Research Article

Formulation and evaluation of sustained release glipizide tablet using different polymers

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ABSTRACT

The glipizide sustained release (SR) tablet was prepared using different hydrophilic polymers such as hydroxypropyl methylcellulose (HPMC) K4M, HPMC K100M, and ethyl cellulose in various proportions. Design Expert software used for formulation of glipizide SR tablet. The SR tablet was prepared by direct compression method. The prepared SR tablets were subjected to thickness, friability, weight variation test, drug content, hardness, and *in vitro* release studies. The drug excipients compatibility was evaluated by Fourier transform infrared (FTIR) and differential scanning calorimetry (DSC) studies. *In vitro* dissolution study shows that F6 formulation was 97% releases the drug in a controlled manner for 16 h. The DSC and FTIR studies revealed that there was no interaction between drug and excipients. Stability studies were carried out for optimized formulation according to ICH guidelines. Using different hydrophilic polymers in various proportions to prepare SR tablets of glipizide having prolonged therapeutic effect with enhanced patience compliance.

Keywords: Direct compression method, ethyl cellulose, glipizide, hydroxypropyl methylcellulose, *in vitro* release, sustained release

Introduction

Sustained release (SR) is types of modified drug delivery system that can be used as an alternative to conventional system. Among different dosage forms, SR drug delivery system widely used.[1] SR system have benefits such as patient compliance, avoid multiple dosing, cost effectiveness, flexibility, increase the plasma drug concentration, avoid side effects, broad regulatory acceptance, and overcome the problems associated with conventional drug delivery system.[2-4] Hydrophilic polymers are becoming very popular in formulating oral sustain release tablets. As the dissolution medium penetrates the SR tablets, the polymer material swells, and it form hydrogel by the time thus it is able to controlled drug release.[5,6] However, the SR tablet by direct technique is a very simple approach in the pharmaceutical field for its ease, compliance, faster production, in comparison with other controlled release systems. Cellulose ethers such as hydroxypropyl methylcellulose (HPMC) and ethyl cellulose are widely used hydrophilic polymers as release retardants.[7,8]

Glipizide is widely used sulphonyl urea antidiabetic agent, for the treatment of patients with type II diabetes.[9] It is a weak acid (pKa = 5.9) practically insoluble in water and acid solution but as per biopharmaceutical classification system it is highly permeable.[10] The oral absorption is uniform, rapid, and complete with nearly 100% bioavailability with an elimination half-life of 2-4 h. Glipizide having a short biological half-life (3.4 ± 0.7 h) requiring it to be administered in 2-3 doses of 2.5-10 mg per day.[11] SR formulations that would maintain plasma levels of drug for 8-12 h might be sufficient for once a day dosing for glipizide. Sustain release products are needed for glipizide to prolong its duration of action and to improve patient compliance. The objective of this study was to develop a matrix system to completely deliver glipizide, in a zero-order manner over an extended period using various hydrophilic polymers. Thus, the study takes into consideration for research study formulate and evaluate the SR tablet of glipizide using different polymers with different ratio and characterized study using SR tablet.

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Materials and Methods

Materials

Glipizide was procured from (Wockhardt Pvt. Ltd., Mumbai), hydroxypropyl methylcellulose (HPMC) K4M, HPMC K100M, ethyl cellulose, lactose, talc, and magnesium stearate an all ingredients and chemicals were used as a laboratory grades were procured from (Research Lab., Fine chemicals industry, Mumbai, Maharashtra, India).

Methods

Formulation of glipizide sustain released (SR) tablet

Weighed all the ingredients and mix all the ingredients in a mortar and triturated it by pestle until the uniformity mixture formed, then added talc and magnesium stearate and again triturated it. After uniform mixture formed ingredients were passed through the sieve no. 20. The direct compression method was utilized for the preparation of glipizide SR Tablet. The tablets were compressed using 8 mm plane faced punches at KBr press tablet compression machine.[10,12,13] Prepared tablet further used for characterization and evaluation study purposed used.

The formula of glipizide SR tablet is shown in the Table 1.

Experimental design

A 3^2 factorial design (Design-Expert® Software, state Stat-Ease, Inc.) was used for preparation of glipizide SR tablet. In this design, two factors were evaluated each at three levels, and experiment trials were performed at all nine possible combination. There are nine batches alloted to performed formulation processed by 3^2 factorial designs. The amount of HPMC K100M code (X1) and the amount of ethyl cellulose code (X2). In this design highest value of ingredients in quantity showed (+) sign, (−) middle value, and (0) lowest value. The coded value of 3^2 factorial designs shown in Table 2. Formulation factorial batches of experiments are shown in Table 3, codes are given F1 to F9 total nine batches.

Characterization

IR spectra

The IR spectra of drug, polymers, and formulation sample were recorded (IR-200 Thermo-electron) using potassium bromide (KBr) pellet method. The sample was triturated in porcelain mortar pestle with dry KBr in ratio (1:100) were pellets prepared at pressure 8 tones. The pellets were scanned over the range of 4000-400 cm and the spectrum obtained at a molecular level.

Differential scanning calorimetry (DSC)

The thermal behavior of glipizide was studied using (Shimadzu DSC TA60WS Thermal Analyzer). Accurately weighed samples of glipizide (5 mg) were hermatically sealed in aluminium panand heated at a constant rate of 10°C/min over temperature range of 150-210°C. The DSC thermogram was recorded and reported.

Evaluation of SR tablets of glipizide

Appearance

The thickness of tablet as a dimensional variable was evaluated. The tablet thickness was controlled within ±5% of average value. The color, odor any other flaws such as chips, cracks, and surface texture are other important morphological characteristics were observed.

Hardness

Tablet hardness is defined as force required to crushing the tablet in diametric compression test. The hardness was measured with Monsanto hardness tester. The tablets were placed diametrically between two plungers and the lower plunger is kept in contact of tablet to read as zero. The upper plunger is forced against a spring by turning the screw until tablet fractures.

Friability

Twenty tablets were weighed and subjected to friability test in Roche friabilator. The pre-weighed sample was placed in friabilator which resolves at 25 rpm for 4 min dropping the tablets through a distance of 6″ with each revolution.

The friability formula is given as:

$$\% F = (1 - W0)/W \times 100 \quad (1)$$

Where,

F is friability,

W0 is the weight of tablets before test,

W is weight of tablets after test.

Table 1: Formula of glipizide SR tablet

Sr. No	Ingredient	Quantity (mg)
1.	Glipizide	10
2.	HPMC K4M	15
3.	HPMC K100M	20
4.	Ethyl cellulose	80
5.	Lactose	159
6.	Talc	2
7.	Magnesium stearate	1
Total weight		290

SR: Sustain released, HPMC: Hydroxypropyl methylcellulose

Table 2: Coded values for 32 factorial designs

Formulation code	Variable	Level
F1	+1	+1
F2	+1	0
F3	+1	−1
F4	0	+1
F5	0	0
F6	0	−1
F7	−1	+1
F8	−1	0
F9	−1	−1

Table 3: Formulation of factorial batches (F1-F9)

Ingredients	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)	F8 (mg)	F9 (mg)
Glipizide	10	10	10	10	10	10	10	10	10
HPMC K4M	15	15	15	15	15	15	15	15	15
HPMC K100M	25	25	25	20	20	20	15	15	15
Ethyl cellulose	90	80	70	90	80	70	90	80	70
Lactose	147	157	167	152	162	172	157	167	177
Talc	2	2	2	2	2	2	2	2	2
Magnesium stearate	1	1	1	1	1	1	1	1	1
Total weight	290	290	290	290	290	290	290	290	290

HPMC: Hydroxypropyl methylcellulose

Weight variation test

Weight variation test is carried out as per USP/NF. The test is carried out by weighing 20 tablets individually and calculating the average weight, and comparing the individual tablet weight with the average weight of 20 tablets. The tablets meet the test if not more than 2 tablets are outside the limit and if no tablet differs by more than 2 times the limit.

The weight variation limits for tablets differ depending on average tablet weight. The limits are specified in the Table 4.

Table 4: Weight variation limits for tablets

Average weight of tablets	Maximum % difference allowed
130 mg or less	10
130-324 mg	7.5
More than 324 mg	5

Drug content

Randomly selected 3 tablets from F6 batch were crushed in a mortar and pestle. The crushed tablet equivalent to 290 mg of glipizide was taken in a 100 ml volumetric flask and dissolved with 7.4 phosphate buffer. The volume was made up to the mark and filtered through Whattman filter paper No.42. The concentration of glipizide was determined by measuring the absorbance at 222 nm.

Drug release study

The drug release rate from glipizide SR tablets was determined using USP apparatus type II (Labindia Analytical, Thane, India). The dissolution test was performed using 900 ml of 7.4 phosphate buffer, for 16 h at 37°C ± 0.5°C and 50 rpm. A sample (5 ml) was withdrawn at a specific interval and replaced with fresh dissolution medium of same quantity. The samples were filtered through a Whattman filter paper. Absorbance of the solutions was measured at 222 nm.

Result and Discussion

Factorial design

Optimization of Glipizide SR tablet was performed using Design Expert software version 9.0.4.1. Design expert plotted the following graphs; predicted versus actual, contour plot, and surface response plot. Analysis of variance (ANOVA) study for formulations was performed by HPMC K4M (A) and ethyl cellulose (B) formulation variables and for percent drug release at 16 h as response. ANOVA results were as summarized in Table 5. Predicted versus actual, contour plot, and surface response plot were given in surface response plot and contour plots shows that drug release decreases with increasing concentration of independent variables HPMC K4M (A) and decreasing concentration of ethyl cellulose (B). The possible reason which may be attributed to this drug release is ability due to its hydrophilic nature (Figures 1-3).

Table 5: ANOVA of glipizide sustained release tablet

Source of variation	Degrees of freedom	Sum of squares (partial)	Mean squares (partial)	F ratio	P value
Model	3	862.07	287.36	6.93	0.0313
A-A	1	440.67	440.67	10.63	0.0224
B-B	1	307.02	307.02	7.40	0.0417
AB	1	114.38	114.38	2.76	0.1576
Residual	5	207.31	41.46	-	-
Correlation total	8	1069.39	-	-	-

ANOVA: Analysis of variance

$$\text{Drug release} = +80.38 + 8.57 * A - 7.15 * B + 5.35 * A * B \quad (2)$$

Characterization

IR spectra

The IR peaks observed in Glipizide and polymers combinations shown in *Figure* 4. In IR study of drug and polymers show all prominent peaks. The IR spectra of glipizide *is characterized* by the absorption of CO-NH stretching at 1640 cm-, at 1370 SO2.NH *stetching*, at 1142 cyclohexyl stretching, 1651 –C=O. In IR spectra of glipizide and polymers shows same absorption patterns that of pure drug. Mentioned *evidences* thus lead to the conclusion that changes *are not seen* as there is no physical interaction between the drug and polymer at *molecular* level.

DSC studies

The endothermic peak at 215°C can be attributed as melting point of glipizide and the endothermic peak at 146°C of the polymer

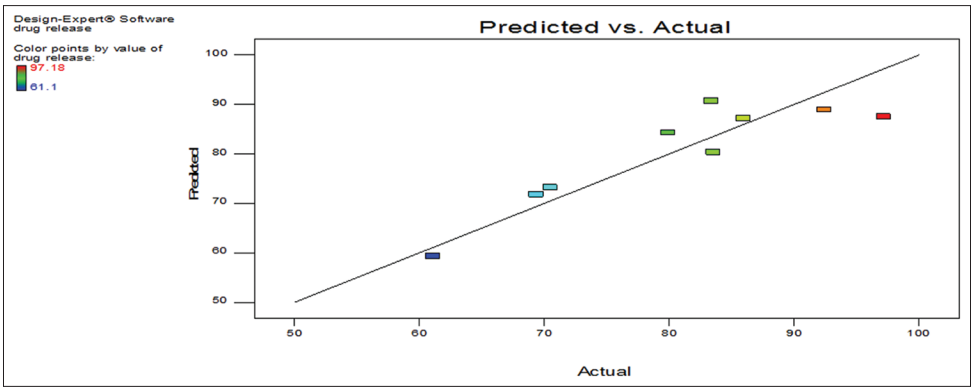

Figure 1: Predicted versus actual value

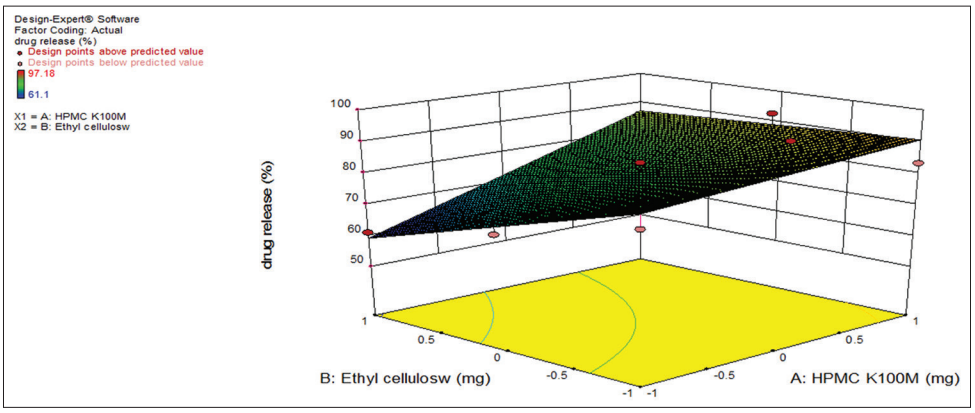

Figure 2: 3D response surface plot showing the relationship between various levels of two factors on % cumulative drug release

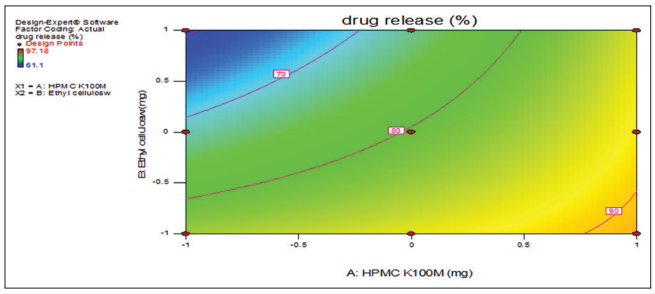

Figure 3: 3D graph showing the influence of two factors on % cumulative drug release

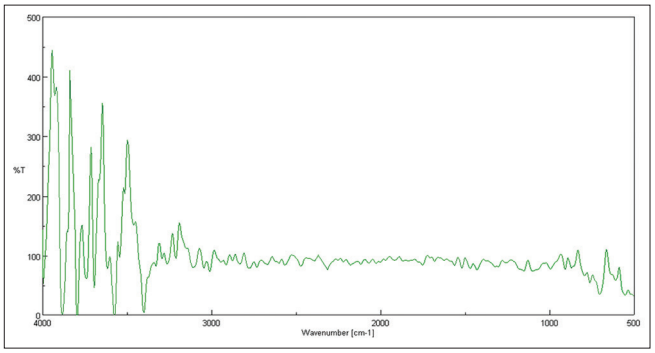

Figure 4: Infrared spectra of glipizide and polymers

can be attributed shown in Figure 5. The thermogram showed that the glipizide, HPMC, and ethyl cellulose are compatible with each other.

Evaluation of glipizide SR tablet (F6) batch

Among the entire 9 batches, F6 batch selected for the further evaluation process. The following are the evaluation parameters for glipizide SR tablet.

Appearance

The tablets from F6 batch was white, circular, and flat faced. The surface texture was smooth. The thickness of tablets of was 2.99 ± 0.02 mm and it was found to be within limit of deviation from average value (not more than 5%).

Hardness

The hardness is important characteristics to be evaluated for handling and transportation properties of the tablets. Hardness of tablets was found to be 4.7-5.3 kg/cm^2.

Friability

Friability is important characteristics to be evaluated for handling and transportation properties of the tablets. The friability of tablets

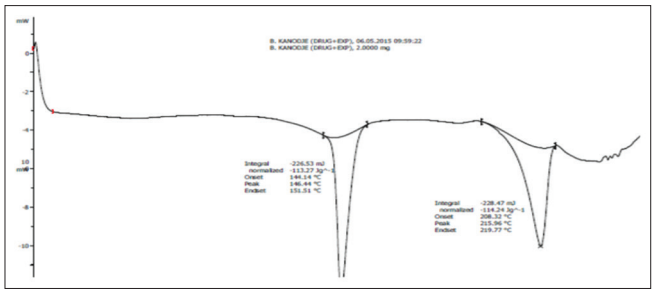

Figure 5: Differential scanning calorimetry thermogram of glipizide and polymers

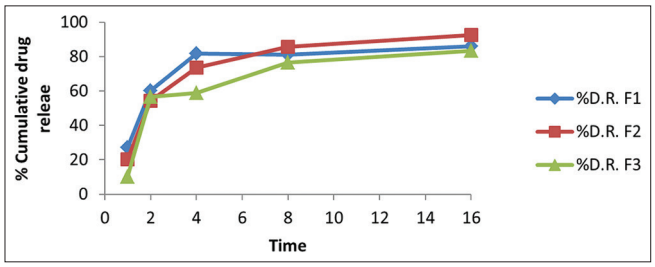

Figure 6: % cumulative drug release of F1, F2, and F3 batches

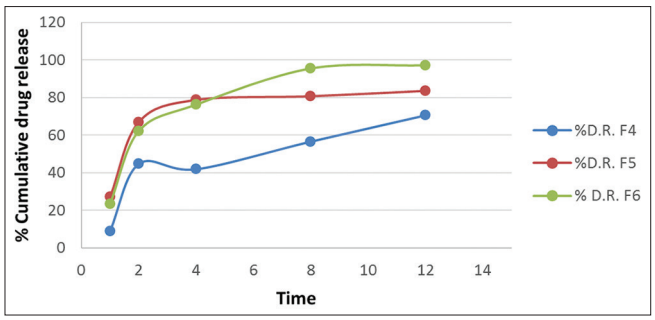

Figure 7: % cumulative drug release of F4, F5, and F6 batches

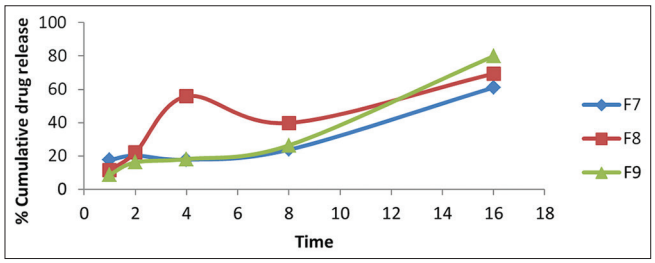

Figure 8: %cumulative drug release of F7, F8, and F9 batches

was <0.5% which indicates good handling and transportation characteristics. The friability of tablets was found to be 0.6%.

Weight variation

According to USP for tablet weighing 290 mg or more not more than two tablets differ from the average weight by 7.5% deviation. The percent deviations in weight variation from average value for all formulations of factorial batches were within limit. The weight variation within limits indicates uniformity in tablet compression and consequently content of drug in unit. Tablet weight within all factorial design batches was not constant because that would require the use of diluents for weight adjustment, which in turn may have caused variation in release profile (Tables 6 - 8).

Table 6: ANOVA study to determine the impact of two polymers on each other

Term	Coefficient	Standard error	Low confidence	High confidence	VIF
Intercept	80.38	2.15	74.86	85.90	
A: Factor 1	8.57	2.63	1.81	15.33	1.00
B: Factor 2	−7.15	2.63	−13.91	−0.40	1.00
A • B	5.35	3.22	−2.93	13.63	1.00

ANOVA: Analysis of variance

Table 7: Regression analysis

Significant terms

Name	P value
A: Factor 1 (HPMC K4M)	0.0224
B: Factor 2 (ethyl cellulose)	0.0417
A • B	0.1576

HPMC: Hydroxypropyl methylcellulose

Drug content

The drug content of SR tablet of glipizide (F6) batch was found to be between 96.86% and 99% the value ensures good uniformity of the drug content in the tablet.

In vitro drug release studies of SR tablets of glipizide

The rate of drug absorption for many drug moieties in the gastrointestinal track is often determined by the rate of dissolution from the tablet. The rate of drug dissolution may be directly related to the efficacy of the tablet product, as well as bioavailability differences between the formulations. This test of dissolution is most of the times useful to specific types of dosage forms such as control release, sustain release, time dependent, and targeted to know the approximate drug release behavior of dosage form in the gastrointestinal (GI) tract. The release profile of formulation F1 to F9 shows % cumulative drug release in 16 hours as shown in Figure 6 (F1-F3), Figure 7 (F4 to F6), and Figure 8 (F7 to F9). Formulations F1, F2, F5, and F6 releases drug up to 20-30% in 1st h and F4, F7, F8, and F9 releases drug in 10-20%. The released of drug sustained by combination of HPMC K100M, and ethyl cellulose. The burst release may be overcome using the two polymers, hydrophilic polymer HPMC K100M, and hydrophobic polymer ethyl cellulose. Formulation F6 shows 97% drug release in 16 h.

Comparison of drug release profile with marketed preparation

The optimized formulation F6 has compared with marketed product according to USP sampling interval. All parameters were found to have good similarity. The prominence was placed on comparison of dissolution profile by determination of similarity factor (f_2) which was in range of 50-100.

Table 8: Evaluation of prepared SR tablets

Formulation	Appearance	Weight variation (mg±SD)	Hardness (kg/cm^2) ±SD	Friability (%)	Thickness (mm)±SD	Drug content
F6	White, circular, 8 mm plane surface	289.62±1.86	4.94±0.9	0.6	2.7±0.2	96.86±1.38

SR: Sustain released, SD: Standard deviation

Table 9: Evaluation of glipizide SR tablets factorial batches (F1-F6)

Formulation code	Weight variation (mg±%SD)	Hardness (kg/mm^2)	Friability (%)	Thickness (mm)±SD	Assay (%)	Drug release
F1	280±0.55	4.7±0.5	0.6	2.5±0.012	91.42	85.96
F2	295±0.45	4.9±0.9	0.94	2.5±0.01	87.4	92.46
F3	286±1.28	5.5±1.30	0.7	2.65±0.05	85.55	83.38
F4	274±0.19	5±1	0.79	2.30±0.02	91.40	70.49
F5	286±0.56	5±1.05	0.9	2.57±0.05	89.27	83.56
F6	287±0.85	4.1±0.17	0.6	2.67±0.0	96.86	97.18
F7	291±1.42	4.86±0.8	0.5	2.71±0.02	96.56	61.10
F8	278±1.41	4.7±0.7	0.74	2.69±0.06	90.41	69.37
F9	284±1.11	4.9±0.9	0.94	2.72±0.06	85.55	79.91

SR: Sustain released, SD: Standard deviation

Table 10: Comparative evaluation of optimized batch with marketed preparation

Evaluation parameter	Developed product batch (F6)	Marketed product (Glynase XL 10 mg, USV Ltd. Mumbai)
Appearance	White, circular, 8 mm flat faced	White, circular, 10 mm, concave faced
Weight variation (±%)	0.854%	1.527%
Drug content (%)	96.86±1.86	99.03±1.12
Hardness (kg/cm^2)	4.94±0.9	6.3±0.045

Table 11: Comparative dissolution profile of developed F6 batch and marketed product

Time (h)	% cumulative drug release Marketed formulation	% cumulative drug release F6 batch tablet
1	21.35	23.42
2	39.39	62.14
4	56.50	76.24
8	63.55	95.48
16	99.12	97.18

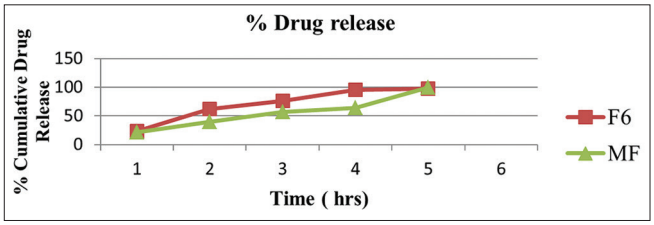

Figure 9: % cumulative drug release F6 batch tablet and market formulation

The optimized batch was compared with the market sample regarding the drug release profile to determine the parallelism between the optimized formulation, i.e., F6 and marketed sample. The detail graph of comparison is shown in Figure 9.

Figure 9 shows release pattern of formulations 6 sample resemble to the market sample product. From results it was cleared that blend has good flow property. Tablet has satisfactory physical properties. Release pattern was found to be complied with USP specifications as well as similar to marketed sample product (Tables 9-11).

Conclusion

The SR system releases drug such as glipizide throughout the GI tract achieving peak drug release level within few hours followed by decreasing release rate over time. The preliminary studies revealed that formulations prepared using polymers HPMC K4M, HPMC K100M failed to retard the release of drug for 16 h through the tablet because of the high solubility of drug. Formulation containing ethyl cellulose retarded the drug release up to some period.

From the release pattern of formulations containing both HPMC K100 and Ethyl cellulose, it could be concluded that only ethyl cellulose worked well and the initial burst was controlled as well as the release of the drug was better in the initial 1-4 h.

Formulations F1, F2, F5, and F6 releases drug up to 20-30% in 1 h. F4, F7, F8, and F9 releases drug in 10-20%. The burst release may be overcome using the two polymers, i.e., hydrophilic polymer HPMC K100M and hydrophobic polymer ethyl cellulose. Formulation F6 shows 97% drug release in 16 h. Formulation and evaluation of glipizide SR tablet using different polymer was successfully developed.

References

1. Bravo SA, Lamas MC, Salamón CJ. *In vitro* studies of diclofenac sodium controlled-release from biopolymeric hydrophilic matrices. J Pharm Pharm Sci 2002;5:213-9.
2. Mishra B, Seena J, Singh S, Sankar C. Development and characterization of matrix tablets of ketorolac trometh amine. Indian Pharm 2003;2:86-9.

3. Reddy KR, Mutalik S, Reddy S. Once-daily sustained-release matrix tablets of nicorandil: Formulation and *in vitro* evaluation. AAPS PharmSciTech 2003;4:E61.
4. George M, Grass IV, Robinson JR. Sustained and Controlled Release Drug Delivery Systems. New York: Marcel Dekker; 1978. p. 124-7.
5. Bonferoni MC, Caramella C, Sangalli ME, Conte U, Pedraz JL. Rheological behaviour of hydrophilic polymers and drug release from erodible matrices. J Control Release 1992;18:205-12.
6. Kurahashi H, Kami H, Sunada H. Influence of physicochemical properties on drug release rate from hydroxyl propyl methylcellulose matrix tablets. Chem Pharm Bull (Tokyo) 1996;44:829-32.
7. Arthur HK. Handbook of Pharmaceutical Excipients. 3rd ed. London: American Pharmaceutical Association; 2000. p. 463-4.
8. Carstensen JT. Theoretical aspects of polymer matrix systems. In: Muller BW, editor. Controlled Drug Delivery. Stuttgart: Wissenschftliche Verlagsgesellschaft; 1987. p. 135-7.
9. Möckel JE, Lippold BC. Zero-order drug release from hydrocolloid matrices. Pharm Res 1993;10:1066-70.
10. Chowdary KP, Rao YS. Design and *in vitro* and *in vivo* evaluation of mucoadhesive microcapsules of glipizide for oral controlled release: A technical note. AAPS PharmSciTech 2003;4:E39.
11. Patel JK, Patel RP, Amin AF, Patel MM. Formulation and evaluation of mucoadhesive glipizide microspheres. AAPS PharmSciTech 2005;6:E49-55.
12. Patil S, Choudhari S, Ratnaparkhi MP. Formulation and evaluation of beta blocker and ACE inhibitor bilayered tablets by direct compression technique. Sch Res Libr 2013;5:164-172.
13. Cantoni J, Tous SS, Bataille B, Prinderre P, Reynier JP, Hansel-Esteller S, *et al*. Formulation and evaluation of sustained release tablets containing antioxidants. Bull Pharm Sci 2010;33:9-18.