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FORMULATION AND EVALUATION OF ZERO-ORDER RELEASE GLIPIZIDE BILAYER MATRIX TABLETS USING NATURAL AND SYNTHETIC POLYMERS

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ABSTRACT

The aim of the present investigation was to develop controlled zero-order release glipizide bilayered matrix tablets using different grades of hydroxy propyl methyl cellulose (HPMC) as novel release modifier along with xanthan gum (XG), guar gum (GG), and karaya gum (KG) as release retardants. Bilayered matrix tablets of glipizide were prepared by wet granulation method. The release rate were modulated by varying concentration of different types of rate controlling material as well as in a combination of two different rate controlling material. After evaluation of physical properties of tablets, the *in vitro* release study was performed in phosphate buffer pH 7.4 upto 12 hrs. The effect of polymer concentration and polymer blend concentration were studied. All precompressional parameters were found to be within acceptable standard limits. It was observed that bilayer matrix tablets contained polymer blend of HPMC/Ethyl cellulose were successfully sustained the release of drug upto 12 hrs. The release data were fit into different kinetic models (zero order, first order and Korsemeyer-Peppas powers law equation). The DSC and FTIR studies demonstrated that there was no interaction between polymers and drug. Stability studies were carried out according ICH guidelines. Stability studies (40±2°C/75±5% RH) for 6 months indicated that glipizide was stable in matrix tablets. All above polymers can be successfully used to achieve desired zero order drug release.

Keywords: Matrix tablets, zero-order release, hydroxy propyl methyl cellulose, xanthan gum, guar gum, and karaya gum.

INTRODUCTION

The synthetic / semi synthetic polymers are quite unfavoured when compared with natural gums, as the natural gums are cost effective, non-toxic, biodegradable, easily available and offer flexibility in manufacturing.

Over the years, considerable efforts have been and continued to be expended in the development of new delivery concepts in order to achieve zero-order or near zero-order release. Examples of altering kinetics of drug release from the inherent non-linear behavior included the use of geometry factors (cone shape, biconcave, donut shape, hemisphere with cavity, core-in cup…), erosion/dissolution control and swelling control mechanisms, non-uniform drug loading and matrix membrane combinations. Some of the systems are difficult or impractical to manufacture [1].

Developing oral controlled release tablets for highly water soluble drugs with constant release rate has always been a challenge to the pharmaceutical technologists. Most of the highly water soluble drugs if not formulated properly, may readily release the drug at a faster rate, and are likely to produce toxic concentration of the drug on oral administration. Though various formulation approaches are used to control the release of water soluble drugs, multilayer matrix tablets are proving to be potential [2]. Glipizide is a second generation sulfonyl urea compound. It is given orally in the treatment of maturity onset diabetes, insulin resistant diabetes and diabetes insipidus. It stimulates the synthesis of insulin from the beta-cells of islets of langerhans, also, increase in the number of beta-cells and decrease the rate of insulin degradation. It is having short biological half-life (3–7 hrs) and frequent administration (usually two times a day) makes a potential candidate for sustained release formulation [3]. The main objective is to formulate glipizide controlled release bilayer matrix tablets using various polymers. And evaluate the usefulness and efficacy of various polymers using the controlled released systems. Bilayer tablets concept has long been utilized to develop sustained release formulation. Such a tablet has a fast releasing layer and may contain one (bilayer), to sustain the drug release. The pharmacokinetic advantage relies on the criterion that, drug release from the fast releasing granules layer leads to a sudden rise in the blood concentration. However the blood level is maintained at steady state, as the drug is released from the sustaining granules layer [4]. The present study is planned, to evaluate the suitability of different polymers for bilayer matrix tablets. Formulations were evaluated with respect to various parameters like (weight variation, hardness, friability, thickness, content uniformity and *in vitro* dissolution rate studies.

MATERIALS AND METHODS:

Materials: Glipizide was procured as gift sample from Cipla Chemicals Pvt. Ltd., Mumbai. Karaya gum, xanthan gum, and guar gum were obtained as gift samples from M/s H.B. Gum Industries Pvt Ltd, Kalol,

Gujarat. HPMC K15M was purchased from M/s S.D. Fine Chemicals Mumbai. All other solvents and reagents were of analytical grade.

Methods:

Preparation of Glipizide bilayer matrix tablets [5]:

The bilayer matrix tablets of glipizide were prepared by the wet granulation method. The drug, polymers and other excipients for both fast release and sustaining layer were passed through sieve #80 before their use in the formulation.

Formulation of the fast release layer: The dose in the formulation for fast release was 1.5mg, the maintenance dose or sustained dose (3.5mg) of glipizide was calculated as per the reported method. The fast release granules were prepared by wet granulation technique by blending glipizide uniformly with lactose and starch by following the formulae as per [Table 1]. The cohesive mass obtained was passed through # 16 and the granules were dried at 60°C for 1 hr in a hot air oven. The dried granules were passed through # 20 and lubricated with magnesium stearate by further blending for 3 min and finally talc was added to the blend.

Formulation of the sustained release layer: The sustaining granules were formulated by the wet granulation technique, mixing glipizide uniformly with matrix materials (HPMC, ethyl cellulose), following the formulae given in [Table 2]. The powders were granulated using sufficient quantity of acetone till a wet mass was formed. The cohesive mass obtained was passed through # 16 and the granules were air dried at room temperature for 6hrs.The dried granules were again sieved by passing through # 22. The granules were mixed with talc and magnesium stearate.

Compression of bilayer tablets: The quantity of granules for the sustained release layer was compressed lightly using a 10 station Rimek tablet compression machine (M/s Karnawati Engg. Ltd. Ahmadabad) using 6.5 mm round, flat and plain punches. Over this compressed layer, required quantity of the fast release layer was placed and compressed to obtain hardness in the range of 5-7 kg cm-2 to form a glipizide bilayer matrix tablets.

Evaluation of bilayer tablets:

The prepared tablets were evaluated for weight variation, hardness, thickness, friability, drug content, and stability studies. Pfizer hardness [6] tester was used for the determination of the hardness. In Weight variation test twenty tablets were selected at a random and average weight was calculated. Then individual tablets were weighed and the weight was compared with an average weight. The tablet was placed in contact between the plungers and the handle was pressed, the force of the fracture was recorded. In this work, for each formulation the hardness of 6 tablets was evaluated. The crown-to-crown thicknesses of ten tablets from each batch were determined using vernier calipers. The Friability [6] of the tablets was determined using Roche friabilator (Electrolab, Mumbai). This device subjects the tablets to the combined effect of abrasions and shock in a plastic chamber revolving at 25 rpm and dropping the tablets at a height of 6 inches in each revolution. Preweighed sample of tablets was placed in the friabilator and were subjected to 100 revolutions. Tablets were dedusted using a soft muslin cloth and reweighed. The friability (F) is given by the formula:

$$F = (1- W_0 / W) \times 100$$

Where, W_0 is the weight of the tablets before the test and W is the weight of the tablet after the test. For determination of drug content at least three tablets from each formulation were weighed individually, pulverized, and diluted to 250ml with sufficient amount of phosphate buffer pH 7.4. After that an aliquot of the filtrate was diluted and analyzed spectrophotometrically at 276nm.

The swelling [7] of the polymers upon hydration by the test medium was determined by a method similar to the equilibrium weight gain method. Representative formulations from each set were analyzed for swelling behavior. The bilayered matrix tablets were weighed and Placed in tarred metallic baskets. These baskets were then immersed in 900 ml of phosphate buffer pH 7.4 and rotated at 100 rpm. At specified time intervals, the baskets containing the bilayered matrix tablets were removed, lightly blotted with tissue paper so as to remove excess water and weighed again. They were then placed back in the dissolution vessel as quickly as possible. The percent degree of swelling was calculated as follows:

$$\text{Percent degree of swelling} = [Ws - Wd / Wd] \times 100$$

Where Ws is the weight of the swollen matrix at time t and Wd is the weight of the dry matrix. The swelling study was done in triplicate for all samples tested.

In vitro release was studied using [8, 9] USP XXIII type dissolution test apparatus (Electrolab TDT 08T) in the speed 900ml of phosphate buffer pH 7.4 for a period of 12 hrs. The dissolution test was performed at 100 rpm and the temperature was set at 37 ^{0} C ± 5^{0}C. At predetermined time intervals over 12 hrs 5 ml samples were withdrawn and assayed spectrophotometrically at 276 nm. After each

sampling equal volume of fresh dissolution medium (5ml) was replaced.

Optimized bilayered matrix tablets were selected for stability studies [7]. The stability studies was carried out according to ICH guidelines at 40 ± 2°C/75 ± 5% RH for three months by storing the samples in (Lab-care, Mumbai) stability chamber.

FTIR Studies

IR spectra for pure drug and formulation F12, F14 and F18 were recorded in a Fourier transform infrared spectrophotometer (FTIR 1615, Perkin Elmer, and USA.) with KBr pellets

DSC Studies

DSC scans of about 5mg; using an automatic thermal analyzer system performed accurately weighed and tablet containing glipizide the same amount of drug. (DSC 60, Shimadzu, Japan) Sealed and perforated aluminium pans were used in the experiments for all the samples. Temperature calibrations were performed using indium as standard. An empty pan sealed in the same way as the sample was used as a reference. The entire samples were run at a scanning rate of 10°C/min from 50-300°C.

RESULT AND DISCUSSION

Precompressional parameters

Precompressional parameter of I.R. layer granules results were compared in the [Table 3] in range between angle of repose (24.22 to 31.45) ,% compressibility between(14.09 to 17.23 %) respectively .The result showed in [Table 3] indicates good flow property and compressibility.

Precompressional parameter of S.R. layer granules those results were compared in the [Table 3], angle of repose (24.02 to 31.91), % compressibility (14.03 to 17.87) respectively. The result showed in [Table 3], indicates good flow property and compressibility.

Postcompressional parameters

The thickness of the tablets was ranged from 5.01mm to 6.32mm. The average percentage deviation of 20 tablets from each formulation was remained within ± 3 %. The hardness and percentage friability of the tablets of all formulation remained in range of 5.22 to 6.79 and 0.32 to 0.89 respectively. Drug content was ranged from 98.12% to 99.99%. The result is depicted in [Table 4].

Table 1: Compositions of IR layer and SR layer of synthetic polymers

Formulation code	Ingredients of IR layer (100mg)			Ingredients of SR layer (150mg)				
	Glipizide and Mannitol solid dispersion 1:2 ratio	Lactose	Starch	Glipizide	HPMC K4	HPMC K15	HPMC K100	EC
F1	6	66	25	3	36	-	-	108
F2	6	66	25	3	108	-	-	36
F3	6	66	25	3	-	36	-	108
F4	6	66	25	3	-	108	-	36
F5	6	66	25	3	-	-	36	108
F6	6	66	25	3	-	-	108	36
F7	6	66	25	3	108	-	-	36
F8	6	66	25	3	36	-	-	108
F9	6	66	25	3	-	108	-	36
F10	6	66	25	3	-	36	-	108
F11	6	66	25	3	-	-	108	36
F12	6	66	25	3	-	-	36	108

** In all the formulations in both IR and SR layer contains 1mg of talc. **** In all the formulations in both IR and SR layer contains 2mg of magnesium stearate.

Table: 2 Compositions of IR layer and SR layer of natural polymers

Formulation code	Ingredients of IR layer (100mg)			Ingredients of SR layer (150mg)				
	Glipizide and Mannitol solid dispersion 1:2 ratio	Lactose	Starch	Glipizide	XG	GG	GK	EC
F13	6	66	25	3	100	30	-	14
F14	6	66	25	3	90	40	-	14
F15	6	66	25	3	30	100	-	14
F16	6	66	25	3	40	90	-	14
F17	6	66	25	3	100	-	30	14
F18	6	66	25	3	90	-	40	14
F19	6	66	25	3	30	-	100	14
F20	6	66	25	3	40	-	90	14
F21	6	66	25	3	-	100	30	14
F22	6	66	25	3	-	90	40	14
F23	6	66	25	3	-	30	100	14
F24	6	66	25	3	-	40	90	14

** In all the formulations in both IR and SR layer contains 1mg of talc. **** In all the formulations in both IR and SR layer contains 2mg of magnesium stearate.

Table 3: Precompressional parameters of IR, and SR layer granules

Formulation code	IR layer granules			SR layer granules		
	Angle of repose (θ) (±SD), n=3	%Compressibility (±SD), n=3	Hausner's ratio, (±SD), n=3	Angle of repose (θ) (±SD), n=3	%Compressibility (±SD), n=3	Hausner's ratio, (±SD), n=3
F1	24.22(0.81)	16.13(0.47)	1.21(0.01)	24.02(0.81)	16.13(0.47)	1.21(0.01)
F2	25.71(0.89)	15.73(0.52)	1.23(0.00)	25.71(0.89)	15.73(0.52)	1.23(0.00)
F3	26.94(0.63)	17.32(0.34)	1.18(0.21)	26.94(0.63)	17.87(0.34)	1.18(0.21)
F4	27.62(0.91)	16.09(0.48)	1.17(0.08)	27.62(0.91)	16.09(0.48)	1.17(0.08)
F5	29.70(0.18)	16.53(0.56)	1.18(0.01)	29.70(0.18)	16.53(0.56)	1.18(0.01)
F6	30.72(0.21)	15.99(0.73)	1.16(0.02)	30.72(0.21)	15.99(0.73)	1.16(0.02)
F7	31.23(0.12)	14.09(0.92)	1.25(0.02)	31.23(0.12)	14.03(0.92)	1.25(0.02)
F8	29.28(0.71)	15.60(0.97)	1.25(0.02)	29.28(0.71)	15.60(0.97)	1.27(0.02)
F9	29.12(0.17)	15.99(0.65)	1.21(0.02)	29.12(0.17)	15.99(0.65)	1.21(0.02)
F10	30.78(0.29)	16.57(0.95)	1.19(0.02)	30.78(0.29)	16.57(0.95)	1.19(0.02)
F11	31.45(0.53)	15.89(0.73)	1.13(0.02)	31.45(0.53)	15.89(0.73)	1.13(0.02)
F12	26.78(0.11)	15.81(0.42)	1.17(0.02)	26.78(0.11)	15.81(0.42)	1.10(0.02)
F13	25.99(0.18)	15.99(0.33)	1.18(0.03)	25.99(0.18)	15.99(0.33)	1.18(0.03)
F14	26.17(0.16)	16.02(0.36)	1.12(0.02)	26.17(0.16)	16.02(0.36)	1.12(0.02)
F15	29.32(0.13)	15.99(0.83)	1.13(0.01)	29.32(0.13)	15.99(0.83)	1.13(0.01)
F16	27.15(0.61)	15.96(0.39)	1.12(0.02)	27.15(0.61)	15.96(0.39)	1.12(0.02)
F17	31.30(0.82)	16.79(0.03)	1.13(0.03)	31.30(0.82)	16.79(0.03)	1.13(0.03)
F18	29.22(0.18)	15.88(0.72)	1.14(0.02)	29.22(0.18)	15.88(0.72)	1.14(0.02)
F19	30.23(0.66)	15.11(0.43)	1.12(0.00)	30.23(0.66)	15.11(0.43)	1.12(0.00)
F20	30.37(0.12)	15.36(0.85)	1.17(0.03)	30.37(0.12)	15.36(0.85)	1.17(0.03)
F21	31.11(0.32)	15.09(0.74)	1.18(0.02)	31.91(0.32)	15.09(0.74)	1.18(0.02)
F22	29.34(0.33)	16.50(0.62)	1.17(0.04)	29.34(0.33)	16.50(0.62)	1.17(0.04)
F23	28.56(0.21)	16.47(0.56)	1.15(0.01)	28.56(0.21)	16.47(0.56)	1.15(0.01)
F24	29.32(0.45)	15.45(0.52)	1.14(0.04)	29.32(0.45)	15.45(0.52)	1.14(0.04)

Note: Values in parenthesis are standard deviation (±SD)

Table 4: Postcompressional parameters of glipizide bilayer tablets

Formulation Code	Hardnes test (Kg/cm^2) (±SD), n=6	Friability(%), (±SD), n=10	Wt. variation (%) n=20	Thickness(mm), (±SD), n=10	Drug content (%), (±SD), n=3
F1	6.28(0.01)	0.32(0.01)	1.91	5.13(0.02)	99.97(0.55)
F2	6.76(0.36)	0.76(0.01)	1.20	5.06(0.02)	98.12(1.20)
F3	6.23(0.01)	0.82(0.01)	1.77	5.15(0.02)	99.04(0.45)
F4	5.36(0.35)	0.49(0.01)	2.15	5.18(0.02)	98.18(0.85)
F5	6.54(0.36)	0.39(0.01)	1.95	5.01(0.02)	99.70(0.45)
F6	6.41(0.36)	0.59(0.01)	2.34	5.21(0.02)	99.47(0.55)
F7	6.40(0.36)	0.66(0.01)	2.41	5.33(0.02)	99.76(0.75)
F8	5.67(0.35)	0.42(0.01)	2.18	5.31(0.02)	98.88(0.62)
F9	6.79(0.36)	0.59(0.01)	1.82	5.22(0.02)	99.99(0.69)
F10	6.45(0.35)	0.65(0.01)	2.34	5.16(0.02)	99.46(0.56)
F11	6.56(0.34)	0.73(0.01)	2.57	5.17(0.02)	99.660.58)
F12	5.22(0.32)	0.32(0.01)	2.79	6.22(.01)	98.81(0.83)
F13	5.63(0.36)	0.89(0.01)	2.78	5.11(0.02)	99.49(0.58)
F14	6.49(0.36)	0.72(0.01)	2.69	5.35(0.02)	98.91(0.67)
F15	6.57(0.32)	0.36(0.01)	1.72	5.17(0.02)	99.96(0.61)
F16	6.54(0.3.3)	0.55(0.01)	1.95	6.32(0.36)	99.88(0.81)
F17	6.78(0.36)	0.75(0.01)	1.33	5.12(0.02)	99.40(0.58)
F18	5.89(0.33)	0.66(0.01)	2.20	5.23(0.02)	99.61(0.54)
F19	5.67(0.32)	0.45(0.01)	1.88	5.43(0.02)	98.94(0.62)
F20	5.59(0.36)	0.59(0.01)	1.78	5.39(0.02)	98.97(0.67)
F21	6.68(0.32)	0.68(0.01)	1.79	5.25(0.02)	99.99(0.49)
F22	6.67(0.22)	0.66(0.01)	2.45	5.22(0.02)	98.96(0.66)
F23	5.89(0.36)	0.45(0.01)	2.39	5.21(0.02)	99.97(0.63)
F24	5.90 (o.34)	0.49 (0.01)	2.29	5.17(0.02)	99.91(0.61)

Note: Values in parenthesis are standard deviation (±SD)

Table 5: Kinetic parameters of matrix tablets

Formula	First- order(r^2)	Zero-order(r^2)	Kors.-Peppas (n)	Kors. -Peppas (r^2)
F1	0.7954	0.9626	0.3423	0.9757
F2	0.8471	0.9869	0.3789	0.9820
F3	0.8802	0.9703	0.3915	0.9872
F4	0.8751	0.9814	0.5012	0.9807
F5	0.8423	0.9840	0.4645	0.9549
F6	0.7991	0.9946	0.5745	0.9770
F7	0.8041	0.9799	0.6351	0.9657
F8	0.8642	0.9987	0.5078	0.9651
F9	0.8085	0.9798	0.5485	0.9659
F10	0.8803	0.9921	0.6589	0.9490
F11	0.8995	0.9894	0.4576	0.9578
F12	0.8723	0.9979	0.6992	0.9501
F13	0.9204	0.9737	0.5689	0.9793
F14	0.8924	0.9876	0.5676	0.9896
F15	0.8956	0.9803	0.6423	0.9848
F16	0.9523	0.9799	0.5786	0.9818
F17	0.8971	0.9806	0.5467	0.9705
F18	0.8750	0.9789	0.5768	0.9873
F19	0.8923	0.9792	0.6734	0.9790
F20	0.9158	0.9785	0.6056	0.9859
F21	0.9255	0.9706	0.5489	0.9416
F22	0.8956	0.9769	0.5167	0.9556
F23	0.8278	0.9698	0.6230	0.9884
F24	0.8496	0.9708	0.5347	0.9867

Table 6: Data after stability study

Formulation Code	Stability period	Drug content (%), (±SD), n=3,	Hardness Test, (Kg/cm^2) (±SD), n=6	Friability (%), (±SD), n=10
F12	30 days	98.81 (0.83)	6.22 (0.01)	0.32 (0.01)
	60 days	98.45 (0.80)	6.72 (0.01)	0.31 (0.01)
	90 days	98.18 (0.81)	6.32 (0.36)	0.55 (0.01)
F14	30 days	98.82 (0.80)	5.72 (0.01)	0.79 (0.01)
	60 days	98.45 (0.80)	5.69 (0.01)	0.78 (0.01)
	90 days	98.07 (0.80)	5.69 (0.01)	0.80 (0.01)
F18	30 days	99.88 (0.81)	6.32 (0.36)	0.55 (0.01)
	60 days	99.10 (0.81)	6.30 (0.36)	0.54 (0.01)
	90 days	98.17 (0.81)	6.30 (0.36)	0.60 (0.01)

Note: Values in parenthesis are standard deviation (±SD)

In vitro dissolution study of all the formulations was carried out using phosphate buffer pH 7.4 upto 12 hrs. All the formulations were prepared by using different synthetic (HPMC, ethyl cellulose) and natural polymers like XG, GG, KG. The polymer chosen are well established and have good swelling properties. Formulations F1 to F4 were prepared by using ratio of drug and mannitol solid dispersion as 1:1. [Figure 1] shows the release profile of formulations F1 to F4. Among all formulations, the F4 formulation with HPMC K4 M shown faster drug release within 12 hrs. With all four formulations, an initial burst release of the drug followed by a steady-state release was observed. As it is bilayered tablets, the drug is released immediately from the IR layer so as to achieve minimum effective concentration. Then the drug is released slowly from the SR layer to maintain the achieved concentration in controlled manner upto 12 hrs. [Figure 2] shows the release profile of formulations F5 to F8. These formulations were prepared by using ratio of drug and mannitol solid dispersion as 1:2. In all four formulations, an initial burst release of the drug followed by a steady-state release was observed. Formulations F5 and F6 which is prepared with HPMC K4 M different ratio. For F5 show 85.13% drug release in 12 hrs, where as the formulation F6 which is prepared with another ratio of HPMC K4 M shows 77.19% drug release in 12 hrs. F7 which is prepared with HPMC K 15 M has show 79.91% drug release in 12 hrs. F8 which is prepared with HPMC K15 M has show 88.94% drug release with in 12 hrs. From the *in vitro* dissolution study it was found that the polymer amount in formulations F5 to F8 was sufficient to sustain the drug release upto 12 hrs. Among these eight formulations, formulations with HPMC K15 M alone show higher initial burst release due to hydration rate of this synthetic polymer relates to its hydroxyl propyl substitutes percentage [10]. HPMC K15 M contains the greatest amount of these groups and produces strongly viscous gel that play an important role in drug release especially at the beginning of the release profile. [Figure 3] shows the release profile of formulations F9 to F14. These formulations were prepared by using ratio of drug and mannitol solid dispersion as 1:3. In these formulation polymers blend HPMC K 100 and HPMC K 4 M grade were used. From the release study it is observed that, from the formulations drug release will be controlled upto 12 hrs. In these formulations as the concentration of HPMC K100 M, decreased the drug release is increased from 98.16% to 99.99%. [Figure 6] shows the release profile of formulations F15 to F18. These formulations were prepared with the drug and mannitol solid dispersion with natural polymer of XG, and GG. From the release study it is observed that, from the formulations drug release will be controlled upto 12 hrs.

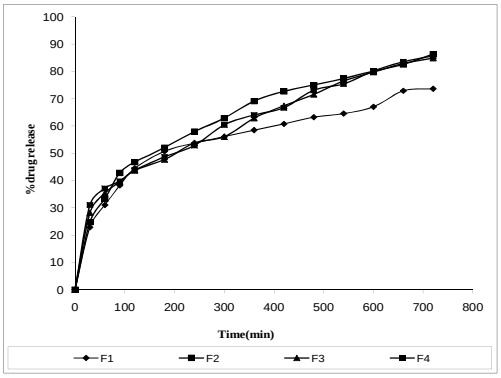

Fig 1: Comparative release profile of formulation F1 to F4.

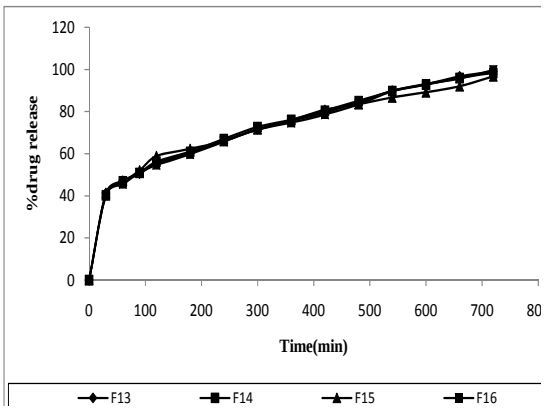

Fig 4: Comparative release profile of formulation F13 to F16.

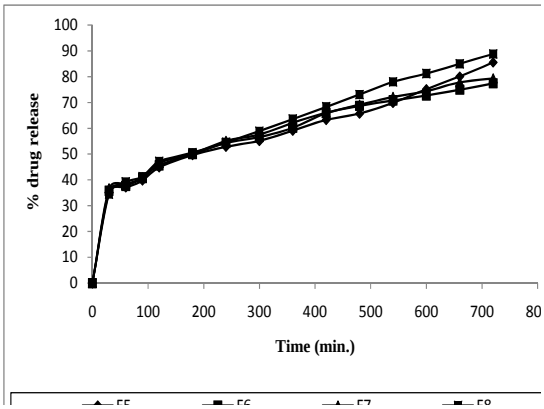

Fig 2: Comparative release profile of formulation F5 to F8.

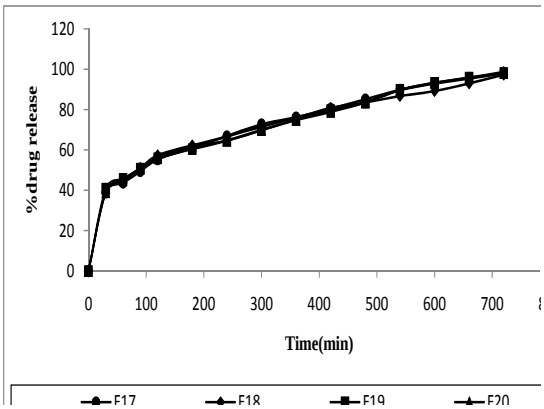

Fig 5: Comparative release profile of formulation F17 to F20.

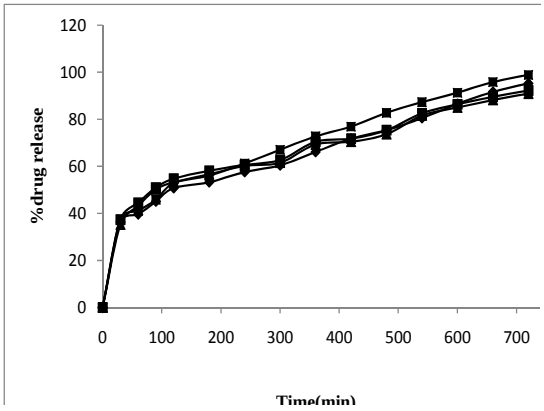

Fig 3: Comparative release profile of formulation F9 to F12.

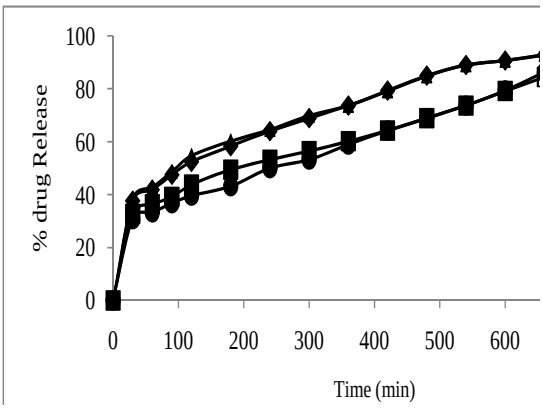

Fig 6: Comparative release profile of formulation F21 to F24.

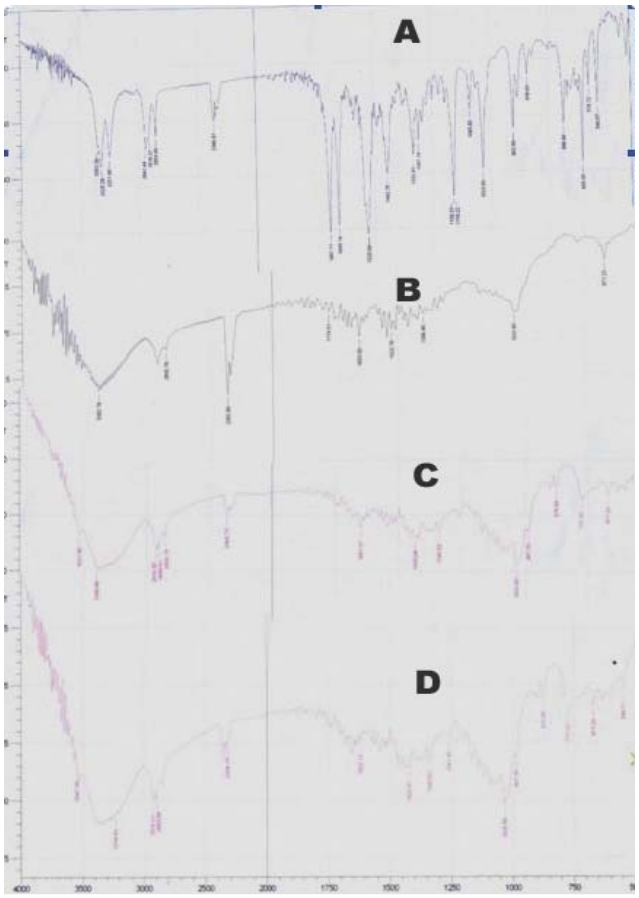

Fig 7: A - FTIR spectra of Glipizide pure drug, B - FTIR spectra of formulation F12, C- FTIR spectra of formulation F14, D - FTIR spectra of formulation F18.

In these formulations as the concentration of XG, decreased the drug release is increased 96.01% to 99.81%. It is mainly due to high swelling rate of GG. [Figure 4] shows the release profile of formulations F19 to F22. These formulations were prepared by using ratios of drug and mannitol solid dispersions 1:3 with natural polymer blend of KG and XG. From the release study it is observed that, from the formulations drug release will be controlled upto 12 hrs. In these formulations, as we increase the concentration of KG, increased the drug release is decreased from 98.37% to 97.03%. It is mainly due to high swelling rate of KG. [Figure 5] shows the release profile of formulations of F23 to F26. These formulations were prepared with the natural polymer blend of GG and KG. In these formulations also the same ratio of drug and mannitol solid dispersion 1:3 were used. From the release study it is observed that from the formulations drug release will be controlled upto 12 hrs. In this formulation, as we increase the concentration of KG increased, the drug release is decrease from 95.07% to 90.90%.It is mainly due to high swelling rate of KG [11].

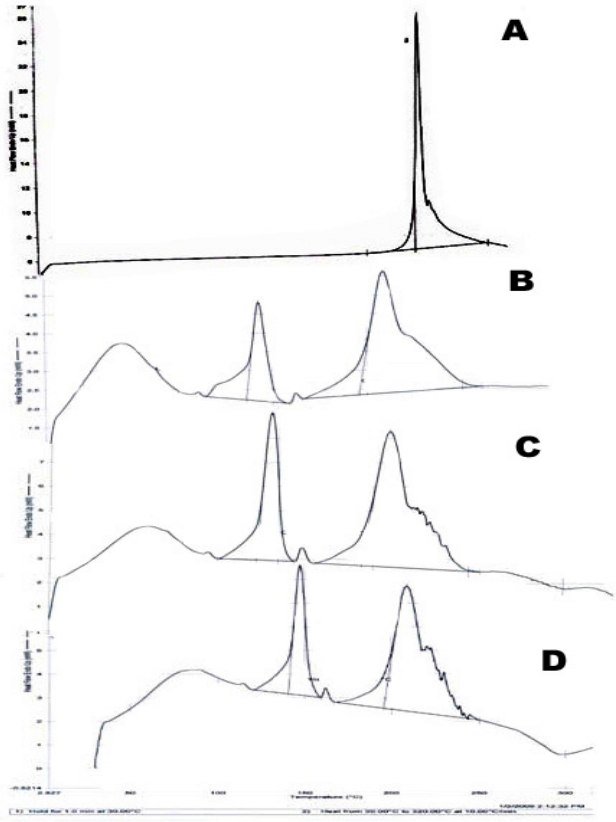

Fig 8: (A) DSC thermogram of glipizide pure drug, (B) DSC thermogram of Formulation F12, (C) DSC thermogram of Formulation F14, (D) DSC thermogram of Formulation F18.

Kinetics drug release result shown in [Table 5] reveals that all formulations follows zero-order kinetics as correlation coefficient (r^2) values are higher than that of first-order release kinetics. The calculated n values from power law equation for drug release profiles Were between 0.3423-0.6922 with a correlation coefficient (r2) values >0.94, suggest that drug release mechanism from bilayered matrix tablets followed non-Fickian (anomalous) transport mechanism.

The stability study of the tablets F12, F14 and F18 were carried out according to ICH guidelines at 40±2°C/ 75±5%RH for three months. [Table 6] shows the drug content; hardness and friability did not vary with accelerated conditions.

FTIR Study

[Figure 13] shows the IR Spectrum of pure drug glipizide shows characteristic absorption band for its different functional groups and various bonds in the following IR region.

NH Stretching - 3251 and 3325 cm^{-1}. Aromatic CH stretching -3060 cm^{-1}.

CH stretching of CH_3, CH_2 groups both symmetric and assymetric - 2854 to 2941 cm^{-1}.

C=O of CONH - 1687 cm^{-1}. NH Bending - 1649 cm^{-1}. C=N - 1610 cm^{-1}.

C=O Ring Stretching - 1550, 1525, 1460 cm^{-1}.

CH bending of CH_3 and CH_2 - 1442 cm^{-1}.

The IR Spectrum of the formulation F 12 which contains the drug and the polymer HPMC shows the characteristic peaks as follows. The broad band ranging from 3100 to 3400 cm^{-1} consists the NH stretching and OH hydrogen bonded. The peaks in the range 2850 to 2940 cm^{-1} may be due to CH stretching both symmetric and assymetric CH_2 and CH_3 groups of the drug and the polymer.

The IR spectrum of F14 formulation. The amide carbonyl group absorption band at 1680 cm^{-1}, NH bending - 1650 cm^{-1}, 1340 cm^{-1} SO_2, 1435 cm^{-1} CH bending of CH_2 and CH_3 groups of drug and polymer. The significant peak at 1033 cm^{-1} may be due to C-O-C. The IR spectrum of F 18 is also in full agreement with the IR spectrum of the formulation F 12 and F 14. In this formulation also no appreciable changes in the position of absorption bands of the respective drug and the polymer is observed.

Hence it can be concluded that, in all the formulations the drug and the polymer are present without under going in structural changes indicating that there is no interaction between the drug and the polymer

DSC study

[Figure 14] shows the DSC thermogramss of the pure Glipizide shows melting point around 214^0 C, which is slightly higher than the literature melting points that is 209^0C may be due to traces of impurities. In the drug procured as a gift sample. However the formulation of the drug in F12, F14 and F18 containing drug and different polymers has given DSC thermogram with sharp melting point in the range 208 -209^0C all most the same melting point collected from the literature that is 208 -209^0C. There is no much change in the nature of thermo gram as well as in the melting point of the drug and the drug with the different polymers it can be concluded no interaction between drug and polymer used in different formulations.

CONCLUSION

In conclusion, following the parameters of bilayer matrix tablets were within acceptable official IP limits. Precompressional parameters of bilayer matrix tablets (angle of repose, % compressibility and hausner·s ratio are in the range of given in official standard, indicated that granules prepared by wet granulation method were free flowing.

The postcompressional parameters of bilayer matrix tablets (hardness, friability, weight variation, thickness and drug content) were within the acceptable official IP limits. The optimized bilayered tablets were selected for DSC and FTIR studies did not show any interaction between the polymer and pure drug. The optimized bilayered tablets formulation were selected for the Stability studies were carried out according to ICH guidelines at 41 ± 2^o C/75±5% RH for three months indicated that the pure drug was stable in layered tablets.

Hence, it is finally concluded that, the bilayer matrix tablet technology can be successfully applied for achieving ideal zero-order release pattern for glipizide using blend of HPMC K100M, HPMC K15M and ethyl cellulose, xanthan gum, guar gum, karaya gum can be used as rate controlling polymers by appropriate selection of the level of polymers in the matrix tablets.

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