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EFFECT OF TWO HYDROPHOBIC POLYMERS ON THE RELEASE OF GLICLAZIDE FROM THEIR MATRIX TABLETS

TALIB HUSSAIN[1]*, TARIQ SAEED[1], AHMAD M. MUMTAZ[1], ZEESHAN JAVAID[2], KHIZAR ABBAS[1], AZEEMA AWAIS[3] and HAFIZ ARFAT IDREES[2]

[1]University College of Pharmacy, University of the Punjab, Lahore, Pakistan
[2]Faculty of Pharmacy and Alternative Medicine, The Islamia University of Bahawalpur, Pakistan
[3]Bahauddin Zakariya University, Multan, Pakistan

Abstract: Gliclazide is an oral hypoglycemic agent, indicated in non insulin dependent diabetes mellitus and in patients with diabetic retinopathy. It has good tolerability and is a short acting sulfonyl urea that requires large dose to maintain the blood glucose level. So development of a sustained release formulation of gliclazide (GLZ) is required for better patient compliance. This study was conducted to assess the effects of different drug polymer ratios on the release profile of gliclazide from the matrix. Oral matrix tablets of gliclazide were prepared by hot melt method, using pure and blended mixture of glyceryl monostearate (GMS) and stearic acid (SA) in different ratios. *In vitro* release pattern was studied for 8 h in phosphate buffer media (pH 7.4). Different kinetic models including zero order, first order, Higuchi and Peppas were applied to evaluate drug release behavior. Drug excipient compatibility was evaluated by scanning with DSC and FTIR. Higuchi model was found the most appropriate model for describing the release profile of GLZ and non-Fickian release was found predominant mechanism of drug release. The release of drug from the matrix was greatly controlled by GMS while SA appeared to facilitate the release of drug from matrix tablets. FTIR results showed no chemical interaction between drug and the polymers, and DSC results indicated amorphous state of GLZ and polymers without significant complex formation. The results indicate that matrix tablets of gliclazide using glyceryl monostearate and stearic acid showed marked sustained release properties.

Keywords: gliclazide, glyceryl monostearate, stearic acid, sustained release, matrix tablets, kinetic models

Administration of least number of daily doses of a dosage form is advantageous for better patient compliance and is achieved if the drug is uniformly released over a desired prolonged period of time. This effect is accomplished using sustained release formulations. Development of oral sustained release dosage form for short acting, highly water soluble drugs with constant release rate remains an exceptionally difficult task to the researchers. These oral dosage forms are now gaining importance because of their predetermined drug delivery rates and especially for drugs which are used for long term therapy (1).

Gliclazide, a second generation oral hypoglycemic agent, was selected as model drug. It shows very low incidence of hypoglycemia during regular treatment, so is considered as a drug of choice in the long term therapy with sulfonylurea for the control of noninsulin dependent diabetes mellitus (2). Oral administration of GLZ tablet reaches peak serum GLZ concentration in a time range of 2 to 8 h approximately and requires a dose of 80-380 mg to be administered three times daily to maintain peak plasma drug concentration. It has been proved to be a short acting drug, so it requires the development of sustained release oral tablets for ease of administration and good patient compliance (3).

Matrix system has shown a great potential towards sustained release pattern. The drug either in dispersed or in dissolved state in a solid polymeric matrix, shows control release for a prolonged period of time. The matrix system requires drug to be uniformly distributed throughout the polymer blend, so the drug released through diffusion from the polymer blend is the rate limiting step for the system. Most of the oral matrix sustained release formulations employ either hydrophilic or hydrophobic polymers for the homogeneous distribution or dissolution of drug and to put a control on its release (4). The study was focused to develop hydrophobic

* Corresponding author: e-mail: dr.talibhussain@hotmail.com, phone No.: 0092-300-6907704

polymers based sustained release matrix tablets of GLZ having various ratios of drug to polymer and polymer to polymer. The polymers selected were glyceryl monostearate and stearic acid and the aim was to evaluate the effect of polymeric concentrations on the release characteristics of the model drug from the matrix. The stability of sustained release tablets was also evaluated by Fourier transform infrared (FTIR) spectroscopy and differential scanning calorimetry (DSC).

EXPERIMENTAL

Materials

Gliclazide was a kind gift from Wilson's Pharmaceuticals, Islamabad, Pakistan. Glyceryl monostearate and stearic acid were provided by Schering (Germany) and Sharooq Pharma (Pakistan), respectively. Magnesium stearate and lactose were purchased from Sigma-Aldrich (Germany) while methanol, potassium dihydrogen orthophosphate and sodium hydroxide were from Merck (Germany). All the chemicals were of analytical grade.

Preparation of matrix tablets

Gliclazide, glyceryl monostearate and stearic acid were weighed separately and accurately. Hydrophobic polymers i.e., GMS and SA were heated on hot plate magnetic stirrer at 60°C. The heated polymers were melted and mixed at a speed of 500 rpm. After fusion of the polymers, GLZ was then added and blended into the molten matrix at a speed of 500 rpm for 1 h to ensure homogeneous mixing while the temperature was maintained at 60°C during this procedure. The molten matrix was then allowed to cool and solidified at room temperature. The solidified matrix was milled and then reduced to granules of uniform shape by passing it through mesh size 20. These granules were mixed with measured quantities of lactose and then subjected to compression under a fixed compressional force to get flat discs of uniform size and hardness. To avoid moisture uptake, these preparations were stored in the desiccators at room temperature till further processing (5). Fifteen different formulations were prepared depending upon the drug to polymer and polymer to polymer ratios as shown in Table 1.

Dissolution studies

According to B.P. 2007 requirements, USP apparatus-II was used for the dissolution test of tablets. Dissolution was carried out at 100 revolutions per minutes with 900 mL medium (phosphate buffer pH 7.4) and was calibrated to the temperature of 37 ± 0.5°C. The samples (5 mL) were withdrawn

Table 1. Composition of matrix tablet using different proportion of gliclazide, stearic acid and glyceryl monostearate.

Formulations	Drug to polymer ratio	Active ingredient (mg)	Polymer ratios		Lactose (mg)
			GMS (mg)	SA (mg)	
F1	1 : 1	100	100	0	20
F2	1 : 1	100	50	50	20
F3	1 : 1	100	0	100	20
F4	1 : 2	66.66	66.66	66.66	40
F5	1 : 2	66.66	33.33	100	40
F6	1 : 3	50	150	0	60
F7	1 : 3	50	112.5	37.5	60
F8	1 : 3	50	75	75	60
F9	1 : 3	50	37.5	112.5	60
F10	1 : 3	50	0	150	60
F11	1 : 4	40	160	0	80
F12	1 : 4	40	120	40	80
F13	1 : 4	40	80	80	80
F14	1 : 4	40	40	120	80
F15	1 : 4	40	0	160	80

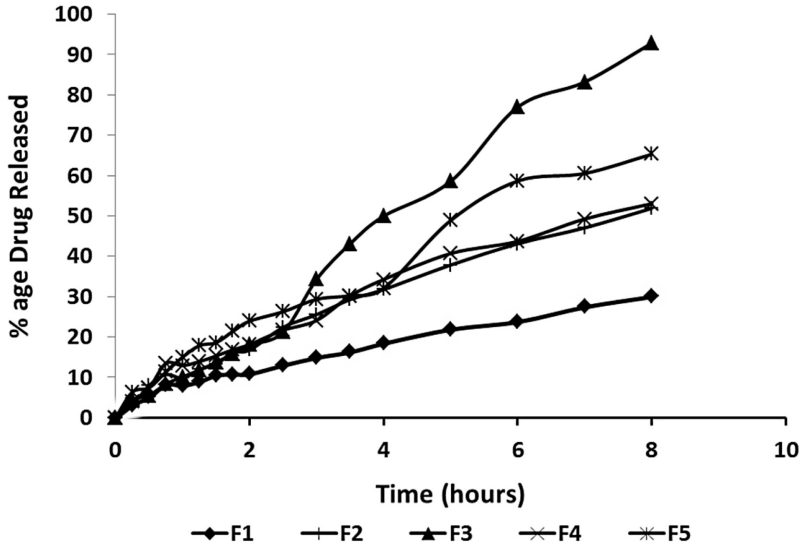

Figure 1. Drug release from formulations F1-F5

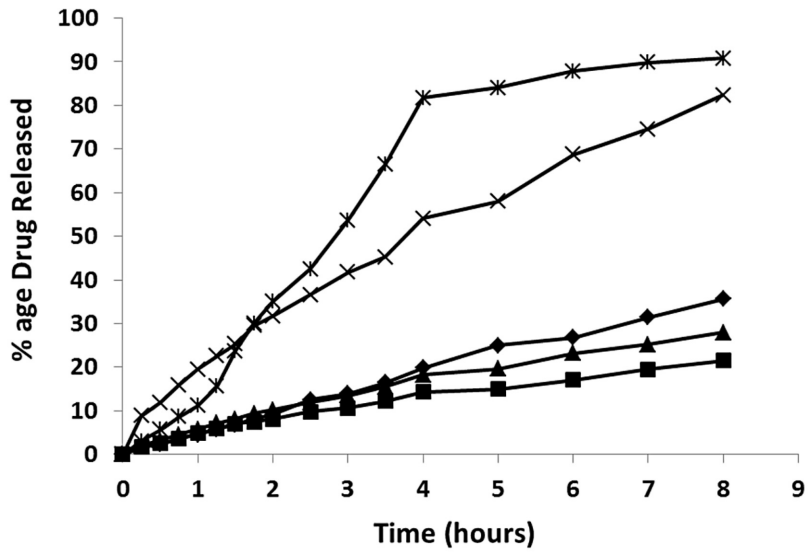

Figure 2. Drug release from formulations F6-F10

from the medium at specific time intervals and filtered through the 0.45 µm membrane filter using Sartorius syringe filtration assembly. The withdrawn sample volume was replaced with equivalent fresh volume of media already maintained at 37°C (6). The concentration of GLZ was determined at λ = 226 and 290 nm using the dissolution medium in the reference cell of the UV spectrophotometer. The absorbance obtained at 226 nm was corrected by subtracting the absorbance measured at 290 nm. A standard curve showing the absorbance of known concentration of gliclazide was prepared and then amount of GLZ released was determined with the help of this standard curve.

Differential scanning calorimetry

Differential scanning calorimeter (Q2000 DSC TA instrument) was used for the analysis of samples. Samples (5.5 mg) were sealed in aluminum pan and DSC thermograms were recorded between temperatures of 30 to 250°C at a nitrogen gas flow rate of 20 mL per min and heating rate of 10°C/min. An empty aluminum pan was used as a reference (7).

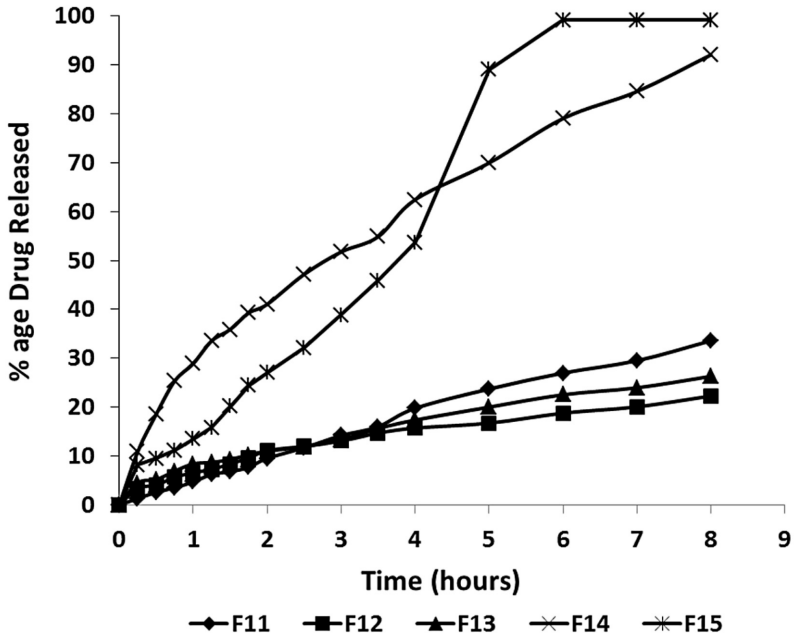

Figure 3. Drug release from formulations F11-F15

Table 2. Percentage drug release, correlation coefficient "r" using different kinetic equations and "n" values of formulations.

Formulation code	% drug released (after 8 h)	Zero order $Qt = K_0t$	First order $Qt = In\ Q_0 - K_1t$	Higuchi $Mt / M\infty = K_Ht^{1/2}$	Korsmeyer-Peppas $Mt / M\infty = Kt^n$	
		r^2	r^2	r^2	r^2	**N**
F1	30.06	0.973	0.674	0.977	0.9826	0.526
F2	51.88	0.982	0.678	0.966	0.97	0.614
F3	92.83	0.988	0.796	0.894	0.91	0.66
F4	53.04	0.977	0.651	0.965	0.98	0.63
F5	65.29	0.975	0.654	0.942	0.99	0.66
F6	35.66	0.995	0.827	0.941	0.77	0.43
F7	21.50	0.970	0.725	0.979	0.91	0.48
F8	27.98	0.979	0.654	0.977	0.98	0.64
F9	82.36	0.977	0.647	0.97	0.94	0.66
F10	90.73	0.905	0.68	0.937	0.91	0.72
F11	33.58	0.993	0.82	0.949	0.91	0.43
F12	22.28	0.933	0.714	0.987	0.96	0.48
F13	26.30	0.965	0.635	0.973	0.99	0.65
F14	92.05	0.947	0.616	0.96	0.99	0.68
F15	99.14	0.958	0.662	0.941	0.98	0.75

Fourier transform infrared spectroscopy

The spectra were collected on FTIR spectrophotometer (Thermo Nicolet 6700) in the range between 400 to 4000 cm^{-1} at 4 cm^{-1} resolution of scan. The small amount of grinded sample was placed on the detector and was compressed to a 12 mm disc by a hydraulic press at 10 tons compression force for 30 s. The infrared spectrum was then analyzed between ranges of 400 cm^{-1} to 4000 cm^{-1} (8).

RESULTS AND DISCUSSION

Release characteristics and kinetic models

Dissolution studies were carried out to find the amount of drug release from the gliclazide matrix tablets. The release profile was generated after 8 h of dissolution study (Figs. 1-3), and then percentage drug release was calculated as shown in Table 2. Different kinetic equations were applied to determine correlation coefficient "r¸" and then were used for interpretation of release pattern as well as the mechanism of drug release from matrix system (9). The best fit model having higher correlation values was found with zero order release model and Higuchi equation. The dissolution data were also fitted according to Korsmeyer Peppas equation to describe the GLZ release mechanism from matrix tablets. In Korsmeyer Peppas equation 'n' is a release exponent which is used to characterize the transport mechanism. The value of n varies from cylinder to sphere, as tablets are near to cylinders so the n value for tablets are as: n = 0.45 for Fickian (Case I) release, > 0.45 but < 0.89 for non-Fickian (anomalous) release and 0.89 for Case II (zero order) release and > 0.89 for super case II type of release (10). The drug release mechanism from these gliclazide matrix tablets could be better revealed as non-Fickian or anomalous diffusion (11). Anomalous transport (non Fickian) refers to the summation of both diffusion and dissolution controlled drug release. The complex nature of the prepared formulations represents the release mechanism from the matrix being controlled by both the diffusion and erosion/dissolution controlled release. This suggests that when this polymer mixture is employed, some extent of swelling as well as dissolution of matrix must be operating within the system, which causes it to deviate from the Fickian release (12). The incorporation of glyceryl monostearate, a hydrophobic surfactant, in the matrix caused an increase in the matrix lipophilicity, thus leading to a decrease in the effective interfacial area between the drug and the dissolution medium. This resulted in a reduction of the matrix wettability (the rate of dissolution medium penetration into the matrix) and consequently leading to a decrease in drug diffusion from the matrix. So it was a possible mechanism for retarding drug release (sustained release) from glyceryl monostearate based matrix system (13, 14).

The release pattern from some GLZ matrix tablets showed fast release due to the presence of hydrogen bonding between free carboxylic acid group (-COOH), that is present in stearic acid and water. The hydrogen bonding formation was also enhanced by the higher molecular dimension of stearic acid that also resulted in elevated GLZ release from the matrix (15). Stearic acid showed the highest release rates in all formulations because of its little hydrophilic nature with the tendency of being hydrated in aqueous medium. Therefore, its matrix showed the highest release in dissolution profile (16).

The microscopic examination of the matrix system, containing pure glyceryl monostearate, after 2 h of dissolution revealed that upon contact with the phosphate buffer medium (pH 7.4), the matrix surface was eroded by the dissolution medium. The particles of drug on surface were released in the dissolution medium leaving the surface brittle and also the values given in Table 2 revealed that with the increase in the amount of glyceryl monostearate the

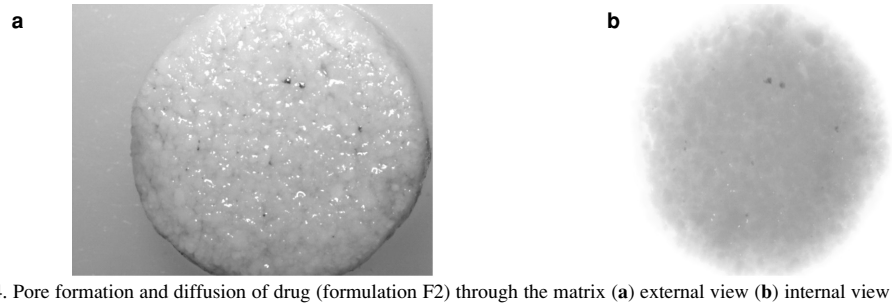

Figure 4. Pore formation and diffusion of drug (formulation F2) through the matrix (**a**) external view (**b**) internal view

drug release was retarded. This complies with the findings of Abdelbary et al. (11). Poorly water-soluble drugs like gliclazide are released predominantly by erosion mechanism (17). Erosion profiles of the matrix were in good correlation with release profiles of the gliclazide, showing erosion controlled release mechanisms (18).

The microscopic examination of the tablets containing combination of glyceryl monostearate and stearic acid after 2 h of dissolution (Fig. 4) suggested that upon contact with the buffer medium (pH 7.4) matrix surface was eroded and glyceryl monostearate showed the retarding effect by delaying the drug release. Stearic acid formed pores in the matrix and appeared to channelize the drug from the wax matrix (19). The porosity of the matrix was decreased with an increase in the concentration of glyceryl monostearate in the matrix (20). The presence of stearic acid in the formulations caused the degradation of tablets because it got ionized in the dissolution medium of phosphate buffer pH 7.4. Stearate anion formed during this process decreased the surface tension of the medium and thus increased the wettability of the dissolving particles. So, pore diffusion and matrix erosion is generally the release mechanism of a drug from hydrophobic matrix tablet (21).

Differential scanning calorimetry

DSC thermogram of pure gliclazide, glyceryl monostearate and stearic acid showed endothermic peaks at 171.73, 65.04 and 55.21°C, respectively, corresponding to their melting points. Thermogram of GLZ and glyceryl monostearate hot melt granules (F1) showed two distinct peaks at 65.40 and 158.72°C. The peak at 65.40°C represents glyceryl monostearate, as it is almost identical to the pure GMS endothermic peak, and is the melting point peak of glyceryl monostearate. The peak at 158.72°C represents gliclazide and describes a shift of gliclazide peak to a lower temperature, indicating that a true complex has not formed between gliclazide and glyceryl monostearate. The enthalpy of drug melting in mixture form (F1) (ΔH –29.25 J/g) was gradually decreased as compared to the pure untreated GLZ (ΔH –103.8 J/g). This phenomenon of enthalpy change could be attributed to the amorphous form of GLZ in hot melt granules. The slightly lower Tm and decrease of enthalpy indicate that the reduction in size during hot melt granulation actually resulted in these changes so it shows the absence of considerable incompatibility between the drug and polymers (22).

The thermogram of gliclazide and stearic acid (F3) hot melt granules showed two peaks. The peak

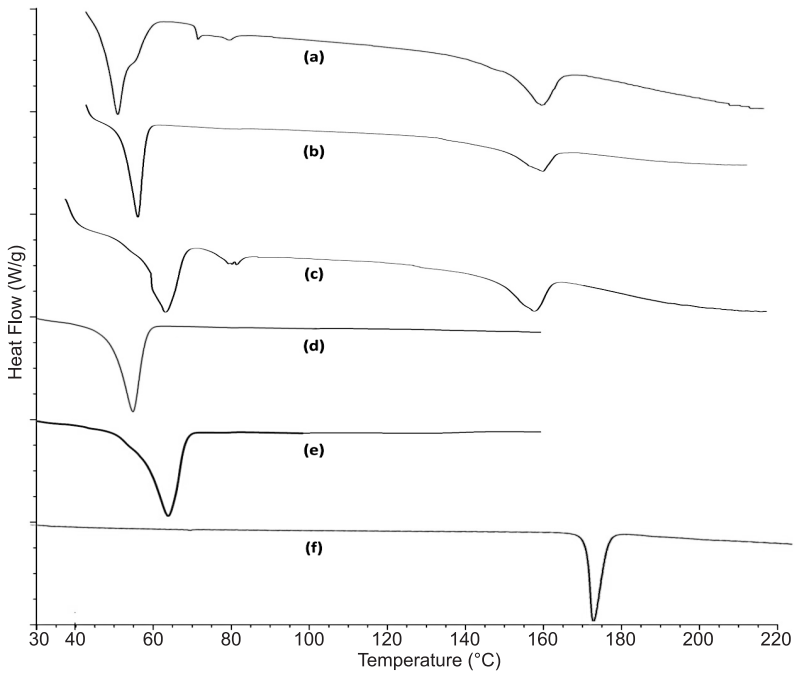

Figure 5. DSC spectra of (**a**) F2, (**b**) F3, (**c**) F1, (**d**) stearic acid, (**e**) glyceryl monostearate, (**f**) gliclazide

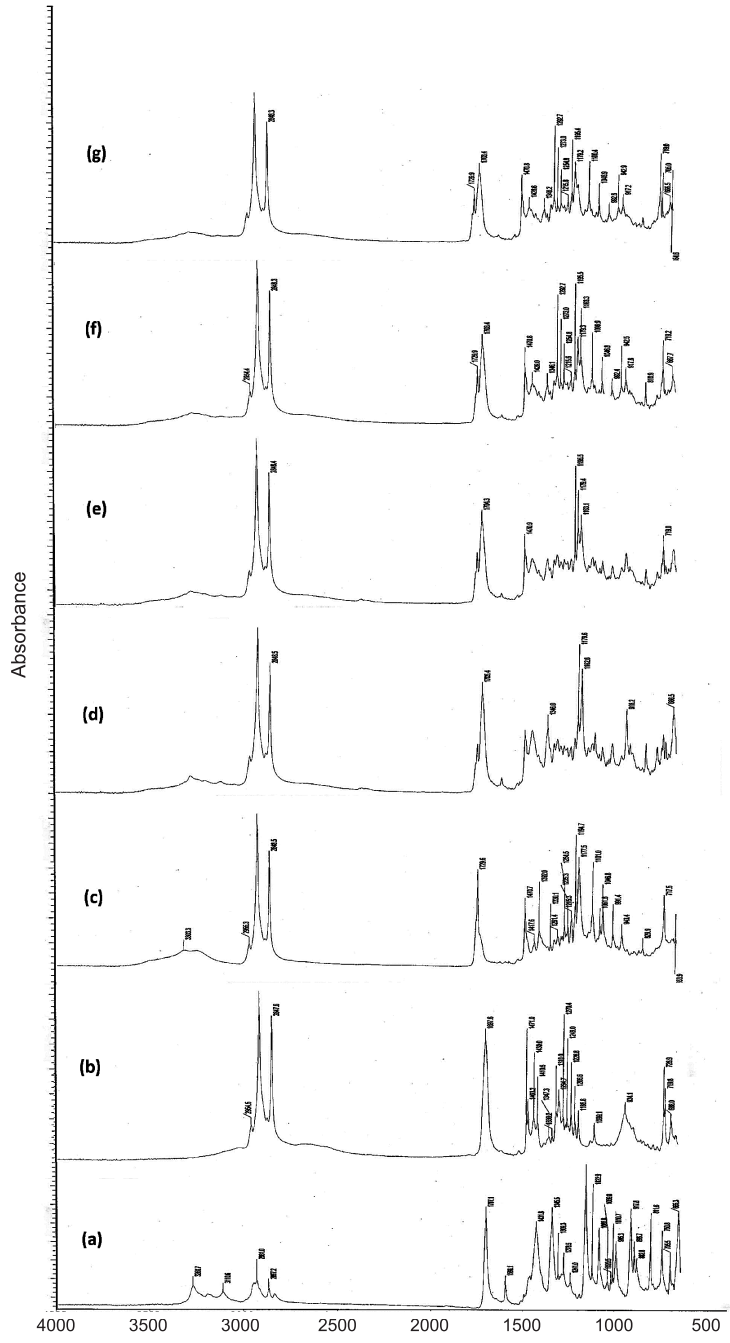

Figure 6. FTIR spectra of (**a**) gliclazide, (**b**) stearic acid, (**c**) glyceryl monostearate, (**d**) F2, (**e**) F4, (**f**) F8, (**g**) F1

at 53.85°C, almost identical to the pure stearic acid endothermic peak, is the melting point peak of stearic acid and the peak at 162.22°C is the shift of gliclazide peak to a lower temperature indicating that no true complex has been formed. The height of this endotherm was reduced considerably in comparison with that of pure gliclazide, thus indicating a fairly strong interaction between the drug and polymer (23). The enthalpy of drug melting in mixture form (F3) (ΔH –24.05 J/g) was also decreased

as compared to the pure untreated form drug (ΔH –103.8 J/g). Also the enthalpy of polymer melting in mixture form (F3) (ΔH –63.44 J/g) was decreased a little as compared to the pure untreated form stearic acid (ΔH –114.10 J/g). Thus, both the drug and the polymer were in amorphous form in hot melt extrudes (24).

The thermal curve of gliclazide, glyceryl monostearate and stearic acid (F2) complex prepared by hot melt method showed two peaks at 51.22 and 159.86°C. The peak at 51.22°C is a broad peak representing both the polymers and is due to the close melting points of the both polymers. Complete disappearance of the glyceryl monostearate melting peak was due to the complete miscibility of the polymer in the melted polymer carrier (22). Similar observations were made by Trotta M. et al., who showed that the location of peaks of glyceryl monostearate particles slightly moved towards lower temperature values as compared to that of the pure bulk glyceryl monostearate material; this happened probably because of the presence of surfactants into the formulation containing glyceryl monostearate (25). The peak at 159.86°C is due to drug melting point indicating that the true complex has not formed in formulation F2 and only interactions are found between the drug and polymers. The enthalpy of drug melting in mixture form (F2) (ΔH –17.41 J/g) was markedly decreased as compared to the pure untreated form (ΔH –103.80 J/g) (26).

Infrared spectroscopy

The evaluation of IR spectrum of GLZ showed that it exhibits characteristic peaks at 2931.0 and 1707.10 cm^{-1} due to N-H and C=O stretching of amide group, respectively. The stretching peaks of S=O were observed at 1345.5 and 1164.37 cm^{-1}. The N-H group is also located at 3268.7 cm^{-1}. These peaks confirm the structure of GLZ. The IR spectrum of glyceryl monostearate exhibited peaks at three positions that are 2915, 2955.3 and 2848.5 cm^{-1}. These peaks are due to -CH_2- stretching vibrations. The carboxyl group (C=O) stretching peak is observed at 1729.6 cm^{-1} (27). The IR spectrum of stearic acid demonstrates peaks at three distinct positions; 2915, 2954.5 and 2847.6 cm^{-1}, showing -CH_2- stretching vibrations. The peaks at 1697.6 and 1430.0 cm^{-1} were due to C=O (from carboxyl group) and O-H (hydroxyl group) band stretching. The symmetric stretching peaks of the carboxylic group –COO appeared distinctly at 1410.5 cm^{-1} and antisymmetric stretching peaks of the carboxylic group –COO appeared distinctly at 1518 cm^{-1}. The CH_2 wagging and twisting vibrations generated the progressional bands that were seen in the region of 1150–1350 cm^{-1}. These confirmed the structure of stearic acid (28).

The IR spectrum of formulation containing gliclazide, glyceryl monostearate and stearic acid (F8) prepared by hot melt technique showed peaks at positions as shown in their individual spectra i.e., peaks at 2931.0 cm^{-1} due to N-H stretching, peaks at 1704.3 cm^{-1} due to C=O stretching of amide group of gliclazide, peaks at 1346.2 and 1163.1 cm^{-1} due to S=O stretching. Shift of peak from 1707.1 to 1704.3 cm^{-1} and 1345 cm^{-1} to 1346.2 cm^{-1} indicates very weak interaction between drug and polymers. In this complex considerable reduction in the intensity of the peak at 1704.3 cm^{-1} indicates weak interaction between drug and polymers as shown in Figure 6.

The aforementioned characters ensure the chemical integrity of gliclazide with polymers in sustained release formulation. Slight shift of peak from 1707.1 to 1705.4 cm^{-1} and 1345 to 1346 cm^{-1} indicated very weak interaction between gliclazide and polymers. The above findings suggest that there were either very weak or almost negligible interactions between the drug and polymers, so the predominant release retarding mechanism was only due to the property of polymer that retarded the drug (29).

CONCLUSION

Sustained release matrix tablets of gliclazide can be prepared from proper blended mixtures of glyceryl monostearate and stearic acid in different ratios by using hot melt extrusion method. If glyceryl monostearate and stearic acid are used in combination, then they develop the ability to retard the release of gliclazide from matrix tablets and it is also evaluated that drug release rate from the matrix is inversely proportional to the amount of rate retarding polymer (glyceryl monostearate). On the other hand, increasing the amount of stearic acid in the matrix increased gliclazide release because of its hydrophilic nature. Most of the sustained release formulations followed Higuchi kinetic model. The mechanism of gliclazide release from formulations was followed by both diffusion and erosion process. DSC results also indicated that complex formation was not significant. FTIR spectroscopy reflected that there was no significant interaction between the polymers and gliclazide, hence it has been proved that the release retardation was exclusively based on the properties of polymers.

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