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FORMULATION AND EVALUATION OF GLICLAZIDE INCORPORATED CELLULOSIC MICROSPHERES FOR SUSTAINED RELEASE DELIVERY

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ABSTRACT

Polymeric microspheres of gliclazide were prepared to provide sustained release delivery of gliclazide to aid in continuous therapy with high margin of safety. Gliclazide was microencapsulated with different polymers namely HPMC K100LV, Ethocel (20 cps) and HPMC K100M by emulsion solvent evaporation technique using acetone as internal phase and liquid paraffin as external phase. Seventeen formulations were prepared using different drug loading and polymeric ratio of which nine formulations were prepared by a 3^2 full factorial design. Each formulation was evaluated for flow properties, particle size, surface morphology, drug entrapment efficiency, drug release and compatibility. Yield (%) for every batch of microspheres was measured. Flow properties of the microspheres were examined by determining bulk density, tapped density, Carr's compressibility index, Hausner ratio and angle of repose. Particle size distribution was examined by sieving and particle size analyzer. Surface morphology was determined by scanning electron microscopy (SEM). *In-vitro* drug release was studied in a paddle type dissolution apparatus (USP Type II Dissolution Apparatus) for a period of 8 hours at 37°C using phosphate buffer (pH 7.4). FTIR and DSC studies established compatibility of the drug with the polymers. Microspheres prepared with Ethocel (20 cps) and HPMC K100M were free flowing than those prepared only with HPMC K100LV. Entrapment efficiencies were within 75.88-99.69%. Microspheres prepared with Ethocel (20 cps) and HPMC K100M showed more sustained release when compared to microspheres prepared with HPMC K100LV only. Increase in drug loading resulted in increased drug release for the microspheres. Kinetic modeling of *in vitro* dissolution profiles revealed the drug release mechanism ranging from diffusion controlled to anomalous type. Ethocel and HPMC K100M in a ratio of 1:3 exhibited better sustained release properties than 1:1 and 3:1 ratios. The release rate of gliclazide from microspheres prepared with Ethocel (20 cps) and HPMC K100M was less than the release rate of gliclazide from microspheres prepared with HPMC K100LV, demonstrating Ethocel and HPMC K100M as suitable polymeric blend for preparing the controlled release formulation for gliclazide whereas, HPMC K100LV was found not suitable candidate when used alone as a polymer.

KEYWORDS: Emulsification-solvent evaporation, Gliclazide, Microsphere, HPMC K100LV, Ethocel, HPMC K100M.

INTRODUCTION

Microencapsulation is a useful method for prolonging drug release from dosage forms and reducing adverse effects. Recently, dosage forms that can precisely control the release rates and target drugs to a specific site have made an enormous impact on the formulation and development of novel drug delivery system. Microencapsulation is the coating of small solid particles, liquid droplets or gas bubbles with a thin film of coating or shell material that have an arbitrary particle size ranging between 1 and 1000 µm.[1,2]

Gliclazide is an oral antihyperglycemic agent used for the treatment of non-insulin dependent diabetes mellitus (NIDDM). It belongs to the sulfonylurea class of insulin secretagogues, which act by stimulating β cells of the pancreas to release insulin. Gliclazide is a BCS Class II drug. It is rapidly absorbed from the GIT. It appears in the blood within 1-2 hrs.[4] Like other drugs of BCS class II, reduction of particle size or increase in surface area will enhance its solubility. At present, patients have to take one or more doses of conventional or sustained release gliclazide tablets to maintain normal plasma glucose levels. Currently, gliclazide tablets available in the market have not yet attained the physiological goal of providing constant plasma glucose levels over an extended period of time to meet the basal needs between meals and during the night. Not only the less local gastric interferences but less chance of dose dumping make microencapsulation one of the best ways to provide

sustain release of drug. Among the cellulosic polymers, hydroxypropyl methylcellulose (HPMC) is one of the most important hydrophilic carrier materials which is used for the preparation of oral controlled drug delivery systems.[5,6] HPMC is biodegradable and highly sweallable, which significantly influences the release kinetics of an incorporated drug. When the dosage form such as microsphere comes in contact with water or biological fluid the drug diffuses into the device, resulting in polymer chain relaxation with volume expansion.[7,8]

MATERIALS AND METHODS

Gliclazide and other excipients such as Methocel K100LV (Colorcon, India), Methocel K100M (Colorcon, India) and Ethocel 20 cps (Colorcon, India) were obtained from ACI Pharmaceuticals Ltd. Acetone, *n*-hexane, Span 80, liquid paraffin, potassium dihydrogen phosphate, sodium hydroxide etc were procured from Merck (Germany).

Preparation of microspheres of gliclazide with cellulosic polymers by solvent evaporation technique.[9]

Polymeric microspheres of gliclazide were prepared according to non-aqueous emulsification solvent evaporation technique using three different cellulosic polymers HPMC K100LV, HPMC K100M and Ethocel 20 cps all of which are insoluble in water; but can dissolve in mixture of organic solvents depending upon the ethoxy contents. Acetone was used as solvent and Span 80 was used as lipophilic surfactant for all the formulations. According to the formulation (Tables 1 and 2), the required amount of polymer was taken in 100ml glass beaker previously containing 10ml acetone. Then the mixture was thoroughly stirred until a clear solution of polymer was formed. The beaker was kept for microsphere preparation. 1ml of Span 80 was taken in properly washed and dried 1000ml plastic beaker. 100ml light liquid paraffin was added to Span 80 and the mixture was stirred at 1000 rpm for 5 minutes. Then required amount of gliclazide powder was added to the respective formulation to form a suspension. Stirring was continued for 10 minutes. Then polymer solution was poured drop by drop into the drug suspension with simultaneous stirring. The stirring was continued until hard, uniform shaped microspheres were formed which required about 3 hours. The container was then kept static to allow the microspheres for settling down. Serial washing of microspheres was carried out with *n*-hexane. Then the microspheres were spread over a filter paper and left for drying in a desiccator for a day. The dried microspheres were kept in a vial with proper identification.

Formulation design

Seventeen batches of microspheres of gliclazide were prepared. Total amount of drug and polymer were kept constant at 2g for each batch. First eight batches of microspheres were prepared using single polymer (HPMC K100LV) where the amount of drug was increased gradually keeping the total amount to 2g. The next nine batches were prepared with a combination of two polymers (Ethocel 20 cps and HPMC K100M) according to a 3^2 full factorial design where the drug loading and the polymeric ratios were considered as independent variables to evaluate their effect on other parameters which are considered as dependent variables.[10]

Table 1 Formulation of microspheres of gliclazide using single polymer (HPMC K100LV).

Table 2: Formulation of microspheres of gliclazide by 32 factorial design using combination of polymers (Ethocel 20 cps and HPMC K100M).

Drug Loading ↓	Polymer (Cellulose)		
	Ethocel-Methocel (1: 3)	Ethocel-Methocel (1: 1)	Ethocel-Methocel (3: 1)
30% (Ploymer-70%)	**GC 11** (0.60g Gliclazide + 0.35g Ethocel + 1.05g Methocel)	**GC 21** (0.6g Gliclazide + 0.70g Ethocel + 0.70g Methocel)	**GC 31** (0.60g Gliclazide + 1.05g Ethocel + 0.35g Methocel)
50% (Ploymer-50%)	**GC 12** (1.0g Gliclazide + 0.25g Ethocel + 0.75g Methocel)	**GC 22** (1.0g Gliclazide + 0.50g Ethocel + 0.50g Methocel)	**GC 32** (1.0g Gliclazide + 0.75g Ethocel + 0.25g Methocel)
70% (Ploymer-30%)	**GC 13** (1.4g Gliclazide + 0.15g Ethocel + 0.45g Methocel)	**GC 23** (1.4g Gliclazide + 0.30g Ethocel + 0.30g Methocel)	**GC 33** (1.4g Gliclazide + 0.15g Ethocel + 0.45g Methocel)

In vitro characterization of polymeric microspheres of gliclazide

Production yield.[11] The yield (%) was determined by dividing the weight of microspheres by weight of total amount used in the formulation, and multiplying it by 100.

Micromeritics study.[13,14] Flow properties were studied by determining the Carr's compressibility index, Hausner ratio and angle of repose. Bulk density and tapped density were determined.

Angle of repose was calculated by fixed funnel method. Accurately weighed microspheres were passed through the funnel fixed on a stand with a white paper placed under it. The microspheres falling through the funnel on

the paper formed a pile. Then the funnel was lowered in such a way so that the tip of the funnel touched the apex of the pile of the microspheres. Then the paper with the microspheres on it was removed, and the height from the base to the funnel was measured. The diameter of the pile of microspheres was measured several times, and the average value was taken as the diameter of the pile. From this the radius was calculated.

Particle size analysis.[15,16] Particle sizes of the microspheres prepared with Ethocel and HPMC K100M combined was determined by laser diffracting particle size analyzer (Partica®5960). The analyzer provided the particle size according to the refractive index of that particle. The particle size distribution was represented as bar diagram as well as in numeric values.

Study of surface morphology by scanning electron microscopy (SEM).[17,18] Scanning electron microscopy was used to study the morphology and surface topography of the microspheres. The samples were scanned using scanning electron microscope (s- 3400N, Hitachi) under different magnification.

***In vitro* dissolution study of microspheres containing gliclazide.**[19,20] *In vitro* dissolution study was performed in a paddle type (Type II) dissolution apparatus. Weighed amount of microspheres containing 100mg drug was taken from each batch of formulation for dissolution purpose. Phosphate buffer of pH 7.4 was used as dissolution media, paddle speed was set at 100 rpm and temperature was maintained at 37°C. The dissolution process was carried out for 8 hours and 10 ml dissolution sample from each dissolution media was withdrawn. Then the amount of drug released and rate constants were analyzed using different mathematical models to evaluate the release mechanism to find the best fit by observing the R^2 value. Korsmeyer-Peppas model was used to determine the 'n' value to make conclusion about the diffusion mechanism. Successive fractional dissolution time for each batch was also measured and analyzed by gg Plot software to observe the effect of drug loading and polymer ratio.

Compatibility studies of drug and polymer within gliclazide microspheres.[21]

Fourier transform infrared spectrophoto- metry (FTIR). The IR spectrum of the pure drug, pure polymers and optimized microsphere formulations were obtained to evaluate the chemical integrity and compatibility of the drug with the polymers in the microspheres.

Differential scanning calorimetery (DSC). DSC study was carried out to evaluate the interaction between the drug and the polymers in the microspheres by using a Differential Scanning Calorimeter (DSC 60, Shimadzu). The specific heat and enthalpies of transition were determined.

RESULTS AND DISCUSSION

Production yield (%) of microspheres. For microspheres prepared with HPMC K100LV, there is a wide variation in the yield (%) value, the lowest value being 76.70% for GH1 (10% drug loading) and the highest one being 95.75% for GH6 (60% drug loading). Microspheres prepared with Ethocel and HPMC K100M, the yield (%) value exhibited lowest variation, with the minimum being 95.85% for GC11 (30% drug loading) where the ratio of polymer (Ethocel: HPMC K100M) was 1:3 and the maximum being 100.15% for GC33 (70% drug loading) where the ratio of polymer (Ethocel: HPMC K100M) was 3:1.

Drug entrapment efficiency. Figure 1 depicts the relationship between the drug entrapment efficiency and the drug loading. The bar diagram exhibits that, when only HPMC K100LV is used as a polymer, the drug entrapment efficiency is maximum for GH1 (10% drug loading) and minimum for GH5 (50% drug loading). The bar diagram also reveals another important fact that the drug entrapment efficiency becomes maximum (97.71%) when the ratio of polymers (Ethocel: HPMC K100M) is 1:3 with 70% drug loading and minimum (82.39%) when the ratio of polymers is 1:1 with 30% drug loading.

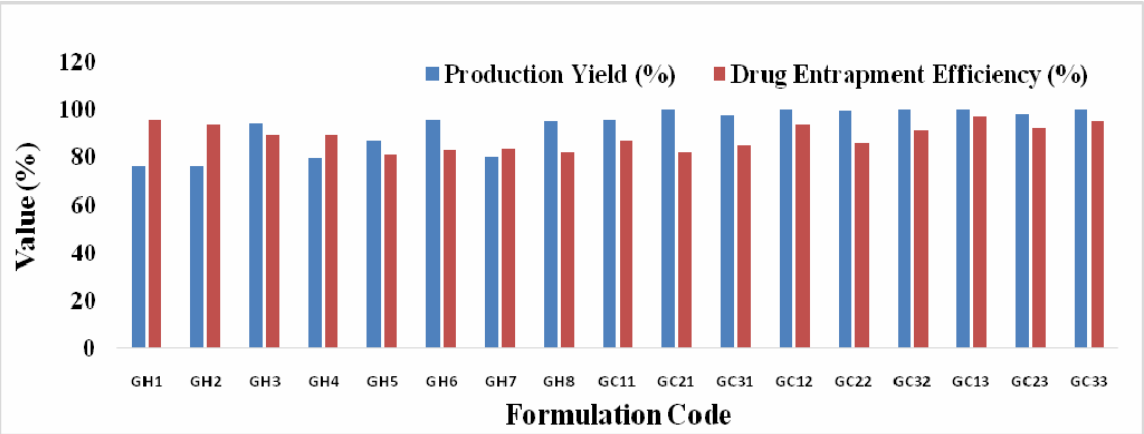


Figure 1: Production yield (%) and drug entrapment efficiency of microspheres.

But irrespective of polymer ratios, the drug entrapment efficiency increases with the increase in the drug loading. So, it can be concluded that, microspheres prepared with HPMC K100M and Ethocel, HPMC K100M when used in its highest amount become more effective for obtaining better drug entrapment efficiency.

Analysis of impact of drug loading and polymer ratio on drug entrapment efficiency using gg plot software (R i386.3.0.0). Figure 2 reveals that, for microspheres prepared with HPMC K100LV, drug entrapment efficiency decreases with increase in drug loading and decrease in percentages of polymer. For batches of microspheres prepared with Ethocel and HPMC K100M, drug entrapment efficiency increases with increase in drug loading and the maximum drug entrapment efficiency is obtained when Ethocel and HPMC K100M were used in 1:3 ratio for all three drug loadings (30%, 50% and 70%), that is the batches of microspheres of GC11, GC21 and GC31 have the highest drug entrapment efficiency.

The model F-value of 117.31 implies that the model is significant. Values of "Prob > F" less than 0.0500 indicate model terms are significant. In this case A, B, B2 are significant model terms. The "Lack of Fit F-value" of 1.68 implies that the Lack of Fit is not significant relative to the pure error. So, it can be can said that both drug loading and ratio of polymer have individualized effect on drug entrapment efficiency of various batches of microspheres prepared with Ethocel and HPMC K100M.

loadings, which can be clarified by a gradual fall up to '0' coded value and gradual rise from '0' coded value along X2 axis in figure 3. Contour plot in figure 4 reveals the different drug loading and.

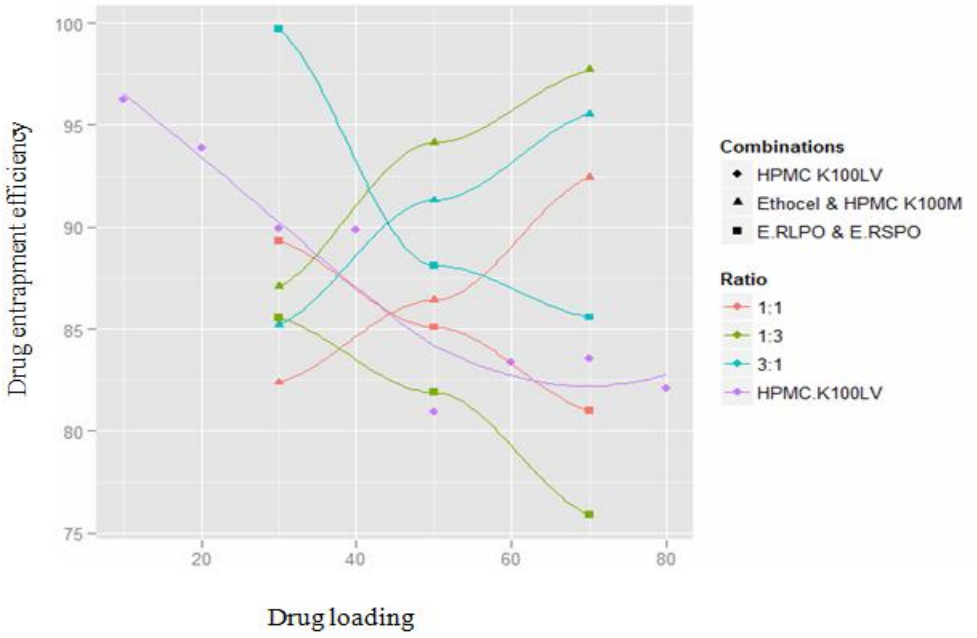


Figure 2: Complex line-plot effect of drug loading and polymer on drug entrapment efficiency.

ANOVA (Analysis of variance) for response surface reduced quadratic model Table 4. ANOVA for drug entrapment efficiency of various batches.

Source	Sum of squares	df	Mean square	F value	P-value Probe>F	
Model	0.011	3	3.631E-003	117.31	<0.001	Significant
A-Drug Loading (Gliclazide)	8.392E-003	1	8.392E-003	271.14	<0.001	
B-Ethocel: HPMC K100M	4.090E-004	1	4.090E-004	13.21	0.0027	
B^2	2.092E-003	1	2.092E-003	67.57	<0.0001	
Residual	4.333E-004	14	3.095E-005			
Lack of Fit	2.028E-004	5	4.057E-005	1.68	0.2583	

Micromeritics study. Particles having excellent flow properties will have value of Carr's Compressibility index, Hausner ratio and Angle of repose in the range of ≤10, 1.00-1.11 and 25-30, respectively. The results in Table 8 indicate that microspheres prepared with HPMC K100LV exhibits poor flow properties. Among the eight batches prepared with HPMC K100LV, the best flow properties were shown by GH4 (40% drug loading) and the worst by GH3 (30% drug loading) which requires aid to flow through the funnel. On the other hand, microspheres prepared with Ethocel and HPMC K100M exhibit improved flow properties. Best flow properties were exhibited by GC31 (30% drug loading) and GC13 (70% drug loading), whereas, the worst exhibited by GC11 (30% drug loading). In GC31, the ratio of polymers (Ethocel: HPMC K100M) was 1:3 and in GC13, the ratio was 3:1 (Ethocel: HPMC K100M). So, it can be concluded that when Ethocel and HPMC K100M were used in combination in preparing microspheres, the higher is the amount of HPMC K100M better is the flow properties.

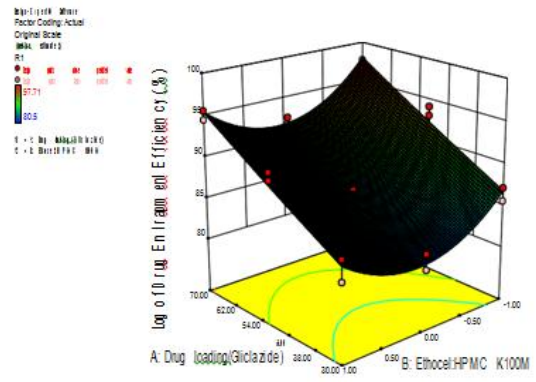


Figure 3: Response surface plot for drug entrapment efficiency for gliclazide microspheres prepared with Ethocel and HPMC K100M.

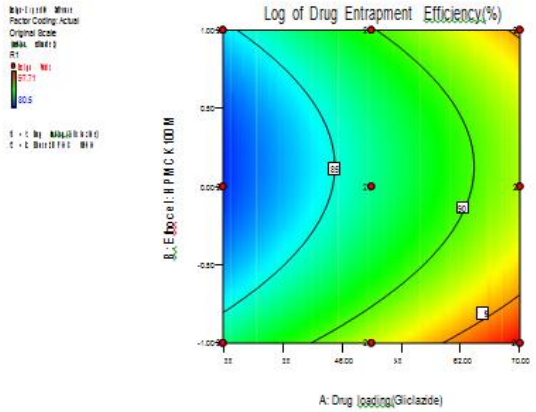


Figure 4: Contour plot for drug entrapment efficiency for gliclazide microspheres prepared with Ethocel and HPMC K100M.

Table 8: Particle size distribution.

Formulation	Mean size (µm)	Median size (µm)	D (v, 0.1) (µm)	D (v, 0.5) (µm)	D (v, 0.9) (µm)
GC11	913.04	924.38	131.94	924.38	1487.09
GC21	1430.00	1403.65	685.00	1403.65	2277.49
GC31	1317.65	1246.24	607.58	1246.24	2182.10
GC12	677.02	729.47	105.34	729.47	1086.29
GC22	1393.36	1372.13	673.30	1372.13	2176.11
GC32	1719.81	1700.45	1054.98	1700.45	2479.53
GC13	472.23	254.24	113.05	254.24	1177.65
GC23	1078.02	1041.64	314.24	1041.64	1835.81
GC33	1321.39	1282.72	605.06	1282.72	2105.87

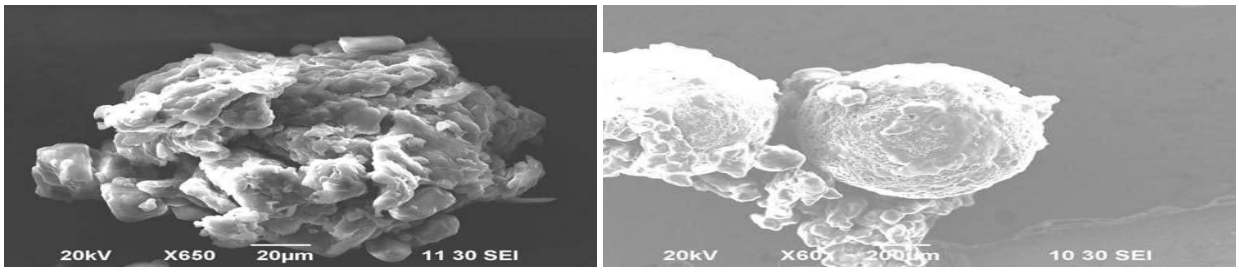
OBSERVATIONS

Scanning electron microscope (SEM). SEM study reveals that, microspheres prepared with HPMC K100LV have pores and cracks in the surface but the microsphere prepared in combination with Ethocel and HPMC K100M have no pores or cracks in their surface. Presence of pores or cracks may cause quick release since these facilitate the penetration of dissolution medium into the microsphere. Nature of the surface influences the stability and dissolution characteristics of the microspheres. If surface is rough, there are more chances of wetting and contact of water with the microsphere than the smoother one.

Effect of polymer on release pattern of gliclazide microsphere. Microspheres of all the seventeen formulations were examined for dissolution pattern. GH3 showed better release retardant properties than the rest of the formulations prepared with HPMC K100LV alone. But, when Ethocel and HPMC K100M were used in combination, 3:1 ratio of Ethocel and HPMC K100M showed better release retardant properties. Ethocel and HPMC K100M when used in 1:3 ratios also exhibited release retardant properties which were better than 1:1 ratio of the two polymers.

Successive fractional dissolution time. Successive fractional dissolution times of seventeen formulations of gliclazide microsphere are discussed below. The $T_{25\%}$,

$T_{50\%}$, $T_{80\%}$ and MDT values were determined to characterize the drug release rate from the microspheres and the retaining efficiency of the polymers. Higher value of MDT indicates higher drug retaining ability of the polymer and *vice-versa*.



A B

Figure 5: Scanning electron microscopic view of microspheres A. Formulation GH5 (Microspheres with HPMC K100LV), B. Formulation GC12 (Microspheres with Ethocel and HPMC K100M).

Table 9: Release rate constants and R^2 values for different release kinetics for all batches of microspheres.

Formulation	Zero order		First order		Higuchi		Korsmeyer-Peppas		Hixson Crowell K0	
	K0	R2	K1	R2	KH	R2	KKP	R2	KHC	R2
GH1	11.93	0.963	-0.421	0.922	35.29	0.987	0.244	0.985	0.183	0.981
GH2	7.846	0.622	-0.309	0.936	27.9	0.837	0.388	0.985	0.179	0.959
GH3	6.53	0.9	-0.106	0.963	21	0.991	0.259	0.985	0.093	0.947
GH4	9.169	0.839	-0.228	0.973	30.35	0.977	0.366	0.977	0.187	0.942
GH5	9.61	0.835	-0.292	0.979	31.85	0.975	0.416	0.977	0.237	0.958
GH6	10.57	0.89	-0.451	0.873	34.24	0.992	0.394	0.988	0.327	0.966
GH7	8.144	0.835	-0.203	0.945	26.58	0.947	0.433	0.918	0.201	0.933
GH8	8.406	0.86	-0.173	0.959	27.44	0.975	0.293	0.932	0.193	0.937
GC11	6.378	0.939	0.097	0.98	19.04	0.994	0.202	0.988	0.087	0.97
GC21	7.003	0.95	0.108	0.982	21.92	0.99	0.176	0.996	0.097	0.976
GC31	4.408	0.908	0.058	0.942	14.14	0.994	0.324	0.99	0.054	0.932
GC12	3.677	0.883	0.046	0.922	11.87	0.979	0.162	0.975	0.053	0.911
GC22	5.942	0.946	0.085	0.98	18.69	0.995	0.151	0.998	0.092	0.971
GC32	4.471	0.88	0.058	0.919	14.51	0.987	0.149	0.986	0.065	0.907
GC13	6.246	0.875	0.088	0.896	19.96	0.951	0.132	0.965	0.108	0.891
GC23	5.191	0.634	0.08	0.697	18.53	0.859	0.316	0.882	0.095	0.677
GC33	4.312	0.911	0.055	0.942	13.79	0.992	0.127	0.986	0.069	0.932

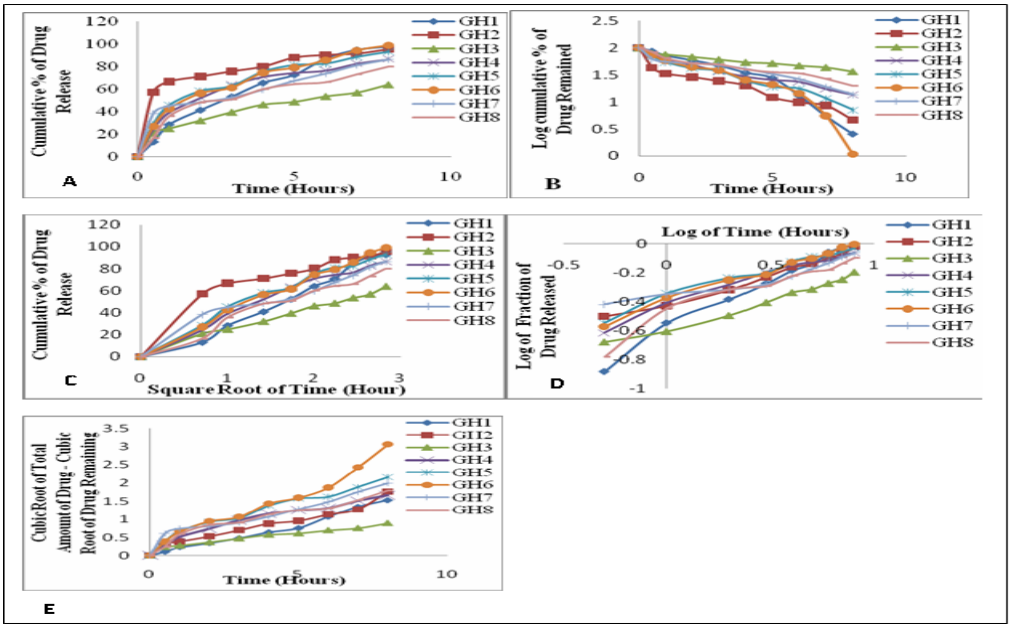


Figure 6: *In vitro* release kinetics of gliclazide microspheres prepared with HPMC K100LV A. Zero order plot,

B. First order plot, C. Higuchi plot, D. Korsmeyer-Peppas plot, E. Hixson-Crowell plot.

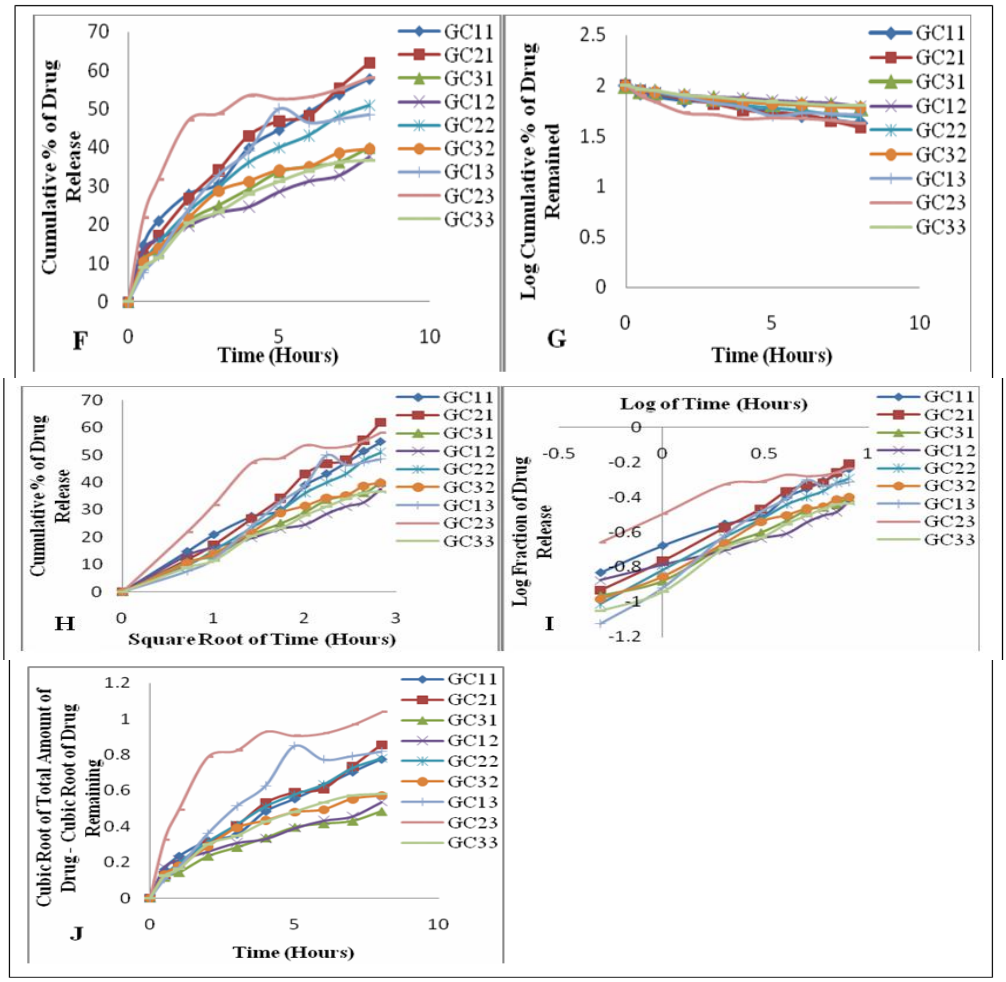


Figure 7: *In vitro* release kinetics of gliclazide microspheres prepared with Ethocel and HPMC K100M F. Zero order plot, G. First order plot, H. Higuchi plot, I. Korsmeyer-Peppas plot, J, Hixson-Crowell plot.

Table 10: Best fitted model and mechanism of drug release from polymeric microspheres.

Formulation	Best fitted model	n value	Release mechanism
GH1	Higuchi	0.698	Non-Fickian/Anomalous transport
GH2	KorsmeyerPeppas	0.403	Fickian transport
GH3	Higuchi	0.403	Fickian transport
GH4	Higuchi and Korsmeyer-Peppas	0.438	Fickian transport
GH5	First order	0.400	Fickian transport
GH6	Higuchi	0.447	Fickian transport
GH7	Higuchi	0.285	Fickian transport
GH8	Higuchi	0.497	Non-Fickian/Anomalous transport
GC11	Higuchi	0.487	Non-Fickian/Anomalous transport
GC21	Korsmeyer-Peppas	0.597	Non-Fickian/Anomalous transport
GC31	Higuchi	0.489	Non-Fickian/Anomalous transport
GC12	Higuchi	0.359	Fickian transport
GC22	Korsmeyer-Peppas	0.598	Non-Fickian/Anomalous transport
GC32	Higuchi	0.501	Non-Fickian/Anomalous transport
GC13	Higuchi	0.717	Non-Fickian/Anomalous transport
GC23	Korsmeyer-Peppas	0.316	Fickian transport
GC33	Higuchi	0.544	Non-Fickian/Anomalous transport

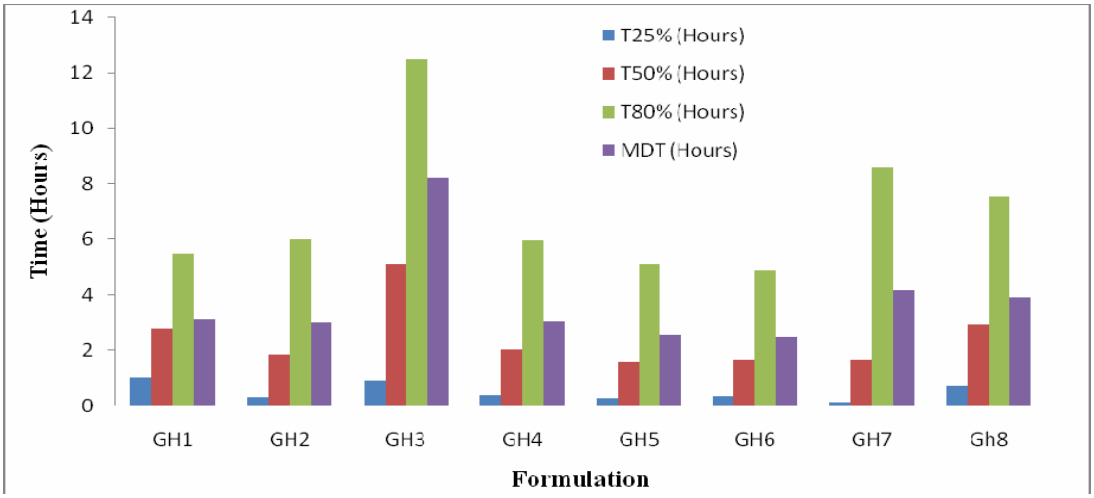


Figure 8: Bar diagram representing successive fractional dissolution time of GH1, GH2, GH3, GH4, GH5, GH6, GH7 and GH8.

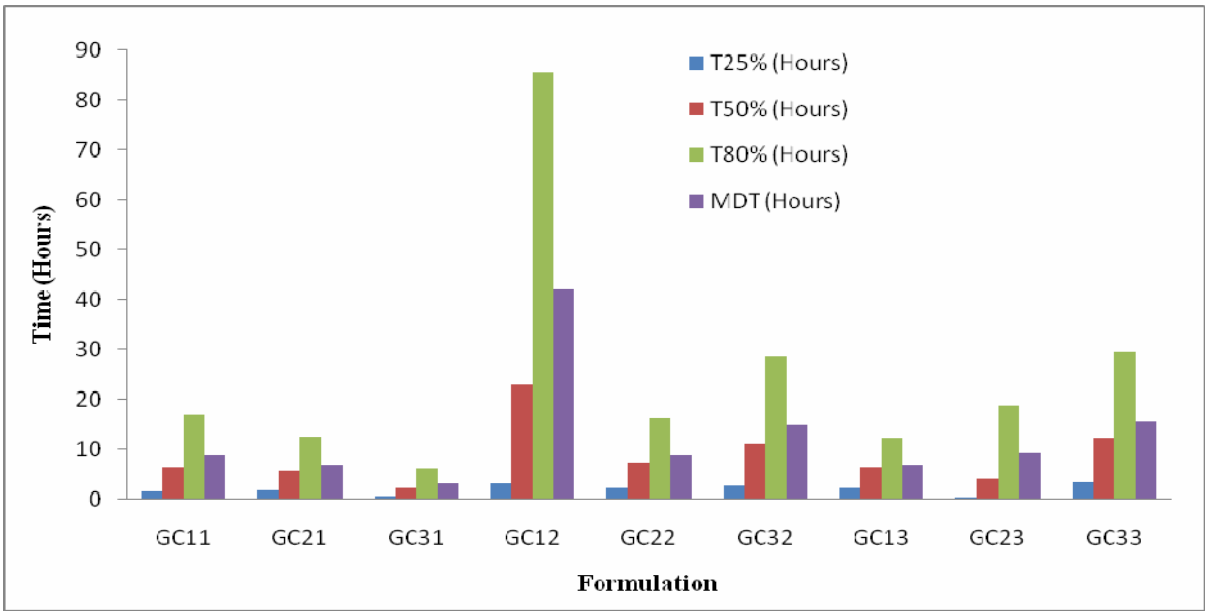


Figure 9: Bar diagram representing successive fractional dissolution time of GC11, GC21, GC31, GC12, GC22, GC32, GC13, GC23 and GC33.

Compatibility studies of drug and polymer within gliclazide microspheres.

Fourier transform infrared spectroscopy (FTIR) study: Fourier transform infrared spectroscopic (FTIR) study was conducted for the pure drug (Gliclazide), sample GH5 (Gliclazide microsphere containing HPMC K100LV) and sample GC23 (Gliclazide microsphere containing mixture of Ethocel and HPMC K100M). Figure 11 represents the FTIR spectrum of pure gliclazide. Many peaks are visible in this spectrum but the most prominent bands are-

1. Secondary amine N-H stretching at 3275.19 cm^{-1} and bending at 1597.09 cm^{-1}.
2. CH stretching at 3113.16 cm^{-1}.
3. Acyclic ketone carbonyl (C=O) stretching at 1709.92 cm^{-1}.
4. SO_2NH stretching at 1354.05 cm^{-1}.
5. Sulphonyl S=O stretching at 1164.06 cm^{-1}.

Here, secondary amine (N-H) possesses one band for stretching at 3275.19 cm^{-1} and one band for bending at 1597.09 cm^{-1}. Rest of the four prominent functional groups of gliclazide possesses one peak for stretching. Figure 12 represents spectrum of GH5, which is a batch of microspheres prepared by using HPMC K100LV. Now if this spectrum is compared with the spectrum of gliclazide, then it is found that peaks for N-H stretching and bending, =CH stretching, carbonyl C=O stretching, SO_2NH stretching and sulphonyl S=O stretching all are present here at 3272.29 cm^{-1}, 1597.09 cm^{-1}, 3113.16 cm^{-1}, 1710.89 cm^{-1}, 1354.05 cm^{-1} and 1164.06 cm^{-1} respectively which indicate the presence of these groups, in other words those are indication of no interaction. Figure 13 represents spectrum of GC23, which is a batch of microsphere prepared with Ethocel and HPMC K100M. Now, if this spectrum is compared with the spectrum of Gliclazide, then it is found that peaks for N-H stretching and bending, =CH stretching,

carbonyl C=O stretching, SO_2NH stretching and sulphonyl S=O stretching all are present here at 3274.22 cm^{-1}, 1597.09 cm^{-1}, 3114.13 n **Differential scanning calorimetric (DSC) study.** The data obtained from all of these samples are viewed here as combined thermogram of drug, polymers and microspheres prepared with Ethocel and HPMC K100LM.

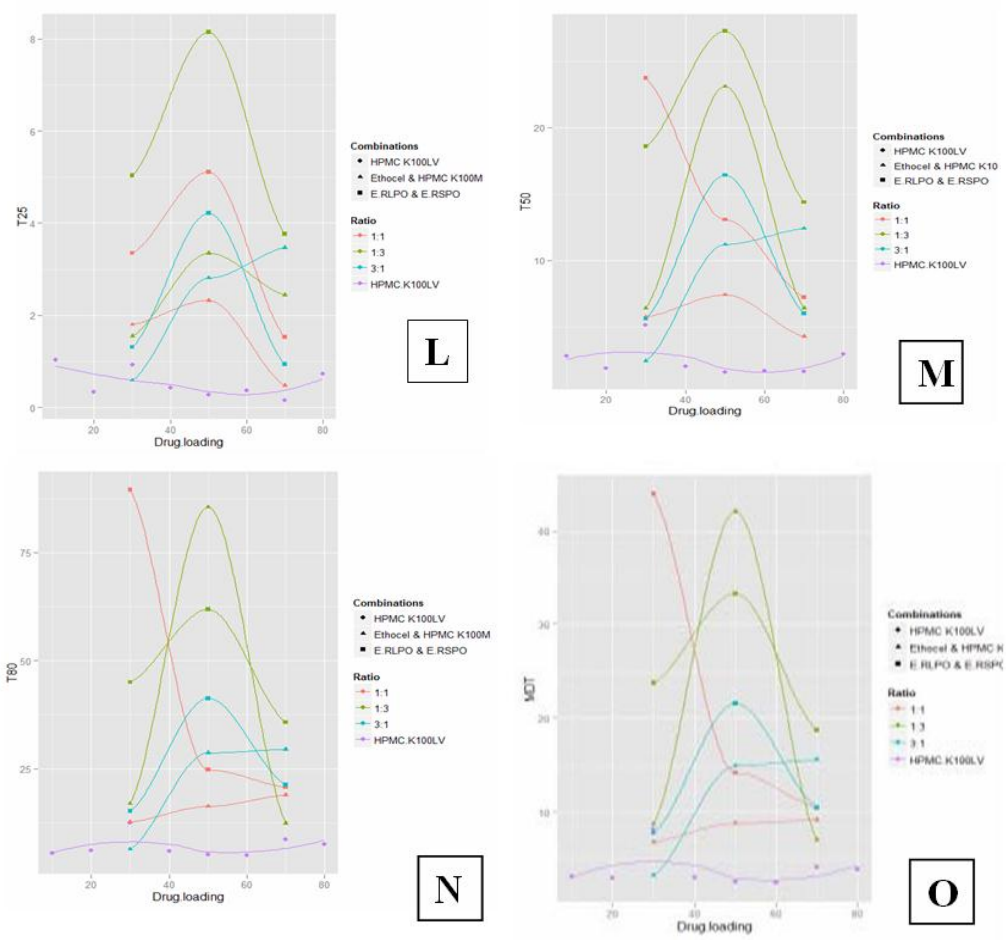


Figure 10: Complex line-plot: L. $T_{25\%}$; M. $T_{50\%}$; N. $T_{80\%}$;O. MDT.

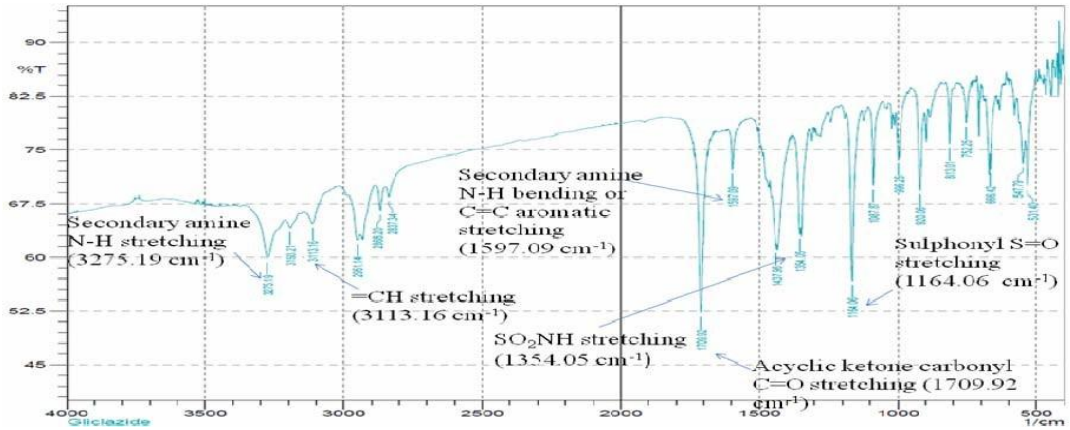


Figure 11: FTIR spectrum of pure gliclazide.

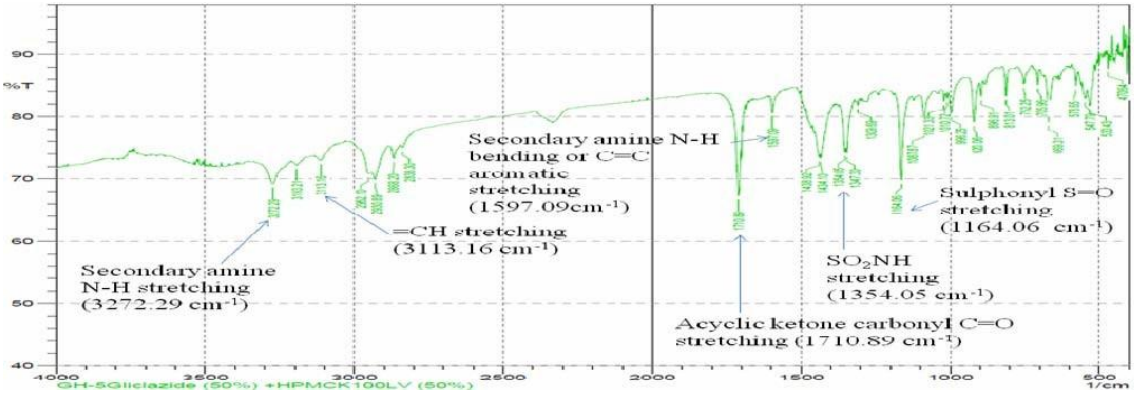


Figure 12: FTIR spectrum of GH5 (gliclazide microsphere prepared with HPMC K100LV).

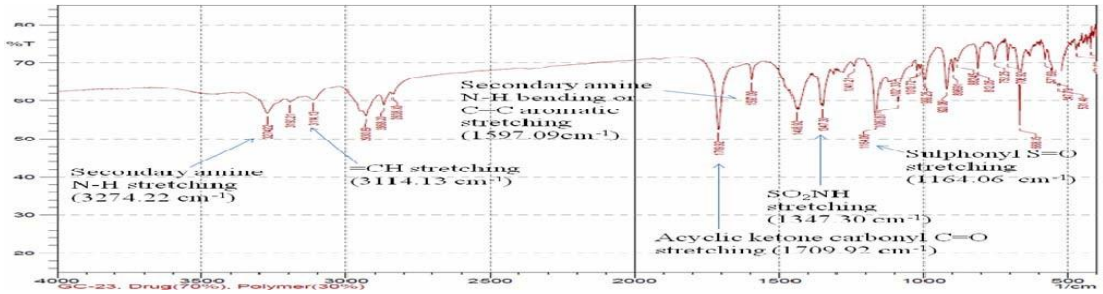


Figure 13: FTIR spectrum of GC23 (gliclazide microsphere prepared with HPMC K100LM and Ethocel).

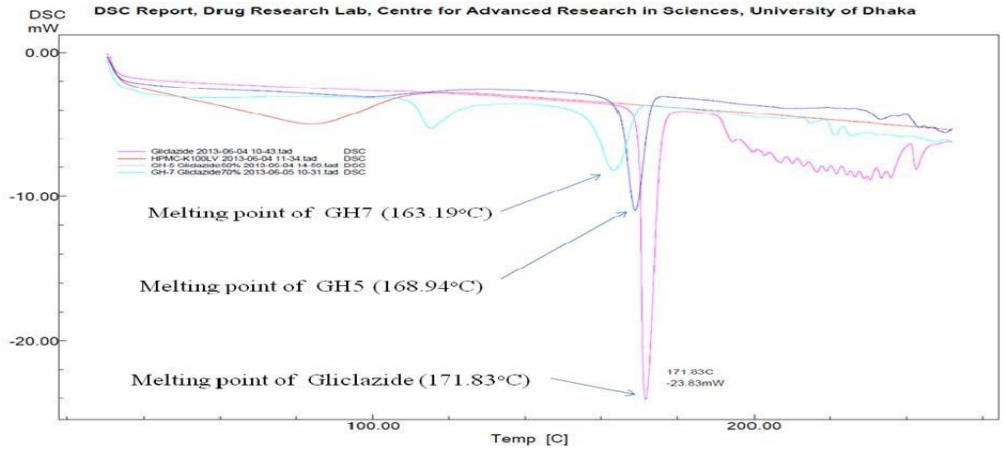


Figure 14: Combined DSC thermogram of pure gliclazide, HPMC K1000LV and two batches of microspheres of gliclazide prepared with HPMC K100LV.

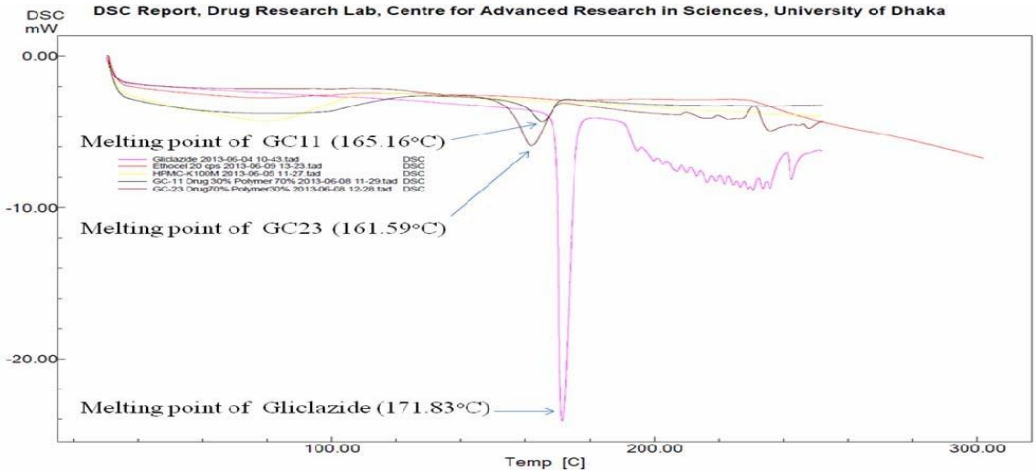


Figure 15: Combined DSC thermogram of pure gliclazide, HPMC K100M, Ethocel and two batches of microspheres of gliclazide prepared with HPMC K100M and Ethocel.

No drastic change occurred to the melting point of the microspheres in comparison with pure gliclazide in case of the microspheres prepared with HPMC K100LV alone or microspheres prepared with Ethocel and HPMC K100M in combination. So it can be said that there is no interaction between drug (gliclazide) and the polymers (HPMC K100LV, HPMC K100M and Ethocel).

CONCLUSION

In this study, polymeric microspheres of gliclazide were prepared successfully by emulsification-solvent evaporation technique. Microspheres prepared with a combination of Ethocel and HPMC K100M were proved to be of good quality compared to the microspheres prepared with HPMC K100LV alone, as all the microspheres fromformer batches possessed spherical like shape and the particle size of most of the batches were within the acceptable size range (1-1000µm).

Various variables like drug loading, polymeric type and polymer ratio (in case microspheres prepared by using mixture of polymers) all have direct effect on different characteristics of the microsphere.

Microspheres prepared with only HPMC K100LV, though have better entrapment efficiency, but cannot retard the release of the drug for a prolonged period. But when Ethocel is blended with HPMC K100M a more sustained release of the drug is obtained. Drug loading also influences entrapment efficiency as well as release rate. The entrapment efficiency increases with increase in drug loading for the microspheres prepared with Ethocel and HPMC K100M. Among three different ratios used (1:3, 1:1 and 3:1), 1:3 ratio of Ethocel and HPMC K100M showed better sustained release properties. Other parameters like surface morphology or particle size are also influenced by drug loading, polymeric property or by the ratio of two polymers.

To optimize the various properties of microspheres by using polymers of different permeability characteristics, a 3^2 factorial design was investigated taking drug loading and polymeric ratio as the independent variables and the various properties of the microspheres like entrapment efficiency, release rate as the dependent variables. This however, opened a newer approach to formulate micro particulate dosage form of optimum *in vitro* characteristics by manipulating drug loading and changing polymeric ratio.

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