



COMPATIBILITY STUDIES OF GLIMEPIRIDE WITH SELECTED EXCIPIENTS FOR THE DEVELOPMENT OF EXTENDED RELEASE FORMULATIONS

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ABSTRACT

The objective of this study was to detect interaction of Glimepiride with selected extended release excipients by DSC and FT-IR and to develop ER tablet by direct compression method. In the first phase of the study, differential scanning calorimeter (DSC) was used as tool to detect any interaction. In the next phase, excipients defined in the prototype formula were tested for their compatibility with Glimepiride using FT-IR. In this study it was possible to observe the interactions of the Glimepiride with magnesium stearate and lactose. In brief, tablets of Glimepiride having an average weight of 150 mg were prepared using varying quantity of HPMC K4M and release studies were carried out in phosphate pH 7.8 for a period of 10 hour to achieve extended release pattern. The tablets were also evaluated for physical properties, kinetic studies and stability studies. FTIR and DSC studies shown there was no interaction between drug, HPMC K4M and other filler excipients. The physicochemical properties of tablets were found within the limits. Formulation F-2 having a composition of 20.0 % w/w HPMC K4M gave a predetermined release for 6 hrs than all other formulations. The kinetic treatment showed that the release of drug follows Zero order followed by Higuchi spherical matrix release and best co-related with Korse-Meyer Peppas models. The optimized formulations were subjected to stability studies and shown there were no significant changes in drug content, physicochemical parameters and release pattern. Results of the present study indicated the suitability of the HPMC K4M hydrophilic matrix polymers in the preparation of extended release formulation of glimepiride.

KEY WORDS

Compatibility, Glimepiride, direct compression, extended release, HPMC.

INTRODUCTION

Extended release dosage forms are terms used to identify drug delivery system that are designed to achieve or prolonged therapeutic effect by continuously releasing medication over the extended period of time after administration of a single dose ^[1, 2]. The objective in designing a sustained release/extended release system is to deliver drug at a rate necessary to achieve and maintain a constant drug blood level. Techniques of thermal and isothermal stress testing (IST) were used to evaluate the compatibility of drug with selected excipients for the development of extended release formulations. The incompatibility between drugs and excipients can alter the physicochemical properties of drugs and hence, can have an effect on its efficacy and safety profile.

Therefore, drug-excipient interaction study at the initial stage of a formulation development should be treated as an imperative exercise to ensure correct selection of excipients and hereby, increasing the possibility of developing a successful dosage form ^[3,4]. In particular, the cost and time constraints associated with the process of pharmaceutical product development have made this type of predictability techniques even more desirable. As the thermo-analytical methods do not yield direct chemical information, Fourier transform infrared spectroscopic (FT-IR) investigations were also used in this work. The compatibility studies using thermal analysis present advantageous to readily available knowledge of any physical and chemical interactions between drugs and excipients which might give rise to changes in chemical nature, stability, solubility,

absorption and therapeutic response of drugs^[5, 6]. Thermal techniques have been increasingly used for quick evaluation of possible incompatibility between formulation components through comparison of thermal curves of pure substances with curve obtained from a 1:1 mixture.

Glimepiride is the first III generation sulphonyl urea it is a very potent sulphonyl urea with long duration of action. It is practically insoluble in water. Soluble in dimethyl formamide, slightly soluble in methanol, sparingly soluble in methylene chloride. It also dissolves in dilute alkali and in dilute acids. Half life is approximately 5 hours following single dose. Completely (100%) absorbed following oral administration. Over 99.5% bound to plasma protein. The highest recommended dose per day is 6-8 mg. Daily doses of glimepiride of more than 6 mg are more effective only in a minority of patients. There is a risk of hypoglycaemia, if starting dose exceeds the daily dose of GLM being taken. Glimepiride is used with diet to lower blood glucose by increasing the secretion of insulin from pancreas and increasing the sensitivity of peripheral tissues to insulin^[7,8]. The aim of the present investigation was to study compatibility of GLM with selected matrix polymers and to prepare extended release tablets by direct compression method.

EXPERIMENTAL

Materials

The glimepiride, sulfonylurea was obtained from Balaji, Drugs, Mumbai-37. Excipients tested were: lactose, microcrystalline cellulose (Blanver), HPMC K4M, lactose (Henrifarma) and Stearic Acid, Magnesium stearate, Calcium carbonate from Loba Chemie, Kolkata. The mixed samples consisted of equal masses of glimepiride and each excipient was weighed individually into amber glass flasks to originate mass of 2.0 g of mixture. Physical mixtures were prepared in proportion 1:1 of glimepiride : excipient by simple mixing.

Methods

Differential scanning calorimetry study

A Mettler Toledo DSC thermal analysis system (Mettler Inc., Schwerzenbach, Switzerland) was used for thermal analysis of the drug-excipient mixtures. Approximately 2-5 mg of GLM and excipient or their binary mixture was examined in the temperature range between 40 °C and 300 °C, in a normal covered Aluminium crucible (three pin holes were applied in the cover). The heating rate was 10 °C min⁻¹. Nitrogen was used as carrier gas at a flow rate of 10 Lh⁻¹ during the DSC investigation^[3, 6].

Fourier transform infrared spectroscopy study

FT-IR spectra of the GLM and its binary mixtures were recorded in the interval 4000–400 cm⁻¹ with an Shimadzu FT-IR instrument (Japan), at 4 cm⁻¹ optical resolution. Standard KBr pellets were prepared from IR grade KBr and 0.5 mg of ATV, or 1.0 mg of binary mixture. The spectra were recorded with the use of software, and all spectral interpretations were done^[3, 12].

Preparation of Extended release tablet of GLM by direct compression

The weighed quantity of GLM was screened through sieve no. # 40. The various excipients were accurately weighed and screened separately using sieve no. # 40. The extended release tablets were prepared by direct compression method using the formula shown in **Table 1**. Accurately weighed quantity of raw materials such as Glimepiride, Lactose, MCC, HPMC K4M, Stearic Acid were sifted through sieve no. #40 and mixed them for 5 minutes. The blended drug-powder was compressed into tablets weighing approx. 150 mg on a single punch tablet machine (Cadmach, Ahmadabad) using a flat-faced non-beveled punch and die set of 8-mm diameter^[10-12].

Evaluation of Pre compression Parameters

It is very important parameter to be measured, since it affects the mass of uniformity of the dose. It is usually predicted in terms of angle of repose, bulk density and tapped density, compressibility index^[9, 13].

Evaluation Post compression Parameters

The formulated tablets were evaluated for the following parameters such as thickness, hardness, friability, weight variation and in-vitro drug release characteristics ^[12, 13].

In Vitro Drug Release studies:

Dissolution studies were carried out for all the formulations combination in triplicate, employing USP - II paddle method and 900ml of pH 7.8 phosphate buffer as the dissolution medium. The medium was allowed to equilibrate to temp. of $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$. Tablet was placed in the vessel and the vessel was covered with the apparatus was operated for 24 hrs in pH 7.8 phosphate buffer at 50 rpm. At definite time intervals, 5 ml of the aliquot sample was withdrawn periodically and the volume replaced with equal volume of fresh dissolution medium. The samples were analyzed spectrophotometrically at 228 nm using UVspectrophotometer ^[8, 16]. And this dissolution data was further treated for kinetic modeling. The in vitro drug release studies are conducted in three times.

Kinetic evaluation of release data

To evaluate the mechanism of drug release the datas were fitted in to various kinetic models such as zero-order, first order, Higuchi and Korsmeyer-Peppas ^[17].

Zero-order

$C = K_0 \cdot t$ (1) expressed in units of concentration/time, K_0 is zero order release constant and t is the time in hrs.

First-order

$\log C = \log C_0 - Kt / 2.303$ (2)

Where C is the concentration, C_0 is the initial concentration of drug, K is the first-order rate constant, and t is the time.

Higuchi

$Q_t = K_H \cdot t^{1/2}$ (3)

Where Q_t is the amount of release drug in time t , K is the kinetic constant and t is the time in hrs.

Korsmeyer peppas,

$M_t / M_{\infty} = K \cdot t^n$ (4)

Where M_t represents amount of the released drug at time t , M_{∞} is the overall amount of the drug total dose. The value of n indicates the drug release

mechanism related to the geometrical shape of the delivery system, if the exponent $n = 0.5$, then the drug release mechanism is Fickian diffusion. If $n < 0.5$ the mechanism is quasi-Fickian diffusion, and $0.5 < n < 0.5$, then it is non-Fickian or anomalous diffusion and when $n = 1.0$ mechanism is non-Fickian case II diffusion, $n > 1.0$ mechanism is non-Fickian super case II.

Stability studies

The stability studies were conducted by storing the optimized tablets at $40 \pm 2^{\circ}\text{C} / 75 \pm 5\% \text{ RH}$ in stability chamber for 45 days. The samples were withdrawn after 45 days and analyzed for various physical tests and drug release study.

RESULTS AND DISCUSSION

Drug-excipient compatibility testing by DSC

In the first phase the compatibility of GLM with different excipients were tested using DSC. Different formulation trials were taken to develop formulation compositions. DSC curve of glimepiride (**Figure 1a**) shows a sharp endothermic peak at 216.33°C that corresponds to melting followed by thermal decomposition. The melting peak of GLM according to Cides et. al 2006 happened to 212.46°C and enthalpy of 94.6 J g^{-1} . The melting peak of GLM when disappeared, or decreased in intensity in drug-excipient binary mixtures, it was confirmed to be physical interaction. DSC curve of GLM + lactose shows only the characteristic endothermic peaks of lactose (**Figure 1b**). DSC curve of the binary mixture revealed interactions between GLM and lactose, which might be physical in nature. This fact is justified because the melting of drug and excipient occur in the same temperature range ($210\text{--}212^{\circ}\text{C}$). In this binary mixture the melting point of the drug and excipient was decreased of 210 to 193.91°C (T_{onset} of physical mixture). The corresponding data of glimepiride-magnesium stearate mixture indicate the occurrence of remarkable interaction, since the endotherm peak of glimepiride shifted from 216 to 192°C (**Figure 1d**). The thermo-analytical data of DSC of GLM and drug-excipients mixtures were presented in **Table 1**.

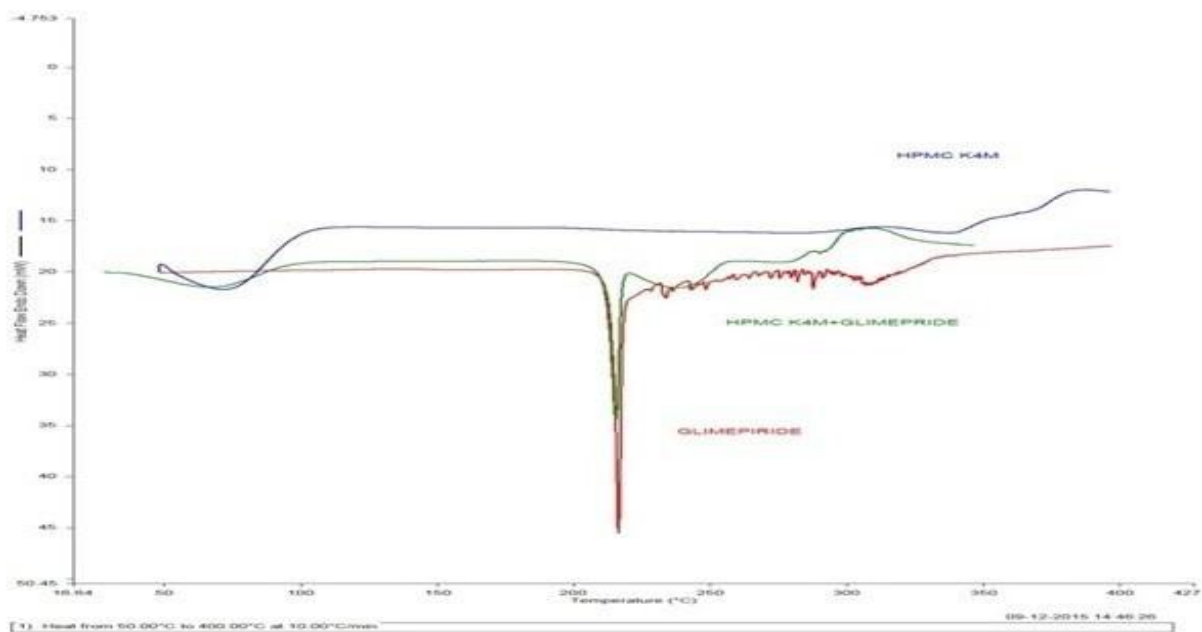


Figure 1. (a) DSC thermogram of GLM, HPMC K4M and their physical mixture

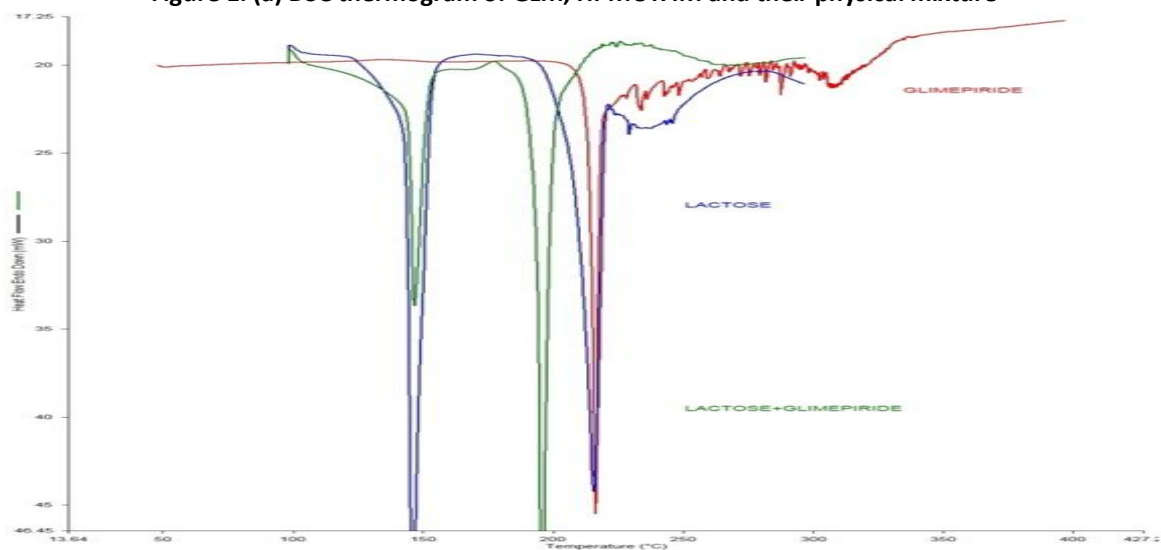


Figure 1. (b) DSC thermogram of GLM, Lactose and their physical mixture

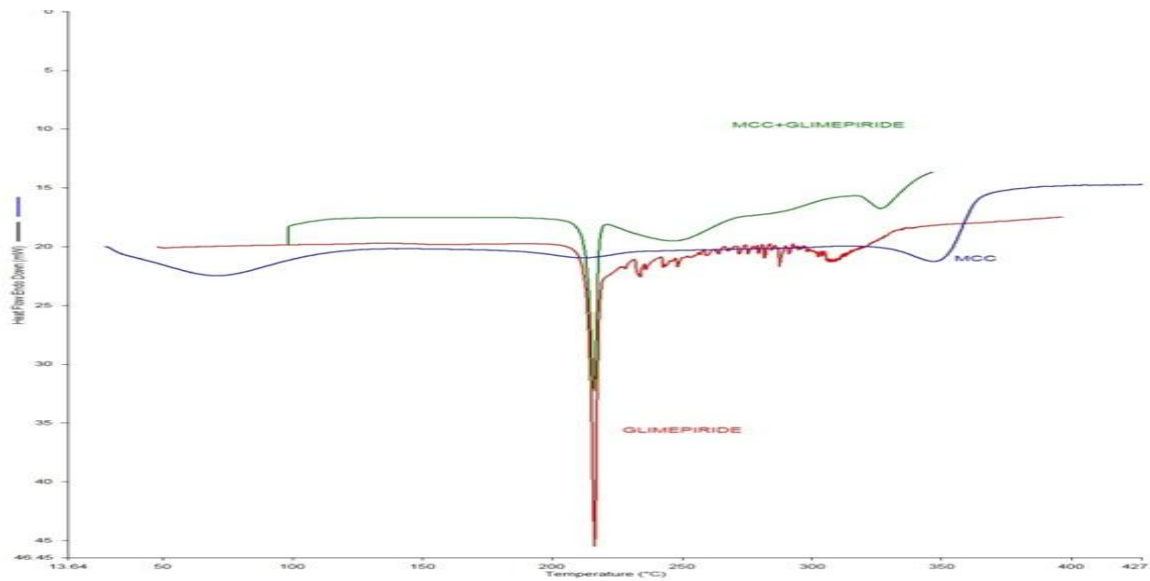


Figure 1. (c) DSC thermogram of GLM, MCC and their physical mixture

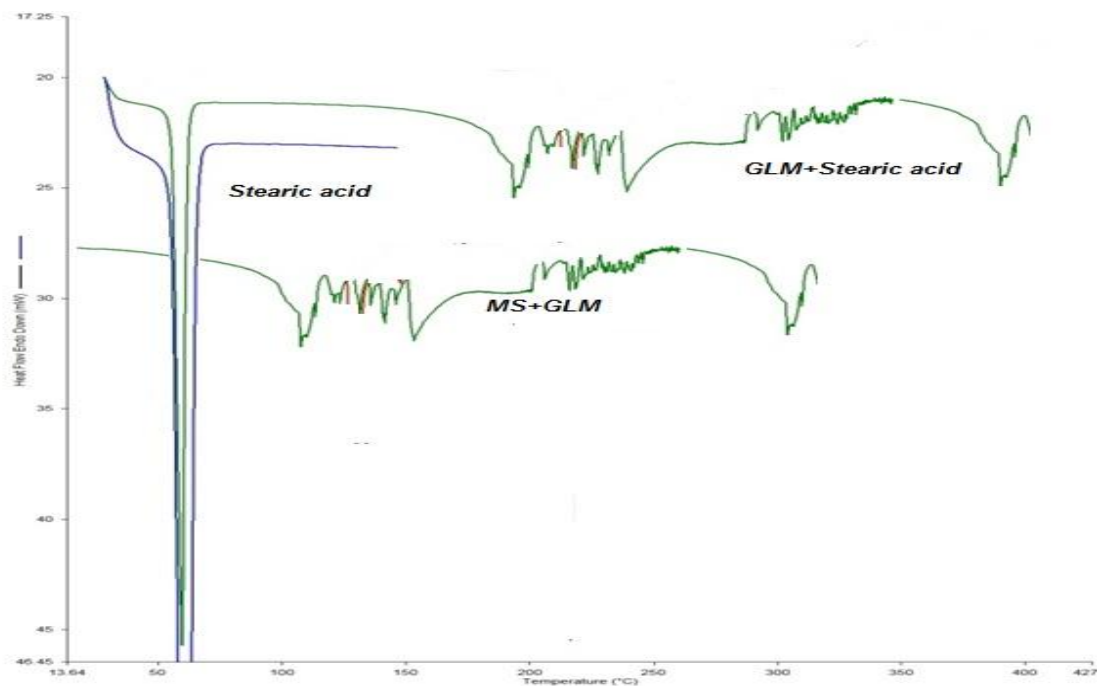


Figure 1. (d) DSC thermogram of GLM, Stearic acid, Magnesium stearate physical mixture

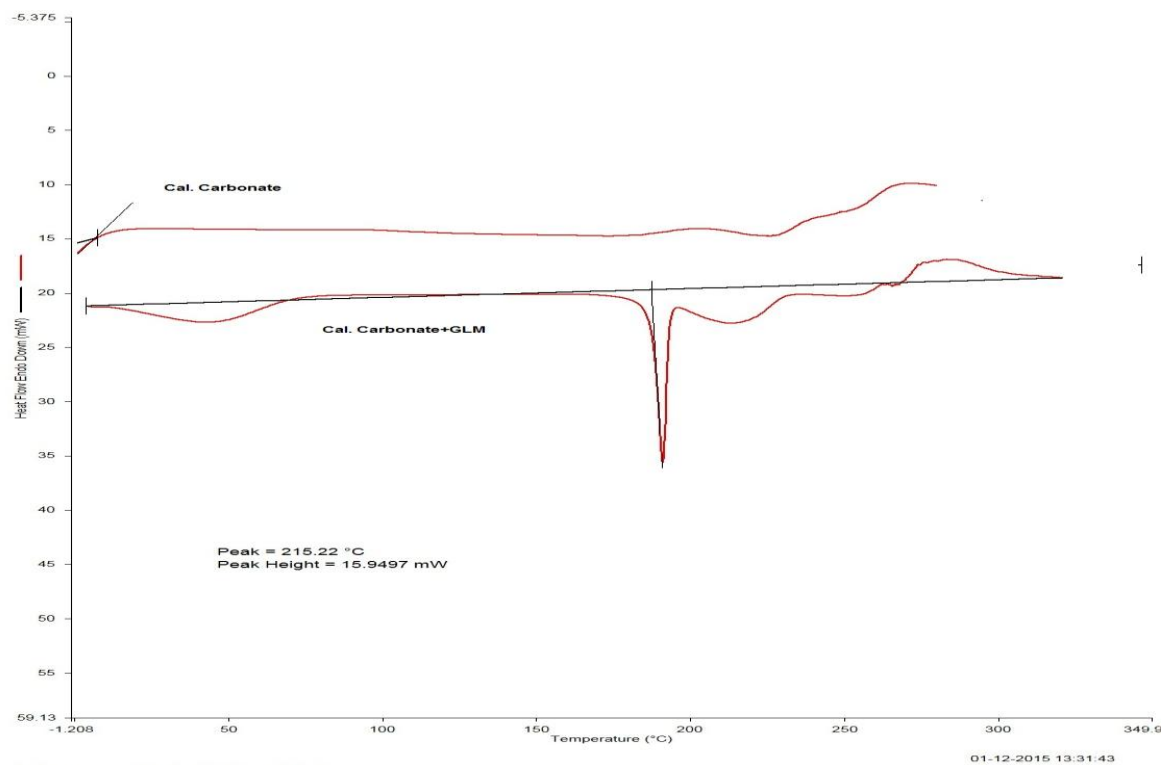


Figure 1. (d) DSC thermogram of GLM and physical mixture with Calcium carbonate.

Table 1: Thermoanalytical data by DSC of GLM and excipients

Drug+Excipients	T _{onset} (fusion)/°C	T _{peak} (fusion)/°C	ΔH _{fusion} /J g ⁻¹
GLM	213.89	216.33	119.31
GLM+ Lactose	193.91	195.46	132.82
GLM+ Magnesium Stearate	213.02	114.25	890.862
GLM+ HPMC K4M	212	215.22	201.604
GLM+ Microcrystalline cellulose	213.02	216.19	73.40
GLM+Magnesium stearate			
GLM + Stearic acid	192.64	193.56	26.65
Glimepiride + Calcium carbonate	206.42	211.46	54.31

Drug–excipient compatibility testing by FT-IR

FT-IR spectra of pure GLM revealed that the principle absorption peaks occurs due to N-H stretching at 3369 cm⁻¹, C-H stretching at 2932-2842 cm⁻¹, C=O stretching at 1707 cm⁻¹ and C-N stretching at 1542 cm⁻¹. IR spectra of GLM, GLM-lactose binary mixture showed the presence of characteristic bands corresponding to drug and excipient. There was no appearance of new bands in IR spectra confirming that it did not occur change in drug structure. FT-IR spectral analysis showed that there

is no appearance or disappearance of any characteristic peaks of pure drug GLM and in the physical mixture of all other extended release excipients which confirms the absence of chemical interaction between drug and polymers. Similar results were observed in the mixtures of GLM and magnesium stearate. Lactose and magnesium stearate which shows incompatibility in DSC studies were found compatible in FT-IR study as characteristic absorption bands of GLM are well

retained in physical mixtures of lactose and MS without any shifting or change in band position.

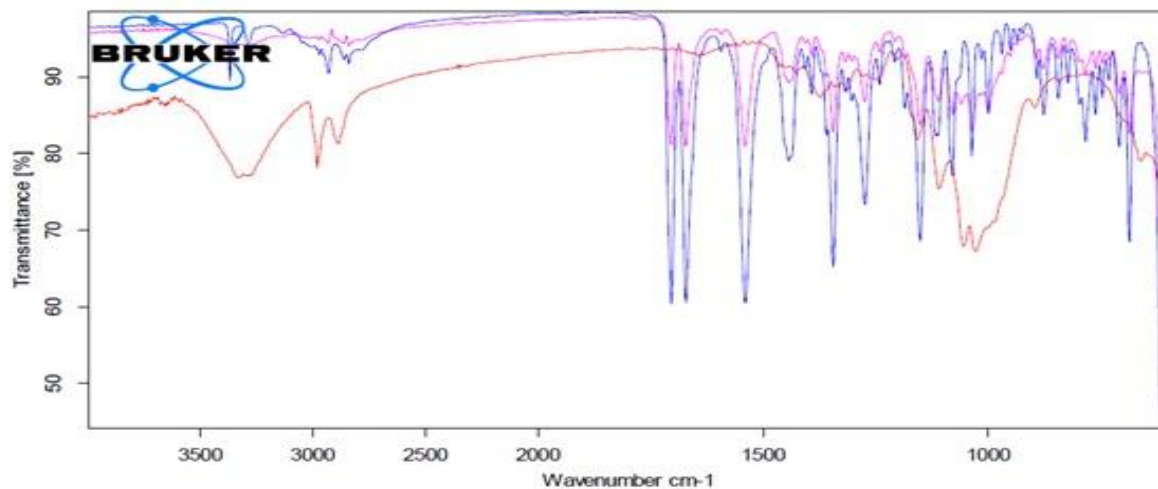
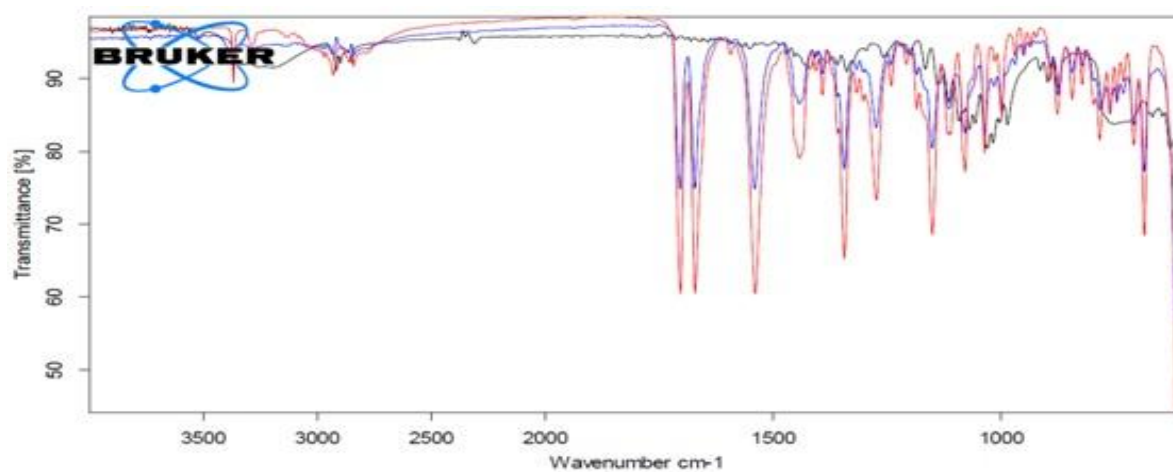
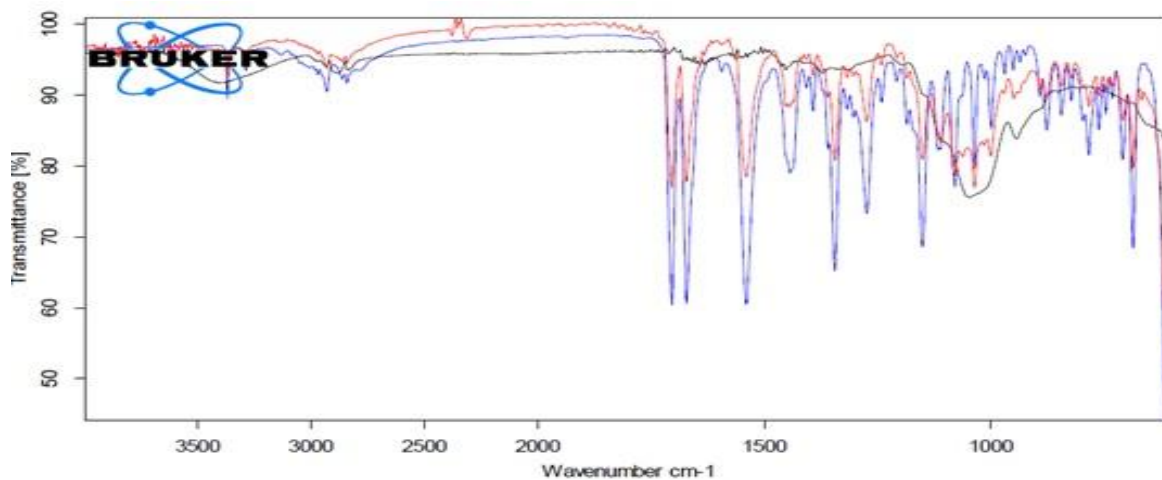


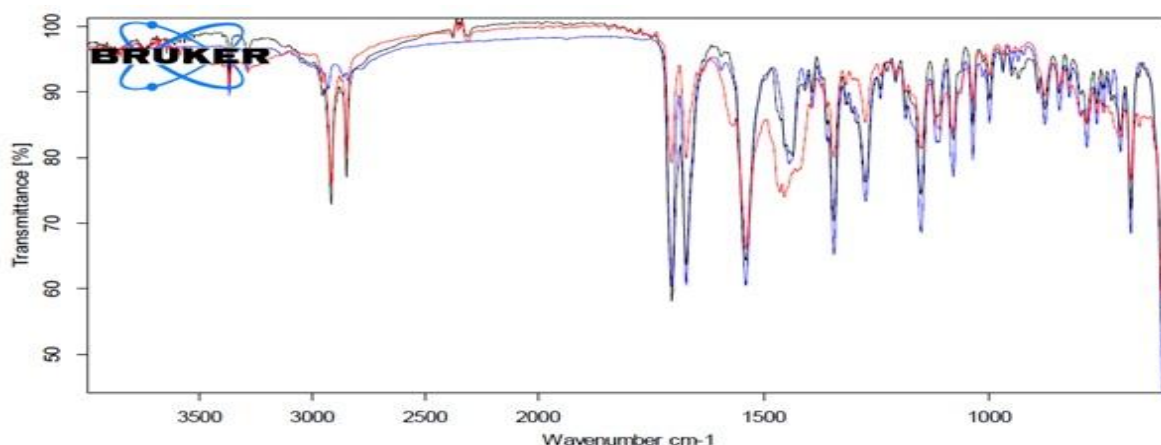
Figure 2. (a) FT-IR spectrum of GLM, blank MCC and CaCO₃ mixture and drug-excipient physical mixture



2. (b) FT-IR spectrum of GLM, lactose and their physical mixture



2. (c) FT-IR spectrum of GLM, HPMC K4M and their physical mixture



2. (d) FT-IR spectrum of GLM, Magnesium stearate, stearic acid and their physical mixtures.

Evaluation of pre-compression properties

Extended release tablet of GLM were successfully prepared by direct compression method using varying quantity of HPMC K4M as hydrophilic swellable release retardant polymer and other excipients found compatible as per the composition shown in **Table 2**. The directly compressible powder blend was evaluated for parameters like bulk density, tapped density, compressibility index, and angle of repose, Hausner ratio as shown in **Table 3**. The bulk density of the powder was in the range of 0.456 to 0.498 gm/ml; the tapped density was in the range of 0.440 to 0.460 gm/ml, which indicates that the powder was not bulky. The angle of repose of the formulations with lactose in larger quantity was

in the range of 15.12° to 18.52°, which indicated good flow of the powder. The Carr's index was found to be in the range of 3.63 to 9.69 indicating moderate to fairer compressibility of the tablet blend. The Hausner ratio lays in the range 0.911 to 0.964 confirming good flow characteristics for direct compression tablets. The results of Hausner's ratio were found to be lesser than 1.25 which indicates better flow properties. The results of angle of repose (<30) indicates good flow properties of the powder. This was further supported by lower compressibility index values. Generally compressibility values up to 15% results in good to excellent flow properties.

Table 2: Formulation composition of GLM extended release tablet

Ingredients (mg)	Coded Formulations							
	F-1 (mg)	F-2 (mg)	F-3 (mg)	F-4 (mg)	F-5 (mg)	F-6 (mg)	F-7 (mg)	F-8 (mg)
Glimepiride	6	6	6	6	6	6	6	6
PVP K30	10	10	10	10	10	10	10	10
Microcrystalline cellulose	30	30	30	30	30	30	45	15
HPMC K4M	22.5	30	37.5	45	52.5	60	60	60
Calcium carbonate	78.5	71.0	63.5	56.0	48.5	41.0	29.0	59.0
Stearic acid	3	3	3	3	3	3	3	3
Total weight	150	150	150	150	150	150	150	150

Table 3: Pre-compression properties of directly compressible powder blend

Formulation code	Angle of repose (θ°)	Tapped density (g/cm^3)	Bulk density (g/cm^3)	Hausner ratio	Carr's index (%)
F-1	15.12	0.440	0.456	0.964	3.63
F-2	16.35	0.445	0.476	0.934	6.96
F-3	17.86	0.449	0.487	0.921	8.46
F-4	18.52	0.451	0.472	0.955	4.65
F-5	16.77	0.454	0.498	0.911	9.69
F-6	17.15	0.453	0.477	0.949	5.29
F-7	19.16	0.460	0.486	0.946	5.65
F-8	16.69	0.463	0.496	0.933	7.12

Evaluation results of post compression properties of tablets

The physical properties of different batches of extended release tablets are given in **(Table 4)**. Tablet mean thickness was almost uniform in all the formulations. The thickness varies between 3.012 ± 0.01 to 3.96 ± 0.03 mm. The prepared tablets in all the formulations possessed good mechanical strength with sufficient hardness in the range of 3.3 ± 0.06 to 3.5 ± 0.06 kg/cm^2 . Friability values below

1% were an indication of good mechanical resistance of the tablets. All the tablets from each formulation passed weight variation test, as the % weight variation was within the pharmacopoeial limits of $\pm 5\%$ of the weight. The weight variation in all the six formulations was found to be 146 ± 2.45 mg to 156.0 ± 2.20 mg. The percentage drug content of all the tablets was found to be between 96.19 ± 0.32 to $98.69 \pm 0.25\%$ which was within the acceptable limits.

Table 4: Post compression properties of prepared tablets

Formulation code	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Weight variation	% of Drug content
F-1	3.321 ± 0.05	3.3 ± 0.06	0.40 ± 0.02	150 ± 2.31	96.27 ± 0.21
F-2	3.045 ± 0.04	3.4 ± 0.02	0.46 ± 0.06	152 ± 2.34	96.59 ± 0.24
F-3	3.012 ± 0.01	3.4 ± 0.04	0.53 ± 0.02	154 ± 2.02	98.21 ± 0.24
F-4	3.564 ± 0.06	3.4 ± 0.04	0.26 ± 0.08	148 ± 2.43	97.62 ± 0.12
F-5	3.875 ± 0.07	3.5 ± 0.07	0.33 ± 0.03	146 ± 2.45	97.53 ± 0.29
F-6	3.964 ± 0.03	3.5 ± 0.01	0.46 ± 0.01	154 ± 2.30	96.19 ± 0.32
F-7	3.854 ± 0.03	3.5 ± 0.03	0.19 ± 0.05	153 ± 2.31	98.69 ± 0.25
F-8	3.210 ± 0.05	3.5 ± 0.06	0.39 ± 0.02	156 ± 2.20	97.56 ± 0.23

Drug release characteristics

For successful extended release of drugs, either soluble or insoluble it is essential that polymer hydration and surface gel layer formation are quick and consistent to prevent tablet disintegration and premature drug release. The dissolution rate profile of all the six formulations showed that a higher amount of HPMC K4M in tablet composition resulted in reduced drug release **(Table 5)**.

Formulation F-2 having a composition of 20.0 % w/w HPMC K4M gave a predetermined release for 6 hrs than all other formulations. So it was concluded that formulation F-2 was the optimized batch because its drug release profile **(Figure 3a)** shows drug release for six hours in predetermined rate. At higher percentage of HPMC in tablets, when in contact with release medium, HPMC may swell and form a thick gel, thus may decrease the size of the

pores present in the tablet and further reducing the drug release. The drug release profile of various tablets was shown in **Figure 3**. Formulation F-2 which showed promising results, were subjected to

stability studies at ambient room conditions for 3 months. After 3 months, extended release tablets did not show any change in physical appearance or drug content.

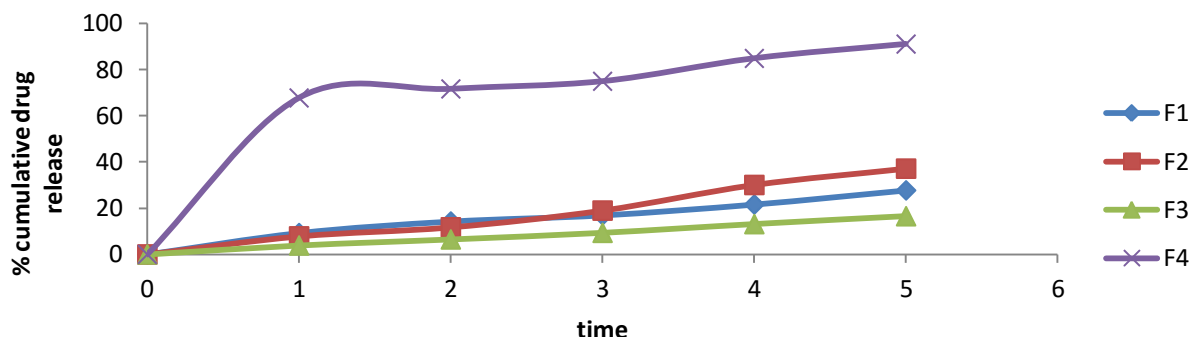


Figure 3 (a): In-vitro drug release profile of F1, F2, F3 and F4 extended release formulations

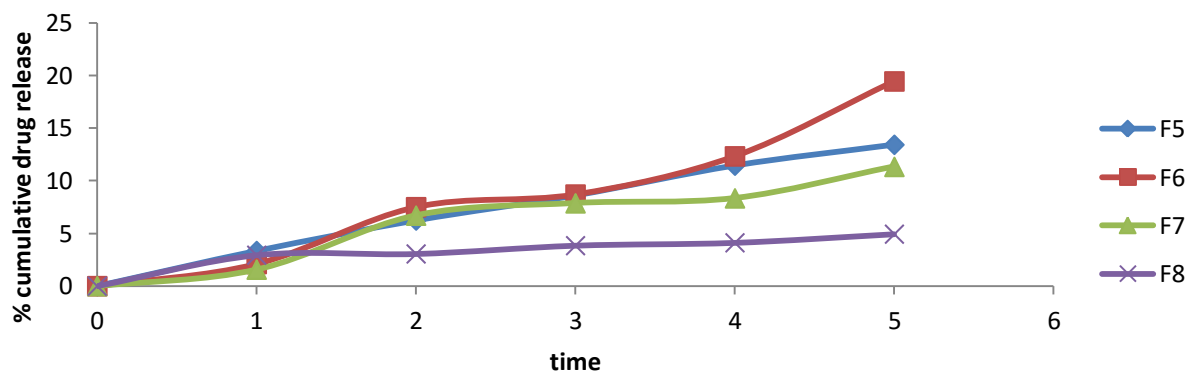


Figure 3 (b): In-vitro drug release profile of F5, F6, F7 and F8 extended release formulations

Release data revealed that optimized batch F2 follow zero-order drug release followed by Higuchi spherical matrix release as good linearity (R^2) was observed with both these models (**Table 6**). However, the best linearity ($R^2 = 0.998$) was obtained in Korse-Mayer peppas models. The

release exponent n was 0.797, which appears to indicate a coupling of the diffusion and erosion mechanism so-called non-Fickian or anomalous diffusion and may indicate that the drug release is controlled by more than one process.

Table 5: In vitro drug release data of various batches of formulations

Time in hrs	% Cumulative drug release							
	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8
1	9.25	7.81	3.87	7.43	6.47	7.3	1.57	2.98
2	14.24	11.73	6.49	7.66	6.24	7.5	6.7	3.06
3	16.92	10.62	7.21	13.41	8.61	8.7	7.8	3.5
4	21.60	30.05	13.12	17.63	9.8	12.33	8.01	4.12
5	27.71	37.11	13.33	19.96	10.5	25.83	11.33	4.94
6	34.27	38.56	16.76	20.30	11.93	31.39	25.28	7.05

12 98.66 94.77 83.29 91.33 106.55 87.19 96.32 99.84

Table 6: Release kinetic data for evaluation of drug release mechanism

FA Code	Zero order		First Order		Higuchi Model		Hixson –crowell model		Korsemeyer-Peppas Model	
	K_0	R^2	K_1	R^2	K_H	R^2	K_3	R^2	n	R^2
F1	4.862	0.982	0.027	0.963	16.59	0.941	0.101	0.841	0.66	0.936
F2	6.834	0.958	0.026	0.506	16.90	0.986	0.33	0.796	0.797	0.998
F3	2.990	0.950	0.012	0.938	8.944	0.928	0.048	0.925	0.820	0.951
F4	3.530	0.928	0.015	0.949	10.51	0.930	0.053	0.959	0.652	0.891
F5	2.473	0.828	0.004	0.584	3.56	0.797	0.067	0.482	0.332	0.779
F6	4.449	0.837	0.028	0.836	16.82	0.746	0.086	0.789	0.821	0.722
F7	2.536	0.771	0.023	0.820	12.59	0.701	0.067	0.756	0.292	0.891
F8	0.756	0.863	0.004	0.716	2.52	0.762	0.016	0.950	0.436	0.758

CONCLUSION

The results showed the utility of thermal analysis as a rapid and convenient method of screening drug candidate and some excipients during pre-formulation studies, because it permits the ascertainment of excipients compatibility or demonstration of drug-excipient interaction or incompatibility. In this study it was possible to observe the interactions of the Glimepiride with magnesium stearate and lactose. It has been revealed that excipient such as HPMC K4M with polyvinyl pyrrolidone as binder, CaCO₃ as filler can be used with direct compression method for versatile extended release technologies. Formulation F-2 having a composition of 20.0 % w/w HPMC K4M gave a predetermined release for 6 hrs than all other formulations. Release study clearly indicates that release rate from the matrix is dependent upon factors including polymer type and level; drug solubility and dose; polymer to drug ratio; filler type and level; particle size of drug and polymer and the porosity and shape of matrix. The optimized formulation was stable after 45 days accelerated stability study as there were no significant changes in drug content, physicochemical parameters and extended release pattern.

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