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FORMULATION DEVELOPMENT OF METFORMIN HCL AND GLIMEPIRIDE SANDWICHED OSMOTIC PUMP TABLET

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ABSTRACT
An attempt was to formulate the immediate release of Glimepiride for 30 mins and control release of Metformin hydrochloride over12hrs of sandwiched osmotic pump tablets by using hydroxypropyl methylcellulose of different viscosity grades (HPMC K4M, HPMC K15M, and HPMC K100M) and disintegrants. The tablets were prepared by wet granulation technique. The granules were evaluated for angle of repose, loose bulk density, tapped and bulk density. It shows satisfactory results. The tablets were subjected to thickness, weight variation, drug content, hardness, friability, and *in vitro* release studies. The *in vitro* dissolution study was carried out for 12 h using USP dissolution apparatus II (paddle) in 900mL pH 6.8 phosphate buffer as dissolution media for Metformin HCL and 0.1N Hcl buffer as dissolution media for Glimepiride [30min]. The release mechanisms were explored and explained with zero order, first order, Higuchi, Korsmeyer peppas equations. Based on drug kinetics release, optimized formulation were selected through comparison with marketed product. It is cleared that the drug release from sandwiched osmotic pump tablets prepared by HPMC K100M provides a better result in preparation of control release formulation of metformin hydrochloride.

KEYWORDS: Diabetes mellitus, Control release, Metformin HCL, Glimepiride, HPMC K100M.

INTRODUCTION

Diabetic Mellitus

Diabetes mellitus is a chronic, complicated metabolic disease that affects a large portion of the world's population. Hyperglycemia, the term for elevated blood glucose levels, is a hallmark of the illness. This happens because the body either doesn't create enough insulin or doesn't use it well enough. The pancreas produces the hormone insulin, which is essential for controlling blood sugar levels and facilitating the uptake of glucose into cells to provide energy.[1,2]

When this process's regular operation is disrupted, it may lead to a number of issues that could affect the body's many organ systems.2. Less than 30% of diabetic patients worldwide achieve glycated hemoglobin (HbA1c) levels of less than 7.0% (53 mmol/mol), suggesting an unmet medical need for more effective glycemic diabetes care. Glycemic control can be achieved with early combination therapy, according to several studies.[2]

Types of Diabetes mellitus

Type 1 diabetes

Type 1 diabetes, also known as juvenile or insulin-dependent diabetes, is an autoimmune disease caused by the body's immune system mistakenly attacking and killing the insulin-producing beta cells in the pancreas. As a result, people with type 1 diabetes produce little to no insulin and require daily injections of insulin to be alive. This illness typically shows symptoms in childhood or adolescence, but it can also appear in adults. The exact cause of type 1 diabetes is still unknown, however it is thought to result from a combination of environmental and genetic factors.[3,4]

Type 2 diabetes

Type-2 diabetes, also referred to as non-insulin-dependent diabetes, accounts for 90–95% of all cases of diabetes and is the most common type. The body's failure to maintain normal blood glucose levels is caused by insulin resistance or inadequate insulin synthesis.[5,4]

Obesity, sedentary activity, and poor diet are among the lifestyle factors that are commonly associated with type-2 diabetes. This syndrome is more common in adults, but it has also been reported in children and adolescents more frequently, which may be related to the growing problem of childhood obesity.[5,6]

Osmotic drug delivery system

The most promising strategy-based medication delivery devices are osmotic devices. The net flow of water across a selectively permeable membrane caused by a variation in the osmotic pressure across the membrane is known as osmosis. It is caused by a differential in the concentrations of solutes across the membrane, which permits water to pass through while rejecting the majority of solute molecules or ions. Osmosis is used to create the best controlled drug delivery system possible.[3,7] These devices use the osmotic pressure produced by osmogen as a driving mechanism to deliver the medicine in a regulated manner.

Both the oral and the implantation routes of delivery are compatible with these systems.[2,7] Compared to alternative controlled drug delivery methods, osmotic pumps provide a number of advantages, including uniform blood concentration, a longer therapeutic impact, ease of formulation and operation, and enhanced patient compliance through more consistent and less frequent dosage. Oral osmotic drug-delivery devices that work well usually have a compressed tablet core covered in a semipermeable membrane coating.[8]

This coating contains one or more delivery apertures that allow the medicine to be released gradually as a suspension or solution. The main components are a medication formulation with a water-swellable polymer and an osmotic agent. The osmotic pressure produced by the membrane coating's permeability and the core's constituent parts determine how quickly the core absorbs water. The drug solution or suspension is forced out of the tablet through one or more delivery ports as a result of the core's volume expansion upon absorbing water.[8,9]

Advantages

The following advantages have contributed to the popularity of osmotic drug delivery systems.

- They typically give a zero order release profile after an initial lag.
- Deliveries may be delayed or pulsed if desired.[13]
- Drug release is independent of gastric pH and hydrodynamic condition.
- The release mechanisms are not dependent on drug.
- A high degree of in-vitro and in-vivo correlation (ivivc) is obtained in osmotic systems.[3,5]

Disadvantages

- High Cost.
- If the coating process is not well controlled there is a risk of film defects, which results in dose dumping.[6,10]
- Hole Size is critical in case of elemetry osmotic system.

Basic components of osmotic drug delivery

An osmotic pump should contain the following components to attain the desired control over the drug release.[10,11]

- Drug
- Osmotic agent
- Polymer
- Delivery orifice
- Semi permeable membrane
- Hydrophilic and hydrophobic polymer
- Surfactants
- Solubiling agent
- Flux regulators

MATERIALS AND METHODOLOGY

Materials: Metformin HCL and Glimepiride were purchased from D M pharma marketing pvt Ltd, Punjab, India. HPMC K100M, polyethylene oxide, and Microcrystalline cellulose were obtained from sigma Aldrich, Bangalore, India. Other excipients are sodium starch glycolate, Magnesium stearate, isopropyl alcohol, and povidone k30 were purchased from Jain impex, Mumbai, India.

METHODOLOGY

Raw material analysis

Determination of calibration curve for Metformin HCL

Preparation of stock solution

100 mg of Metformin HCL was weighed separately and transferred in 100 mL volumetric flasks. The drugs were dissolved in 50 mL of distilled water by sonication and then the volume was made up to the mark with the same solvent to obtain final concentration 1000 µg mL-1 of the component.[12]

Preparation of standard solution

Powder of twenty tablets, containing 500 mg Metformin HCl, was weighed. A quantity of powder equivalent to 10 mg of Metformin HCl was taken in different 10 mL volumetric flasks containing about 5 mL distilled water for analysis and sonicated for 15 min. After sonication, the volume was made up to the mark with the same solution to obtain sample stock solution of Metformin HCL. Suitable aliquots of 1000 mg mL-1 solution were diluted up to the mark with water to get the concentration range of 10, 20, 30, 40 and 50 mg mL-1 for Metformin HCL.[12,13] The absorbance was measured at 232 nm.

Determinaion of calibration curve for Glimepiride

Preparation of stock solution

Standard solution of Glimepiride was prepared by transferring accurately weighed 10 mg of drug into a 100 ml volumetric flask and the volume was made up to 100 ml using chloroform as an solvent to get the concentration of 100µg/ml.[10,13]

Preparation of standard solution

From the standard stock solution fresh aliquots were pipette out and suitably diluted with chloroform to get final concentration in the range of 5-30 µg/ml.[14,15] The solutions were scanned under 200-400 nm wave length range and a sharp peak was obtained at 226nm.

Calibration curve was plotted by taking absorbance on yaxis and concentration of solution on x-axis.

Solubility study

For Metformin HCL

An excess amount of the drug was added to 10 mL volumetric flask having different media (i.e. distilled water, simulated gastric fluid pH-1.2, simulated intestinal fluid pH-6.8, and simulated intestinal fluid pH-7.4). Drug was added to this till saturation occurred and shaken at room temperature for 48 h.[12,16] After that, samples were filtered, appropriately diluted and analyzed at 232nm using UV visible spectrophotometer.[16]

For Glimepiride

Solubility study of drug was performed using different solvents such as methanol, ethanol, dimethyl sulfoxide, ethyl acetate, Dichloromethane (DCM) and N-Methyl-2-Pyrrolidone. Samples were shaken on a rotary shaker at 37ºC for 24 hours. The two phases are then separated by filtration. Amount of solute in supernatant is then determined using UV spectrophotometric analysis at the corresponding λmax of each solvent.[17]

Incompatibility study

Differential scanning colorimetry

Compatability study were performed using differential scanning colorimetry.

Diffrential scanning calorimeter study of samples was carried out on a differential scanning calorimeter (model DSC60plus, Shimadzu analytical instrument, India). The thermal analysis was performed in a nitrogen atmosphere at a heating rate of 10°C/min over a temperature range of 30–300°C. Alumina was employed as the reference standard.[17,18] The onsets of melting points and enthalpies of fusion of samples were automatically calculated by the instrument.

Preformulation studies

1. Bulk Density (Db)

It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weight powder (passed through standard sieve # 20) into a measuring cylinder and initial weight was noted and calculated according to the formula mentioned below.[14,17] It is expressed in g/ml and is given by.

Db = M/ Vb

Where, M - mass of powder

Vb - bulk volume of the powder.

2. Tapped Density (Dt): The volume was measured by tapping the powder for 750 times and the tapped volume was noted if the difference between these two volumes is less than 2%. If it is more than 2%, tapping is continued for 1250 times and tapped volume was noted.[82] It is expressed in g/ml and is given by.

Dt = M / Vt

Where, M - mass of powder

Vt - tapped volume of the powder.

3. Angle of Repose

It is defined as maximum angle possible between the surface of the pile of powder and the horizontal plane.[18]

= tan-1θ (h / r) - angle of repose.θ

Where, h - height in cms

r - radius in cms.

Table 1: Angle of repose and powder flow property.

S.NO	Angle of repose	Type of flow
1	<20	Excellent
2	20-30	Good
3	30-34	Passable
4	>34	Poor

4. Carr's index (or) % compressibility

It indicates the powder flow properties. It is expressed in percentage and is given by formula.[19]

I=DT-DB/DTX100

Where, Dt - tapped density of the powder

Db - bulk density of the powder.

Table 2: Percentage compressibility and flow property.

S.NO	Percentage compressibility	Flow property
1	5-12	Excellent
2	12-16	Good
3	18-21	Passable
4	23-35	Poor
5	33-38	Very poor
6	>40	Very very poor

5. Haussner's ratio

Hausner‟s ratio is an indirect index of ease of powder flow. It is calculated by the following formula.

Hausner's ratio = DT/DB

Where, Dt - tapped density,

Db - bulk density.

Lower Hausner‟s ratio (<1.25)indicates better flow property than higher ones >1.25).[17,19]

FORMULATION OF SANDWICHED OSMOTIC PUMP TABLET

Preparation of Glimepiride layer

Wet granulation method

The immediate release Glimepiride layer was prepared by the wet granulation method. Accurately weighed quantities of glimepiride, lactose monohydrate, and MCC PH101 are mixed thoroughly and passed through

sieve no40. A binder solution of IPA and povidone k30 is prepared. Then, the binder solution is mixed with the screened powders thoroughly and dried in a tray dryer at 45ºC for 30 minutes. After drying, the dried granules are sifted through sieve no.20. Then, the remaining ingredients are blended with the dried granules for 5 minutes. Magnesium stearate is passed through sieve no. 60 and mixed with the blended granules.[20]

Preparation of Metformin HCL layer

Wet granulation method

The controlled release metformin HCL layer was prepared by the wet granulation method. Accurately weighed amounts of metformin HCL, lactose monohydrate, and cabosil were mixed thoroughly and sifted through sieve no 30. A binder solution of IPA and povidone k30 was prepared. Then, the binder solution was mixed with the screened powders and dried in a tray dryer at 45ºC for 15 minutes. After drying, the dried granules were sifted through sieve no. 40. Then, the remaining ingredients were blended with the dried granules for 5 minutes. Magnesium stearate was passed through sieve no. 60 and finally mixed with the blended granules.[21]

Preparation of polymer layer

The polymer layer was prepared by direct compression method. Weighed accurately polyethylene oxide, talc, and brilliant blue were mixed and passed through sieve no 40.[20.22]

Post compression

The compression of sandwiched osmotic pump tablet was done by using Cadmach double compression machine. It was compressed by layer one after the other. Both the drug layer and polymer layer were identified by white colour of metformin HCL, light yellow colour of Glimepiride and blue colour of polymer layer[middle layer].[21]

Punch specification

Punch diamension: 20 x 9mm
Punch shape: concave
Upper plane: break line
Lower plane: plane

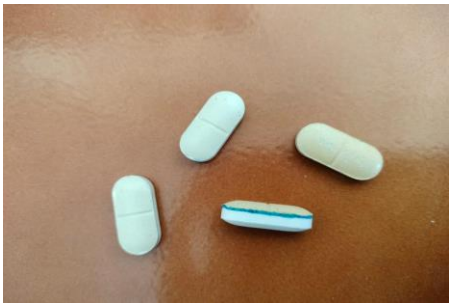

Fig. 1: Sandwiched osmotic pump tablet.

Table 3: Metformin HCL layer.

S.NO	Ingredients[mg]	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
1	Metformin HCL	500	500	500	500	500	500	500	500	500	500
2	Lactose monohydrate	148.6	109.6	70.6	148.6	109.6	70.6	148.6	109.	70.6	90.6
3	Cabosil	7.8	7.8	7.8	7.8	7.8	7.8	7.8	7.8	7.8	7.8
4	Povidone k30	30	30	30	30	30	30	30	30	30	30
5	IPA	120	120	120	120	120	120	120	120	120	120
6	HPMC K4M	78	117	156	-	-	-	-	-	--	-
7	HPMC K15M	_	_	_	78	117	156	_	_	_	_
8	HPMC K 100M Premium	_	_	_	-	_	_	78	117	156	136
9	Cabosil	7.8	7.8	7.8	7.8	7.8	7.8	7.8	7.8	7.8	7.8
10	Magnesium Stearate	7.8	7.8	7.8	7.8	7.8	7.8	7.8	7.8	7.8	7.8
11	Tablet weight [mg]	780	780	780	780	780	780	780	780	780	780

Table 4: Glimepiride layer.

S.NO	Ingredients[mg]	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
1	Glimepiride	1	1	1	1	1	1	1	1	1	1
2	Lactose monohydrate	50	50	50	50	50	50	50	50	50	50
3	MCC PH 101	59.4	58.2	57	59.4	58.2	57	59.4	58.2	57	57
4	Povidone k30	3.6	3.6	3.6	3.6	3.6	3.6	3.6	3.6	3.6	3.6
5	IPA	5	5	5	5	5	5	5	5	5	5
6	CrospovidoneXL10	3.6	4.8	6	_	_	_	_	_	_	_
7	Croscarmellose Sodium	_	_	_	3.6	4.8	6	_	_	_	_
8	Sodium starch glycolate	_	_	_	_	_	_	3.6	4.8	6	6
9	Cabosil	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2
10	Iron oxide	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
11	Magnesium Stearate	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2
12	Tablet weight [mg]	120	120	120	120	120	120	120	120	120	120

Table 5: Polymer layer [100mg]

S.NO	Ingredients[mg]	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
1	Polyethylene oxide	75	75	75	75	75	75	75	75	75	75
2	Talc	24.7	24.7	24.7	24.7	24.7	24.7	24.7	24.7	24.7	24.7
3	Brilliant blue	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25

EVALUATION

- Weight variation
- Hardness
- Thickness
- Friability
- Drug content
- Dissolution test
- Separation time analysis
- Swelling index study
- Osmotic pressure study

Weight Variation

Twenty tablets were selected randomly from the lot and weighed individually to check for weight variation and average weight was calculated. The deviation of each tablet from average weight was calculated and percent deviation was computed. Weight variation specification as per IP.[21,23]

Thickness

The thickness in millimeters was measured individually for 10 preweighed tablets by using vernier calipers. The average thickness was reported.

Hardness

Tablet hardness was measured by using electrolab hardness tester. The crushing strength of the 10 tablets with known weight and thickness of each tablet was recorded in kilopond (kp) and the average hardness was noted.

Friability (F)

Twenty tablets were selected from each batch and weighed. Each group of tablets was rotated at 25 rpm for 4 min (100 rotations) in the electrolab tablet friabilator. The tablets were then dust and re-weighed to determine the loss in weight. Friability was then calculated as percent weight loss from the original tablets. The friability (F) is given by the formula.[24]

F=initial weight –final weight /initial weight x 100

Drug content

For metformin HCL

Preparation of phosphate buffer pH 6.8

Weighed accurately about 6.8 gm of potassium dihydrogen orthophosphate in a 1000 ml beaker, added sufficient water to dissolve, and made up the volume with water. Adjusted pH to 6.8 with 1 M sodium hydroxide.

Standard preparation

Weighed accurately about 50mg of Metformin HCl WS in a 100ml volumetric flask, added 50ml of phosphate buffer pH-6.8 to dissolve with the aid of ultrasound, and made the volume 100ml with phosphate buffer pH-6.8. Transferred 1ml of this solution to a 100ml volumetric flask and made the volume 100ml with phosphate buffer pH-6.[21,24]

Sample preparation

Crushed the content of 20 tablets to a fine powder and weighed equivalents to 50 mg of Metformin HCl into a 100 ml volumetric flask. Added 50 ml of phosphate buffer pH-6.8 to dissolve with the aid of ultrasound and made the volume 100 ml with phosphate buffer pH-6.8. Filtered the solution through Whatman filter paper no. (1). Transferred 1 ml of this solution to a 100 ml volumetric flask and made the volume 100 ml with phosphate buffer pH-6.8. The absorbance of the standard and sample solution was measured at about 232 nm using phosphate buffer pH-6.8 as a blank in the reference cell.

For Glimepride

Standard preparation

Weighed accurately about 50 mg of Glimepiride to 100 ml volumetric flask, added 5 ml of diluents[DMF] to dissolve with the aid of ultrasound and make volume with diluents. Transferred 10 ml of this solution to 50 ml volumetric flask and madeup volume with IPA.[19,22]

Sample preparation

Crushed the content of 20 tablets to a fine powder and weighed accurately quantity of powder equivalent to about 5 avg weight(equivalent to 5 mg of glimepiride) of tablet to a 50 ml volumetric flask, added 5 ml of diluents[DMF] to dissolve it and madeup volume with IPA. The solution were filtered through whatman filter paper no. 1. The absorbance of standard and sample solution was measured at about 226nm using IPA as a blank in the reference cell.

***In-vitro* dissolution test**

Dissolution study of contolled release and immediate release of different tablet formulations were carried out separately.[24,25]

Preparation of phosphate buffer PH 6.8 solution

Weighed accurately about 6.8 gm of potassium dihydrogen orthophosphate in a 1000 ml beaker, added sufficient water to dissolve, and made up the volume with water. The pH was adjusted to 6.8 with 1 M sodium hydroxide**.**

Dissolution conditions

Apparatus : USP Type II (Paddle type)
Medium : 6.8 pH phosphate buffer
Rpm : 100

Volume : 900ml
Temp : 37.5°C

Standard preparation
Weighed accurately about 28mg of Metformin HCl in 100ml volumetric flask, added 50ml of dissolution medium to dissolve with the aid of ultrasound and make volume 100ml with dissolution medium. Transfered 2 ml of this solution to 100ml volumetric flask and make up volume with phosphate buffer.

Procedure
The study was carried out for 12 hours. 10 ml of samples were withdrawn at the time interval of 1,3,6, 10,12th hour. Filtered through whatman filter paper no. 1. Replace 10ml of dissolution medium. Transferred 2 ml of this filtrate to 100 ml volumetric flask and make volume with dissolution medium. The absorbance of standard and sample solution was measured at about 232nm using dissolution medium as a blank in reference cell.[88]
The percentage of Metformin HCl release was calculated using following formula.
=Test abs/std abs x std wt/100x std dilution factor x 900/label claim x test dilution x purity%/100 x 100

Glimepiride
Standard procedure
Weighed accurately about 50mg of Glimepiride in a 100ml conical flask and added 5ml of DMF, then made up the volume to 100ml with IPA. Transferred 1ml into a 100ml conical flask and made up the volume to 100ml with IPA. Again transferred 1ml into a 100ml flask and made up the volume with IPA. The absorbance of the standard was measured at about 226nm.

Procedure
Accurately weighed preparations equivalent to 10 mg of Glimepiride were added to 900 ml of dissolution media (1.2 HCL buffer) in a USP dissolution apparatus II (Paddle type) and stirred at a speed of 50 rpm at 37±0.5°C.After 5min transferred into phosphate 6.8 buffer and samples were withdrawn at 10, 20, 30 minutes and replaced by 5 ml of fresh dissolution media (37°C). The collected samples were analyzed after suitable dilution at 226 nm using UV-visible spectrophotometer against the blank.[26]

Separation time analysis
All the formulations was taken separately into 500ml beaker containing water and time was noted for separation of Glimepiride layer from polymer layer in sandwiched osmotic pump tablets.

Swelling index
The initial weight of the tablets W1 were noted and placed individually into petridish containing 10ml of PH 6.8 buffer. The weight of the tablets W2 was noted after every 2hr for 8hr after wiping out the excess of water using filter paper.[27]
The swelling index was calculated by using the formula.
Swelling index=W2 – W1/W1 X100
Where
W1-Initial weight
W2-Final weight

Osmotic pressure study
Procedure: Fiske model 210 Micro –Osmometer used[26]
1. A sample of the dissolution fluid to be tested was drawn into the 20µl pipette.
2. The pipette tip was inserted into the bottom of a sample tube smoothly, and the sample was ejected without splashing or spraying it.
3. The sample was visually inspected. If there are any voids or bubbles in the sample, the sampling procedure was repeated to ensure a bubble-free sample.
4. The loaded sample tube was gently placed into the sample well.
5. The measuring head was fully lowered into the sample tube.
6. The test was initiated by pressing the [TEST] button as indicated on the user interface.

Kinetics Analysis
The results of in vitro release profile obtained for all the formulations were plotted in modes of data treatment as follows.
1. Zero - order kinetic model - Cumulative % drug released versus time.
2. First – order kinetic model - Log cumulative percent drug remaining versus time.
3. Higuchi‟s model - Cumulative percent drug released versus square root of time.
4. Korsmeyer equation / Peppa‟s model - Log cumulative percent drug released versus log time.[25,27]

EVALUATION OF OPTIMIZED FORMULATION
The optimized formulation were selected on the comparison of all formulation with *I*nvitro kinetics release of drug. The optimized formulation were evaluated for all physical parameters are weight variation, thicknesss, hardness, friability, drug content as per I.P specifications.

Effect of agitational rates on drug release
In order to study the effect of agitation intensity, release studies was performed for optimized formulations in dissolution apparatus at various rotational speed of 50, 100, and 150 RPM and the Invitro release studies of the tablets were conducted.

Effect of Osmogen concentration on drug release
Optimized formulation were subjected to release studies in dissolution media containing NaCl of various strength of buffer solution normal buffer, 8.5g, 15,20,25] to confirm the release mechanism by osmosis. Release studies were performed in 1000 ml of osmotically active medium using USP-II dissolution apparatus at 100

rpm.[28] The release was studied at predetermined time interval.

Effect of pH on drug release

To study the effect of pH of release medium in the drug release of optimized formulation, the *In-vitro* release study was carried out in different pH of buffer solution of pH 6.8 phosphate buffer, pH 1.2 phosphate buffer, and pH 4 phosphate buffer in USP type II dissolution apparatus. The release was studied at predetermined time intervals.[27,28]

STABILITY STUDIES

Procedure

In the present study, stability studies were carried out at 40ºC ± 75ºC for a specific time period up to 30 days for formulation F10. For stability study, the tablets were placed in an ambered coloured vials and sealed with aluminium foil, sample containers were placed in desiccators and evaluated for physiochemical parameter, drug content and drug release study.[29]

RESULTS AND DISCUSSION

Standard calibration curve of Metformin HCL and Glimepride

Standard curve for Metformin HCL and Glimepiride was performed and mentioned in the table.

Table 6: Standard calibration curve for Metformin HCL.

S.NO	Concentration[µg/ml]	Absorbance[nm]
1	10	1.102
2	20	2.280
3	30	3.215
4	40	4.541
5	50	5.710

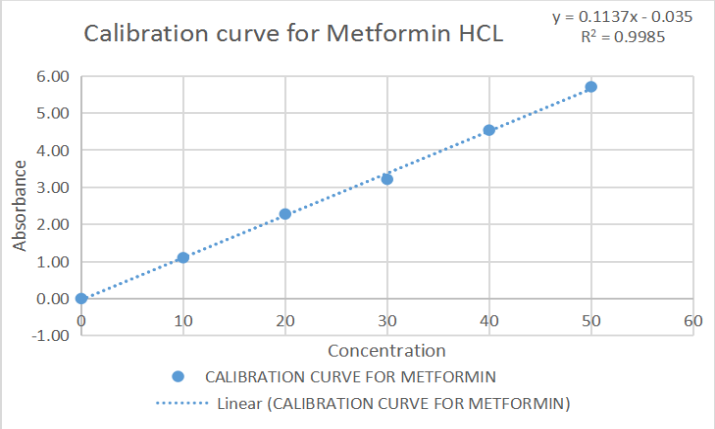

Fig. 2: Calibration curve for Metformin HCL.

The calibration curve was plotted by using water as a solvent. 20mg of the metformin HCL was weighed and diluted with water in a 10ml volumetric flask. From this stock solution 0.01mlwas taken and diluted into10ml. From the above solution, a range of concentration 10 to 50 µg/ml were prepared and the absorbance was measured at 232nm against a blank using a UV spectrophotometer. The calibration curve was shown in figure.2 and regression value $R^2 = 0.9985$.

Table 7: Standard calibration curve for Glimepiride.

S.NO	Concentration[µg/ml]	Absorbance[nm]
1	5	0.085
2	10	0.178
3	15	0.258
4	20	0.351
5	25	0.430

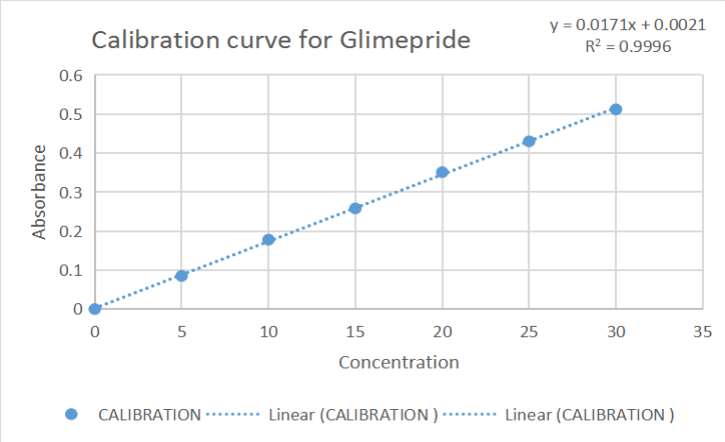

Fig. 3: Calibration curve for Glimepiride.

The calibration curve was plotted by using choloform as a solvent. 20mg of the Glimepiride was weighed and diluted with choloform in a 10ml volumetric flask. From this stock solution 0.01mlwas taken and diluted into10ml. From the above solution, a range of concentration 5 to 30 µg/ml were prepared and the absorbance was measured at 226nm against a blank using a UV spectrophotometer. The calibration curve was shown in figure.3 and regression value $R^2 = 0.9996$. Hence Metformin HCL and Glimepiride obeys Beers Lambert's Law.

Solubility analysis

The solubility study for Metformin HCL and Glimepiride were performed by using various solvents and measured. Thus the results shown in tabular column[8 & 9].

Metformin HCL was freely soluble in water.

Table 8: Metformin HCL.

Solvent	Saturation solubility (µg/mL)
SGF pH 1.2	256
SIF pH 6.8	282
SIF pH 7.4	156

Table 9: Glimepiride.

Solvents	Solubility (mg/mL)
Methanol	3.0±0.15
Ethanol	3.0±0.15
Dimethylformamide (DMF)	57.0±2.85
Ethyl Acetate	1.0±0.05
Dichloromethane (DCM)	5.0±0.25

Differential scanning colorimentry analysis

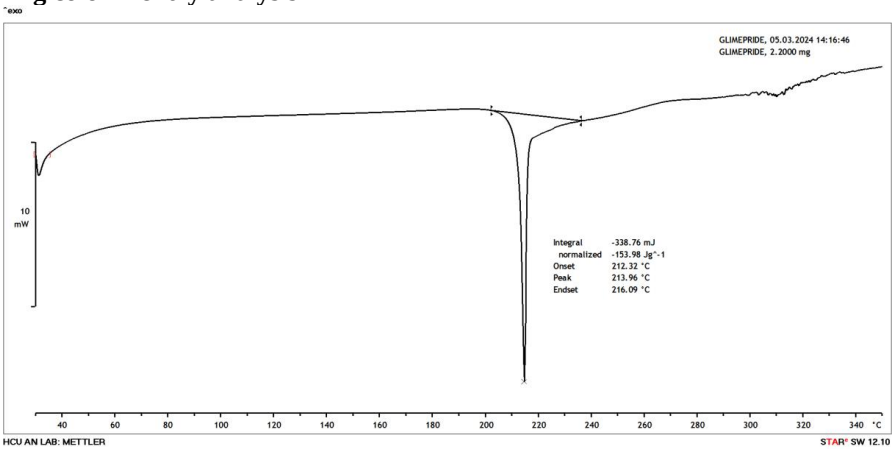

Fig . 4: Glimepiride.

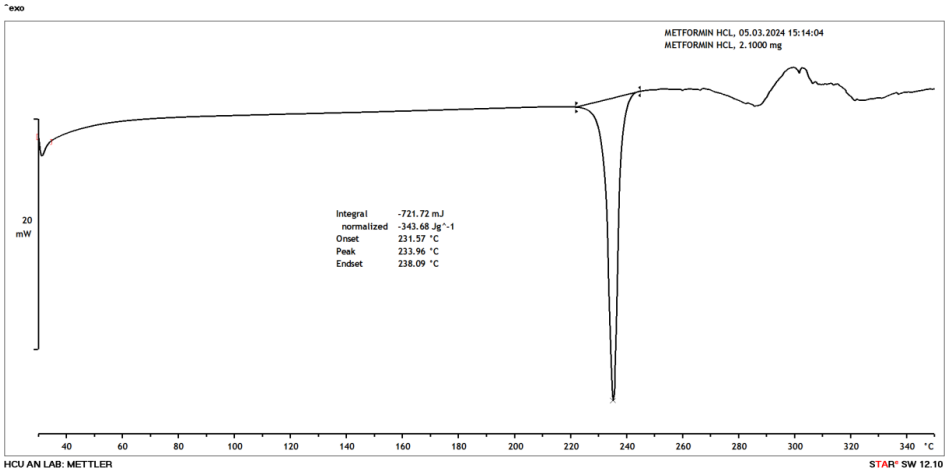

Fig. 5: Metformin HCL.

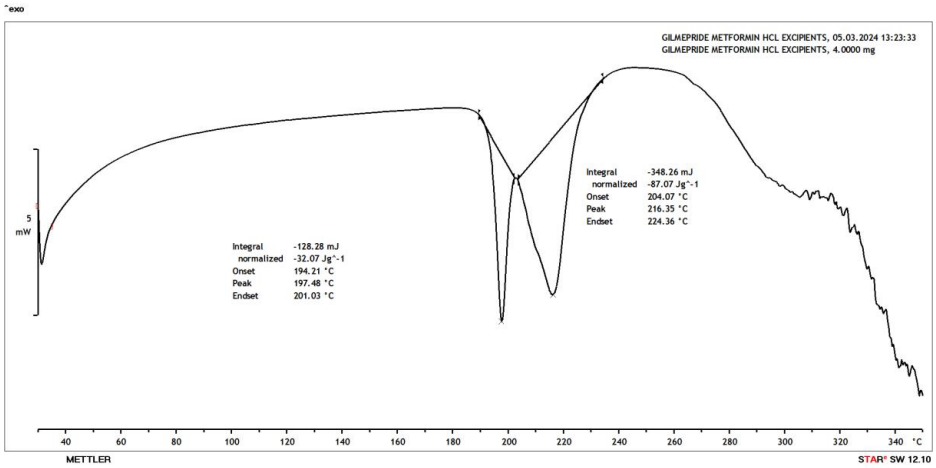

Fig. 6: Metformin HCL and Glimepiride with excipient.

The comparative study of graph were obtained for pure drug of Glimepiride and Metformin HCL and combination drug with excipients was shown in the figure [4 to 6] respectively. Pure metformin hydrochloride exhibited characteristic endothermic peak at 213.96ºC, pure Glimepiride exhibited characteristic endothermic peak at 233.9ºC and combination drug with excipients exhibited characteristic endothermic peak at 197.48, 216.35. This proves the fact that there is no potential incompatibility of the drug with the polymers used in the formulations.

Preformulation study

Micromertics analysis

The tablets of different formulations were subjected to preformulation studies such as angle of repose, bulk density, tapped density, hausner's ratio, carr's index as per IP. The results are shown in the table no:7 and 8.

1. Angle of repose: The angle of repose for the blended powders was shown in the table 7&8. The angle of repose was found to be in the range of Metformin HCL 26.13 to 31.59, Glimepiride 24.87 to 27.52 with good flow property.

2. Bulk density and Tapped density: The bulk density and tapped density values are shown in the table 7&8. The value was found to be in the range of bulk density- Metformin HCL 0.541 to 0.568, Glimepiride 0.449 to0.465, Tapped density- Metformin HCL 0.643 to 0.670, Glimepiride 0.513 to 0.530.

3. Compressibility index: The compressibility index values are measured from the bulk density and tapped density. The values was shown in the table 7&8 and found to be in the range of Metformin HCL 13.44 to 15.61, Glimepiride 9.81 to 14.97.

4. Hausner's ratio: The hausners ratio values are measured by the ratio of tapped density to the bulk density. The value was found to be in the range of Metformin HCL 1.13 to 1.19, Glimepiride 1.12 to 1.20.

Table 10: Metformin HCL Micromeritics results.

Formulation code	Angle of repose [degree]	Bulk density[gm/ml]	Tapped density[gm/ml]	Hausner's ratio[%]	Carr's index[%]
F1	31.59	0.58	0.662	1.16	13.77
F2	30.8	0.557	0.659	1.19	15.52
F3	31.71	0.57	0.643	1.13	15.61
F4	29.54	0.568	0.663	1.18	14.21
F5	27.82	0.545	0.661	1.17	13.75
F6	28.15	0.55	0.673	1.15	13.44
F7	29.11	0.58	0.658	1.15	13.76
F8	30.8	0.547	0.659	1.16	14.22
F9	26.82	0.543	0.661	1.14	13.70
F10	28.13	0.541	0.670	1.19	13.43

Table 11: Glimepiride Micromeritics results.

Formulation code	Angle of repose [degree]	Bulk density[gm/ml]	Tapped density[gm/ml]	Hausner's ratio[%]	Carr's index[%]
F1	25.78	0.453	0.524	1.16	13.17
F2	25.20	0.449	0.515	1.15	12.6
F3	24.96	0.450	0.540	1.20	15.97
F4	25.67	0.465	0.519	1.19	9.81
F5	27.46	0.452	0.522	1.14	12.74
F6	26.52	0.457	0.513	1.12	13.10
F7	25.34	0.438	0.517	1.15	11.07
F8	24.87	0.457	0.515	1.19	12.5
F9	25.72	0.459	0.529	1.17	13.15
F10	25.92	0.462	0.530	1.18	14.97

Evaluation

All the formulations are evaluated for weight variation, thickness, hardness, friability, drug content as per IP specifications and further processed.

Table 12: physical parameters.

Formulation code	Weight variation [mg]	Thickness[mm]	Hardness[kg/cm^{2}]	Friability [%]
F1	1058.5	6.8	11.1	0.47
F2	1060.2	6.83	11.7	0.46
F3	1057.2	6.95	12.3	0.51
F4	1061.5	6.89	11.9	0.49
F5	1055.2	6.92	12.2	0.51
F6	1059.2	6.9	13	0.47
F7	1056.1	6.80	11.5	0.45
F8	1049.3	6.95	12	0.48
F9	1050.2	6.89	13.4	0.53
F10	1057.8	6.93	12.6	0.47

Table 13: percentage of drug content.

Formulation code	Metformin HCL [%]	Glimepiride[%]
F1	96.24	94
F2	95	91.34
F3	96.78	96
F4	98.13	97.07
F5	96	95.23

F6	97.45	95
F7	95.3	92.15
F8	93	96
F9	98.67	99.21
F10	99.53	100.28

Invitro drug release analysis

The percentage of Invitro drug release for both Glimepiride and Metformin HCL from formulations F1 to F10 were carried out using various polymer of HPMC K4M, HPMC K15M, HPMC K100M premium in Metformin layer and various disintegrant of crospovidoneXL10, Croscarmellose sodium, sodium starch glycolate in Glimepiride layer. Among these formulations, the release rate was decreased in the following polymer order: HPMC K4M < K15M < K100M. It was varied in percentage ranged from 83 to 98% within 30mins for immediate release of Glimepiride and from 88 to 99% over 12 hr for control release of Metforrmin HCL.

Formulation 1.

Formulation F1 has shown that drug release 83% upto 3hrs of Metformin HCL due to concentration of HPMC K4M[78mg] and 81% of Glimepiride due to concentration of crospovidoneXL10[3.6mg].

Table 14: *Invitro* release of Metformin HCL with Glimepiride from F1.

% Drug release			
hours	**Metformin HCL**	**Mins**	**Glimepiride**
1	60	5	29
3	83	10	53
6	-	20	69
10	-	30	81
12	-		

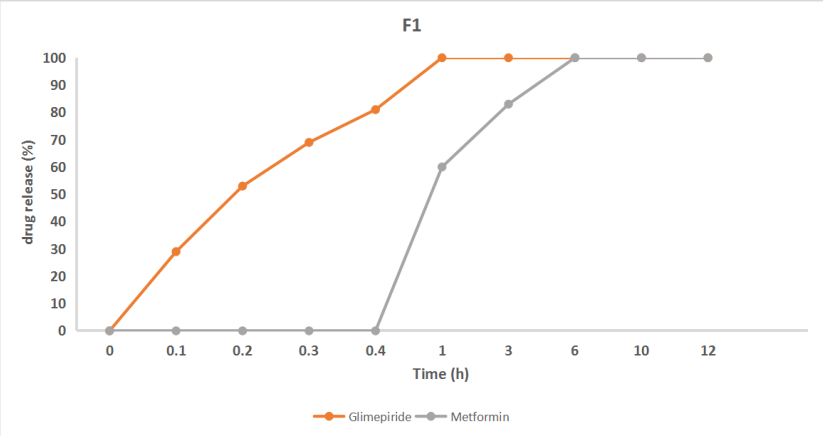

Fig 7: *Invitro* release of Metformin HCL with Glimepiride F1.

Formulation 2

Formulation F2 has shown that drug release 89% upto 6hrs of Metformin HCL due to concentration of HPMC K4M[117mg] and 83% of Glimepride due to concentration of crospovidoneXL10[4.8mg].

Table 15: *Invitro* release of Metformin HCL with Glimepiride from F2.

% Drug release			
Hours	**Metformin HCL**	**mins**	**Glimepiride**
1	45	5	38
3	57	10	57
6	89	20	71
10	-	30	83
12	-		

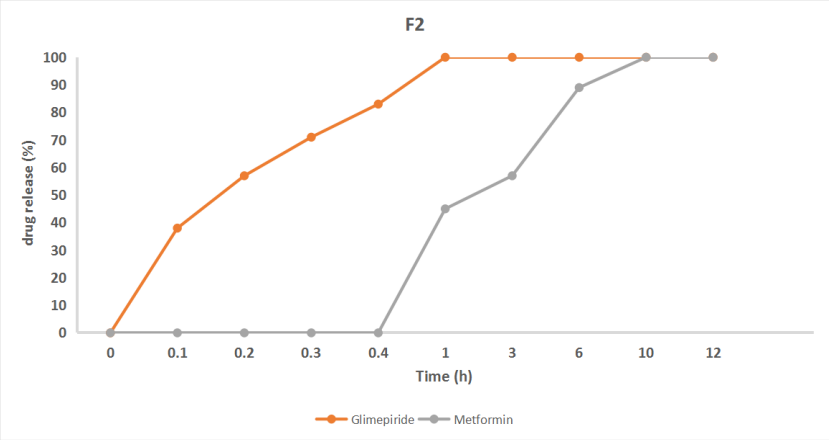

Fig 8: *Invitro* release of Metformin HCL with Glimepiride F2.

Formulation 3

Formulation F3 has shown that drug release 90% upto 10hrs of Metformin HCL due to concentration of HPMC K4M[156mg] and 85% of Glimepiride due to concentration of crospovidoneXL10[6mg].

Table 16: *Invitro* release of Metformin HCL with Glimepiride from F3.

% Drug release			
Hours	**Metformin HCL**	**mins**	**Glimepiride**
1	38	5	34
3	57	10	59
6	73	20	70
10	90	30	85
12	-		

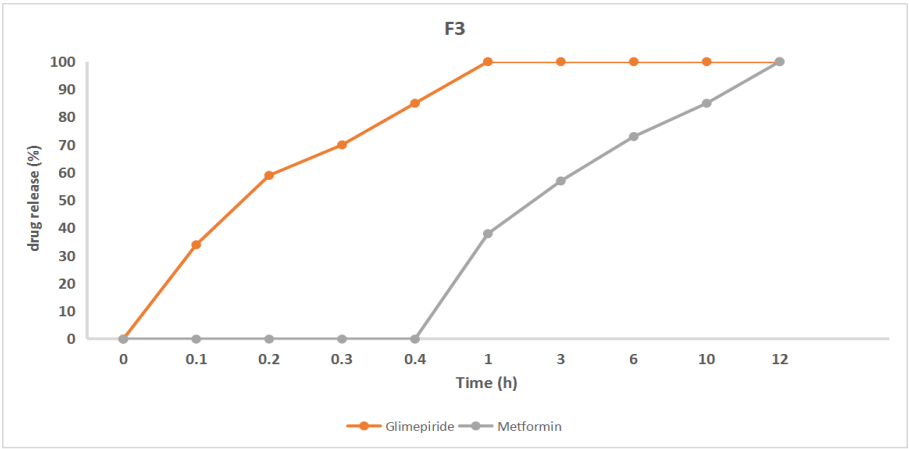

Fig 9: *Invitro* release of Metformin HCL with Glimepiride F3.

Formulation 4

Formulation F4 has shown that drug release 88% upto 3hrs of Metformin HCL due to concentration of HPMC K15M[78mg] and 83% of Glimepiride due to concentration of croscarmellose sodium[3.6mg].

Table 17: *Invitro* release of Metformin HCL with Glimepiride from F4.

%Drug release			
Hours	**Metformin HCL**	**mins**	**Glimepiride**
1	61	5	30
3	88	10	62
6	-	20	75
10	-	30	83
12	-		

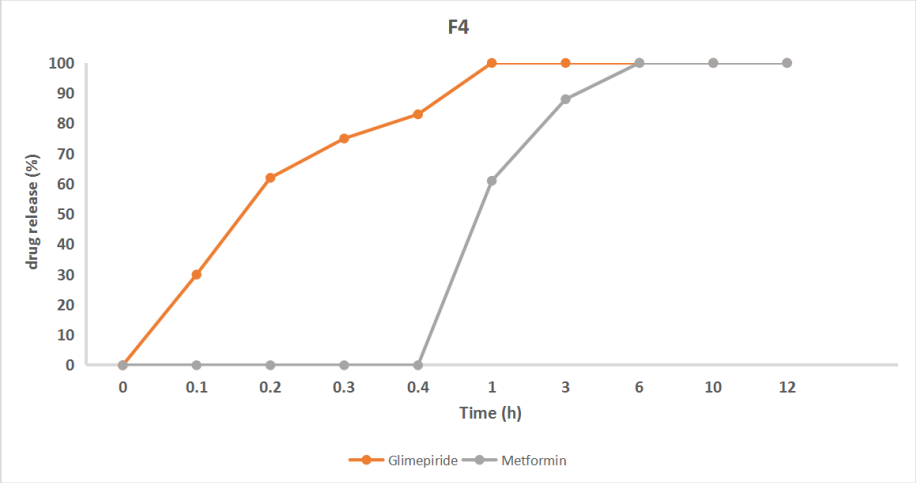

Fig 10: *Invitro* release of Metformin HCL with Glimepiride F4.

Formulation 5

Formulation F5 has shown that drug release 101% upto 6hrs of Metformin HCL due to concentration of HPMC K15M[117mg] and 87% of Glimepiride due to concentration of croscarmellose sodium[4.8mg].

Table 18: *Invitro* release of Metformin HCL with Glimepiride from F5.

%Drug release			
Hours	**Metformin HCL**	**Mins**	**Glimepiride**
1	**48**	**5**	**33**
3	**73.4**	**10**	**64**
6	**101**	**20**	**74**
10	**-**	**30**	**87**
12	**-**		

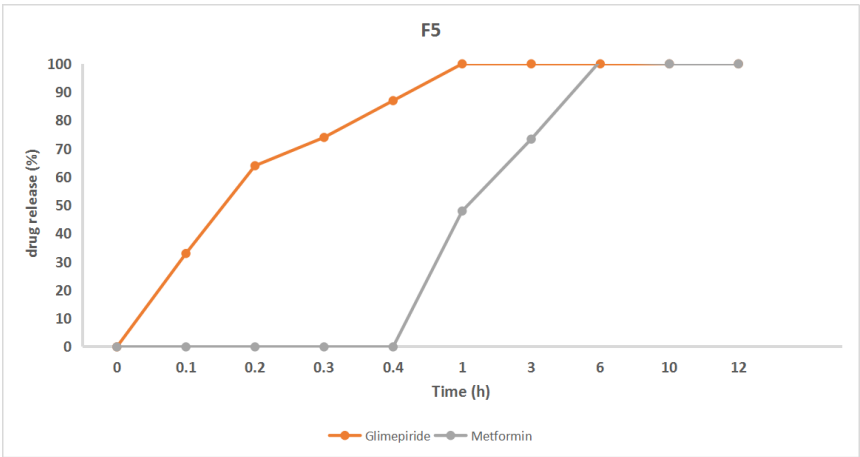

Fig 11: *Invitro* release of Metformin HCL with Glimepiride F5.

Formulation 6

Formulation F6 has shown that drug release 91% upto 12hrs of Metformin HCL due to concentration of HPMC K15M[156mg] and 83% of Glimepiride due to concentration of croscarmellose sodium[6mg].

Table 19: *Invitro* release of Metformin HCL with Glimepiride from F6.

%Drug release			
Hours	**Metformin HCL**	**Mins**	**Glimepiride**
1	31	5	38
3	47	10	69
6	59	20	77
10	73	30	91
12	91		

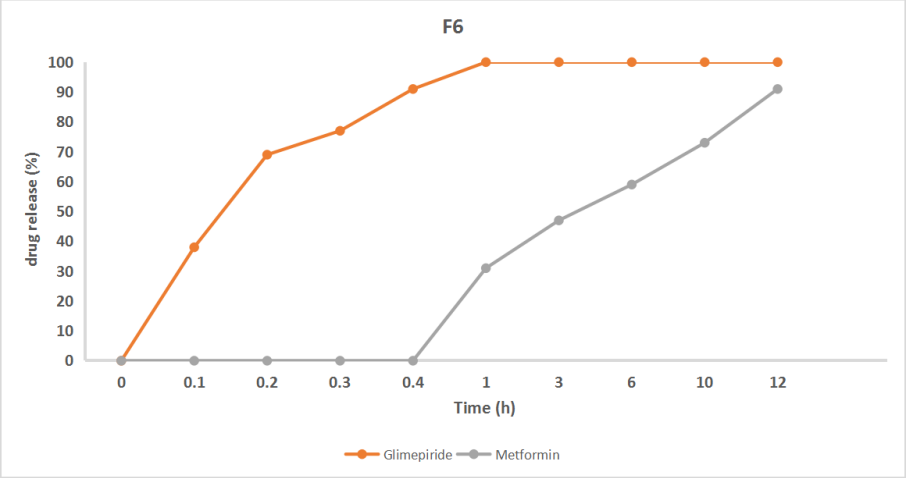

Fig 12: *Invitro* release of Metformin HCL with Glimepiride F6.

Formulation 7

Formulation F7 has shown that drug release 88% upto 3hrs of Metformin HCL due to concentration of HPMC K100M premium [78mg] and 86% of Glimepiride due to concentration of sodium starch glycolate[3.6mg].

Table 20: *Invitro* release of Metformin HCL with Glimepiride from F7.

% Drug release			
Hours	**Metformin HCL**	**Mins**	**Glimepiride**
1	56	5	28
3	88	10	59
6	-	20	73
10	-	30	86
12	-		

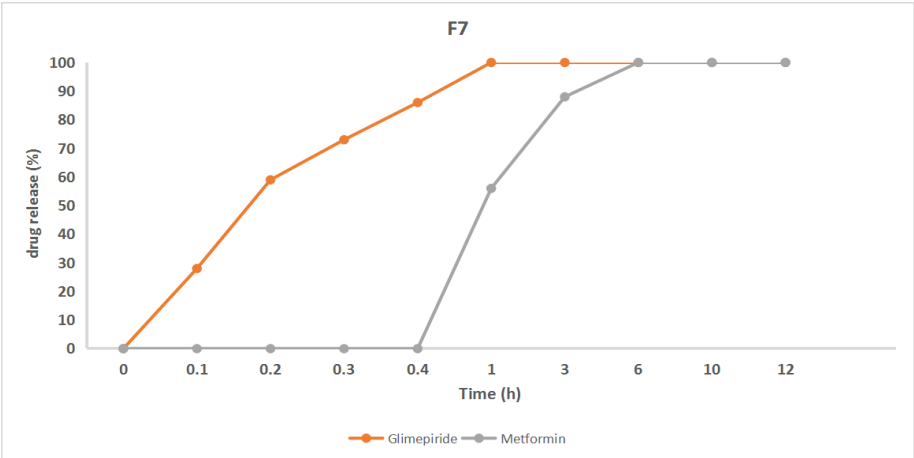

Fig .13: *Invitro* release of Metformin HCL with Glimepiride F7.

Formulation 8

Formulation F8 has shown that drug release 96.7% upto 6hrs of Metformin HCL due to concentration of HPMC K100M Premium[117mg] and 92% of Glimepiride due to concentration of sodium starch glycolate[4.8mg].

Table 21: *Invitro* release of Metformin HCL with Glimepiride from F8.

%Drug release			
Hours	**Metformin HCL**	**Mins**	**Glimepiride**
1	47.6	5	31
3	75	10	67
6	96.7	20	82
10	-	30	92
12	-		

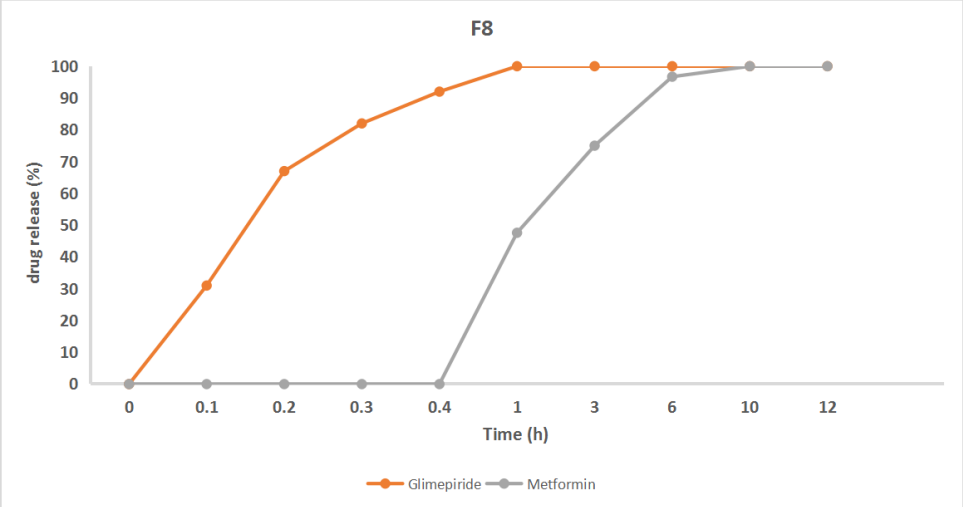

Fig. 14: *Invitro* release of Metformin HCL with Glimepiride F8.

Formulation 9

Formulation F9 has shown that drug release 93.5% upto 12hrs but it was released above the time limit of Metformin HCL due to concentration of HPMC K100M Premium[156mg] and 98% of Glimepiride due to concentration of sodium starch glycolate[6mg] and it was satisfactory release of Glimepiride.

Table 22: *Invitro* release of Metformin HCL with Glimepiride from F9.

%Drug release			
hours	**Metformin HCL**	**Mins**	**Glimepiride**
1	40	5	33
3	65	10	71
6	71	20	86
10	82	30	98
12	93.5		

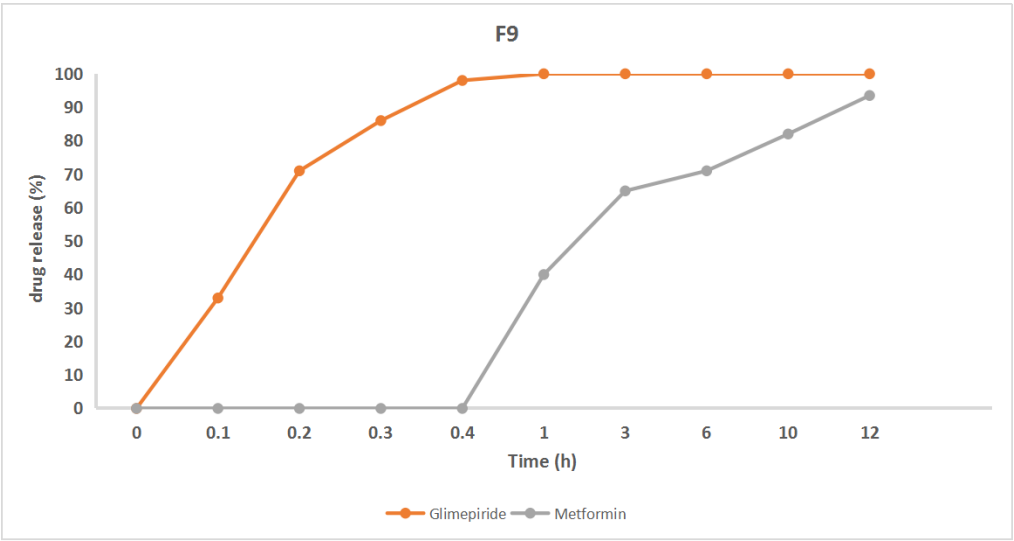

Fig.15 *Invitro* release of Metformin HCL with Glimepiride F9.

Formulation 10

Formulation F10 has shown that satisfactory drug release 99% over 12hrs of Metformin HCL due to reduce concentration of HPMC K100M Premium[136mg] from F9 formulation and 98% of Glimepiride due to same concentration of F9 sodium starch glycolate[6mg]. F10 formulation has showed an optimal formulation due to its closest profile to the target in terms of marketed release formulation. Formulation F10 shows immediate release of Glimepiride followed by controlled release of Metformin HCL with good stability.

Table 23: *Invitro* release of Metformin HCL with Glimepiride from F10.

%Drug release			
hours	**Metformin HCL**	**Mins**	**Glimepiride**
1	9.0	5	33
3	25.20	10	71
6	51	20	86
10	86.0	30	98
12	99		

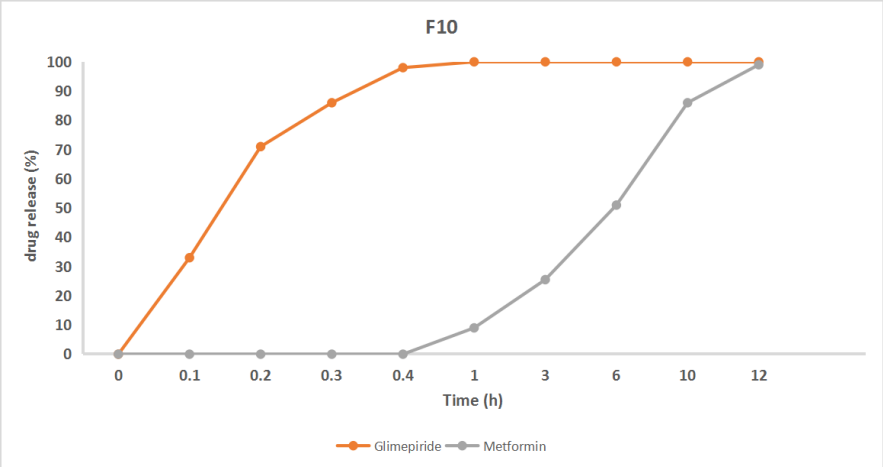

Fig.16: *Invitro* release of Metformin HCL with Glimepiride F10.

Separation time

The separation time for all formulation of glimepiride layer from polymer layer were mentioned in table 24.

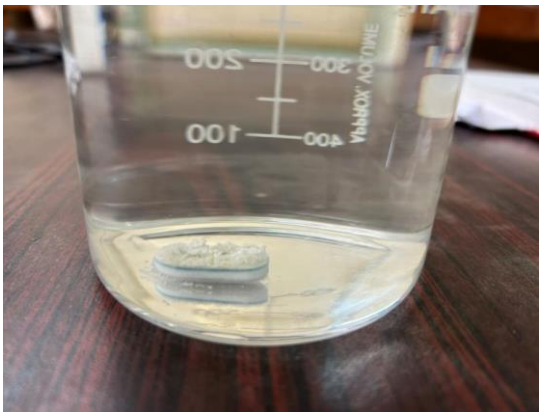

Fig.17: Separation layer of Glimepiride.

Table 24: Separation time for formulations.

Formulation code	Separation time[min]
F1	7
F2	9
F3	10
F4	9
F5	12
F6	11
F7	10
F8	12
F9	13
F10	13

Swelling index study

All the formulations swelling studies were carried out for 8hrs. The swelling index ranged between 124 to 161. Thus the formulations F 10 exhibited acceptable value [153] compared to others.

Table 25: swelling index.

Formulation code	Swelling index
F1	129
F2	125
F3	151
F4	127
F5	132
F6	154
F7	129
F8	139
F9	161
F10	153

Osmotic pressure analysis

All the formulations were studied for osmotic pressure, hence the formulation F10 containing lactose monohydrate as a osmogen in the tablet with acceptable concentration[90mg] and they formed micro cavities in the semi permeable membrane has come out successfully to comply with the controlled release formulation. The osmotic pressure exerted by the osmogen in the core tablet and the amount of solutes in the semipermeable membrane speed up the drug release. Thus the results were mentioned in the table 26.

Table 26: Osmotic pressure result.

Formulation code	Osmolarity [mOsm/L]
F1	487
F2	454
F3	359
F4	472
F5	443
F6	343
F7	473
F8	469
F9	349
F10	372

Kinetics release analysis

The drug release values of the optimized formulation was applied to various dissolution models (zero order, first order, Higuchi model, Korsmeyer- peppas model) to study the kinetics of drug release and compared with marketed product to find best fit model. The correlation coefficient value were obtained for higuchi's model(0.9144), zero order kinetics [0.9991] and korsmeyer-peppa's model[0.9970] for optimized formulation F10. The F10 'n' value of 0.5703 peppa's model followed non fickian diffusion controlled release. Thus the result shows that optimized formulation 10 followed zero order release kinetics, higuchi' model, korsmeyar- peppa's model and found to be better.

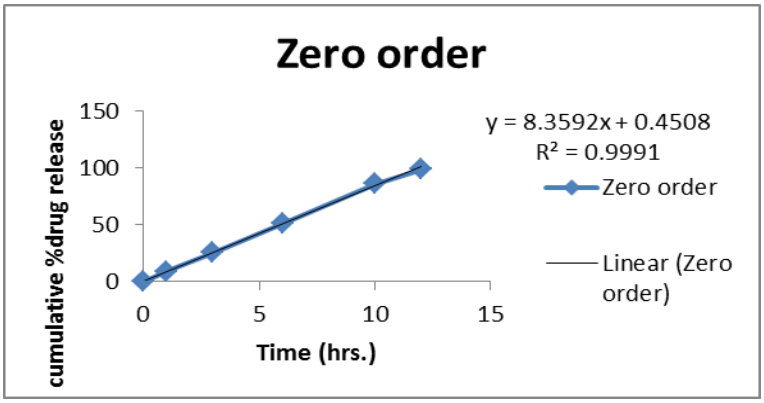

Fig .18: Zero order model.

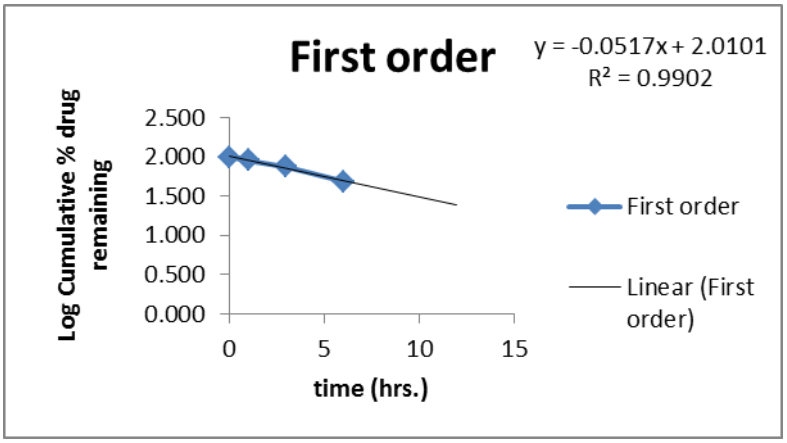

Fig .19: First order model.

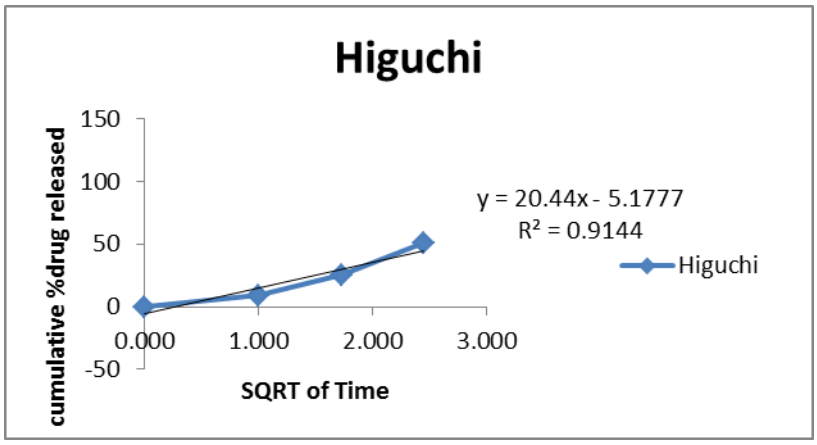

Fig .20: Higuchi model.

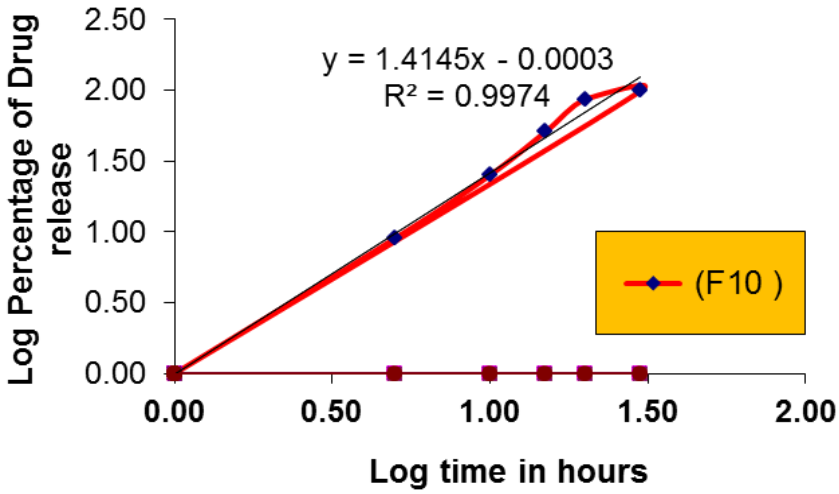

Fig.21: kors peppas model.

Optimized Formulation

Comparison of marketed product and optimized formulation

All the formulations were studied for Invitro drug release kinetics analysis. The formulation F10 was considered as optimized formulation based on that comparison of all formulation with marketed product.

Table 27: comparison of marketed vs optimized formulation.

Time [h]	Marketed product %	Optimized formulation %
1	9.60	9.0
3	25.96	25.20
6	51.83	51.00
10	87.00	86.23
12	97.00	99.00

F2 :Similarity Factor [limit : 50-100]	95
F1 :Dissimilarity Factor [limit:0-15]	2

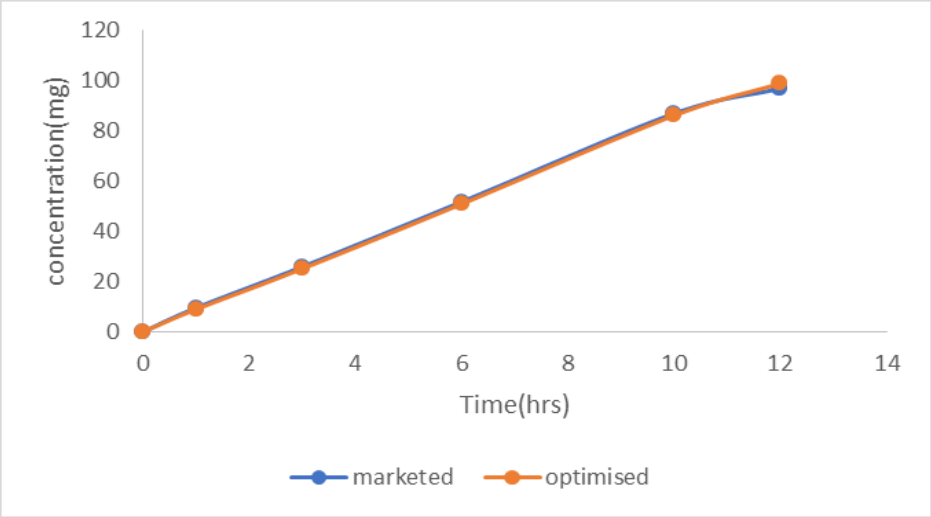

Fig. 22: comparison of optimized formulation vs marketed product.

Evaluation of optimized formulation

Table 28: physical parameters.

S.NO	Optimized formulation
Weight variation [mg]	1057.8
Thickness[mm]	6.93
Hardness[kg/cm^2]	12
Friability%	0.47
Drug content	
Metformin HCL	99.53%
Glimepiride	100.28%

Table 29: Effect of pH on drug release results.

Time[hrs]	Cumulative % drug release		
	0.1NHCL buffer 1.2	HCL buffer 4	Phosphate buffer6.8
1	15	16	19
3	32	31.2	34
6	63.2	60	67
10	86	83.1	86
12	94	95	98.7

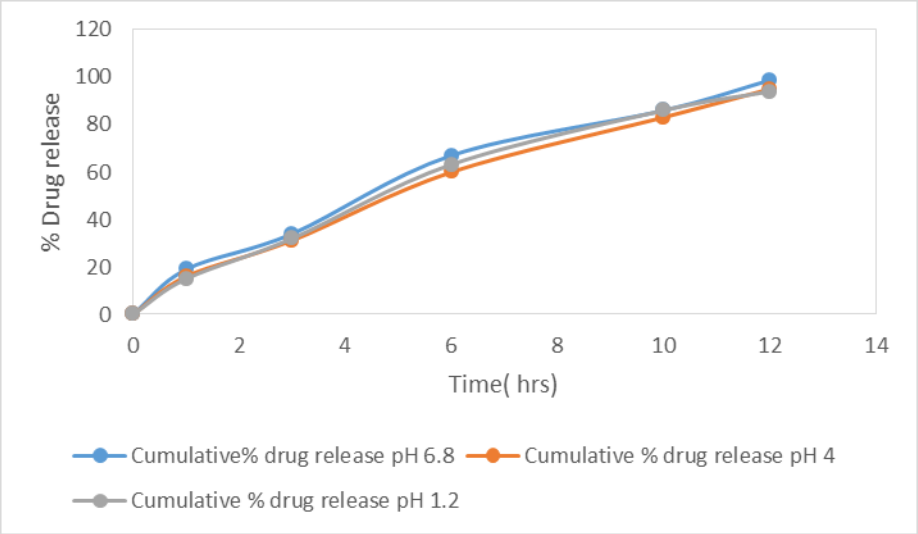

Fig. 23: Effect of pH.

The amount of drug released was not greatly influenced by effect of pH and it was pH independent on drug release of optimized formulation F10. The percentage drug release of various pH1.2 -94%, pH4-95%, pH6.8 - 98.7%. The graph were shown in the Figure23.

Table 30: Effect of agitation rates on drug release results.

Time[hrs]	Cumulative % drug release		
	50 RPM	100 Rpm	150 Rpm
1	27	29.2	26
3	40.1	43	42
6	55	57	54.8
10	89.3	91.5	90
12	96	99	95

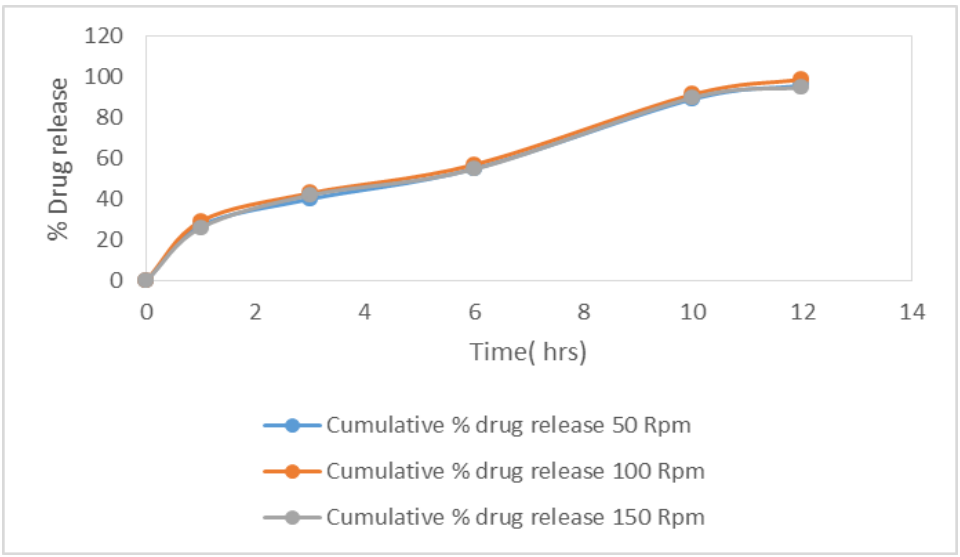

Fig. 24: Effect of Rpm.

It was not greatly influenced by rotational speed. The release profile of Metformin HCL from the optimized F10 was fairly independent of the agitational intensity 50, 100, and 150 rpm of the release media, and hence, it can be concluded that the release was independent of the hydrodynamic conditions of the body. The graph were mentioned in the Figure 24.

Table 31: Effect of Osmotic pressure on drug release.

Time [hrs]	Cumulative % drug release				
	Normal buffer solution I	Buffer solution II[8.5g NaCl]	Buffer solutionIII [15g NaCl]	Buffer solution IV [20gNaCl]	Buffer solution V[25g NaCl]
1	33	31	29	29.3	27
3	56.1	53.4	52	50	50.7
6	75	70	68.4	65.4	65
10	87.3	82	80.1	78	72
12	99	93	89	86	83.3

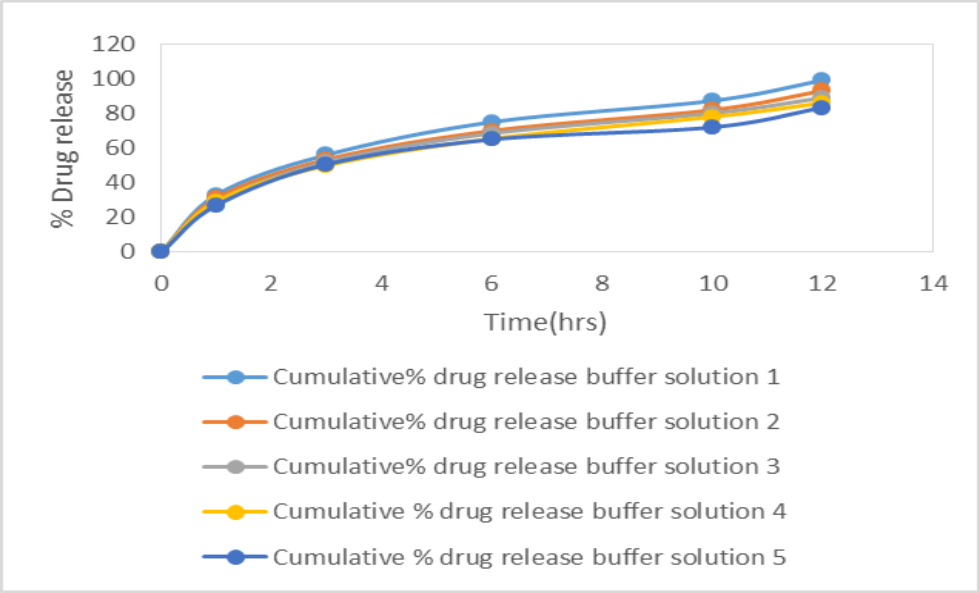

Fig 25: Effect of Osmotic pressure.

Metformin HCL release from the formulation decreased as the osmotic pressure of the media increased was shown in Figure 25. hence the delivery system is dependent on osmotic pressure. The drug release from the optimized formulation was increased as osmotic pressure of the media decreased.

Stability Study

The stability study of the formulation F10 were placed in an ambered coloured vials and sealed with aluminium foil, and sample containers were placed in stability chamber at 40ºC/75% RH for one month. The sample were collected after one month and were evaluated for drug content, physicochemical parameters, *Invitro* drug release.

Table 33: physicochemical data.

Physicochemical paramaters	1st month
	40ºC
Colour	No characteristics change
Thickness	
Hardness	
Friability	

Table 34: Percentage of drug content and drug release.

Month	Drug	% drug content	% drug release
		40ºC	40ºC
1 month	Metformin HCL	99.87	98.24
	Glimepiride	100.7	99.60

CONCLUSION

Sandwiched osmotic pump tablet of Metformin HCL and Glimepiride was successfully developed using wet granulation method with combination of hydrophilic polymer, superdisintegrant, and osmogen. The optimized formulation F10 were satisfactory in terms of physical

parameters [hardness, weight variation, thickness, friability, drug content, swelling index, and Invitro drug release]. The hydrophilic polymer HPMC K100M controlled the release of Metformin HCL over 12 hrs with 98% and immediate release of Glimepiride upto 30 mins with 99% in formulation F10 and it is considered as optimized formulation based on *Invitro* drug kinetics release profile. The optimized formulation F10 follows zero order kinetics, first order kinetics and korsmeyer peppa's model with diffusion controlled release. The drug release from the optimized formulation was increased as osmotic pressure of the media decreased and pH independent. The optimized formulationF10 were stable after one month with physicochemical parameters, drug content, and Invitro drug release.

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