Original Article

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A VALID ADVANCE TECHNIQUE DESIGNED FOR GLIBENCLAMIDE AND METFORMIN HCL INTO IMMEDIATE AND EXTENDED RELEASE BILAYERED TABLET

[*,1]Aiswarya R, [2]Suresh A G, [1]Parthiban K G

[*,1]J.K.K.M.M.R.F College of Pharmacy, Komarapalayam, Namakkal (dt), TN, India - 638 183.

[2]C.L.Baid Metha College of Pharmacy, Thorapakkam, Chennai, TN, India - 600 097.

Abstract

The present study was to establish Bi-layer tablets containing Metformin hydrochloride as extended release layer and Glibenclamide as immediate release layer for the treatment of type II diabetes mellitus. Extended release layer was prepared by wet granulation method using HPMC 100 and ethyl cellulose as polymers. Immediate release layer were prepared by using super disintegrants such as sodium starch glycolate and cross carmellose sodium. The granules were evaluated for bulk density,tapped density, compressibility index,and hausner's ratio. The granules showed satisfactory flow properties. The tablets were subjected to weight variation test, hardness test, friability test, drug content test ,wetting time and water absorption test. All the tablets were passed the tests. The *in-vitro* release studies were carried out in phosphate buffer of PH 6.8 for 12 hours using USP-type II paddle apparatus. The *in-vitro* release profiles of drug from sustained release layer could be best expressed by Higuchi's equation as plots showed high linearity (R2> 0.988). The formulations (F12, F27) having immediate release layer produces effect within 30 minutes followed by sustained release (98.90%) at 12 hours.

Keywords: Bi-layer tablet, Glibenclamide,Metformin hydrochloride,Higuchis equation.

Introduction

Metformin hydrochloride is a highly water-soluble anti-hyperglycemic agent used in the treatment of type II (non-insulin-dependent) diabetes mellitus. It is the only agent specifically affecting elevated plasminogen activator (PAI) - levels both in hypertriglyceridemia and in noninsulin dependent diabetes.[1] In spite of its favorable clinical response metformin hydrochloride suffers from certain drawbacks of which, the most prominent being the high dose[2] (1.5-2.0 g/day), low bioavailability (40-60%), short biological half-life (0.9-2.6 h) which requires repeated administrations of high doses to maintain effective plasma concentrations,[3] and high incidence of gastro intestine tract side effects (30% cases) such as abdominal discomfort, nausea, and diarrhea, may occur during the treatment.[4] Gastrointestinal absorption of metformin is incomplete under fasting conditions in combination with rapid

Author for Correspondence:
Aishwarya R,
J.K.K.M.M.R.F College of Pharmacy,
Ethirmedu, B.Komarapalayam,
Namakkal Dt, Tamilnadu, India- 638 183.
Email: ais_sakthi7@yahoo.co.in

elimination and 20–30% of an oral dose is recovered in feces. Bioavailability decreases as the dose increases, suggesting some form of saturable absorption process and need for twice to three times a day administration which can also reduce patient compliance and hinder more successful therapy.[5]

Glibenclamide is a second generation sulphonyl urea capable of stimulating insulin release, but are not capable of acting on insulin resistance, and metformin hydrochloride able to act on insulin resistance, whereas they are not able to stimulate insulin secretion.[6]

Rationale for combination of glibenclamide with metformin hydrochloride, suggests the use of combined formulations of medicaments capable of finding a remedy for both the deficiency in insulin secretion and the insulin resistance condition. Reduces the incidence of secondary failure of mono therapy and also increases the patient compliance by administering the drug in a single dosage form[7] 5mg of glibenclamide and 500mg of metformin hydrochloride is suitable for the treatment of type II diabetes mellitus at any time of the progression of the disease, from its onset to most severe cases. In sudden occurrence of hyperglycemia, a dose of 5mg of glibenclamide is required to reduce the hyperglycemic effect and 500mg of metformin hydrochloride is required to sustain the normal glycemic level for the type II diabetic patient.[8]

The primary goal of our work is to produce a sustained release preparation with more uniform maintenance of blood plasma active concentration. Thus, potentially avoiding undesirable peaks and troughs associated with multiple immediate release preparations, and to reduce frequent dosing interval of the drug.

Therefore, it is an **object** to produce a bilayer tablet with two different release profiles with glibenclamide as immediate release layer and metformin hydrochloride as a sustain release layer to provide a desired pharmacokinetic and therapeutic action.

Materials and Methods

Materials

Metformin Hydrochloride, Glibenclamide were received as gift samples from Arvind Remedies ltd. Chennai. Sodium starch glycolate, Crospovidone, and Croscarmellose sodium were obtained from Sigma Aldrich, Bangalore. Hydroxy propyl methyl cellulose 100 purchased from Rolex Laboratory Reagent. Ethyl cellulose, and Povidone (PVP – K30) were purchased from Lab Chemicals, Chennai. Microcrystalline cellulose, Colloidal Silicon dioxide (Aerosil), and Magnesium stearate was obtained from Paxmy specialty chemicals, Chennai. Lactose, Talc and Manitol were purchased from Chemspure, Chennai. All other chemicals and reagents used were analytical grades purchased from S.d. Fine Chemicals ltd, Mumbai

Methods

Characterization of active pharmaceutical ingredient and polymer using FT – IR

Metformin hydrochloride, Glibenclamide, and their mixture discs were prepared by pressing their respective drug, polymer and superdisintegrant with potassium bromide by using FT – IR Spectrophotometer MB 104 Boman Canada. Spectrum was observed between 4000^{-1}cm to 500^{-1}cm under the operational conditions.

Thermal analysis for characterizing interaction between drugs and excipients

Differential scanning colorimetry

Thermograms were obtained for the mixture of drugs and its excipients were done with NETZSCH DSC 204 in the range from 23.9°C to 237.9°C, and their melting point and glass transition temperature were detected.

Analysis of excipients compatibility by stability studies

The active ingredients metformin Hcl, glibenclamide alone and mixtures of active ingredients with various excipients in the ratio 1:1 and 1:0.5 and 1:0.3 were taken in glass vial and kept at various conditions (40°C / 75%RH and 50°C / 90% RH) and studied in open and closed vials for a period of 1 month.

Preparation of immediate release granules

Glibenclamide, lactose, manitol, micro - crystalline cellulose, and super disintegrant were sifted through 40#. Sifted materials were mixed thoroughly in a porcelain mortar for 15 minutes and granulated with PVP K30 in ethanol as a binder solution. Granules were dried in hot air oven at 50°C for 30 minutes and passed through 20#. Prepared granules were lubricated with magnesium stearate and aerosil previously passes through 60#. Prepared granules were compressed with round shaped concave punches for initial assessments in an average weight of 200mg per tablet.

Preparation of sustained release granules

Metformin hydrochloride, microcrystalline cellulose and HPMC 100 / Ethyl Cellulose were sifted through 40#. Sifted materials were mixed thoroughly for 15 minutes in a porcelain mortar and granulated with PVP K30 in Isopropyl alcohol as a binder solution. Granules were dried in hot air oven at 50°C for 30 minutes and passed through 20#. Prepared granules were lubricated with magnesium stearate, Talc and aerosil previously passes through 60#. Prepared granules were compressed with round shaped concave punches for initial assessments in an average weight of 800mg per tablet.

Table no. 1: Formulation of glibenclamide immediate release layer

S. No	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
1	Glibenclamide	5	5	5	5	5	5	5	5	5	5	5	5
2	Sodium starch glycolate	6	8	10	12	-	-	-	-	-	-	-	-
3	Crospovidone	-	-	-	-	6	8	10	12	-	-	-	-
4	Croscarmellose sodium	-	-	-	-	-	-	-	-	6	8	10	12
5	Povidone K 30	10	10	10	10	10	10	10	10	10	10	10	10
6	Microcrystalline cellulose	73	73	73	71	71	71	69	69	69	67	67	67
7	Mannitol	50	50	50	50	50	50	50	50	50	50	50	50
8	Lactose	50	50	50	50	50	50	50	50	50	50	50	50
9	Aerosil	02	02	02	02	02	02	02	02	02	02	02	02
10	Magnesium stearate	04	04	04	04	04	04	04	04	04	04	04	04
	Total	200	200	200	200	200	200	200	200	200	200	200	200

Table no. 2: Formulation of metformin hydrochloride sustained release

S.No	Ingredients	F13	F14	F15	F16	F17	F18	F19	F20	F21	F22	F23	F24	F25	F26	F27
1	Metformin hydrochloride	500	500	500	500	500	500	500	500	500	500	500	500	500	500	500
2	HPMC 100	100	125	150	175	200	-	-	-	-	-	100	50	100	100	100
3	Ethyl cellulose	-	-	-	-	-	100	125	150	175	200	50	100	100	100	100
4	Microcrystalline cellulose	160	135	110	85	60	160	135	110	85	60	110	110	60	55	50
5	PVP K 30	20	20	20	20	20	20	20	20	20	20	20	20	20	25	30
6	Talc	08	08	08	08	08	08	08	08	08	08	08	08	08	08	08
7	Aerosil	04	04	04	04	04	04	04	04	04	04	04	04	04	04	04
8	Magnesium stearate	08	08	08	08	08	08	08	08	08	08	08	08	08	08	08
9	Isopropyl alcohol	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
	Total	800	800	800	800	800	800	800	800	800	800	800	800	800	800	800

Preparation of bilayer tablet

Both immediate and sustained release layer granules were compressed as a single layer tablets in different formulations and their results were interpreted, optimized and chosen for bilayer tablet. Optimal formulation from both the layers was compressed with caplet shaped plain punches in an average weight of 1000mg per tablet.

Evaluation for immediate release granules[9]

Angle of repose

The diameter of powder cone was measured and the angle of repose was calculated using the following equation

$$\tan\theta = \frac{h}{r}$$

Where,

h = Height of the cone;

r = Radius of surface area of the pile.

Bulk density and tapped density

Bulk density and tapped density were calculated using the formula given below,

$$Bulk\ density = \frac{W}{V_0};$$

$$Tapped\ density = \frac{W}{V_f}$$

Where,

W = weight of the powder;

V_0 = initial volume;

V_f = final volume

Compressibility index

The compressibility index was calculated with the following equation,

$$compressibility\ index = 100\,X\left(\frac{(V_0 - V_f)}{V_0}\right)$$

Hausner's ratio

Hausner's was calculated with the following formula

$$Hausner\ ratio = \frac{V_0}{V_f}$$

Evaluation of immediate release tablet

Weight variation friability hardness and thickness were evaluated.

***Invitro* disintegration test**[10]

Six immediate release glibenclamide tablets were selected randomly from each formulation for disintegration test. The test was carried out in 0.1N hydrochloric acid buffer at 37 ± 0.5°C for 3 minutes at 24 to 26°C. The complete disintegration of the tablet with no palpable mass in the apparatus was measured in seconds.

Drug content[11]

Twenty tablets were triturated. Weighed accurately a quantity of powder containing 20mg of glibenclamide and shaken with 40ml of 0.1M methanolic hydrochloric acid, heated gently and centrifuged. To the extract 0.1M methanolic hydrochloric acid was added to produce 100ml and measured the absorbance at 300nm.

***Invitro* dissolution test**

Dissolution studies were carried out by USP type II method at 37 ± 0.5°C, taking 900ml of pH 1.2 hydrochloric acid buffer at 50 rpm. The test sample 5ml was withdrawn at specific interval (5, 10, 15, 20, and 30minutes) and replaced with fresh dissolution medium. The test sample was filtered and the concentration of the dissolved drug was determined using UV spectrophotometer at 300nm. Six tablets were selected for this test and their mean ± standard deviation was calculated.

Wetting time and water absorption ratio (R)[12]

A tablet was placed on the wet tissue paper placed in a dish containing 6ml of water, and the time for complete wetting was measured and water absorption ratio was calculated using the formula.

$$R = \frac{100(W_a - W_b)}{W_b}$$

Where,

W_a = weight after water absorption;

W_b = weight before water absorption

Evaluation of sustained release tablet

Precompresssion parameters such as angle of repose, bulk density, tapped density, compressibility index, Hausners ratio and the physical parameters such as weight variation, friability, hardness and thickness were evaluated as it was evaluated in immediate release tablet.

Drug content[13]

Twenty tablets were triturated. Weighed accurately a quantity of powder containing 0.1gm of metformin hydrochloride, and shaken with 70ml of water for 15 minutes, diluted to 100ml with water and filtered. To the 10ml of filtrate 100ml water was added for dilution. From this diluted solution 10 ml was further diluted with 10ml of water and measured the absorbance at 232nm.

***In vitro* dissolution test**

In vitro dissolution studies were carried out using USP type II apparatus at 50 rpm. The dissolution medium consisted of 900ml pH 1.2 hydrochloric acid buffer for first two hours and then it was replaced with 900ml of 6.8 phosphate buffer maintained at 37 ± 0.5°C. Withdrawn suitable volume of medium and it was replaced with fresh buffer, absorbance was measured at 233nm.

Kinetic analysis of dissolution data

The rate and mechanism of release of drug were analyzed by fitting the dissolution data into the zero order equation,

$$C = K_0 t$$

Where,

K_0 is the zero order rate constant expressed in units of concentration/time and t is the time in hours.

For the first order,

$$LogC = LogC_0 - Kt/2.303$$

Where,

C_0 is the initial concentration of drug,

K is the first order constant, and t is the time.

For Higuchi's model,

$$Q = Kt^{1/2}$$

Where, K is the constant reflecting the design variables of the system and t is the time in hours.

For Korsmeyer equation,

$$Log\left(\frac{M_t}{M_\infty}\right) = Log\ k + n\ Log\ t$$

Where,

M_t the amount of drug released at time t,

M_∞ is the amount drug release after infinite time, K is a release rate constant and n is the diffusional exponent.

Evaluation of bilayer tablet

Bilayer tablets were evaluated for weight variation, friability, hardness, and thickness. Drug content of both drugs in bilayer tablet was measured by separating both layer of bilayer tablet and measured individually.

***Invitro* dissolution test**

In vitro dissolution studies were carried out using USP type II apparatus at 50 rpm. The dissolution medium consisted of 900ml pH 1.2 hydrochloric acid buffer for first two hours and then it was replaced with 900ml of 6.8 phosphate buffer maintained at 37 ± 0.5°C. Withdrawn suitable volume of medium and it was replaced with fresh buffer at specific intervals absorbance was measured at 300nm for glibenclamide and 233nm for metformin hydrochloride.

Results and discussion

Characterization of active pharmaceutical ingredient and polymer

Glibenclamide and metformin hydrochloride and their respective mixtures were analyzed under IR spectra and their results confirm the identification sample which is compared with the reference standard.

Thermal analysis for characterizing interaction between drug and excipients

DSC was done for the mixture of drug and excipients. Result showed there were presence of an exothermic peak at 170° C this attributes to the presence of glibenclamide and thermal curve for metformin hydrochloride exhibited a sharp endothermic effect, at 221.6° C. The DSC profiles for ethyl cellulose, and hydroxypropyl methyl cellulose K100, were typical of amorphous substances, showing dehydration band in the 134.2 – 137.8°C and between 150 - 160°C temperature range when compared with standard and indicates no changes observed between the drug and excipients.

Analysis of Drug Excipient compatibility studies

The drug-excipient compatibility studies were determined in different ratios under humidity cabinet at different temperature and humidity for the period of four weeks and the results showed that there was no physical change in state, colour and odour.

Evaluation of immediate release granules

The bulk and tapped density of the formulations F1 – F12 in immediate release granules, ranged from 0.308 to 0.329 and 0.341 and 0.367 respectively. Angle of repose of the formulations (F1 – F12) was found to be between the limit 25° - 30° showing excellent flow character. The % of carr's index was found to be 6.26 – 11.74%, indicating an excellent flow character for immediate release formulations F1 – F12. Hausner's ratio in the range of 1.12 – 1.18 shows good flow properties, and the formulations F1, F2, F5, F6, and F7 depicts the result 1.12, 1.13, 1.13, 1.12, and 1.13 respectively. And the formulations F3, F4, F8, F9, F10, F11, and F12 produced a result of 1.11, 1.11, 1.09, 1.10, 1.09, 1.06, and 1.06 respectively which showed an excellent flow character.

Table no. 3: Evaluation of immediate release layer granules

Formulation	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Bulk density (g/ml)	0.323	0.325	0.334	0.333	0.308	0.312	0.314	0.324	0.310	0.314	0.327	0.329
Tapped density (g/ml)	0.362	0.367	0.373	0.372	0.349	0.350	0.355	0.356	0.341	0.345	0.349	0.351
Carr's index (%)	10.77	11.44	10.45	10.48	11.74	10.85	11.54	8.98	9.09	8.98	6.30	6.26
Hausner's ratio	1.12	1.13	1.11	1.11	1.13	1.12	1.13	1.09	1.10	1.09	1.06	1.06
Angle of repose (°)	30.52	28.30	29.42	29.29	28.21	28.70	27.12	27.14	26.56	27.64	27.69	26.00

Evaluation of immediate release layer tablet

The weight variation of tablets in the immediate release formulation F1 – F12 was observed to be within the limit ± 5%. Friability of immediate release formulations were ranging from 0.26 – 0.94% w/w, the values depicts friability is within and passes limit which is not more than 1% w/w, indicating the sufficient mechanical integrity and strength of prepared tablets. Hardness of about 3 – 4 kg/cm^2 is optimum for immediate release tablet. Hardness for the formulations F1 – F12 ranges from 3.90 – 4.20 kg/cm^2 which are very much in the limit. All the formulations in immediate release layer tablets passes the limit and produced necessary hardness. The thickness for F1 – F12 ranges from 4.93 – 5.21mm variations were found less than 5%.

In the immediate release formulations wetting time and water absorption ratio for F1, F4, F7, and F10 containing sodium starch glycolate < F2, F5, F8, and F11 prepared with crospovidone < F3, F6, F9, and F12 prepared with croscarmellose sodium. From this observation croscarmellose sodium provides less wetting time and water absorption ratio compared with sodium starch glycolate and crospovidone due to the fibrous structure of croscarmellose sodium.

The disintegration times for formulation F1 – F12 was compared that indicates the formulation F12 containing croscarmellose sodium 12mg disintegrated the fastest with no mass left and had good hardness.

Drug content lies between 93.40 – 103.80%. Results show all formulation containing drugs were within the limit (90 – 110%).

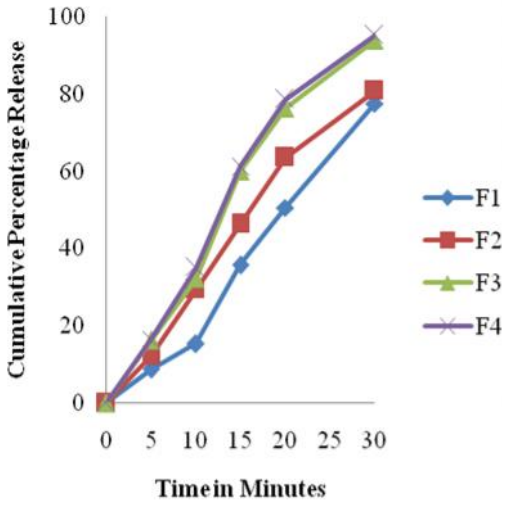
Invitro dissolution of immediate release layer glibenclamide

The dissolution study of immediate release layer formulation F1–F12 revealed the cumulative percentage release of their respective formulations. From the dissolution results obtained F3, F6, F9, and F12 prepared with croscarmellose sodium released the drug faster than the other formulations as the concentration of superdisintegrants increases there was an increase in release percentage of the drug.

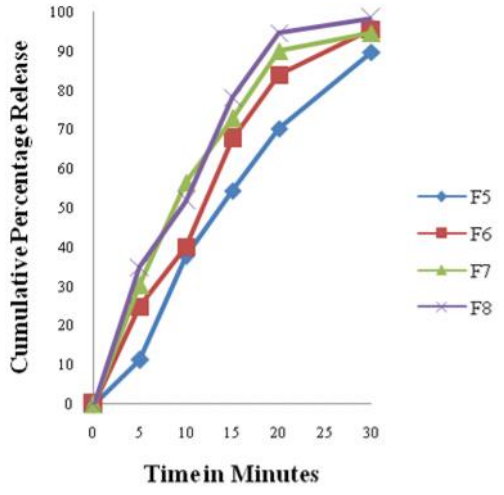
Table no. 4: Evaluation parameters of immediate release layer tablets

Formulation	Weight variation (mg) ± s.d	Friability (%)	Hardness (kg/cm^2)	Thickness (mm)	Wetting time (sec)	Water absorption ratio	Disintegration time (sec)
F1	201.6±0.57	0.26	4.23±0.15	4.94±0.12	121	71.42	348±1.00
F2	201.3±0.57	0.43	4.13±0.20	5.00±0.07	53	61.90	92.3±2.51
F3	202.0±1.00	0.75	4.00±0.20	5.01±0.24	49	52.38	47.6±1.53
F4	201.3±1.52	0.86	4.16±0.21	5.19±0.06	91	70.00	191.3±1.53
F5	201.3±1.52	0.31	4.00±0.20	5.17±0.05	49	60.00	80.3±0.58
F6	201.0±1.73	0.54	4.10±0.17	5.08±0.19	47	52.38	46.3±1.53
F7	199.3±3.51	0.81	4.16±0.06	5.17±0.06	59	68.42	180±1.00
F8	197.6±3.21	0.94	4.20±0.17	5.17±0.05	48	57.14	79.3±4.50
F9	199.6±1.52	0.33	4.20±0.10	5.01±0.10	45	45.00	29.3±0.58
F10	201.3±1.15	0.45	3.96±0.21	4.93±0.03	57	65.00	101.6±1.53
F11	199.3±2.51	0.63	4.06±0.15	5.12±0.09	46	55.00	76.3±1.53
F12	200.0±3.00	0.87	4.10±0.10	5.21±0.08	36	35.00	26±1.00

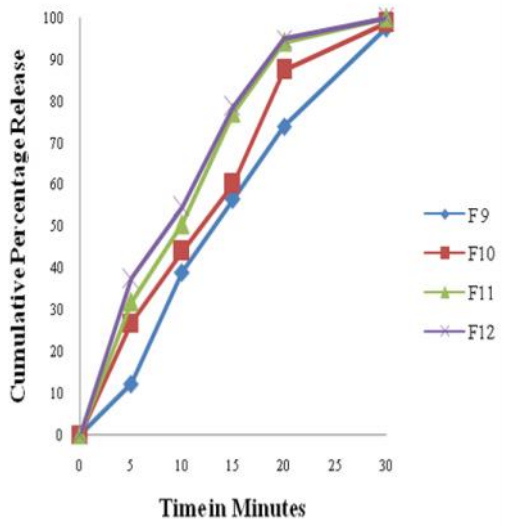
Graph 1



Graph 2



Graph 3



Evaluation of sustained release granules

Bulk density was ranged from 0.143 to 0.160, tapped density ranges from 0.154 to 0.190 for F13 – F27. Angle of repose for F13 – F27 produced an excellent flow character except the F16, F17, and F22, which depicts a good flow character (31° - 35°). Compressibility index for the sustained release formulations F13 – F27 was founded in the range of 0.62 – 9.35% which has an excellent flow character except, the formulations F16, F17, F20, F21, and F22. Hausners ratio F13 –F17 showed an excellent flow character except F16, F21, F17 and F22.

Table no. 5: Evaluation of sustained release layer granules

Formulation	F13	F14	F15	F16	F17	F18	F19	F20	F21	F22	F23	F24
Bulk Density (g/ml)	0.160	0.159	0.158	0.144	0.143	0.159	0.153	0.159	0.154	0.155	0.152	0.154
Tapped density(g/ml)	0.164	0.169	0.174	0.181	0.190	0.160	0.163	0.179	0.185	0.196	0.154	0.159
Carr's index (%)	2.43	5.91	9.19	20.44	24.73	0.62	6.13	11.17	16.75	20.91	1.29	3.14
Hausner's ratio	1.02	1.06	1.10	1.25	1.32	1.00	1.06	1.12	1.20	1.26	1.01	1.03
Angle of repose (°)	25.94	26.56	28.81	32.57	34.43	25.46	27.75	29.89	30.52	33.69	25.34	25.40

Evaluation of sustained release layer tablet

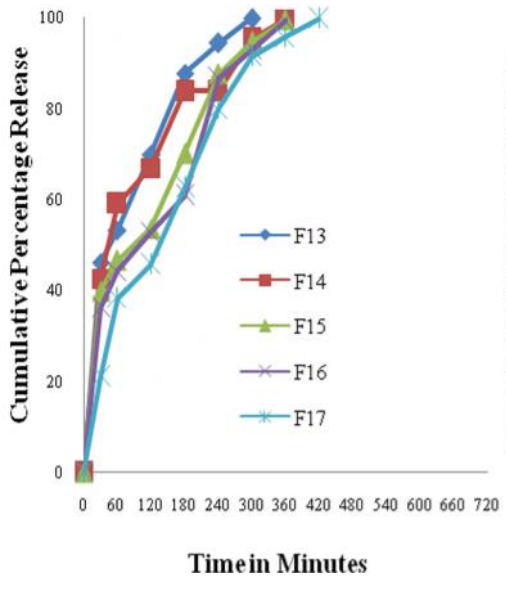
The dissolution study data of sustained release formulation F13 – F27 demonstrates the release percentage of the drug in 12 hours time period. Formulations F13, F14, F15, F16, and F17 prepared with HPMC K100 alone could not able to sustain the release not more than 7 hours; F17 released 99.81% of metformin hydrochloride. And the formulations F18, F19, F20, F21, and F22 prepared with ethyl cellulose could not able to sustain the drug release for not more than 8 hours; F22 released 99.85% of metformin hydrochloride. From the above observation, as the concentration of polymer increases, release of the drug decreases in either of the polymers. Hence the use of single polymer could not able to sustain the drug release for 12 hours in different ratios, combination of both hydrophilic and hydrophobic polymer were used to retard metformin hydrochloride for 12 hours. Formulation F23, F24, and F25 were prepared with combination of hydrophilic HPMC K100 and hydrophobic ethyl cellulose at different polymer ratios, and the drug release was sustained for 12 hours. Formulation F23, F24, and F25 released 99.85, 99.88, and 99.69% of metformin hydrochloride at 12^{th} hour respectively. It was observed from the formulations F25, F26 and F27 on varying the

concentration of PVP K30 there is variation in the drug release. Sustained release layer formulation F25, F26 and F27 prepared with 20, 25, and 30 mg of PVP K30 and polymer in the ratio of 1:1 released 99.69, 99.46 and 98.90% of drug. From the data obtained, PVP K 30 shows an effect on drug release. In the increase in concentration of PVP K 30 release of the drug from the tablet is decreased by increasing the binding and hardness properties of the tablet. 1:1 polymer ratio of HPMC K100 and ethyl cellulose was the optimum concentration for retarding metformin hydrochloride release which sustains the drug release for 12 hours. And the results were tabulated in tables and the results are plotted in graphs.

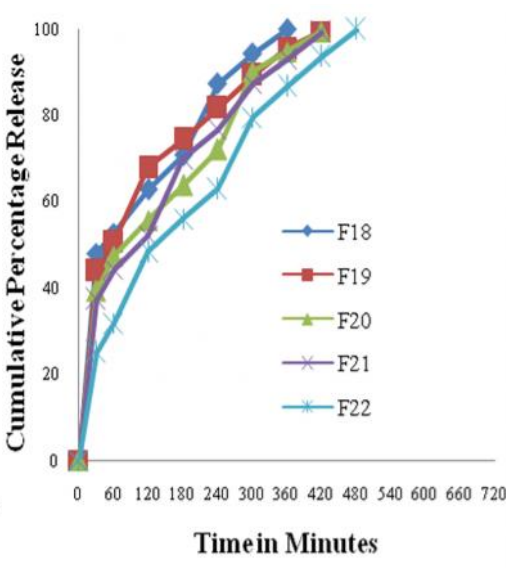
Table no. 6 : Evaluation parameters of sustained release layer tablets

Formulation	Weight variation (mg) ± S.D	Friability (%)	Hardness (Kg/cm^2)	Thickness (mm)
F13	800.3±0.59	1.10	3.53±0.06	6.23±0.03
F14	800.6±1.53	1.07	3.70±0.10	6.04±0.02
F15	799.6±0.58	0.96	3.96±0.15	6.01±0.01
F16	799.3±0.58	0.91	4.10±0.10	6.10±0.01
F17	801.6±2.31	0.75	4.33±0.17	5.99±0.01
F18	801.3±0.58	1.03	4.00±0.00	6.21±0.01
F19	799.6±1.15	1.00	3.93±0.15	6.07±0.02
F20	802.0±1.73	0.87	4.10±0.10	6.02±0.02
F21	799.3±2.08	0.64	4.53±0.05	6.10±0.01
F22	799.6±2.51	0.37	5.10±0.10	6.02±0.02
F23	800.3±1.53	0.87	4.23±0.15	6.07±0.02
F24	800.6±0.58	0.71	4.80±0.10	5.98±0.12
F25	803.3±2.51	0.63	5.03±0.05	6.19±0.01
F26	803.0±3.46	0.66	5.30±0.10	6.02±0.02
F27	799.3±0.58	0.59	5.43±0.06	6.08±0.01

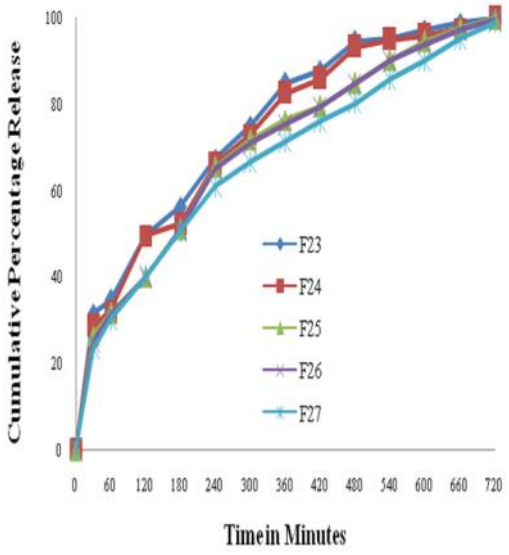
Graph 4



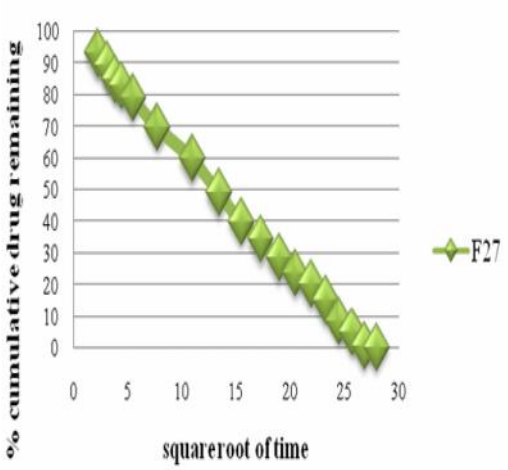
Graph 5



Graph 6



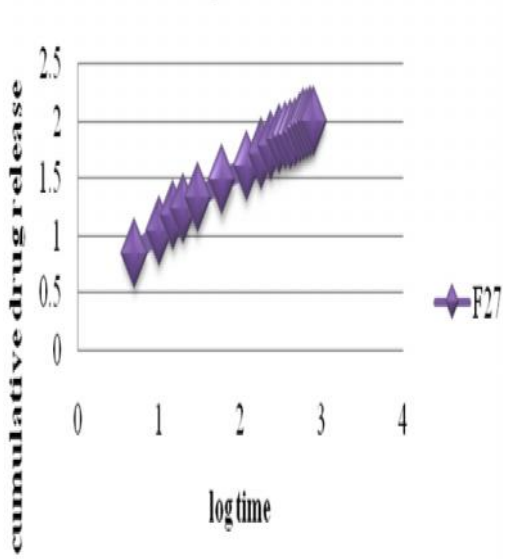
Graph 7: Higuchi diffusion kinetics



Mechanism of drug release

In the optimized sustained release formulation (F27), calculated regression coefficients for zero order, first order and higuchi model were 0.932, 0.782, and 0.998 respectively. Therefore the release seems to fit the higuchi model. To explore the release pattern, results of the Invitro dissolution data were fitted to korsmeyer-peppas equation, which characterizes the transport mechanism. The value of release exponent for the optimized formulation was 0.510 indicated release governed by anomalous transport (non-fickian) diffusion. Release kinetics values are given in table and their graphs were given in graphs.

Graph 8: Korsmeyer peppas equation



Optimization of bilayer tablet

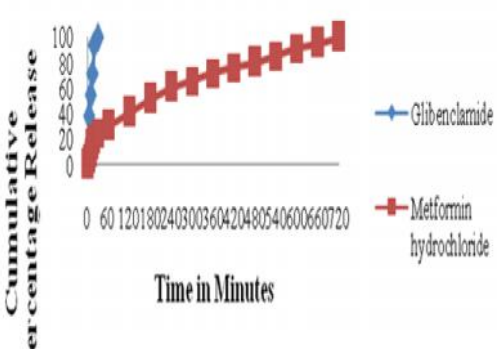
Bilayer tablet was compressed by selecting a formulation from immediate and sustained release layer tablet with the aid of data gathered from the evaluation of both the layers of tablet. Immediate release layer was optimized by comparing their disintegration, wetting time, water absorption ratio and with dissolution data. In this, formulations F12 has the least disintegration time, wetting time and water absorption ratio and it released 99.91% of glibenclamide at 30 minutes which is faster than the other formulations of immediate release layer tablet. Sustained release layer was optimized by comparing their hardness, friability and dissolution data. The formulation F27 prepared with 1:1 polymers ratio showed a suitable hardness and friability and sustained metformin hydrochloride (98.90%) for a period of 12 hours and the rest of the

formulation fails to sustain. By above data formulation F12 for immediate release and formulation F27 for sustained release was optimized for the compression of bilayer tablet.

Evaluation of optimized bilayer tablet F28

Weight of the bilayer tablets was 1.023 ± 0.020 gm, hardness was 6.10 ± 0.10 kg/cm^2, thickness was 6.13 ± 0.03mm, friability was found to be 0.54%. Values of the hardness and friability indicated good handling properties of prepared bilayer tablet. The drug content in the bilayer matrix for glibenclamide and metformin hydrochloride was found to be 99.60%. Invitro dissolution for the formulation F28 was showed 99.94% of release of glibenclamide in 30 minutes as immediate release and 99.28% of metformin hydrochloride in 12 hours as sustained release. Bilayer tablet values and graph are shown in table and graph respectively.

Graph 9: Dissolution for formulation – F28



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