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Formulation Development and Evaluation of Bilayer Floating Tablet of Antidiabetic Drugs

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ABSTRACT

The main aim of present study is to formulate and evaluate bilayer tablets of Metformin Hydrochloride and Sitagliptin Phosphate as fixed dose combination tablets for effective treatment of type II diabetes mellitus. Here, an attempt was made to reduce the dose, dosage frequency, dose related gastrointestinal side effects of metformin and to improve its bioavailability which in turn improve the patient compliance. Preformulation studies including drug excipient compatibility were conducted for both drugs. Different formulations of sustained release, floating Metformin Hcl tablets were prepared by using hydrophilic polymers like HPMC K100 and Sodium CMC and were evaluated. Sitagliptin immediate release formulations were prepared using crosspovidone, croscarmellose sodium and sodium starch glycolate as superdisintegrants and were evaluated. Based on the in vitro dissolution data F7 and S9 were selected as the best formulations from Metformin and Sitagliptin formulations respectively. Bilayer tablets were prepared by slightly compressing Metformin layer (F7) and then final compression was made by placing Sitagliptin layer (S9) layer on it with final hardness 6.5 kg and they were evaluated. From the bilayer tablet Sitagliptin layer disintegrated in 52 sec, Metformin layer started floating after 5.2 min and gave total floating time 18-24 hrs with good swelling index, good post compression parameters. In vitro dissolution study of bilayer tablet was done in USP type II along with UV spectrophotometer gave cumulative % drug release of Sitagliptin as 99.15% at 30 min and 97.65 % of Metformin at 12 hrs. From the study, it was found that, combination of HPMC K100 and Sodium CMC gave good sustained release for 12 hrs. Among the 3 superdisintegrants used sodium starch glycolate showed good disintegration of sitagliptin layer.

Keywords: Bilayer tablets, Fixed dose combination, Hydrophilic polymers, Superdisintegrants, Metformin, Sitagliptin.

INTRODUCTION

Diabetes is one of the most prevailing and advancing diseases in the world having affected 6.6% of the world population. Metformin hydrochloride is the most widely used oral Anti Diabetic drug in the world. Metformin shows high aqueous solubility and low cell membrane permeability. The usual dosage for Metformin is 250–500 mg 3-4 times daily, up to a maximal of 2.5 g/day. The absolute bioavailability of Metformin hydrochloride is 50–60% and is having short biological half-life of 6.2 hrs. The use of Metformin therapy has the high incidence of gastrointestinal side effects. Frequent dosing schedule leading to high GI side effects and high daily dose makes its use unsuccessful, thus it is reasonable to formulate sustained release Metformin tablets to prolong its duration of action and to reduce total dose of drug administered as well as the incidence of adverse side effects, thus improving the patient compliance.

A conventional oral sustained release formulation releases most of the drug content at colon. Since Metformin has absorption window in stomach & upper part of GIT up to intestine, there is a need to develop gastro retentive sustained release formulation which, In contrast to conventional extended-release Metformin tablets reported in the literature gives extended plasma concentration time profiles, increased bioavailability with lower C max and greater T max.

The combination of a DPP-4 Inhibitor with Metformin allows a broad and complementary spectrum of anti-diabetic actions. This combination does not increase the risk of hypoglycemia, do not promote weight gain, and do not cause adverse effect caused by various other oral anti diabetic combinations. Both the drugs have a complimentary and possibly additive effect on glycemic control and reduced glycosylated haemoglobin (HbA(1c)) levels [1].

Bi-layer tablet is suitable for sequential release of two drugs in combination, separating two incompatible substances. Typically, an immediate release granulate is first compressed followed by the addition of a controlled release element which is compressed onto. the. initial tablet, this gives characteristic. Bi-layer.effect to the final.dosage form. In the case of bi-layered tablets drug release can be rendered almost unidirectional [1].

HPMC is the mostly used non-ionic water soluble polymer showing pH independent and desired drug release profiles for a wide range of drugs, provide robust formulation, global availability, cost-effective manufacture. HPMC is typically used as the primary polymer, and other approved polymer(s) have been added to enhance functionality and as a tool to modulate the drug release profile [2].

Sodium Carboxy Methyl Cellulose (Na CMC) has been reported to have synergistic hydrogen-bonding interactions with HPMC7. Freely soluble cationic drugs have been reported to be released slower from combinations of HPMC and Na CMC matrices than when formulated with HPMC alone.

Superdisintegrants are the agents that promote fast disintegration of the tablets by increasing water penetration and dispersion of the matrix15. Here, in this study cross povidone, croscarmellose sodium, sodium starch glycolate were used a superdisintegrants and were evaluated for their effect on dissolution and disintegration of Sitagliptin layer. Fixed dose combinations (or) combination therapy (Two or more active ingredients in one dosage form) offer several advantages such as lower cost, improved efficacy, better compliance as number of doses/ pills per day decreases, and fewer side effects. Thus, currently focus is shifting fast to fixed dose combinations in the form of bi layer (or) multi-layer dosage forms to treat diseases like Diabetes, Hypertension, Tuberculosis, HIV etc.

MATERIALS AND METHODS

Materials

Metformin hydrochloride and sitagliptin phosphate were obtained as gift samples from (Micro Labs, Goa, India). HPMC K100M, sodium carboxy methyl cellulose, lactose, microcrystalline cellulose, pre gelatinised starch, croscarmellose sodium, sodium starch glycolate, crosspovidone, sodium bi carbonate, magnesium stearate, isopropyl alcohol, ferric iron oxide red was collected from S.D Fine Chemicals, Mumbai.

Methodology

The bilayer tablets of Metformin Hcl and Sitagliptin Phosphate were developed in two stages. Blends of immediate release layer of Sitagliptin Phosphate and sustained release layer of metformin Hcl were prepared separately. The individual layers were optimized based on the in vitro dissolution data and bilayer tablets were prepared by using the optimized formulae.

Preformulation

Preformulation studies were conducted for both drugs Metformin Hydrochloride and Sitagliptin Phosphate. For both the drugs Preformulation characteristics like Description, Solubility, melting point, Bulk density, tapped density, Angle of repose, Hausner's ratio, Compressibility index were performed.

IR absorption spectrum of Metformin Hcl and Sitagliptin Phosphate were recorded using potassium bromide (KBr) pellet method at resolution of 4cm-1 for its authentication and to study principle peaks using FT-IR spectrophotometer (FT-IR 8400S, Shimadzu). UV absorbance maximum for metformin Hcl and sitagliptin were

determined by dissolving the pure drug samples in 0.1 N Hcl (pH 1.2) and scanned in the wave length range of 400 – 200 nm in spectrum mode by using lab India UV spectrophotometer.
Assay was performed for both the drugs by following respective methods given in the pharmacopoeias. Calibration curve of Metformin Hydrochloride was constructed by measuring the absorbance of different concentrations of drug (1,2,3,4,5 µg/ml) in 0.1 N Hcl at 233 nm. Calibration curve of Sitagliptin Phosphate was constructed by measuring the absorbance of different concentrations of drug (10, 20, 30, 40.....100 µg/ml) in 0.1 N Hcl at 267 nm. A graph was plotted by taking concentration on X axis and absorbance on Y axis [3-5].

Drug Excipient Compatibility
The compatibility of drugs with their respective excipients was studied by FT-IR spectroscopy. The scanning was performed at scanning speed 2 mm/sec with resolution of 4 cm-1 over the region 4000-400 cm-1. The scans were evaluated for presence of principle peaks of drug, shifting and masking of drug peaks and appearance of new peaks due to polymer interaction.

Formulation and Development of Metformin Floating SR Layer
The dose of Metformin Hcl for sustained release was taken as 500 mg. Metformin SR layer tablets was prepared by wet granulation. Appropriate quantities of Metformin HCl, and excipients like HPMC K100 M, Sodium CMC, PVP K 30 and Sodium Bicarbonate were measured accurately (table no---) and all the measured powders were sifted through Sieve no # 40. The above sifted materials were mixed rapidly for 5 min and again passed through sieve no 40. Iso Propyl Alcohol having 2% w/v amount of PVP K- 30 was used as the granulating liquid and the solution was added to the mixture in step 2 and was kneaded for 2-5 min, then the kneaded mass was passed through sieve no # 20 to obtain the granules. The granules obtained in step 3 were dried in a tray drier at 50°C for 2 hrs. The dried granules were lubricated uniformly with weighed quantities of magnesium stearate.

The above granules were compressed into tablets by CADMACH multi station tablet compression machine by using 9 mm punch. In Batch F1 to F3, HPMC K100M was used as the sustained release polymer and in Batch F4 & F5 sodium CMC was used and in F6 – F8 combination of HPMC K100M and sodium CMC was used as Polymer and in Batch F9 & F10 only HPMC K100M was used as the release retarding polymer.

Sitagliptin Immediate Release Layer
Sitagliptin immediate release layer tablets were prepared by Direct Compression method. Sitagliptin and other excipients like pre gelatinised starch, microcrystalline cellulose, cross povidone, croscarmellose sodium, sodium starch glycolate, poly vinyl pyrollidine were sifted through sieve no 40 #. The sifted powders were thoroughly mixed for approximately 5 min and again passed through sieve no 40 # for maintaining uniformity in particle size.
Above mixture was lubricated for 2 min with magnesium stearate which was already passed through sieve 60. The colour iron oxide red (0.125% w/w) was passed through the sieve number # 100 and added to the above mixture and blended uniformly to ensure uniform colour. Then the tablets were compressed by using CADMACH multistation compression machine with 6mm bi concave punches. For Batches F1 to F3 crospovidone, F4 to F6 croscarmellose sodium and in F7 to F9 sodium starch glycolate were used as super disintegrants [6].

Evaluation of the Blends
The Metformin SR granules for wet granulation and Sitagliptin directly compressible blend were evaluated for various pre-compression parameters like Angle of repose, Bulk density, tapped density, Carr's index, Hausner's ratio etc.

Evaluation of the compressed tablets
Both Metformin and Sitagliptin tablets were evaluated for post compression parameters like hardness, weight variation, friability, drug content uniformity etc. The Metformin SR tablets were evaluated for in vitro buoyancy test for determining floating lag time, total floating time, swelling study for measuring the percentage water uptake and in vitro dissolution study. Sitagliptin IR tablets were evaluated for in vitro disintegration study and in vitro dissolution study. From the in vitro dissolution study, best formulations were selected and their percentage drug release was compared with that of marketed tablets (Glucophage XR and Januvia).

Preparation of Bilayer Tablets
Bilayer tablets were prepared by taking best formulations from both the individual layers. Granules of Metformin layer were first introduced into the die cavity, a slight compression was made and then Sitagliptin blend was

introduced into the die cavity followed by final compression with optimum hardness to form the bi layer tablets. Here compression was made by using 16 station tablet compression machine (Cadmach, India) with 12 mm capsule shaped punches. Bilayer tablets were prepared and evaluated for various post compression parameters and in vitro dissolution.

Evaluation of Bilayer Tablets

All the post compression parameters like thickness, hardness, weight variation, friability, content uniformity of both the drugs were measured.

Dissolution study

The dissolution study of bi layer tablets was performed over a 12 hr period using USP type II (paddle) Dissolution Testing Apparatus (Electrolab). 900ml of 0.1N Hcl was used as dissolution medium agitated at 100 RPM, at temperature of 37± 0.5 0 C. 10 ml samples were withdrawn at 5,10,15,20,30,40,60 min for 1 hr to estimate the release of Sitagliptin, and at 1, 2, 4, 6, 8, 10, 12 hrs for estimating Metformin release. Same volume of dissolution medium was replaced at every time interval, Samples were filtered by whatman filter paper no. 41. The samples were analyzed for Metformin Hcl and Sitagliptin by UV Spectrophotometry at their respective λ max values 233 nm and 267 nm.

The samples collected for first hour were analyzed for Sitagliptin content at 267 nm in UV spectrophotometer by keeping the solution containing Metformin Hcl formulation as blank to minimize the interference. The samples collected for 1 – 12 hrs were analyzed for the release of Metformin Hcl at 233 nm in UV spectrophotometer by keeping the solution containing Sitagliptin formulation as blank to minimize the interference. From in vitro dissolution study the percentage drug release of both the drugs were compared with their respective marketed tablets. By using the % drug release data various kinetic equations were calculated and the mechanism of drug release was estimated.

RESULTS AND DISCUSSION

The Preformulation studies of both drugs Metformin HCl and Sitagliptin are present in the table no - 03. From the observations, Metformin, has shown poor compressibility and poor flow, Sitagliptin shows good flow properties therefore wet granulation was preferred for Metformin SR layer tablets and direct compression for Sitagliptin IR layer tablets. From the UV spectrum, the absorption maximum of Metformin was found to be 233 nm, and for Sitagliptin it was found to be 267 nm. Calibration curve of both drugs were plotted by measuring absorbance at their respective absorption maxima with 0.1 N HCl as solvent. Both the drugs obeyed Beer – Lambert's law by giving good correlation coefficient. Calibration curves of both drugs were shown in figures no 01 – 02. From the spectra, it was confirmed that there is no interaction between drug and polymers because the IR spectra of all physical mixtures retains the principal drug peaks at 1624.12, 1570.11, 1062.81, 937.44 cm-1 for Metformin. From the FTIR studies it was observed that there were no interactions between drug and their respective excipients. FTIR spectra were shown in figures 3-4.

Table-1: Preformulation characters of Metformin and Sitagliptin

Sr No.	Metformin Hydrochloride		Sitagliptin phosphate	
1	Bulk density	0.56 g/cc	Bulk density	0.64 g/cc
2	Tapped density	0.64 g/cc	Tapped density	0.79 g/cc
3	Hausner's ratio	1.14	Hausner's ratio	1.23
4	Angle of repose	42.6^0	Angle of repose	33.2^0
5	Carr's index	12.5 %	Carr's index	18.98%

Table-2: Data for calibration curve of Metformin HCl showing absorbance at 233 nm

Sr No.	Concentration (µg/ml)	Absorbance at 233nm
1	0	0.00
2	1	0.09
3	2	0.18
4	3	0.265
5	4	0.357
6	5	0.434
	Slope	0.087
	Regression coefficient	0.999

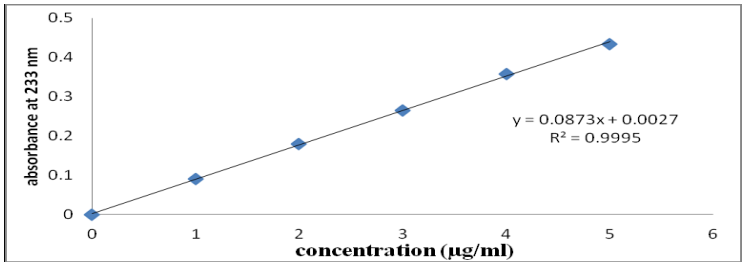

Figure-1: Calibration curve of Metformin HCl

Table-3: Data for calibration curve of sitagliptin showing absorbance at 267 nm

Sr No.	**Concentration (µg/ml)**	**Absorbance at 267nm**
1	0	0.00
2	10	0.037
3	20	0.073
4	30	0.111
5	40	0.149
6	50	0.186
7	60	0.221
8	70	0.260
9	80	0.296
10	90	0.332
11	100	0.371
	Regression coefficient	1.000

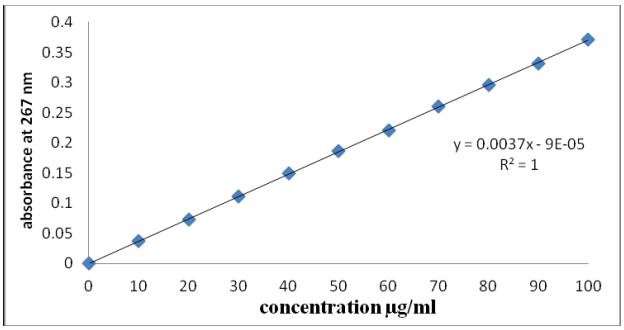

Figure-2: Calibration curve of Sitagliptin

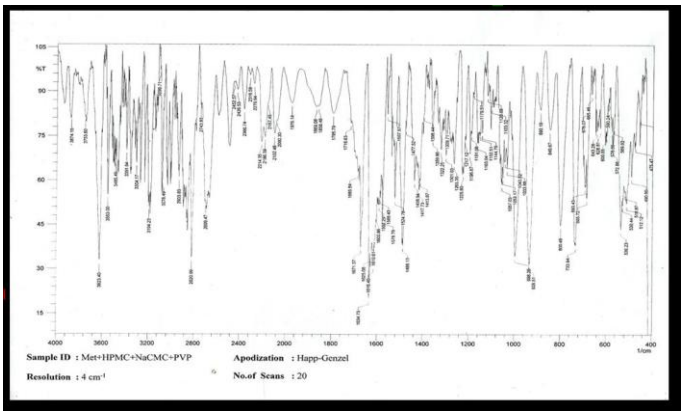

Figure-3: FTIR Spectrum of Metformin and Excipients

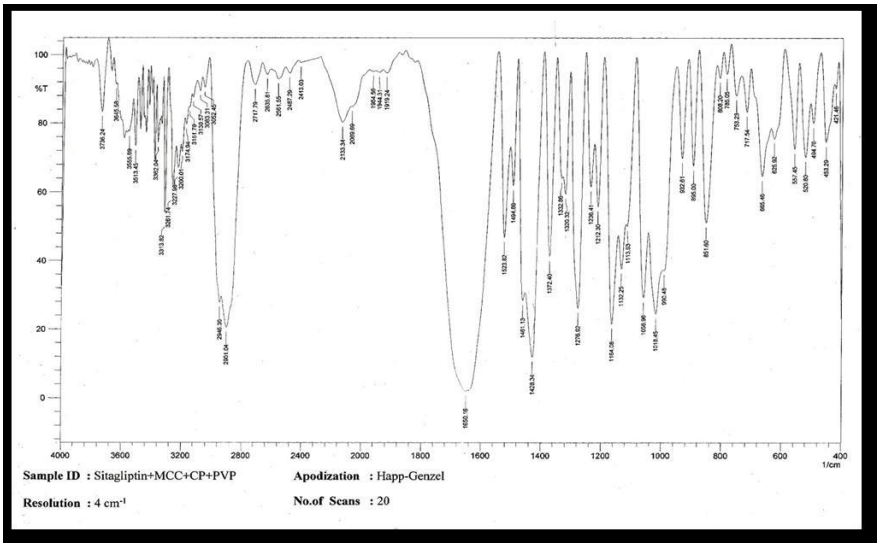

Figure-4: FTIR Spectra of Sitagliptin And Excipients

Sr. No.	Solution pH	Solubility (mg/ml)
1	Deionized water, adjusted to pH 1.2	912.23

2	Deionized water, adjusted to pH 4.5	879.03
3	Deionized water, adjusted to pH 6.8	378.68
4	Deionized water, adjusted to pH 7.4	71.65

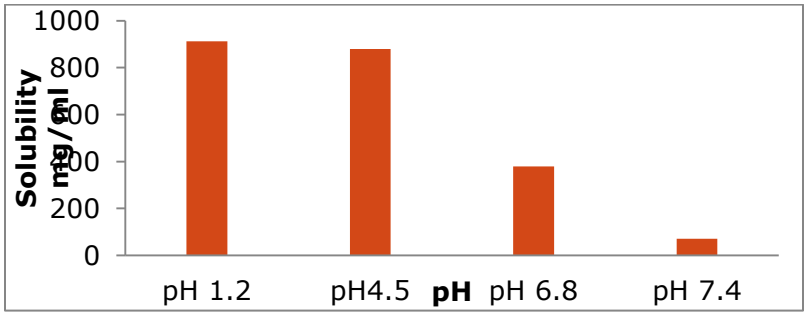

Figure-5: Solubility Analysis

Evaluation of the blends

Various physical properties of Metformin SR tablets blend were evaluated and reported in table no 07. Results indicates good flow properties with angle of repose ranging between 20.06 - 22.970. The Hausner's ratio 1.1055 – 1.1662 and Carr's index 14.52 -16.62 % indicates good flow of metformin granules [7-10]. Results of physical properties of sitagliptin blend table no - 08 indicates good flow properties with angle of repose of 22.49 - 25.58, Hausner's ratio of 1.12- 1.40 and Carr's index of 11.38-17.64 which shows good and excellent flow properties respectively.

Table-4: Pre-compression parameters of Metformin HCl Granules

Formulation Code	Angle of Repose (θ) (± SD)	Bulk Density (g/cc) (± SD)	Tapped Density (g/cc) (± SD)	Carr's Index (%) (± SD)	Hausner ratio (± SD)
F1	20.80±0.11	0.754±0.07	0.878±0.05	15.09±0.06	1.1644±0.05
F2	20.06±0.08	0.781±0.09	0.899±0.09	15.10±0.05	1.1510±0.07
F3	22.33±0.16	0.843±0.09	0.9302±0.11	15.68±0.09	1.1055±0.05
F4	22.97±0.12	0.735±0.12	0.836±0.08	14.52±0.06	1.1374±0.09
F5	20.68±0.09	0.764±0.14	0.891±0.09	16.62±0.13	1.1662±0.06
F6	22.16±0.11	0.782±0.08	0.902±0.08	15.34±0.08	1.1542±0.09
F7	21.83±0.12	0.767±0.09	0.883±0.13	15.12±0.11	1.1512±0.07
F8	21.62±0.09	0.781±0.12	0.895±0.09	14.59±0.05	1.1459±0.05
F9	20.85±0.13	0.792±0.15	0.910±0.11	14.89±0.05	1.1489±0.07

Table-5: Pre-Compression Parameters of Sitagliptin Blend

Formulation code	Angle of repose (θ) Mean ±S.D	Bulk density (gm/cc) Mean±S.D	Tapped density (gm/cc) Mean ±S.D	Carr's index Mean ±S.D	Hausner's ratio Mean ±S.D
F1	25.58±0.31	0.74±0.01	0.99±0.02	17.64±1.2	1.40±0.02
F2	25.08±0.45	0.78±0.08	0.98±0.01	16.21±1.62	1.32±0.02
F3	24.47±0.21	0.78±0.06	0.96±0.08	16.66±0.79	1.15±0.01
F4	23.72±0.23	0.85±0.047	0.98±0.04	13.31±0.78	1.15±0.01
F5	23.40±0.15	0.86±0.047	0.99±0.04	12.50±0.44	1.14±0.05
F6	23.29±0.17	0.86±0.022	0.97±0.04	11.38±1.20	1.13±0.01
F7	22.68±0.09	0.88±0.047	0.98±0.01	13.84±0.90	1.12±0.01
F8	22.77±0.15	0.87±0.098	0.99±0.04	11.49±0.53	1.13±0.06
F9	22.49±0.08	0.88±0.021	0.98±0.01	12.54±0.42	1.12±0.05

EVALUATION OF TABLETS

Metformin floating SR tablets:

The prepared tablets were evaluated for parameters such as Weight variation, Hardness, Friability, Thickness, Floating behavior, density, drug content and *in vitro* dissolution profile. From the results reported in Table no: 09 Thickness was found to be in the range of 4.8 to 4.9 mm. Hardness of the tablets was in the range of 6.0 ± 0.2 to 6.5 ± 0.4 kg/cm2 which was sufficient for the handling of tablets throughout the shelf life. Percentage % friability was between 0.28 – 0.46 % and complies with pharmacopoeial limit of F< 1%. Weight variation was less than 5% which is a pharmacopoeia limit. Drug content of Metformin Hcl found to be in the range of 98.94 ±0.42 to 101.03 ±0.31%, was within the limit as per I.P and ICH guidelines. All the formulations (F1 – F8) having 10 mg sodium bi carbonate floated around 4.8 to 7.0 min depending upon their apparent viscosity. The formulations F9 and F10 containing 25 mg and 50mg have shown the floating lag times of 3.0, 2.5 min respectively (table no 10). This shows that increase in sodium bi carbonate concentration decreases floating lag time. The total floating times of all the formulations were up to 24 hrs. The formulations F9 & F10 shown less total floating time due to the increase in the concentration of the effervescent agent. The density values of all the formulations were measured and were found to be in the range of 0.845 g/cc to 0.933 g/cc. Since the density of all the tablets was less than that of gastric fluids they have shown good floating property. In the present study, F1 – F3 having HPMC K100 M shows more swelling than F4 & F5 having Sodium CMC because of high viscosity of HPMC. Then from F6-F9 the combination of two polymers increases swelling due to the synergistic increase in viscosity. Higher swelling index was found for tablets of batch F8 containing HPMC K100 M (100mg) and sodium CMC (75mg), results were given in table no - 11. Thus, the viscosity of the polymer had major influence on swelling process, matrix integrity, as well as floating capability, hence from the above results it can be concluded that linear relationship exists between swelling process and viscosity of polymer.

Table-6: Results For In Vitro Buoyancy Test and Density of the Metformin HCl Tablets

Sr No.	Formulations Code	Tablet density (g/cc)	Floating lag time (min) average (n-3)	Total Floating Time (Hr)
1	F1	0.856	5.4	>24
2	F2	0.924	5.9	>24
3	F3	0.845	7.0	>24
4	F4	0.916	5.0	>24
5	F5	0.924	5.2	>24
6	F6	0.933	4.8	>24
7	F7	0.856	4.9	>24
8	F8	0.867	5.2	>24
9	F9	0.886	3.0	12-24
10	F10	0.882	2.5	12-24

Table-7: Percentage Swelling Index of Metformin HCl Tablets

Sr No.	Time (hr)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	1	20.27	22.43	26.21	18.48	20.11	18.06	19.24	20.64	21.56
2	2	36.09	44.60	45.12	30.12	33.16	29.18	30.19	32.72	35.46
3	3	51.02	55.57	59.56	47.23	48.32	46.70	49.12	52.16	45.42
4	4	62.47	72.22	73.89	54.42	60.06	60.04	62.21	63.09	59.42
5	5	72.09	85.11	85.06	63.15	71.51	73.56	74.79	75.99	70.43
6	6	90.26	94.56	95.45	80.12	82.45	95.76	96.61	97.52	86.34

DISSOLUTION STUDY

From the table no. 12, it can be noted that in the formulations FI – F3 HPMC K100M was used as the release retarding polymer, being a hydrophilic swellable polymer it gradually swells with floating and sustains the release of the drug up to 12 hrs. From F1 to F3 the drug release rate decreases as the concentration of HPMC K100M increase from 100 mg to 150mg. In F1 as the concentration of HPMC K100M was 100 mg 97.03% of drug released in 10 hrs. Among F1, F2, F3 as the concentration of HPMC K100M increases % drug release decreases. Further the trials were taken by taking sodium CMC as the rate retarding polymer. Formulations F4, F5 having 100mg and 150 mg of sodium CMC respectively shows more % drug release than same concentrations of HPMC K 100M. From F4 to F5 as the viscosity of sodium CMC increases the drug release decreases. In these formulations, the drug release was not

comparable to the marketed tablets at the end of 12 hrs. Further in formulations F6 to F8 high viscosity polymer HPMC K100M was taken in combination with sodium CMC. Here HPMC concentration was kept constant and sodium CMC was increased in the range of 3.7 % - 10.4% w/w. Freely soluble drugs have been reported to be released slower from combinations of HPMC and Na CMC matrices than with HPMC alone, as the combination increases the viscosity due to a synergistic effect of the two polymers. Therefore, in F6 – F8 as the concentration of sodium CMC increases from 3.7 % - 10.4% w/w the cumulative % drug release decreases. Here F7 shows better drug release by releasing 98.73% at the end of 12 hrs. Then further trials were taken to determine the effect of increasing concentrations of sodium bi-carbonate on floating lag time and % drug release. In formulations F9 to F10 as the concentration of sodium bicarbonate increases from 25 mg to 50 mg floating lag time decreased from 4.5-5.0 min to 3.0 and 2.5 min respectively. The drug release profile of F9 and F10 were compared with F3 having the same composition, results shows increase in % drug release by releasing 93.52 and 96.75 for F9 and F10 respectively when compared to F3 (91.25%) [10-14]. Hence, F7 was selected as the best formulation.

Table-8: Drug Release Profile of formulations F1 – F9

Sr.No	Time	Cumulative Percent Drug Release								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1	0	0	0	0	0	0	0	0	0	0
2	1	35.23	30.11	28.46	33.38	30.23	29.23	22.06	20.56	30.35
3	2	52.62	47.15	43.65	50.29	48.66	45.05	34.50	31.23	46.12
4	4	69.11	59.61	57.62	67.24	62.46	61.43	51.21	48.47	58.65
5	6	82.36	72.48	70.54	79.56	74.41	78.2	71.02	68.25	74.24
6	8	91.74	81.69	79.52	88.32	83.62	87.23	82.31	78.85	82.21
7	10	97.03	89.54	87.35	98.63	89.65	96.46	92.84	89.34	89.36
8	12		94.85	91.25		94.57		98.73	95.52	93.52

Table-9: Comparison of F7 with Glucophage XR Tablets

SrNo	Time	Cumulative Percent Drug Release	
		F7	Glucophage XR
1	0	0	0
2	1	22.06	24.65
3	2	34.50	36.54
4	4	51.21	54.68
5	6	71.02	70.85

6	8	82.31	80.56
7	10	92.84	91.24
8	12	98.73	97.45

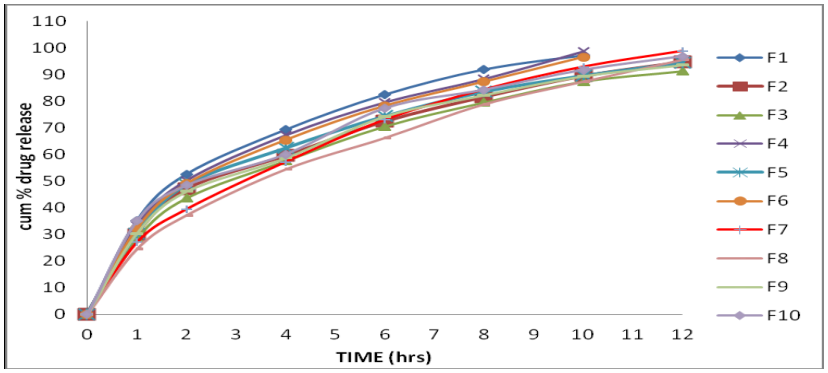

Figure-9: Comparative Drug Release Profile of F1 – F9

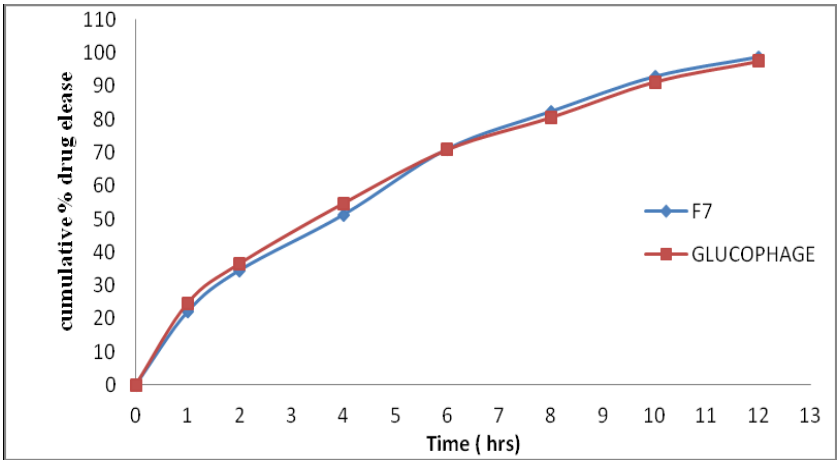

Figure-10: Comparison of F7 with Glucophage XR Marketed Formulation

Evaluation of Sitagliptin IR Tablets

The prepared tablets were evaluated for parameters such as Weight variation, Hardness, Friability, Thickness, Floating behaviour, density, drug content and *in vitro* dissolution profile. From the results reported in table no 14 weight variation was found to be < ±7.5%. which is the pharmacopoeia limit. Hardness of all formulations was in the ranged of 3.3 to 3.6 kg/ccm2. The friability values of none of the formulations exceeded 1% the results of friability indicate that the tablets were mechanically stable. Thickness of all the formulations was between 2.7 to 2.9 mm showing uniform tablets. Drug content was uniform ranging from 97.56 ±1.1to 101.61 ±0.73. From the table, no 15 we can notice that from S1 to S3 as Crospovidone concentration increases from (2-5%) disintegration time decreases gradually. Similarly, from S4 – S6 as the concentration of CrosCarmellose Sodium increases from (2-5%) disintegration time decreases proportionally. Among the 2 superdisintegrants Croscarmellose Sodium gives less disintegration time of 56 sec. Furthermore in formulations S7 - S9 Sodium Starch Glycolate was used as the superdisintegrants 2- 4%, as the concentration increases disintegration time decreases. Among the three superdisintegrants used SSG was the better disintegrant showing lesser DT time around 54 sec.

Table-10: Post Compression Parameters of Sitagliptin IR Tablets

Formulation	Average Weight mg (n=20)	Hardness Kg/cm2 (n=3)	Thickness mm(n=3)	Friability% (n=20)	Drug Content (%)
S1	250.03 ±1.64	3.4 ± 0.3	2.8 ± 0.07	0.58	99.03±0.31
S2	251.14 ±1.91	3.3± 0.6	2.9 ± 0.05	0.48	99.86 ±0.70
S3	250.06 ±1.02	3.3 ± 0.2	2.8 ± 0.11	0.36	99.27 ±1.02
S4	250.52 ±2.83	3.5 ± 0.2	2.7 ± 0.08	0.56	101.61 ±0.73
S5	251.05 ±1.61	3.6 ± 0.4	2.8 ± 0.08	0.53	98.83 ±0.41
S6	249.12 ±3.90	3.4 ± 0.3	2.7 ± 0.13	0.54	100.83±1.13
S7	252.05 ±1.24	3.2 ± 0.2	2.9 ± 0.15	0.39	98.94 ±0.42
S8	250.09 ±1.61	3.3 ± 0.2	2.8 ± 0.09	0.48	97.56 ±1.1
S9	250.08 ±1.02	3.5 ± 0.4	2.9 ± 0.07	0.51	99.63 ±0.62

Table-11: Disintegration Time for Sitagliptin IR tablets

Sr no	Formulation	Disintegration time (sec)
1	S1	98 ± 2.52
2	S2	75 ± 1.02
3	S3	58 ± 2.85
4	S4	92 ± 1.75
5	S5	69 ± 1.96
6	S6	56 ± 2.35
7	S7	84 ± 2.64
8	S8	59 ± 2.13
9	S9	54 ± 3.61

Dissolution study

From the table, no - 16 In the formulations S1 – S3 Cross Povidone was used as superdisintegrant in different proportions of 2%, 4%, 5% respectively. Therefore, the drug release becomes faster from S1 to S3 with S3 showing

95.43 % after 30 min. From S4 – S6 Cross carmellose sodium was used as super disintegrant in different proportions of 2-5% respectively. Therefore, the drug release becomes faster from S4 to S6 with S6 showing 97.73% after 30 min. Thus, from formulations S1 to S6 it can be inferred that crosscarmellose sodium was a better disintegrant giving faster release when compared to cross povidone. The % drug release of 5% of CCS in formulation S6 was not comparable to the marketed Sitagliptin IR tablets. In formulations S7 – S9 sodium starch glycolate was used as the superdisintegrant 2- 4% accordingly the % drug release increases with S9 giving 99.64 % at the end of 30 min. Among the three superdisintegrants used SSG has shown better drug release comparable to the marketed Sitagliptin IR from Januvia 50mg. Hence S9 was selected as best formulation of Sitagliptin IR Layer.

Table-12: Comparative Dissolution Profile for formulations (S1 – S9)

SrNo	Time	Cumulative Percent Drug Release								
		S1	S2	S3	S4	S5	S6	S7	S8	S9
1	0	0	0	0	0	0	0	0	0	0
2	5	31.89	33.56	35.45	34.63	35.32	36.55	35.47	37.22	38.55
3	10	64.47	67.22	69.62	67.24	69.35	70.64	68.61	70.36	72.64
4	15	79.05	82.30	84.41	80.74	83.51	86.76	85.73	88.65	89.64
5	20	89.35	90.68	92.52	91.50	92.41	94.36	90.12	95.37	97.86
6	30	95.84	94.55	95.43	95.10	96.65	97.73	94.24	97.64	99.64
7	40	98.70	----	----	99.57	----	----	----	----	----
8	60	----	----	----	----	----	----	----	----	----

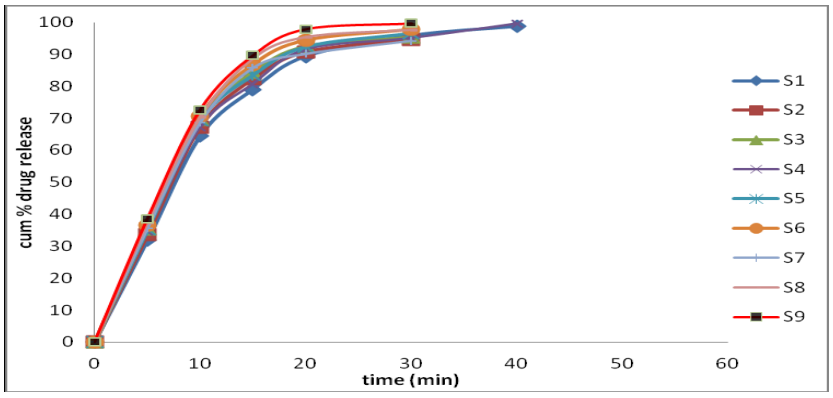

Figure-11: Comparative drug release Profile for Sitagliptin IR formulations (S1- S9)

Table-13: Comparison of S9 with Marketed (Januvia 50 mg)

SrNo	Time	Cumulative Percent Drug Release	
		F7	Januvia 50 mg
1	0	0	0
2	5	38.55	41.65
3	10	72.64	75.17
4	15	89.64	91.42
5	20	97.86	97.52
6	30	99.64	98.64
7	40	----	----
8	60	----	----

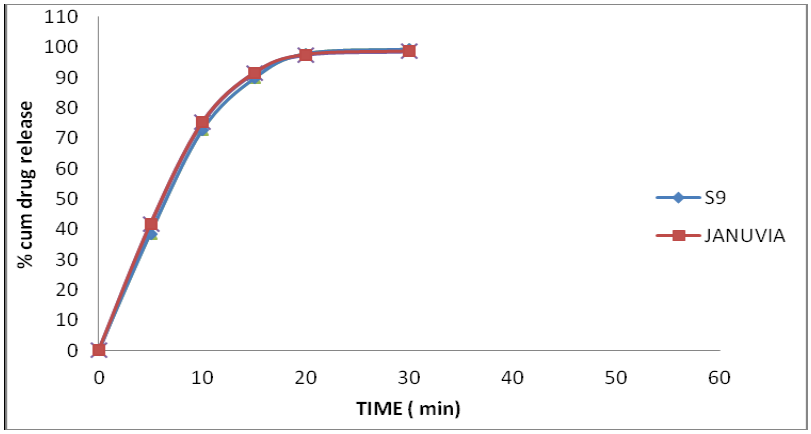

Figure-12: Comparison of Drug Release Profile of S9 with Marketed Tablets

Evaluation of Bilayer Tablets

The bilayer tablets prepared by combining F7 of Metformin SR layer and S9 of Dapagliflozin IR layer were evaluated for floating behaviour, swelling index, hardness, friability, weight variation, drug content uniformity etc. When the tablet was immersed in a 0.1 N HCl solution at 37 ^{0}C, it sank at once in the solution, the Dapagliflozin layer starts to disintegrate immediately and slowly carbon dioxide gas started to generate from the floating layer containing sodium bi-carbonate due to a chemical reaction (Floating lag time). Each formulation started to float at different floating lag times. The floating tablets slowly swelled due to the presence of hydrophilic water swellable polymers like HPMC K100M and sodium CMC. Average floating lag time of bilayer tablets was 5.2 min with total floating time of up to 18-24 hrs table 18. Percentage swelling index was found to be increasing with time due to the increased water uptake by hydrophilic polymers HPMC K100M and Sodium CMC. Physical examination of the tablets shows that the bi - layered tablets were capsule shaped with bisect on one side, with clear differentiation of

the two layers with colorless Metformin HCl layer and Dapagliflozin layer having pale red colour. The thickness of tablets was found to be 6.5 ± 0.63 mm and was uniform in the batch. The hardness of the tablets was found to be 6.7 ± 0.5 kg/cm2 and was sufficient for the handling throughout the shelf life. Percentage weight loss (or) % Friability was measured and found to be in the range of 0.75 % and was within the pharmacopoeial limit that is less than 1% (F< 1%). The tablets passed the weight variation test as per USP limits as they have shown less than 5% of deviation from their weight. Drug contents of Metformin Hcl and Dapagliflozin in the bilayered tablet were found to 99.67 ±0.42 and 99.63 ±0.7 respectively. For both drugs their drug contents were within the limit as per I.P and ICH guidelines and have shown good content uniformity. Dissolution profile of bilayer tablets was reported in table no 22. Dissolution was performed in 0.1 N Hcl for 12 hrs and % drug release was calculated by UV– spectroscopic method, Dapagliflozin release occurred initially for 30 min by giving 99.15 % drug release. Here, drug release was calculated by measuring absorbance by keeping Metformin formulation as blank. Metformin drug release was measured up to 12 hrs from first hour by keeping Dapagliflozin formulation as a blank. Metformin gave 97.65 % drug release at the end of 12 hrs.

Table-14: Floating Behaviour of the bi layer tablets

Sr.No	Floating lag time (avg) (n=3)	Total floating time (avg) (n=3)	Tablet density (n=3) (g/cc)
1	5.2 Min	18- 24 hrs	0.846

Table-15: Swelling Study of Metformin layer

Sr No.	Time (hr)	% Swelling Index (avg) (n = 3)
1	1	20.24
2	2	30.19
3	3	50.12
4	4	63.21
5	5	74.79
6	6	97.61

Table-16: Post compression parameters of the Bilayer tablets

Formulation	Average Weight mg (n=20) (± SD)	Hardness Kg/cm2(n=3) (± SD)	Thickness mm(n=3) (± SD)	Friability %(n=20) (± SD)	Drug content (n=3)	
					Metformin HCl	Dapagliflozin

Bi Layer Tablet (F7 + S9)	945.07 ±1.38	6.7 ± 0.5	6.5 ± 0.63	0.75	99.67 ±0.42	99.63 ±0.7

Table-17: Disintegration test for Sitagliptin IR layer

Sr no	Disintegration time (sec) (n=6) (avg± SD)
1	52 ± 2.5

Table-18: In Vitro Drug Release Profile of the Bi - Layered Tablet

Sr. No	Time intervals	Cumulative % drug release	
		Dapagliflozin	Metformin HCl
1	0 min	0.00	0
2	5 min	37.85	-
3	10 min	72.05	-
4	15 min	88.64	-
5	20 min	97.20	-
6	30 min	99.15	-
7	40 min	100.10	-
8	60 min	-	21.56
9	2 h	-	33.75
10	4 h	-	52.40
11	6 h	-	71.02
12	8 h	-	81.31
13	10 h	-	92.20
14	12 h	-	97.65

Table-19: Comparison of drug release from Bilayer tablet with marketed formulations

S no	Time intervals	Cumulative percentage drug release			
		S9	F7	Glucophage +Januvia	
1	0 min	0.00	-	0	-
2	5 min	37.85	-	41.65	-
3	10 min	72.05	-	75.17	-
4	15 min	88.64	-	91.42	-
5	20 min	97.20	-	97.52	-
6	30 min	99.15	-	98.64	-
7	40 min	100.10	-		-
8	60 min	100.32	21.56		24.65
9	2 h	100.33	33.75		36.54
10	4 h	100.46	52.40		54.68
11	6 h	100.39	71.02		70.85
12	8 h	101.32	81.31		80.56
13	10 h	101.35	92.20		91.24
14	12 h	101.38	97.65		97.45

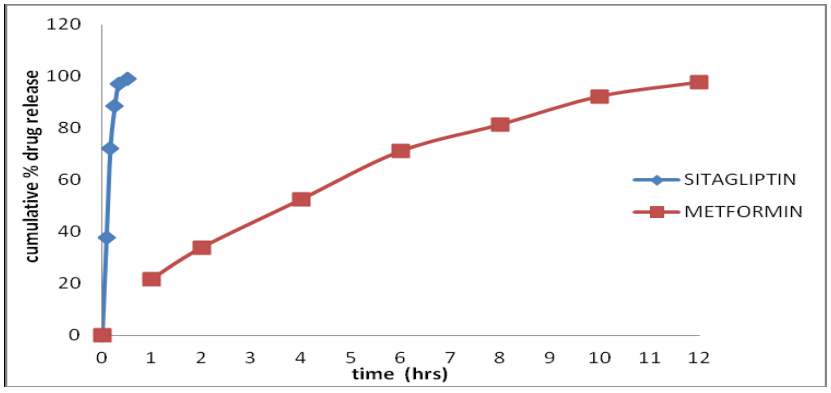

Figure-13: In Vitro Drug Release Profile of the Bilayer Tablet (S9 – F7)

Kinetic study for Metformin SR layer of Bilayer Tablet

Evaluation of mechanism of drug release was done for the Metformin Hcl floating SR layer of the bi layer tablet (F7). In vitro drug release date was fitted into various kinetic models.

Mechanism of drug release

In order to understand the complex mechanism of drug release from the SR matrix system, the % in vitro release was fitted into Korsmeyer-peppas model and the release exponent value (n) was interpreted for mechanism of drug release. The release exponent value (n) thus obtained was 0.617 therefore, we can conclude that it follows Non Fickian Diffusion mechanism. The F7 formulation exhibited First order, Higuchi mechanism.

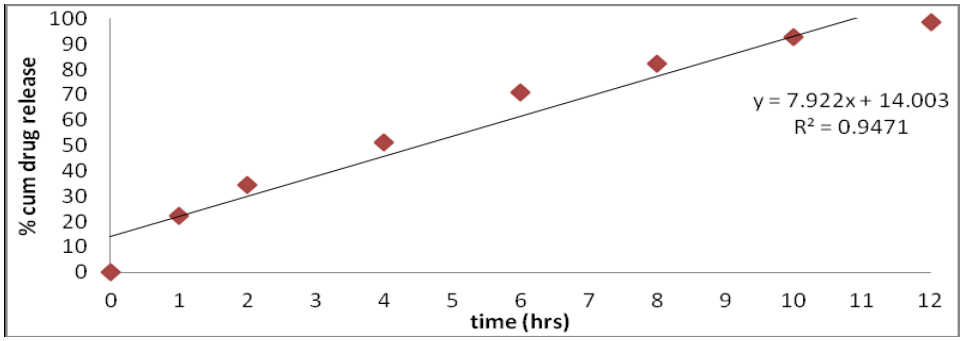

Figure-14: Zero order graph

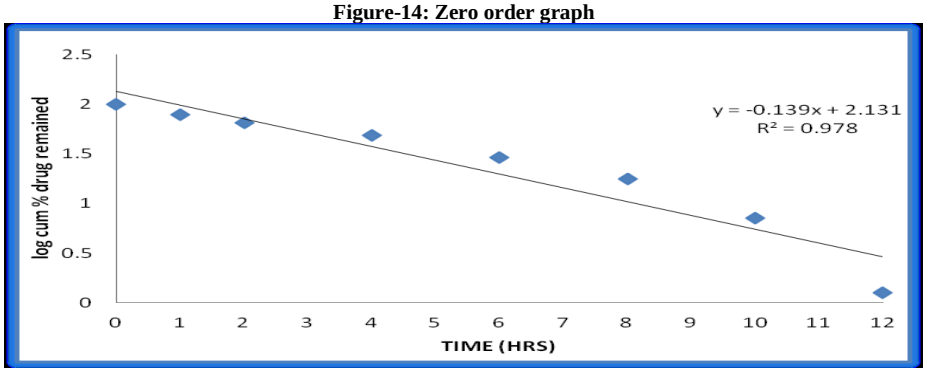

Figure-15: First order Graph

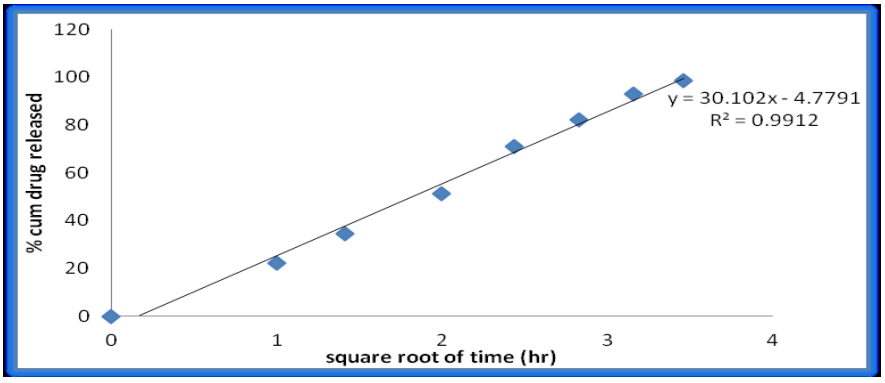

Figure-16: Higuchi Model

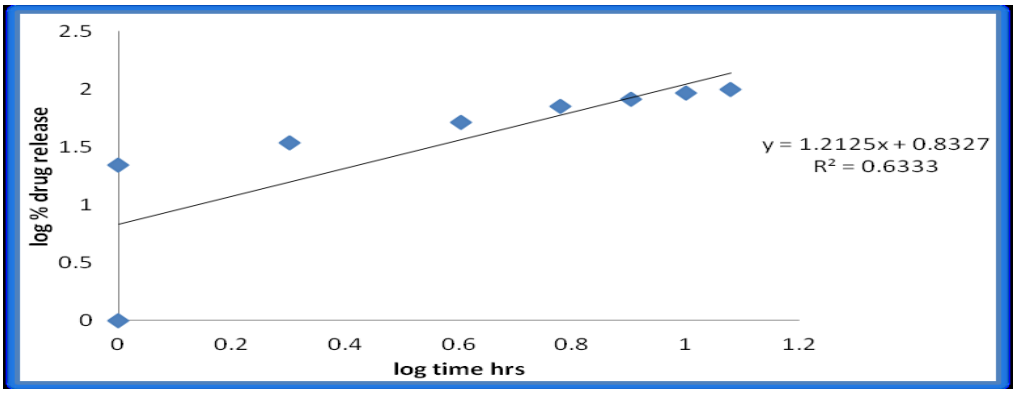

Figure-17: Korsmeyer – peppas model

Table-20: Data for Kinetic Studies

Sr No.	Time	√T	Log T	% CDR	log % CDR	Cum % drug remained	Log % cum drug remained
1	0	0	0	0	0	0	0
2	1	1.00	0	22.06	1.343	77.94	1.891
3	2	1.414	0.3010	34.5	1.537	65.50	1.816
4	4	2.00	0.602	51.21	1.709	48.90	1.689
5	6	2.44	0.7781	71.02	1.851	28.98	1.462
6	8	2.848	0.903	82.31	1.915	17.68	1.247
7	10	3.162	1.00	92.84	1.967	7.16	0.854
8	12	3.464	1.0791	98.73	1.994	1.27	0.103

Table-21: Results of kinetic studies for optimized formulation F7

Sr No.	Formulation	Zero order R2	First order R2	Higuchi R2	Koresmeyer peppas R2	n	Mechanism of drug release
1	F7	0.947	0.978	0.991	0.633	0.617	First order non fickian diffusion

Stability studies

The selected formulation was evaluated for stability by conducting accelerated stability studies. The formulation were stored at 40o C at 75% RH for 3 months and analyzed for their physical parameters and drug content and in vitro drug release studies at every one month interval. The data were shown in the table 2

Table-22: Characteristics of bi layered Tablet during stability studies

Time interval	Drug content (%w/w)		Hardness (Kg/cm2)	Friability (%)
	Metformin HCl	Dapagliflozin		
After one month	99.68±0.42	99.63 ±0.62	6.60 ± 0.64	0.31
After two months	98.90 ± 0.12	99.35 ±0.45	6.50 ± 0.55	0.31
After three months	98.45 ± 0.08	98.94 ±0.67	6.5 ± 0.43	0.32

Table-23: In vitro drug release profile of Metformin HCl layer

Time in hours	Cumulative % drug release		
	1st month	`2nd month	3rd month
0	0.00	0.00	0.00
1	22.06	22.25	22.3
2	34.5	33.75	33.90
4	51.21	50.80	50.55
6	71.02	70.84	70.43
8	82.31	82.07	81.75
10	92.84	92.41	92.06
12	98.73	98.26	98.05

Table-24: In Vitro Drug release profile of Sitagliptin layer

Time in hours	Cumulative % drug release		
	1st month	`2nd month	3rd month
0	0	0	0
5	38.46	38.32	38.85
10	72.60	72.05	71.95

15	89.54	89.25	89.20
20	97.72	97.05	97.04
30	99.44	99.20	99.15

CONCLUSION

From this study by preparing bilayer tablets, it was concluded that we could reduce the total dose, dosage frequency, dose related side effects, and improve the bioavailability of Metformin which in turn improves the patient compliance. Thus, a fixed dose combination tablet of Metformin and Sitagliptin were designed as bilayer tablets which will have good patient compliance over their individual marketed counterparts. However, further clinical studies are needed to access the utility of this system.

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