"Formulation and Evaluation of Saxagliptin Immediate Release and METFORMIN Hydrochloride Sustained Release Tablet"

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Abstract

The objective of the present study was to develop Saxagliptin immediate release and Metformin hydrochloride sustained release tablets formulated employing Hydroxy Propyl Methyl Cellulose polymer and Carmellose sodium polymer, the drug release behavior of the tablets was investigated. Metformin hydrochloride sustained release tablets were prepared by wet granulation methods. The granules were evaluated for bulk density and drug content. The tablets were subjected to Thickness, Dimension, Weight variation test, Hardness, Friability. Saxagliptin was coated to the surface of Metformin hydrochloride sustained release tablets as drug coating. An inner seal coating and outer protective coating optimized to enhance the Saxagliptin drug release and stability of formulation from moister absorbance. Formulation was optimized on the basis of acceptable tablet properties and in vitro drug release. The results of dissolution studies indicated that formulation F_6 the most successful of the study. The results of the dissolution study showed maximum drug release up to 10 hours and the mechanism of the in vitro kinetic release of Metformin hydrochloride was studied by using Zero order, First order, Hixson-Crowell, Higuchi and Korsmeyer-Peppas model. The in vitro release of Metformin hydrochloride sustained release was found diffusion through the swell able matrix polymer. Stability studies of the formulation F_6 showing successful formulation of Saxagliptin 2.5mg immediate release and Metformin hydrochloride 500mg sustained release tablets.

Keywords: Hydroxy Propyl Methyl Cellulose, Carmellose sodium, sustained release.

Introduction

Type 2 diabetes is the most common form of diabetes, accounting for 90 - 95% of cases. Metformin is the first drug doctors usually recommend for people with type 2 diabetes who need to take medication. However, limitations of multiple dosing and risk of triggering gastrointestinal symptoms make its dose optimization difficult. Sustained release dosage forms are designed to achieve a prolonged therapeutic effect by continuously releasing drug over an extended period of time after administration of a single dose.

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The advantages of sustained release dosage forms over conventional forms include the less fluctuation in drug blood levels, frequency reduction in dosing, enhanced convenience and compliance, reduction in adverse side effects and reduction in overall health care costs. The rate of drug release from solid dosage form may be modified by the technologies, which in general are based on modifying drug dissolution through the use of barrier coatings and controlling drug diffusion rates from dosage forms. Generally the different techniques employed to fabricate the modified release dosage forms are coated beads, granules and microspheres, multi tablet system, micro encapsulated drug, complex formation, ion exchange resins, and embedding drug in slowly eroding or hydrophilic matrix system. Saxagliptin is a dipeptidyl peptidase-4 (DPP-4) inhibitors offer new opportunities for oral therapy after failure of Metformin. The present study was designed to develop the oral immediate release Saxagliptin and sustained release Metformin hydrochloride tablet formulation. To develop a suitable Saxagliptin 2.5mg immediate release and Metformin hydrochloride 500mg sustained release tablet formulation. Evaluation of Saxagliptin 2.5mg immediate release and Metformin hydrochloride 500mg sustained release tablet formulation. *In vitro* evaluation of matrix tablets for the release characterization.

Materials and Methods

Metformin Hydrochloride was procured by Wanbury limited (Mumbai, India), Saxagliptin Hydrochloride dihydrate was was procured by Glenmark generics ltd (Mumbai, India), Hypromellose (Methocel K-100MCR) was was gifted by the dow chemical company (Mumbai, India), Carmellose sodium (Cekol LVD) was gifted by Signet chemical co.pvt.ltd (Mumbai, India), Hypromellose (Methocel E15cps) was gifted by Taian Ruital cellulose co. Ltd. (India), Microcrystalline cellulose(Avicel PH102) was gifted by FMC Biopolymer Ltd (Mumbai, India), Magnesium Stearate and Opadry pink was gifted by Colorcon India.

Drug Excipients Compatibility Study

Drug Excipients Compatibility Study by FTIR

Weighed amount of drug (3mg) was mixed with 100mg of potassium bromide (dried at 40-0°C), which was then compressed under 10-tonn pressure in a hydraulic press to form a transparent pellet. Similarly, the pellets of polymers that in combination with the drug was prepared and scanned from 4000-400cm^{-1} in IR spectrophotometer.

Table no. 1: Drug Excipients Compatibility Studies

S.No.	Drug + Excipients	Ratio	Physical description	Condition (40^{0}c/75%RH)			
				1W	2W	3W	4W
1.	Metformin HCl	-	White powder	✓	✓	✓	✓
2.	D*+ Carmellose Sodium	1:1	Brownish white powder	✓	✓	✓	✓
3.	D* + HPMC K100MCR	1:1	White powder	✓	✓	✓	✓
4.	D* + HPMC 15cps	1:1	Off white powder	✓	✓	✓	✓
5.	D* + MCC PH102	1:1	Off white powder	✓	✓	✓	✓
6.	D*+Magnesium stearate	1:0.5	White powder	✓	✓	✓	✓

D* refers to Metformin HCl Compatable

Table no. 2: Drug Excipients Compatibility Studies

S.No.	Drug + Excipients	Ratio	Physical description	Condition (30^0c/65%RH)			
				1W	2W	3W	4W
1.	Metformin HCl	-	White powder	✓	✓	✓	✓
2.	D*+ Carmellose Sodium	1:1	Brownish white powder	✓	✓	✓	✓
3.	D* + HPMC K100MCR	1:1	White powder	✓	✓	✓	✓
4.	D* + HPMC 15cps	1:1	Off white powder	✓	✓	✓	✓
5.	D* + MCC PH102	1:1	Off white powder	✓	✓	✓	✓
6.	D*+Magnesium stearate	1:0.5	White powder	✓	✓	✓	✓

D* refers to Metformin HCl Compatable

Table no. 3: Drug Excipients Compatibility Studies

S.No.	Drug + Excipients	Ratio	Physical description	Condition (25^0c/60%RH)			
				1W	2W	3W	4W
1.	Metformin HCl	-	White powder	✓	✓	✓	✓
2.	D*+ Carmellose Sodium	1:1	Brownish white powder	✓	✓	✓	✓
3.	D* + HPMC K100MCR	1:1	White powder	✓	✓	✓	✓
4.	D* + HPMC 15cps	1:1	Off white powder	✓	✓	✓	✓
5.	D* + MCC PH102	1:1	Off white powder	✓	✓	✓	✓
6.	D*+Magnesium stearate	1:0.5	White powder	✓	✓	✓	✓

D* refers to Metformin HCl Compatible

From the above results, it was concluded that there is no interaction between the drug and excipients used.

Evaluation of API and Final Blend For Compression [1-5]:

Lubricated blends were evaluated for following parameters

- Bulk density
- Tapped Density
- Carr's Index
- Hausner's ratio

Determination of Bulk Density (D_b):

Anaccurately weighed quantity of powder, which was previously passed through BSS #18, was transferred into graduated cylinder. After pouring the powder into graduated cylinder the powder bed was made uniform without disturbing. Then the volume was measured directly from the graduation marks on the cylinder as ml. The volume measured was called as bulk volume and the density is calculated by following formula.

$$\text{Bulk Density} = \frac{\text{Weight of powder}}{\text{Bulk Volume}}$$

Determination of Tapped Density (D_T):

After measuring the bulk volume the same measuring cylinder was kept into tap density apparatus. The tap density apparatus was set to 300 taps drops per minute and operated for 500 taps. Volume was noted as (V_a) and again tapped for 750 times and volume was noted as (V_b). The difference between V_a and V_b not greater than 2% then V_b is considered as final tapped volume. The tapped density was calculated by the following formula.

$$\text{Tapped Density} = \frac{\text{Weight of powder}}{\text{Tapped Volume}}$$

Compressibility index (C.I):

Compressibility index of granules was calculated from the following formula.

$$\text{Compressibility index} = \frac{Dt - Db}{Dt} * 100$$

Where D_t is tapped density and D_b is bulk density.

Table no.4: compressibility index limit.

Effect of Carr's Index and Hausner's Ratio on flow property		
Carr's Index (%)	**Flow Character**	**Hausner's Ratio**
≤10	Excellent	1.00-1.11
11-15	Good	1.12-1.18
16-20	Fair	1.19-1.25
21-25	Passable	1.26-1.34
26-31	Poor	1.35-1.45
32-37	Very Poor	1.46-1.59
≥38	Very very Poor	≥1.6

Hausner's ratio:

Hausner's found that the ratio of tapped density to bulk density was related to inter particle friction and as such, could be used to predict powder flow Properties. Low Hausner's ratio means that the drug has high Flowability. It was calculated using equation given below.

$$\text{Hausner's Ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Table No.5: Formulation of Metformin sustained release and saxagliuptin immediate release tablet

S. No.	Ingredient	Batch number (All weight in mg)					
		F_1	F_2	F_3	F_4	F_5	F_6
	DRY MIX						
1.	Metformin HCl	500.00	500.00	500.00	500.00	500.00	500.00
2.	Hypromellose (Methocel K-100MCR)	----	----	----	----	50.00	50.00
3.	Carmellose sodium (Cekol LVD)	----	----	10.00	10.00	20.00	20.00
	BINDER(For spraying)						
4.	Hypromellose (Methocel E15cps)	----	----	20.00	30.00	30.00	30.00
	Carmellose sodium (Cekol LVD)	15.00	20.00	----	----	----	----
5.	Purified water	qs	qs	qs	qs	qs	qs
	PRE-LUBRICATION						
6.	Microcrystalline cellulose(Avicel PH102)	230.00	225.00	215.00	205.00	195.00	195.00
7.	Hypromellose (Methocel K-100MCR)	275.00	275.00	275.00	275.00	225.00	225.00
	LUBRICATION						
8.	Magnesium Stearate	10.00	10.00	10.00	10.00	10.00	10.00
	TOTAL(core tablet weight)	1030.0	1030.0	1030.0	1030.0	1030.0	1030.0
	COATING						
	Inner seal coating I						
9.	Opadry pink	NA	NA	NA	NA	---	30.00
10.	0.1N Hydrochloric acid	NA	NA	NA	NA	---	200.00
	TOTAL (Seal coated)						1060.0
	drug in coating layer II						
11.	Saxagliptin Hydrochloride dehydrate	NA	NA	NA	NA	3.20	3.20
12.	Opadry pink	NA	NA	NA	NA	26.80	26.80
13.	0.1N Hydrochloric acid	NA	NA	NA	NA	300.00	300.00
	TOTAL (Drug coated)					1060.0	1090.0
	Outer protecting layer III						
14.	Opadry pink	NA	NA	NA	NA	30.00	30.00
15.	0.1N Hydrochloric acid	NA	NA	NA	NA	130.00	130.00
	TOTAL(Film coated)	NA	NA	NA	NA	1090.0	1120.0

NA- Not Applied, All weight in mg.

Evaluation of Tablets [6-7]**:**

Formulated tablets were evaluated for following parameters.

A. Physiochemical Parameter Evaluation

- Average weight
- Thickness
- Dimensions
- Hardness
- Friability
- Weight variation

B. Assay
C. Drug content uniformity
D. In-vitro drug release (Dissolution study)

Thickness:

The thickness of the tablet is mostly related to the tablet hardness and can be used as initial control parameter. 20 tablets were randomly selected from each formulation and their thicknesses were measured by using vernier calipers. Thickness values were reported in millimeters.

Dimensions:

The dimension of the tablet is mostly related to the shape and size of tablet and can be used as initial control parameter. 20 tablets were randomly selected from each formulation and their dimensions were measured by using vernier calipers. Dimensions values were reported in millimeters.

Hardness:

The crushing strength of the tablet was measured using Benchsiever series hardness tester by placing the tablet between the anvils and measuring the force required to break the tablet. The average hardness and standard deviation was determined and results were tabulated.

Friability:

This friability test was carried out by placing 10 core tablets in friabilator (Electrolab). Ten tablets were weighed and rotated at 25 rpm for four minutes (100 rotation). The tablets were then dedusted and reweighed. The friability was calculated as the percentage weight loss.

$$\text{Percentage friability} = \left\{\frac{(\text{Initial weight} - \text{Final weight})}{\text{Initial weight}}\right\} \times 100$$

Weight Variation:

20 tablets of all batches were collected randomly during compression and weight of individual tablets was carried out using electronic balance. Weight value was reported in milligram. The average weight and standard deviation of 20 tablets was calculated, the batch passes the test of weight variation test if not more than two of the individual tablet weight deviates from the average weight by more than the percentage shown in the table and none deviate by more than twice the percentage shown.

Table no.6: Percentage deviation allowed under weight variation

S.No.	Average weight of tablet (mg)	Maximum percentage of deviation allowed (%)
1	130 or less	10
2	130- 324	7.5
3	More than 324	5

$$\% \text{ Deviation} = \frac{\text{Individual weight - Average weight X 100}}{\text{Average weight}}$$

Uniformity of content for Saxagliptin:

Ten tablets were weighed individually and placed in ten separate 250 ml conical flask containing 100 ml of 0.1NHCl (pH 1.2). The flasks were shaken for 6 hrs and volume made with 0.1N HCl. The solution was filtered through whattmann filter papers and 10 ml of filtrate was taken and diluted with a mixture of 0.1% TFA and Water (80:20), and appropriate dilution was made and sample was analyzed at 220 nm using HPLC. The results were tabulated.

Assay

Saxagliptin:

Ten randomly selected tablets were weighed and powdered. The powder was transferred to 250 ml conical flask containing 100 ml of 0.1NHCl (pH 1.2). The flask was shaken for 6 hrs and volume made with 0.1N HCl. The solution was filtered through whattmann filter papers and 10 ml of filtrate was taken and diluted with a mixture of 0.1% TFA and Water (80:20), and appropriate dilution was made and sample was analyzed at 220 nm using HPLC. The results were tabulated.

Table no.7: Chromatographic conditions for Assay & Content Uniformity of Saxagliptin:

Column	BRD 129
Wavelength	220nm
Runtime	60 minutes
Mobile Phase A	Buffer:Methanol (90:10)
Mobile Phase B	ACN: Methanol (70:30)
Flow Rate	1.0ml/minute
Injection Volume	20µl
Column Temperature	30ºC

Metformin Hydrochloride:

Ten randomly selected tablets were weighed and powdered. The crushed powder equivalent to 100mg was transferred to 100 ml conical flask containing 70 ml of Water. The flask was shaken for 2 hrs and volume made with water. The solution was filtered through whattmann filter papers and 10 ml of filtrate was taken and diluted with water to 100ml and appropriate dilution was made and sample was analyzed at 232 nm using UV. The results were tabulated.

In-vitro drug release studies:

The in vitro dissolution studies were carried out using USP XXII dissolution apparatus type II (Paddle type) at 100 rpm. Dissolution test was carried out for a total period of 10 hrs using pH 6.8 Phosphate Buffer dissolution media 1000ml at 37 ± 0.5^0 C for 10 hrs, 10 ml of the sample was withdrawn at regular interval and replaced with the same volume pre-warmed (37 ± 0.5^0C) fresh dissolution medium. The samples withdrawn were filtered through 0.45µ membrane filter, and the drug content in each sample was analysed after suitable dilution. Drug Release of Metformin Hydrochloride was measured at 232nm by UV visible spectrophotometer. Drug Release of Saxagliptin was measured at 220nm by HPLC.

***In Vitro* Drug Release Kinetic Study** [8-11]:

The dissolution data were subjected to release kinetic study. Drug dissolution from solid dosage form has been described by kinetic models in which the dissolved amount of drug (Q) is compared to the Drug content (%) function of the test time (t). Some analytical and kinetic models of the Q versus t commonly used are Zero order, First order, Hixson-Crowell, Higuchi and Korsmeyer-Peppas model to study the in vitro kinetic release mechanism.

Stability Studies [12-15]**:**

One selected fabricated tablet batch was stripping packaged and kept at RT & 40°C with 75% RH. Samples were withdrawn at 0, 30 days.

Condition were used for stability studies

- 40°C/75RH analysed till a period of 30 days.

Hardness, Friability, Drug content and In vitro release studies were carried out for the tablets after 30 days period.

Results and Discussion

Drug Excipients Compatibility Study by Ftir

From the results, it was concluded that there is no interaction between the drug and polymers used in the formulation.

Figure No. 1: IR Spectrum of Metformin Hydrochloride

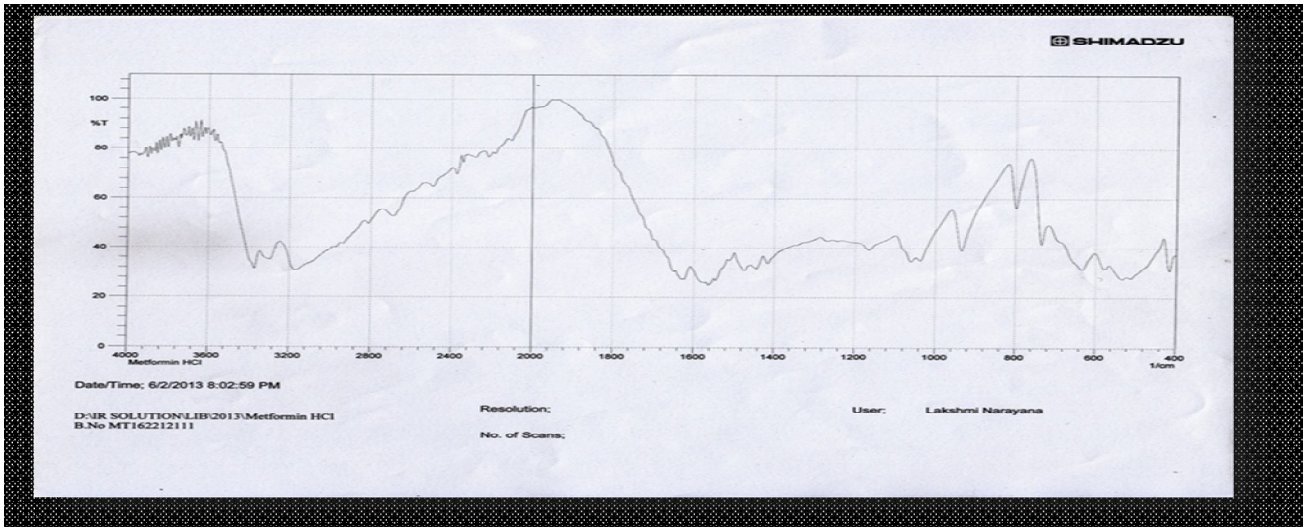


Figure No. 2: IR Spectrum of Metformin Hydrochloride + Hypromellose K100M

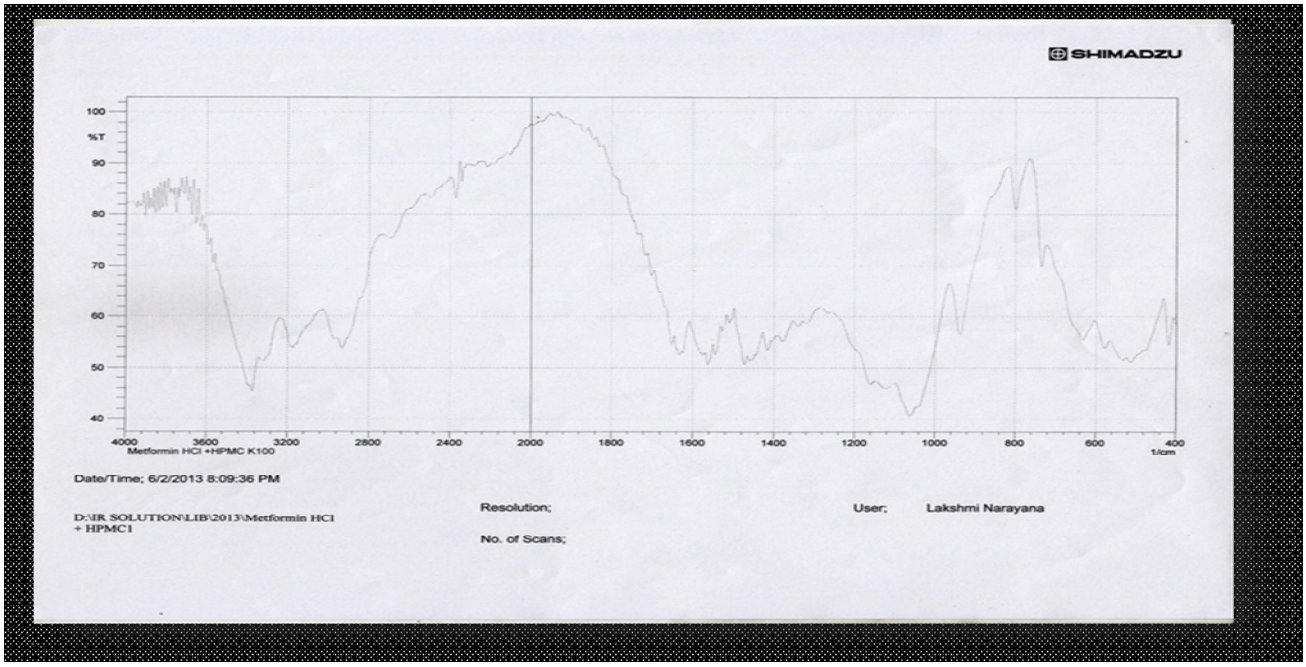
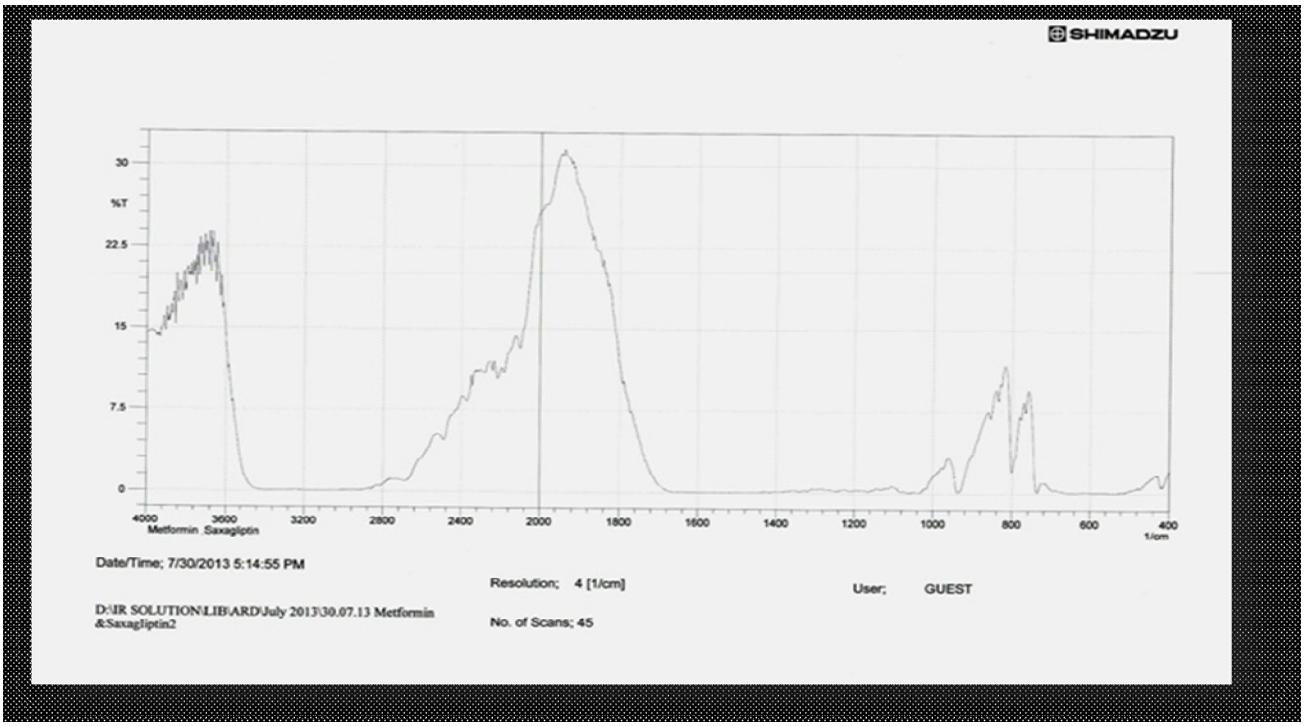


Figure No. 3: IR Spectrum of Metformin Hydrochloride + Saxagliptin



Evaluation of the Powder Blend

The granules obtained for the trial batches (F_1- F_6) were evaluated for flow property of the blend. Bulk density, taped density, Carr's index and Hausner's ratio were tabulated for the blend. Capping and sticking were not observed.

Table no. 8: evaluation of powder blend

Evaluation of Powder Blend of Batches F_1 to F_7				
Powder Blend	**Bulk Density (g/ml)**	**Tapped Density (g/ml)**	**Carr's Index (%)**	**Hausner's Ratio**
F_1	0.46	0.58	20.68	1.26
F_2	0.47	0.57	17.54	1.21
F_3	0.44	0.52	15.38	1.18
F_4	0.46	0.53	13.21	1.15
F_5	0.44	0.50	12.00	1.13
F_6	0.46	0.52	11.53	1.13

From the Carr's index and Hausner's ratio values obtained for granules of batches F_1- F_6, the powder blends were found to have good flow and compressibility properties.

Evalution of Uncoated Tablet (Metformin Hydrochlorid Table no.9: Evaluation of the tablets

		Evaluation Of Tablets of Batches F_1 To F_6				
Trial Batch	**Target weight (mg)**	**Average Weight(mg)**	**Hardness (N)**	**Thickness (mm)**	**Dimension (mm)**	**Friability (%)**
F_1	1030.00	1032.12mg	46 -67N	7.34 -7.42	19.1×9.1	0.54%
F_2	1030.00	1031.34mg	65 – 78N	7.31 – 7.39	19.1×9.1	0.37%
F_3	1030.00	1029.45mg	86 – 96N	7.23 – 7.29	19.1×9.1	0.24%
F_4	1030.00	1030.45mg	145 – 165N	7.18 – 7.25	19.1×9.1	0.14%
F_5	1030.00	1030.80mg	156 – 178N	7.14 – 7.23	19.1×9.1	0.08%
F_6	1030.00	1031.34mg	165 – 176N	7.13 – 7.21	19.1×9.1	0.10%

Assay and Content Uniformity

Table no.10: Assay and Content Uniformity

Batch Number	**% Drug Content**		**% Content Uniformity of Saxagliptin**
	Metformin hydrochloride	**Saxagliptin**	
F_1	98.8	NA	NA
F_2	100.21	NA	NA
F_3	99.89	NA	NA
F_4	99.56	NA	NA
F_5	100.1	98.6	100.2
F_6	99.86	99.63	99.98

The percentage drug content and percentage content uniformity of all the formulation were listed in the table no. 17.

In-Vitrodrug Release Studies

Table no.11: In-vitro drug release studies of Batches F_4 to F_6

Time (hrs)	% Drug Release					
	Batch No.					
	F4		F5		F6	
	Metformin Hydrochloride	Saxagliptin	Metformin Hydrochloride	Saxagliptin	Metformin Hydrochloride	Saxagliptin
5mins	NA	NA	NA	31.78	NA	36.73
10mins	NA	NA	NA	45.89	NA	79.42
15mins	NA	NA	NA	56.35	NA	84.12
20mins	NA	NA	NA	68.09	NA	97.46
30mins	21.66	NA	13.21	76.24	11.60	99.03
1	40.85	NA	28.79	NA	26.13	NA
2	59.31	NA	44.83	NA	42.26	NA
3	71.68	NA	56.18	NA	53.77	NA
4	85.37	NA	68.15	NA	64.02	NA
6	94.50	NA	82.36	NA	79.31	NA
8	96.43	NA	92.67	NA	87.56	NA
10	98.78	NA	95.84	NA	93.67	NA

NA: Not Applied

From the above formulation F_4 was giving the fast release result of Metformin hydrochloride and f5 showing controlled release of Metformin hydrochloride till 10 hours but Saxagliptin release arrested due to direct attachment of Saxagliptin with controlled release polymers. F6 showing controlled release of Metformin hydrochloride till 10 hours and Saxagliptin release within 30 minutes as conventional release.

% Drug Release Profile of Saxagliptin IR and Metformin hydrochloride SR formulation:

Figure No.4: % Drug Release Profile of Saxagliptin Batches F5 and F6

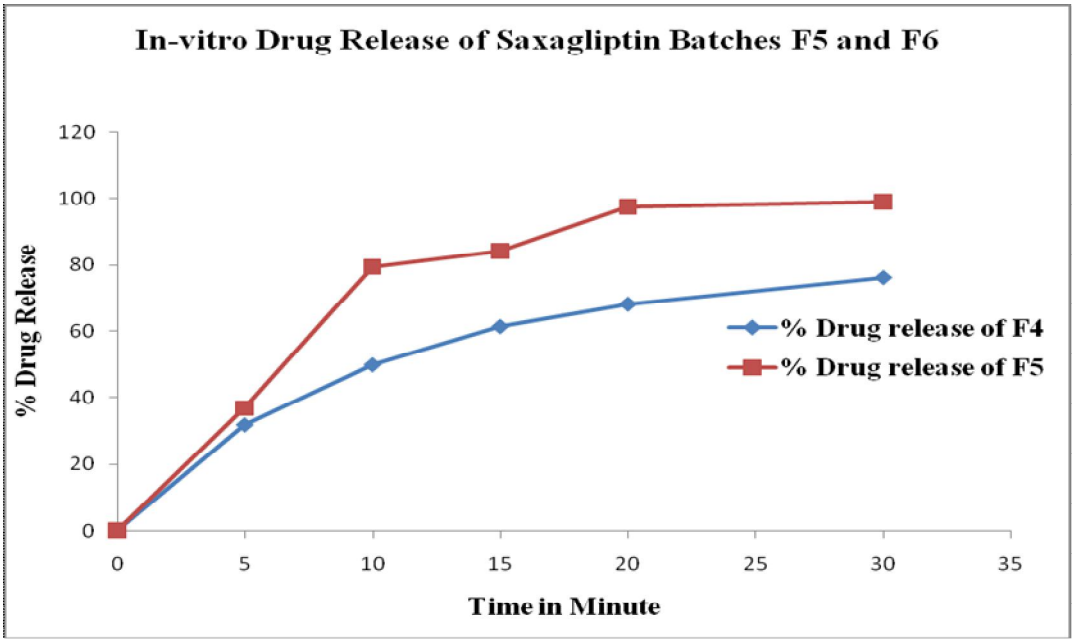
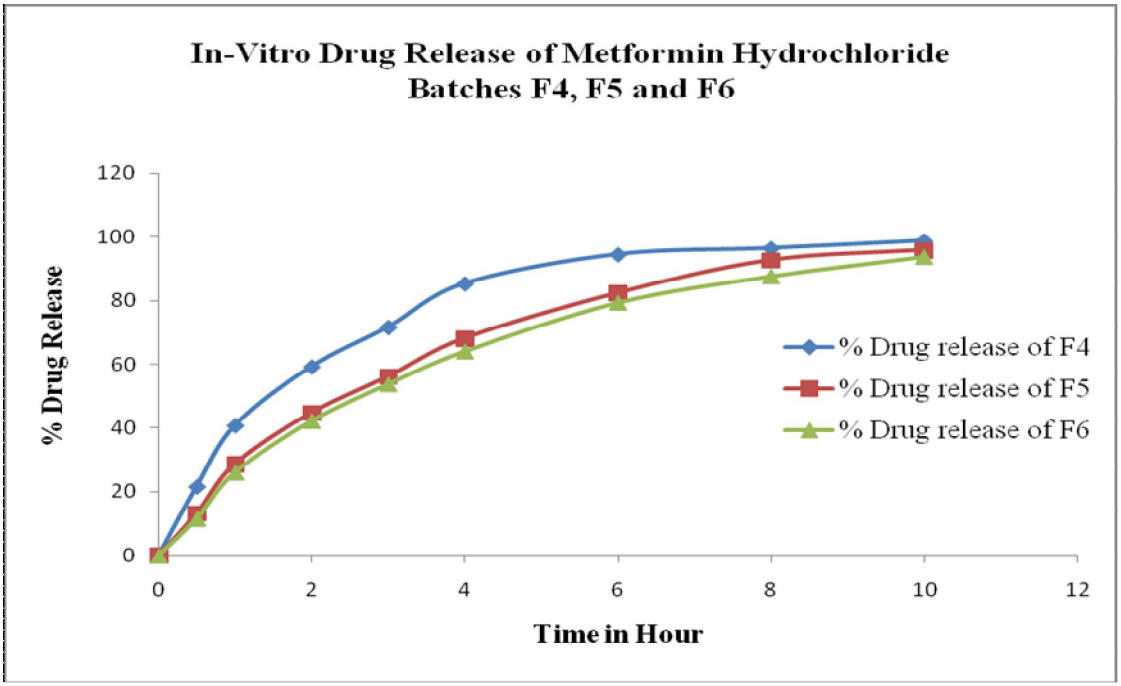


Fig. No.5: % Drug Release Profile of Metformin Hydrochloride Batches F4, F5 and F6



Kinetics of Metformin Hydrochloride sustained released formulation:

The optimised batch F_6 was subjected to graphical treatment to assess the kinetic of drug release from matrix tablet. The optimised formulation F6 was subjected to Zero order, First order, Hixson-Crowell, Higuchi and Korsmeyer-Peppas model to study the in vitro kinetic release mechanism.

From, *in vitro* kinetic release mechanism study it was found that the drug released kinetic of the sustained release formulation of optimised batch F6 follow diffusion mechanism for drug release from the matrix tablet .

Table no.12: Zero order kinetic Model

S. No.	Time in hour	Cum.% Drug release
1.	0.5	11.6
2.	1	26.13
3.	2	42.26
4.	3	53.77
5.	4	64.02
6.	6	79.31
7.	8	87.56
8.	10	93.68

Figure No.6: Zero order kinetic Model

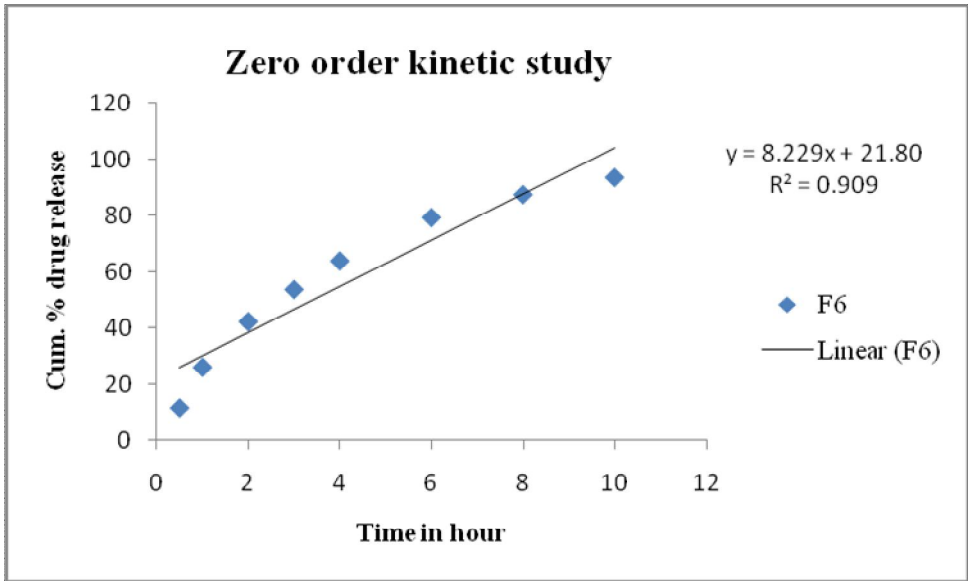


Table no.13: First order kinetic Model

S. No.	Time in hour	Log Cum.% Drug retained
1.	0.5	1.946
2.	1	1.868
3.	2	1.761
4.	3	1.664
5.	4	1.556
6.	6	1.315
7.	8	1.094
8.	10	0.801

Figure No.8: First order kinetic Model

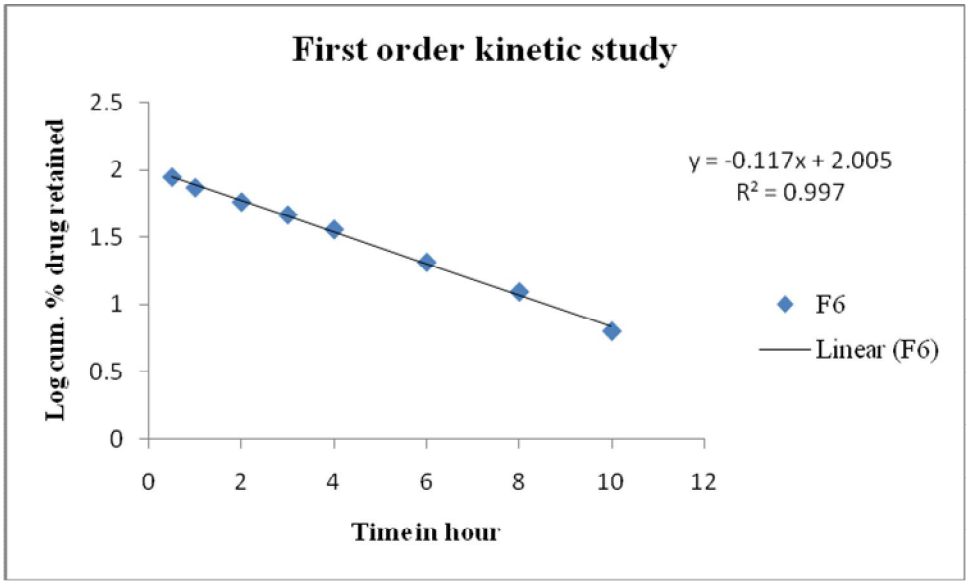


Table no.14: Higuchi matrix model

S. No.	√Time in hour	Cum.% Drug released
1.	0.707	11.6
2.	1	26.13
3.	1.414	42.26
4.	1.732	53.77
5.	2	64.02
6.	2.449	79.31
7.	2.828	87.56
8.	3.162	93.67

Figure No.9: Higuchi matrix model

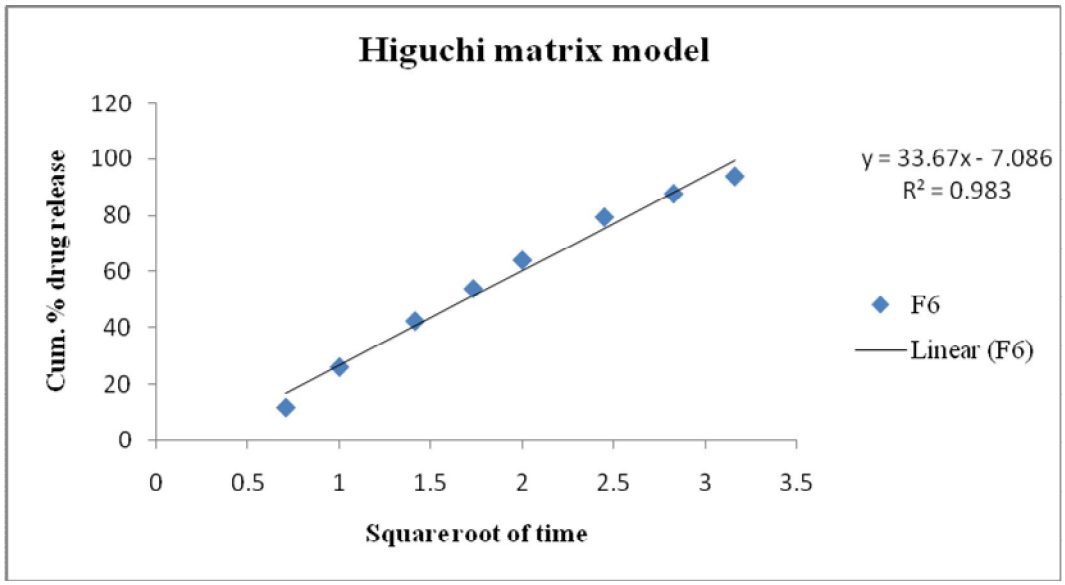


Table no.15: Korsmeyer and Peppas model

S. No.	Log Time	Log Cum.% Drug released
1.	-0.301	1.064
2.	0	1.417
3.	0.301	1.625
4.	0.477	1.73
5.	0.602	1.806
6.	0.778	1.899
7.	0.903	1.942
8.	1	1.971

Figure No.10: Korsmeyer and Peppas model

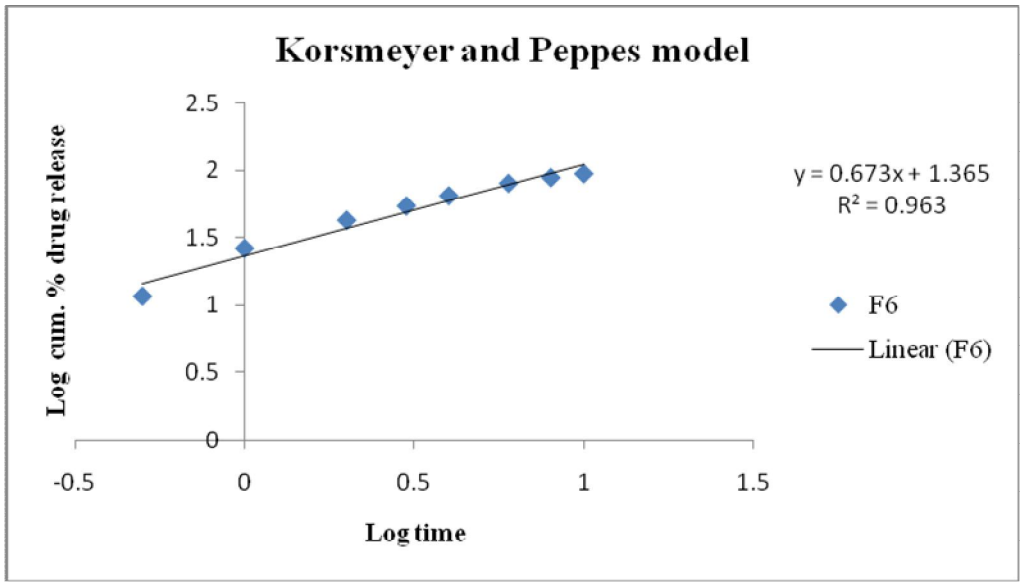
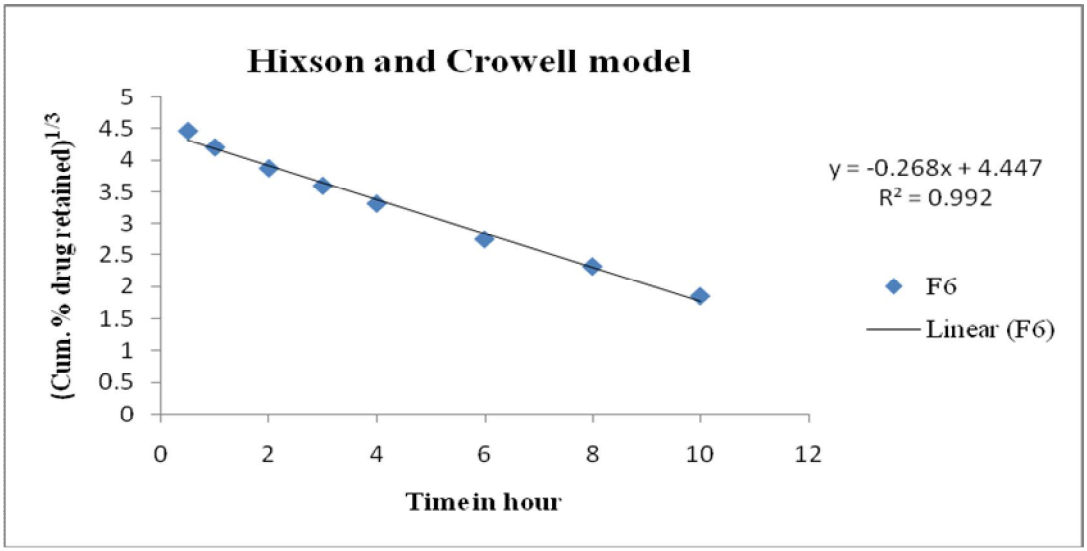


Table no.16: Hixson and Crowell model

S. No.	Time in hour	(Cum.% Drug retained)$^{1/3}$
1.	0.5	4.454
2.	1	4.195
3.	2	3.865
4.	3	3.589
5.	4	3.309
6.	6	2.745
7.	8	2.317
8.	10	1.849

Figure No.11: Hixson and Crowell model



Stability Study

Stability study tests are used to find out whether the formulations are maintaining their quality during the storage period or not. Stability study tests are used to find out the best formulation. It can be studied by applying a stress to the formulation such as temperature, humidity and light. Here stability study was conducted for F6 at 40°C/ 75% RH. The quality control tests were carried out at the end of the one month. Following the same procedure as described previously.

Table No.16: Stability test data for batch number F_6 at 40°C/ 75% RH

Sl.No.	Evaluation test	Initial	After 1 month
1	Weight of the tablets (mg±SD)	1030.0 ± 2.5	1030.0 ± 3
2	Thickness (mm± SD)	7.19 ± 0.02	7.21 ± 0.01
3	Hardness (N)	165-176N	150-165N
4	Assay	99.82 %	99.79 %
5	% Drug Release	100 %	99 %

Among all the batches, Batch no. F6 was taken for stability study.

From this batch the required quantity of tablet (to perform all evaluation tests) were taken. The tablets were expressed to an environmental condition of 40°C/ 75% RH for a period of 1 month. The tablets were evaluated for all parameter (Hardness, Thickness, Weight Variation, % Drug content and in vitro drug dissolution) and were found to be within the acceptable limits. The results are shown in table no. 16.

Summary and Conclusion

Metformin hydrochloride and Saxagliptin are used as anti – diabetic drug. Both compounds exert pharmacodynamic complementary actions. Their co-administration improves blood glucose control (fasting plasma glucose, postprandial glucose and glycated hemoglobin) more potently than either compound separately. The present work was aimed to Formulation, Development and Evaluation of Saxagliptin 2.5mg immediate release and Metformin 500mg sustained release tablet.

The drug and polymers were subjected to physical compatibility studies for period of a month and were found to be compatible with each other. Hypromellose (Methocel K-100MCR) and Carmellose Sodium (CEKOL LVD) were used as controlled Release polymer. Six batches (F_1-F_6) of formulation were prepared by Wet granulation method in the present study. Metformin hydrochloride sustained release 500 mg tablets formulated and Saxagliptin 2.5mg drug coated on the surface of sustained release tablets.

The immediate release of Saxagliptin was optimised in batches F_5 and F_6 formulation and it found satisfactory by applying inner seal coating on surface of Metformin hydrochloride sustained release tablets. A outer protective layer proposed on Saxagliptin drug coating to protect the drugs from moister absorbance. The Tablets of all batches carried the test of Percentage Weight variation, Thickness, Friability, Hardness, % Drug Release, Assay and Content Uniformity. The result obtained in the formulation indicated that the batch F_6 was giving the best release results and in the most optimum trial than other trial. The in vitro kinetics release mechanism of the Metformin hydrochloride sustained release tablets of optimised batches F_6 was studied by graphical and statical models of Zero order, First order, Hixson-Crowell, Higuchi and Korsmeyer-Peppas model.

In vitro kinetic release of Metformin hydrochloride tablets were follow the studies of First order kinetic model, hence the release mechanism of the Metformin sustained release tablets were found diffusion mechanism from the swell able matrix tablets. The tablets of batch F_6 were subjected to stability studies, (Weight Variation, Hardness, Friability, Thickness and Assay) at the end of one month complied within the standard values. From the result obtained, it was observed that the batch F_6 is the best in terms of the release rate studies; hence the batch F_6 was considered of the best formulation. The stability studies of the tablets indicated that the tablets are stable. From the above result, it may be concluded that Saxagliptin 2.5mg immediate release and Metformin 500mg sustained release tablet may be prepared beneficially. From the present studies, it can be concluded that Saxagliptin 2.5mg immediate release and Metformin 500mg sustained release tablet can be prepared successfully.

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