water soluble drugs are prepared as oral sustained release dosage form cause problems like they may be released more rapidly and result in toxicity if not prepared in appropriate fashion.[2] Many methods are there to formulate oral sustained release dosage form among which matrix system is most appropriate due to consistency, validation, scale up and cost effective.[3] Microcrystalline cellulose and PVP were used as diluents and binder respectively. Oral CR systems present a variety of benefits above conventional dosage forms that include decrease in dosage rate, patient ease, minimum toxicity and improved patient compliance[4] On the other hand, more constant level of drug in the blood constant flow with minimum peak-valley is reached, achieve greater efficacy. Conventional dosage forms release drugs according to criminal order which produces the rise and fall of drug concentrations and therapeutic level change. While dosage forms with controlled release of the drug release rate to zero, which gives order a steady drug concentration.[5] Although, the dosage forms of prolonged release also have some demerits. A process for manufacturing extended release dosage form is expensive which makes these products expensive than the conventional dosage forms. It decreased *in vitro / in vivo* bioavailability and free unequal. Other factors that we have considered are motility of the GIT, difference in pH and absorption. Among sulfonylurea class, Glipizide is an oral blood glucose lowering drug. It is not soluble in both alcohol and water with a pKa value of 5.9, but it is highly soluble in 0.1 N NaOH. The registered trademark of glipizide gits is glucotrol xl. It is formulated as a controlled release tablet once a day for oral use and is prepared as 2.5,5, or 10 mg of the glipizide.[6] By activating the insulin release from pancreas, Glipizide severely lower the blood glucose and this effect is dependent upon beta cells functioning. Extra-pancreatic effects also can have crucial role in hypoglycaemic oral sulfonylurea's mechanism of action by enhancing insulin sensitivity and a decreasing the production of glucose. The glipizide mechanism of lowering blood glucose by long-term therapy is not understood clearly. Insulin stimulation is by glipizide as a response to meal is of utmost importance thing.[7] 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. SR formulations that would maintain plasma levels of drug for 8 to 12 hrs might be sufficient for once a day dosing for Glipizide. SR products are needed for glipizide to prolong its duration of action and to improve patient compliance.

METHODS AND MATERIALS

MATERIALS

Glipizide (AA Pharmaceuticals, Pakistan) Guar Gum and HPMC K15(Colorcon, India), microcrystalline cellulose (PH 101), Aerosil and magnesium stearate (Merck, Germany).

METHOD OF PREPARATION TABLET

This is suitable as well economical method for tablet manufacturing. As before direct firmness was restricted to only compression of single compound into a compact mass. Presently it is a process of preparation of tablet by compressing the blend of excipients and active material. In this method wet or dry granulation of blend mixture is not compulsory.[8] So this procedure is consist of four steps that is the milling of non-active and active ingredients, powder mixing, blend in a mixer, powder lubrication with a appropriate lubricant and finally compression of blend to

form tablet. With the addition of microcrystalline cellulose and lactose of different grades make this process more suitable and convenient.

METHOD OF ANALYSIS STANDARD PREPARATION

100 mg of reference standard were weighed and dissolved in 100 ml of 7.4 buffer to make the concentration of 1 mg/ml. Serial dilution was done to make the final concentration of 0.01 mg/ml.[9]

SAMPLE PREPARATION

10 ml of the samples were withdrawn at the time interval of 0.5 hr, 1 hr, 2 hr, 3 hr, 4 hr, 5 hr, 6 hr, 7 hr and 12 hr. The samples withdrawn were replaced by equal amount of dissolution medium.[10]

DISSOLUTION

The release of glipizide from sustained release formulation was studied using Elecrolab dissolution apparatus. For each test, six formulations was placed in the flask containing 900 ml 7.4 buffer, dissolution medium, at 37±2°C at 50 rpm. Ten ml aliquot of the medium was sampled at predetermined time of 12 hours.[11] the sample was filtered and the concentration of glipizide was determined by measuring ultraviolet absorption at 276 nm. The mean of six determinants was used to calculate drug release from each formulation.

PHYSICAL TESTS OF TABLETS

In order to determine the uniformity in weight of tablets, 20 tablets of each formulation were randomly collected and weighed using class "A" weight balance and their percentage variation was deter-mined. The weight variation of all tablets was well within the acceptable limits of BP 2002, indicating that the filling of die cavity for tablets was uniform. All the formulations were tested and the deviation was not greater than 7%.[12] The result of tablets weight variation is presented in Table 3. Hardness of tablets was also determined using Erweka Hardness Tester. Ten tablets of each formulation were used and the average hardness value was determined.[13] the tablets of each formulation were also subjected to friability testing employing Pharma Test Friabilator. Ten tablets were placed in tumbling chamber and rotated precisely for 4 min at a speed of 25 rpm. The weight of 20 tablets prior to their placement in the chamber and at the end of the test was recorded. The percent age weight loss was then calculated. Triplicate measurements were conducted for each formulation. The acceptable limit of weight loss was not more than 1.00%.[14]

IN VITRO DRUG RELEASE CHARACTERISTICS

The dissolution studies were performed for the formulated Glipizide tablets over a period of 12 hours using USP dissolution test apparatus.[15]

Drug release was assayed by dissolution test under the following conditions: n=3 USP type II dissolution apparatus (paddle method) at 50 rpm 900 ml of phosphate buffer pH 6.8 for 12 hours, maintained at

The result in uniformity of the weight, hardness, Thickness, Friability, Drug content of the tablets are shown in the above table. All the tablets of the different batches compiled with the official requirements of uniformity of weight as the weights varied between 200.71 ± 1.02 to 199±1.33mg. The Hardness of the tablets ranged from 5.1±0.236 to 5.04±0.09 kg/cm^2.

The friability values were less than 0.8% indicating that the matrixes were compact and hard. The thickness of the tablets ranged from 2.17±0.078 to 2.23±0.078mm.

All the formulations satisfied the contents of the drug as they contained above 91.29±0.98% of Glipizide and good uniformity in drug content was observed. Thus all the physical attributes of the prepared were found to be practically within official limit.

The technique of Spectrophotometry is utilized frequently in laboratories for determination of compound concentration in solution. To determine the absorbance of glipizide, different concentration of glipizide was made and observes the readings of absorbance at 274nm.These results shows that drug follow beers law.

The calibration data showed that the beer's lambered law was followed by drug; different dilution of the drug was prepared and checked by spectrophotometer (Figure 2) which indicated the value of regression was

Table 1: composition of tablet Glipizide using different proportion of polymers

Formulation	Glipizide (mg)	HPMC K15 (mg)	Guar Gum (mg)	PVP (mg)	Aerosil (mg)	Magnesium Stearate (mg)	Lactose (mg)	Total weight (mg)
F_1	5	20	-	5	0.5	0.5	179	210
F_2	5	30	-	5	0.5	0.5	169	210
F_3	5	40	-	5	0.5	0.5	159	210
F_4	5	50	-	5	0.5	0.5	149	210
F_5	5	60	-	5	0.5	0.5	139	210
F_6	5	-	20	5	0.5	0.5	179	210
F_7	5	-	40	5	0.5	0.5	159	210
F_8	5	-	60	5	0.5	0.5	139	210
F_9	5	-	80	5	0.5	0.5	119	210
F_{10}	5	-	100	5	0.5	0.5	99	210
F_{11}	5	20	100	5	0.5	0.5	79	210
F_{12}	5	30	80	5	0.5	0.5	89	210
F_{13}	5	40	60	5	0.5	0.5	99	210
F_{14}	5	50	40	5	0.5	0.5	109	210
F_{15}	5	60	20	5	0.5	0.5	119	210

Table 2: granules properties

Formulation trial	Angle of repose	Loose bulk density (gm/ml)	Tapped bulk density (gm/ml)	Compressibility index (%)	Total porosity (%)
F1	24.12	0.42	0.553	15.08	24.01
F2	25.12	0.442	0.532	14.07	23.09
F3	24.34	0.412	0.512	12.06 0.08	24.05
F4	24.23	0.453	0.522	11.06	22.02
F5	24.09	0.432	0.502	14.00	23.13
F6	24.33	0.422	0.512	12.06	27.21
F7	24.44	0.411	0.598	13.11	24.12
F8	22.98	0.411	0.532	14.09	26.09
F9	23.23	0.422	0.509	13.23	20.54
F10	24.45	0.411	0.522	15.12	26.32
F11	24.98	0.422	0.512	14.08	22.29
F12	23.98	0.410	0.533	12.03	21.19
F13	23.45	0.397	0.521	11.04	26.75
F14	23.12	0.432	0.512	14.05	25.09
F15	24.33	0.422	0.512	12.06	27.21

Table 3: Physical Evaluation of Matrix Tablets

Code	Hardness (Kg/cm)	Thickness (mm)	Weight variation mg)	Friability %	Drug content %
F1	5.1 ± o.236	2.23 ± 0.078	200.71 ± 2.87	0.29 ±0.15	93.28 ± 1.99
F2	5.04 ± 0.104	2.19 ± 0.053	200.42 ± 1.35	0.32 ± 0.09	95.35 ± 1.14
F3	5.06 ± 0.185	2.22 ± 0.087	199.9 ± 1.33	0.17 ± 0.13	96.34 ± 2.18
F4	5.1 ± 0.109	2.22 ± 0.074	200 ± 1.54	0.19 ± 0.07	91.29 ± 0.98
F5	5.1 ± 0.167	2.18 ± 0.087	200.4 ± 1.45	0.24 ± 0.07	97.35 ± 0.43
F6	5.04 ± 0.09	2.17 ± 0.078	200.2 ± 1.6	0.22 ± 0.14	98.88 ± 0.88
F7	5.1 ± o.236	2.23 ± 0.078	200.71 ± 2.87	0.29 ± 0.15	93.28 ± 1.99
F8	5.04 ± 0.104	2.19 ± 0.053	200.42 ± 1.35	0.32 ± 0.09	95.35 ± 1.14
F9	5.06 ± 0.185	2.22 ± 0.087	199.9 ± 1.33	0.17 ± 0.13	96.34 ± 2.18
F10	5.1 ± 0.109	2.22 ± 0.074	200 ± 1.54	0.19 ± 0.07	91.29 ± 0.98
F11	5.1 ± 0.167	2.18 ± 0.087	200.4 ± 1.45	0.24 ± 0.07	97.35 ± 0.43
F12	5.04 ± 0.09	2.17 ± 0.078	200.2 ± 1.6	0.22 ± 0.14	98.88 ± 0.88
F13	5.06 ± 0.185	2.22 ± 0.087	199.9 ± 1.33	0.17 ± 0.13	96.34 ± 2.18
F14	5.1 ± 0.109	2.22 ± 0.074	200 ± 1.54	0.19 ± 0.07	91.29 ± 0.98
F15	5.1 ± 0.167	2.18 ± 0.087	200.4 ± 1.45	0.24 ± 0.07	97.35 ± 0.43

Table 4: Calibration curve concentrations of Glipizide

Sr no	Concentration mcg/ml	Absorbance
	5 mcg/ml	0.1813
	10 mcg/ml	0.3612
	15 mcg/ml	0.5361
	20 mcg/ml	0.7362
	25 mcg/ml	0.9269
	30 mcg/ml	1.1900

Table 5: FTIR wave length chart of Glipizide.

Sr. no.	Standard IR Peaks for Glipizide and Blend	Corresponding IR ranges	Vibrational Modes
1	1687.41	1670-1820	C=O (stretch)
2	1684.84	1670-1820	C=O (stretch)
3	1525.42	1400-1600	C=C (stretch)
4	1442.49	1400-1600	C=C (stretch)
5	1329.68	1325-1250	C-N (stretch)
6	1157.08	1020-1250	C-N (stretch)
7	1085.73	1020-1250	C-N (stretch)
8	1031.73	1020-1250	C-N (stretch)
9	902.52	910-665	N-H (wag)
10	838.88	900-675	C-H

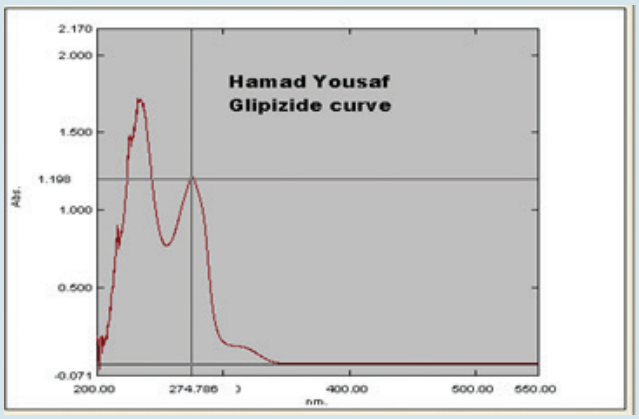


Figure 1: UV spectrum of Glipizide.

Table 6: FTIR wave length chart of Glipizide and HPMC.

Sr. no.	Standard IR Peaks for Glipizide and Blend	Corresponding IR ranges	Vibrational Modes
1	1684.52	1820-1670	C=O (stretch)
2	1645.95	1680-1620	C=C (stretch)
3	1525.42	1600-1400	C=C (stretch)
4	1442.49	1600-1400	C=C (stretch)
5	1154.19	1020-1250	C-N (stretch)
6	1030.77	1200=1000	C-N (stretch)
7	901.56	910-665	N-H (wag)

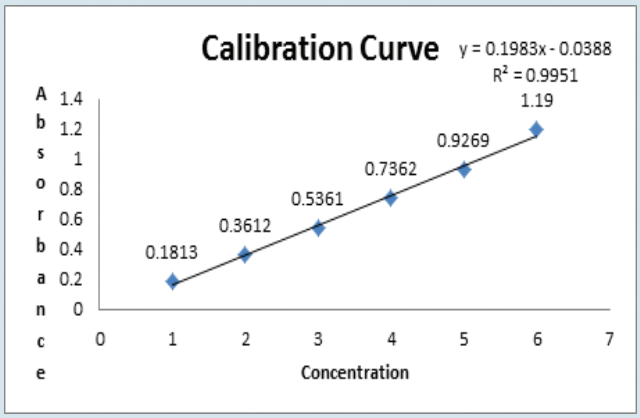


Figure 2: Calibration curve of Glipizide.

Table 7: FTIR wave length chart of Blend

Sr. no.	Standard IR Peaks for Glipizide and Blend	Corresponding IR ranges	Vibrational Modes
1	1684.52	1820-1670	C=O (stretch)
2	1648.84	1680-1620	C=C (stretch)
3	1522.52	1600-1400	C=C (stretch)
4	1439.60		
5	1157.08	1020-1250	C-N (stretch)
6	1030.77	1200=1000	C-N (stretch)
7	902.52	910-665	N-H (wag)
8	754.99		

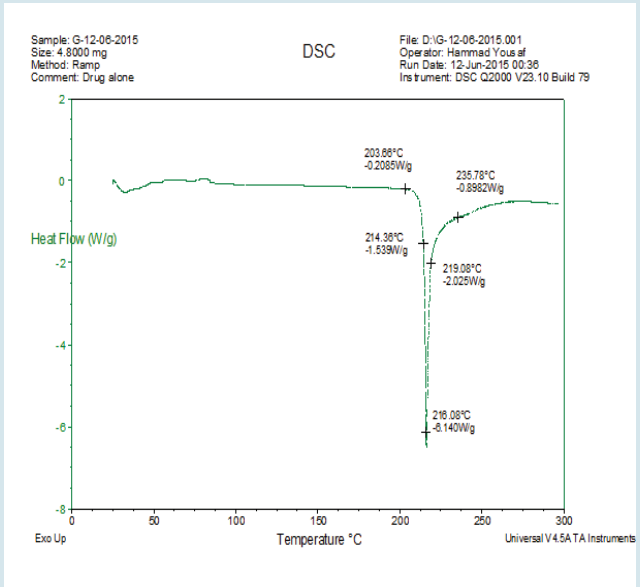


Figure 3: DSC of Glipizide.

Table 8: Kinetic Modeling of F_{14} Formulation

F_{14} Formulation Kinetic Modeling		
Sr. No.	Order & Model	R^2
1	First order	0.950
2	Zero order	0.960
1	KorsmeyerPeppas	0.962
2	Higuchi	0.962

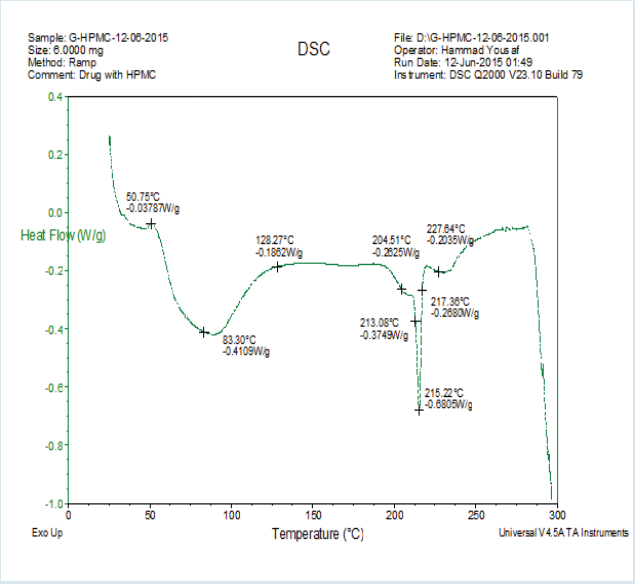


Figure 4: DSC of Glipizide + HPMC.

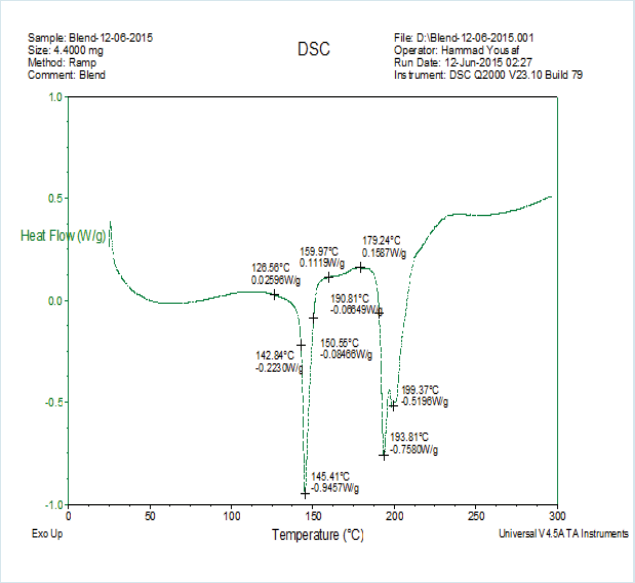


Figure 5: DSC of Blend.

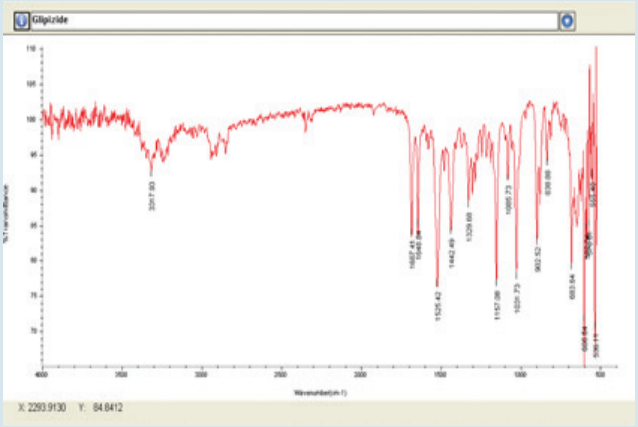


Figure 6: FTIR of Glipizide.

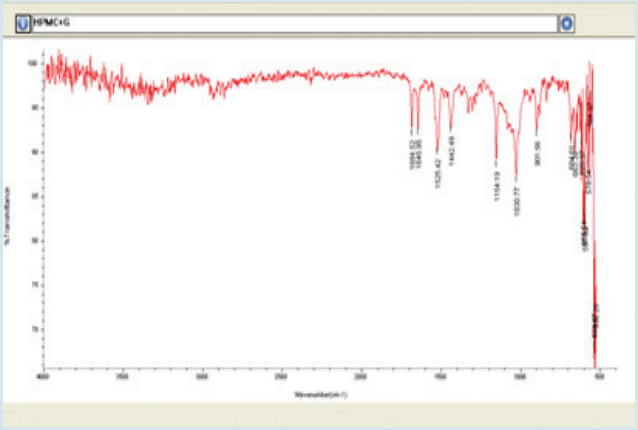


Figure 7: FTIR of Glipizide and HPMC.

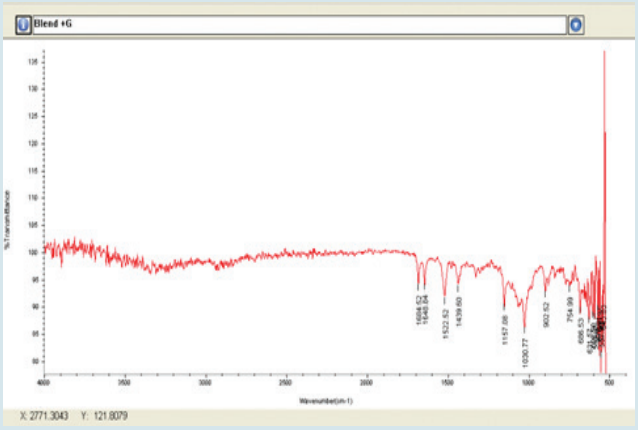


Figure 8: FTIR of Glipizide and Blend.

0.992, slope 73.68.these values were within the limits of ICH guideline.

DSC STUDY

Figure 3 shows pure Glipizide DSC thermogram which showed a sharp melting endo-therm at 216,08 C with a normalized energy of -6.140 J/g.

FTIR STUDY

Drug release studies

In-vitro release of the tablets was done in phosphate buffer of pH 7.4. Absorbance was measured by UV spectrophotometer.

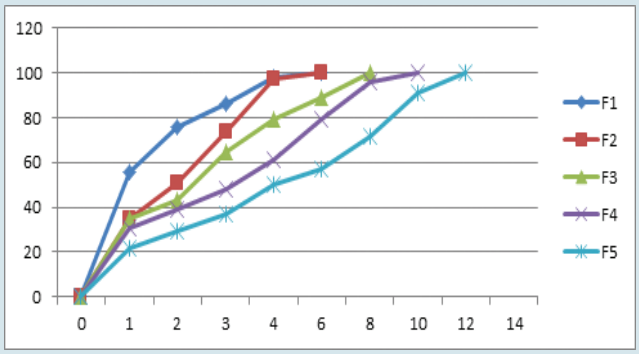


Figure 9: *In vitro* drug Release profile of Glipizide from matrix tablets based on HPMC using phosphate buffer7.4.

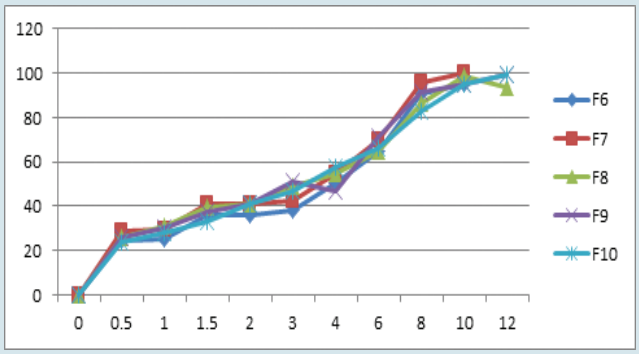


Figure 10: *In vitro* drug Release profile of Glipizide from matrix tablets based on Guar Gum using phosphate buffer 7.4.

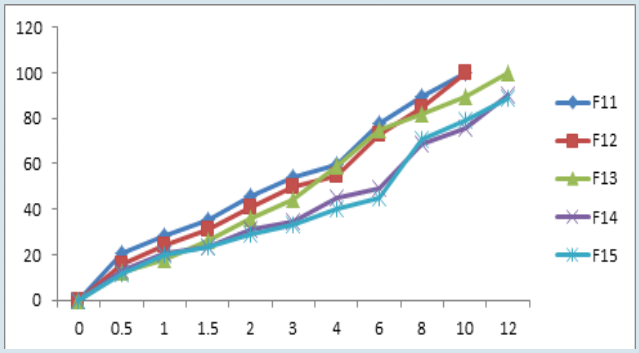


Figure 11: *In vitro* drug Release profile of Glipizide from matrix tablets based on HPMC and Guar Gum using phosphate buffer 7.4.

On the basis of comparison of dissolution data of the test formulations & standard, percentage release of drug was predicted. It was observed that release of drug in phosphate buffer PH 6.8 was slow. As the concentration of HPMC in formulation F_1 to F_5 gradually increased and in F_6 to F_{10} concentration of Guar Gum increased, now we have seen in F_{12} formulation the quantity of HPMC and Guar Gum was enough for the required release.

Effect of Increasing Concentration of HPMC and Guar Gum on Release of Drug

HPMC and Guar Gum was used in several concentrations to produce the matrix tablet. In F_1 to F_5 formulations HPMC alone in 1:4, 1:6, 1:8, 1:10 and 1:12 ratio respectively was used and an increase trend of sustained effect in release was observed. In F_6 to F_{10} formulations, Guar Gum alone in 1:4, 1:8, 1:12, 1:16 and 1:20 ratio respectively was used and again an increase sustained effect in release was observed.

ANALYSIS OF RELEASE DATA OF F_{14} FORMULATION

Regression coefficient R^2 were determined by mathematical models of release kinetics by incorporating data of 12h release of all formulations and release constant k was also determined by slope of graph. To evaluate the drug release mechanism first order, zero order, Hixson Crowell Equation, Higuchi model & korsmeyer model were used. F_{14} formulations followed zero and Higuchi model in the distill water suggested the release of drug was through diffusion.

PHARMACOKINETIC MODELING OF F_{14} FORMULATION

Dissolution Equivalency Test

Formulation F_5 and F_{14}

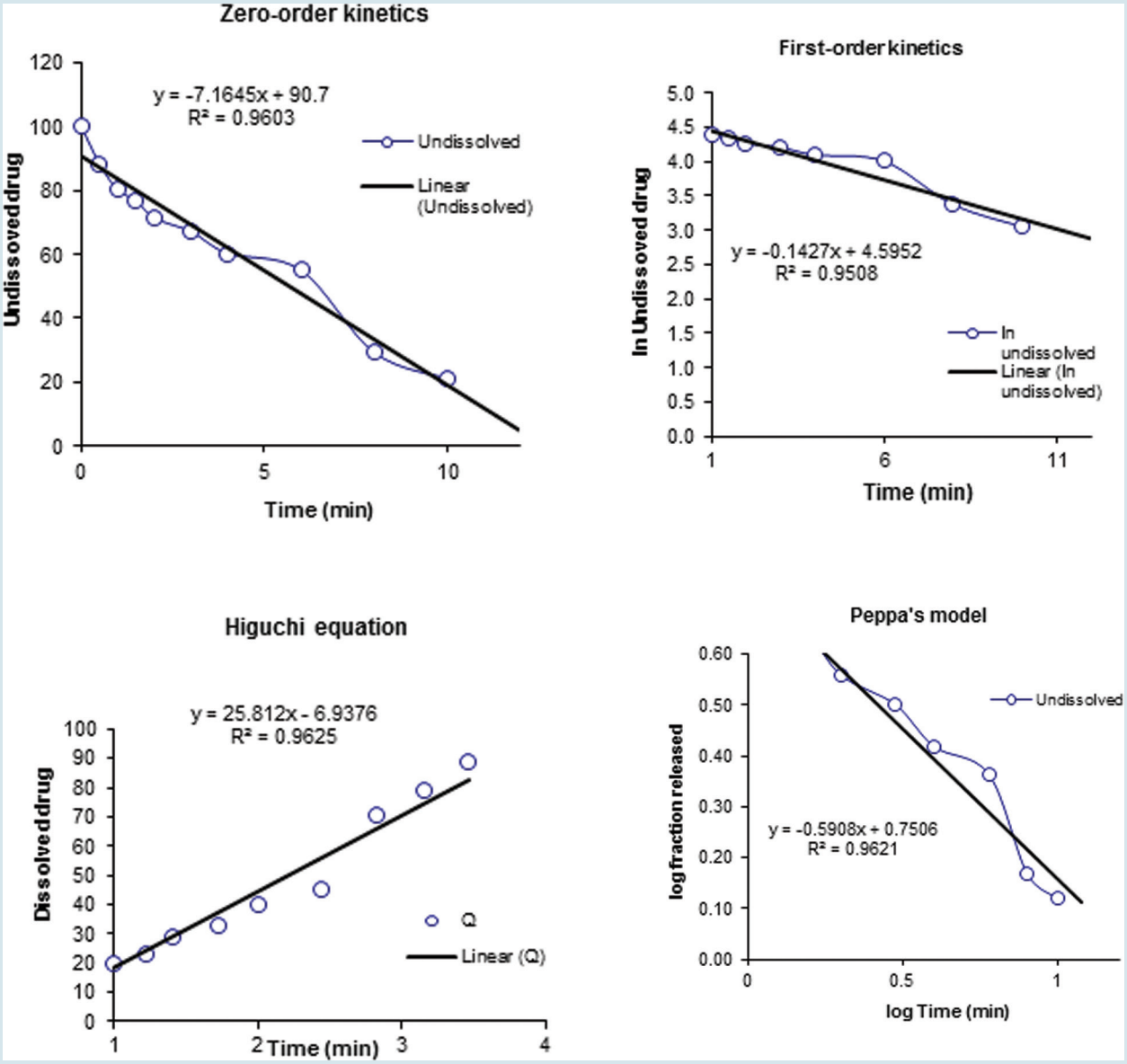
Similarity factors value of f_1 is less than 15 and f_2 is more than 50 indicate that both the formulations are similar proposals.

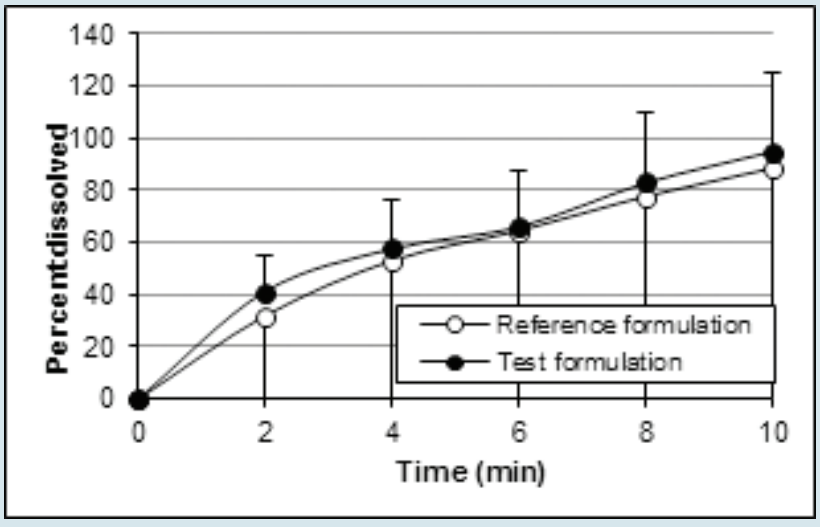
Formulation F_{10} and F_{14}

Similarity factors value of f_1 is more than 15 and f_2 is less than 50 indicate that both the formulations are not of similar proposals.

CONCLUSION

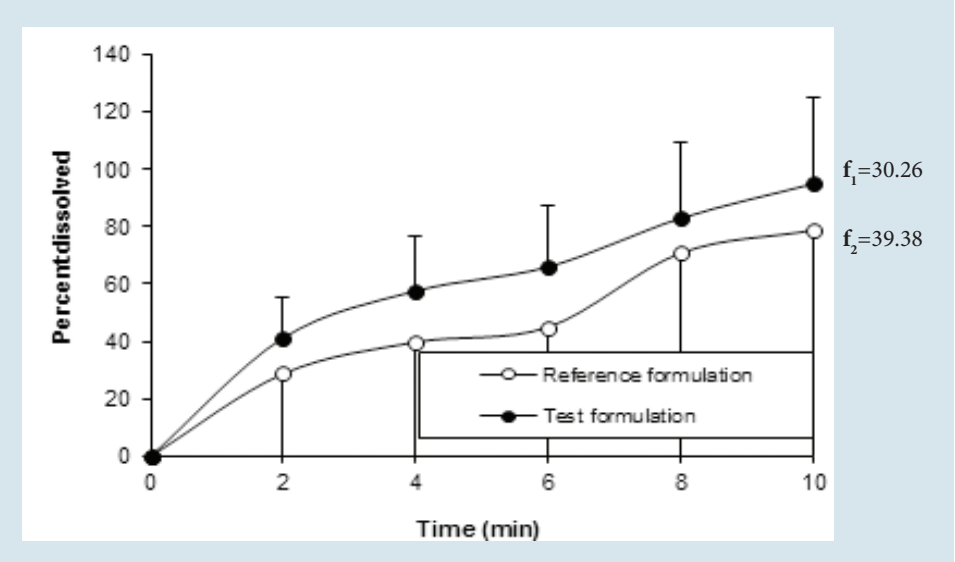
Matrix extended release tablets of glipizide using mixture of natural a nd semi-synthetic polymers are formulated with direct compression technique. Pre-compression, as post-compression parameters were observed and were found to be within official limits. FTIR indicated no interaction or alteration of the structure. They compared different formulations. HPMC and Guar Gum was used in several concentrations to produce the matrix tablet. In F_1 to F_5 formulations HPMC alone in 1:4, 1:6, 1:8, 1:10 and 1:12 ratio respectively was used and an increase trend of sustained effect in release was observed. In F_6 to F_{10} formulations, Guar Gum alone in 1:4, 1:8, 1:12, 1:16 and 1:20 ratio respectively was used and again an increase sustained effect in release was observed. The formulations as F_1 to F_5 had increasing concentration of HPMC (from 9.5% to 28.57%). Although the release of the drug was slow up to 12 hours, but these preparations were not as good as F_6 to F_{10} containing increasing concentrations of guar gum as a natural polymer. All these formulations have shown better results than HPMC containing formulations. Formulations F_4 and F_5 were sustained up to 12 hours that showed improved support properties attributed to HPMC. Guar gum is used as the main polymer formulations F_6 to F_{10}. It is a natural polymer, but the results were better than the HPMC. Drug release was delayed and it took more than 12 hours for the full release of drugs especially to F_9 and F_{10}. In future studies, with glipizide mixture of HPMC (semi-synthetic polymer) and guar gum (natural polymer) in 1: 4: 20, 1: 6: 16, 1: 8: 12,





f_1 = 8.43

f_2 = 61.09



1: 10: 8 and 1:12: 4 respectively. Comparing F_{14} (containing guar gum and HPMC), it is seen that the results were better than the formulations containing guar gum and HPMC alone. These preparations release the drug slowly and sustained up to 12 hours. In the formulation, it was used F_{14} mixture of HPMC and guar gum. Since both polymers were highly effective to maintain the slow release of drug from matrix tablets, these formulations incurred more than 12 hours. It indicates release has been improved by incorporation of the polymer mixture. It suggests that a mixture of polymers 2 works better than the individual polymers. From the release profiles of the drug over, it can be concluded that prolonged effect is highly dependent on the nature and concentration of the polymers. Combination has better effects than the individual polymers. Guar gum when used in higher concentration delayed the release of the drug so profitably, should be further investigated for this type of preparations. Kinetic modeling has also been applied to all formulations. In comparison, it can be concluded that all the formulations followed zero-order kinetics indicating that drug release is independent of concentration. They also followed the Higuchi model indicates that the drug has been released by the diffusion process. The value of n from Korsmeyer Peppas model suggested that all formulations have followed the behavior of non-Fickian release means that the drug has been released both by diffusion and erosion mechanisms controlled.

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CONFLICT OF INTEREST

No conflict of interest.

ABBREVIATION USED

SR: Sustained release; **CR:** Controlled release; **HCl:** Glipizide hydrochloride; **HPMC:** Hydroxy propyl methyl cellulose.

REFFERENCES

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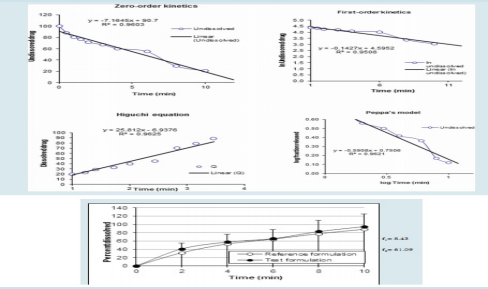
PICTORIAL ABSTRACT



SUMMARY

- Sustained release dosage forms are the formulations which release the therapeutically active agents for longer period of time at expected rate after its single dose administration. Matrix extended release tablets of glipizide using mixture of natural and semi-synthetic polymers are formulated with direct compression technique. Kinetic modeling has also been applied to all formulations. In comparison, it can be concluded that all the formulations followed zero-order kinetics indicating that drug release is independent of concentration. They also followed the Higuchi model indicates that the drug has been released by the diffusion process.

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