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Studies on Formulation and Evaluation of Inlay Tablet for Delivery of an Antidiabetic Drug

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ABSTRACT:
The main objective of the present research work was to develop a inlay tablet containing immediate release core tablet of Glyburide and sustained release cup portion of Metformin Hydrochloride, which is used as an Anti-hyperglycemic agent. Metformin Hydrochloride has biological half-life nearly about 6 hours, so an attempt was made in the direction of preparation and optimization of a combination of sustained release and immediate release in a single tablet. Hydroxy propyl methyl cellulose K100 and Hydroxy propyl methyl cellulose K4M were used as retarding materials and in immediate release sodium starch glycolate, cross carmellose sodium and crospovidone was used as a super disintegrants to give the faster release of Glyburide. Final formulation showed release of drug up to 95.75% in 8 hours. The formulation IT3 was prepared based on optimization and stability study showed no significant changes when stored at 40^{o}C/75%RH for three months according to ICH guidelines. FTIR and DSC studies revealed that there was no interaction between the drugs and polymers. In this study optimized formulation IT3 released the drug till 8 hours.

Keywords: Hyperglycemia, inlay tablet, Glyburide, metformin hydrochloride, immediate release, sustained release, wet granulation.

Introduction:

Amongst the various routes of drug delivery, Oral drug delivery has been known for decades as the most widely utilized route of administration among all the routes that have been explode for systematic delivery of drug via various pharmaceutical products of different dosage form. Oral route is the most convenient and usually the safest and least expensive, it is the one most often used.[1] Popularity of oral route may be ease of administration as well as traditional belief that by oral administration the drug is well adsorbed as food stuff ingested daily. [2] Inlay tablet is a type of layered tablet in which instead the core tablet being completely surrounded by coating, top surface is completely exposed. Tablet compressing was done with core rod tooling in which only one surface of core is expose to outside and other drug is incorporated in cup portion. While preparation, only the bottom of the die cavity is filled with coating material and core is placed upon it. The main body portion may consist of an uncoated granulation which is compressed around the enteric coated inlay portion In this modification the main body portion of the tablet is first released and assimilated in the gastrointestinal tract while the enteric coating protects the inlay portion for a predetermined period of time so as to provide time delayed or sustained medication.[4] Some advantages of inlay tablet is Dosage form comprising of an active ingredient as modified release and an active

ingredient as immediate release can be prepared. Plasma level can be maintained constant and within the therapeutic window throughout the period of treatment and Dosage frequency of highly water soluble drugs con be reduced providing same efficacy.[5] Recently immediate release tablets have started gaining popularity and acceptance as a drug delivery system, mainly because they are easy to administer, has quick onset of action is economical and lead to better patient compliance. They are also a tool for expanding markets, extending product life cycles and generating opportunities. [6] Diabetes mellitus (DM) is a metabolic disorder resulting from a defect in insulin secretion, insulin action, or both. Insulin deficiency in turn leads to chronic hyperglycaemia with disturbances of carbohydrate, fat and protein metabolism. The aim of present investigation was to prepare inlay tablet of Glibenclamide and Metformin Hydrochloride to ensure satisfactory drug release with the use of blends of release polymers, filler, diluent, Superdisintegrant and lubricants. Tablets prepared by wet granulation method.

Material and methods:

Glyburide, Metformin Hydrochloride, Microcrystalline cellulose, Lactose, Sodium Starch Glycolate Cross Carmellose sodium, Crospovidone, HPMC K4M and K100, Magnesium Stearate and Talc were received as gift sample from research laboratory, Mumbai India.

Table 1: Formulation of Immediate release core tablet of Glyburide

Ingredients	Batches								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Glyburide	5	5	5	5	5	5	5	5	5
Sodium Starch Glycolate	4	5	6	-	-	-	-	-	-
Cross Carmellose Sodium	-	-	-	4	5	6	-	-	-
Crospovidone	-	-	-	-	-	-	4	5	6
Lactose	55	54	53	55	54	53	55	54	53
Microcrystalline Cellulose	30	30	30	30	30	30	30	30	30
PVP K 30 Solution	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Magnesium Stearate	2	2	2	2	2	2	2	2	2
Talc	4	4	4	4	4	4	4	4	4
Total	100	100	100	100	100	100	100	100	100

Table 2: Formulation of sustained release outer cup portion of Metformin Hydrochloride

Ingredients	Batches								
	IT1	IT2	IT3	IT4	IT5	IT6	IT7	IT8	IT9
Metformin Hydrochloride	500	500	500	500	500	500	500	500	500
HPMC K4M	40	50	60	40	50	60	40	50	60
HPMC K100	40	40	40	50	50	50	60	60	60
Lactose	62	52	42	52	42	32	42	32	22
PVP K 30 solution	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Magnesium Stearate	5	5	5	5	5	5	5	5	5
Talc	3	3	3	3	3	3	3	3	3
Total	650	650	650	650	650	650	650	650	650

Pre-formulations studies:

Calibration curve of Glyburide

In 0.1N HCl: 100 mg of Glyburide was weighed accurately and transferred to 100 ml volumetric flask and drug was then dissolved and diluted up to the mark with 0.1 N Hydrochloric acid. This was the standard stock solution of Glyburide (100µg/ml). Appropriate quantities of aliquots (0.2 ml to 2 ml) of the standard solution were taken in 10ml volumetric flasks. These were then diluted with distilled water to make solutions of concentration of 2-20µg/ml and absorbance of solutions was recorded at λmax 300 nm.

Calibration curve of Metformin Hydrochloride

In 0.1N HCl: 100 mg of Metformin Hydrochloride was weighed accurately and transferred to 100 ml volumetric flask and drug was then dissolved and diluted up to the mark with 0.1 N Hydrochloric acid. This was the standard stock solution of Metformin hydrochloride (100µg/ml).

Appropriate quantities of aliquots (0.2 ml to 2 ml) of the standard solution were taken in 10ml volumetric flasks. These were then diluted with distilled water to make solutions of concentration of 2 to 20 µg/ml and absorbance of solutions was recorded at λmax 233 nm.

Solubility studies of Glyburide and Metformin Hydrochloride:

An excess amount of the drug was taken and dissolved in a measured volume of solvent in a glass vial to get a saturated solution. The solution was sonicated and kept at room temp for the attainment of equilibrium. The concentration of Glyburide and Metformin Hydrochloride of in the filtrate was determined spectrophotometrically by measuring at λmax 229 nm and 233 nm respectively.

Assay of Glyburide

Weigh accurately about 0.4 g and dissolve in 100 ml of ethanol (95 per cent) with the aid of heat; titrate with 0.1 M sodium hydroxide using 1 ml of dilute phenolphthalein solution as indicator until a red colour is obtained.

1 ml of 0.1 M sodium hydroxide is equivalent to 0.04940 g of Glyburide.

Assay of Metformin Hydrochloride

Weigh accurately about 60 mg, dissolve in 4 ml of anhydrous formic acid, add 50 ml of acetic anhydride. Titrate with 0.1 M perchloric acid, determining the end-point potentiometrically (2.4.25). Carry out a blank titration.

1 ml of 0.1 M perchloric acid is equivalent to 0.008281 g of Metformin Hydrochloride

FTIR Studies

The drug-polymer and polymer-polymer interactions were studied by FTIR spectrometer, Perkin-Elmer Japan. Two percent (w/w) of the sample, with respect to a potassium bromide (KBr; SD Fine Chem Ltd., Mumbai, India) disc, was mixed with dry KBr. The mixture was ground into a fine powder using an agate mortar and then compressed into a KBr discs in a hydraulic press at a pressure of 10000 psi. The characteristic peaks were recorded.

DSC studies

Differential Scanning Calorimetry was performed in order to characterize the physical state of drug and polymer. Thermogram was obtained using DSC. About 5mg of sample was weighed, crimped into an aluminium pan and analyzed at a scanning temperature range from 50ºC - 300ºC at the heating rate of 2ºC/min under nitrogen flow of 25ml/min.

Characterization of Inlay Tablet

Hardness

The hardness of the tablets was determined using Monsanto Hardness tester. It is expressed in Kg/cm^2. Three tablets were randomly picked from each formulation and the mean and standard deviation values were calculated.

Thickness

It was determined by weighing three film formulations individually on a digital balance (Shimadzu). The average value was taken as a weight of the films.

Weight variation

The tablets were selected randomly from each formulation and weighed individually to check for weight variation using digital balance. The U.S Pharmacopoeia allows a little variation in the weight of a tablet.

Friability

The friability of tablets was determined by using Roche Friabilator. It is expressed in percentage). Twenty tablets were initially weighed ($W_{initial}$) and transferred into friabilator. The friabilator was operated at 25 rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again (W_{final}). The percentage friability was then calculated.

Drug Content

The equivalent weight of 100mg Glyburide and metformin hydrochloride from the powdered tablet were dissolved in 100 ml of methanol and diluted with methanol to get 10.0 µg/ml (Theoretical weight) The content uniformity were determined by using UV-VIS spectrophotometer at λmax 300 nm and 233 nm for Glyburide and metformin hydrochloride respectively.

Swelling Index

Swelling study was performed for the floating sustained release layer tablets. The accurately weighed tablets were placed in USP dissolution apparatus II containing 900ml of 0.1 N HCl maintained at 37 ± 2^0C and allowed to swell up to constant weight. The tablets were removed, blotted with filter paper, and changes in weight were measured. The experiments were carried out in triplicate. The degree of swelling (Swelling index) was then calculated.

In vitro drug release studies

The dissolution test for the tablets was carried out by using USP apparatus II, 900ml of 0.1 N HCl and the paddle was rotated at 50 RPM for the first 2 hour. And then 0.1N HCl was replaced by phosphate buffer of pH 6.8 and the paddle was rotated continuously for upto 24 hours. Samples for immediate release layer were collected at the interval of 0, 30 and 60 min and for sustained release layer at the interval of 0, 1, 2, 4, 6 and 8 hours. The collected samples were analyzed at λmax 300 nm for Glyburide and λmax 233 nm for Metformin Hydrochloride by using UV spectrophotometer.

Stability study.

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors. The International Conference on Harmonization (ICH) Guidelines titled “Stability Testing of New Drug substance and Products” (QIA).

Table 3: Storage Conditions for different cases of Stability studies

Study	Storage conditions	Minimum time period covered by data at submission.
a. General Case		
Long term*	25ºC ± 2ºC/ 60% RH± 5% RH Or 30ºC ± 2ºC/ 65% RH± 5% RH	12 months
Intermediate**	30ºC ± 2ºC/ 65% RH± 5% RH	6 months
Accelerated	40ºC ± 2ºC/ 75% RH± 5% RH	6 months
b. Drug substances intended for storage in refrigerator		
Long term	5ºC ± 2ºC	12 months
Accelerated	25ºC ± 2ºC/60% RH± 5% RH	6 months
c. Drug substances intended to be stored in freezer		
Long term	-20ºC ± 5ºC	12 months

* It is up to the applicant to decide whether long-term stability sturdies are performed at 25°C ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH.

** If 30°C ± 2°C/65% RH ± 5% RH is the long-term condition, there is no intermediate condition.

Stability studies were carried out at 40ºC ± 2ºC and 75% RH ± 5% RH for the selected formulation for the period of 3 months. Formulation was evaluated for their physical appearance, drug content and *in vitro* dissolution time at specified intervals of time.

Result and Discussion

LOD

Table 4: Results for Loss on drying

Sr.no.	Drug	Specification	Observation
1.	Glyburide	Not more than 0.5 % w/w	0.37% w/w
2.	Metformin Hydrochloride	Not more than 0.5% w/w	0.25%w/w

Solubility studies

Table 5: Solubility studies of Pure drugs in various solvents

Sr.no.	Solvents used	Glyburide	Metformin Hydrochloride
1.	Distilled water	Insoluble	Freely soluble
2.	Ethanol	0.98 mg/ml	2.74 mg/ml
3.	Methanol	4.3 mg/ml	10.34 mg/ml
4.	Dimethyl Sulfoxide	Soluble	Soluble

Assay of pure drugs

Table 6: Results for Assay of pure drugs

Sr.no.	Material	Specification	Inference
1.	Glyburide	99 - 101%	99.4%
2.	Metformin Hydrochloride	98.5 - 101%	98.9%

UV spectroscopic analysis of Glyburide

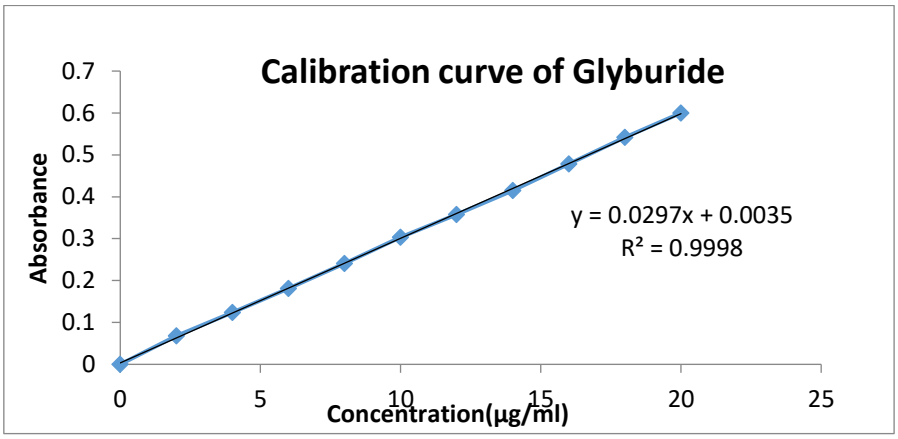

Figure no. 1: Calibration curve of Glyburide in 0.1 N Hydrochloric acid

UV spectroscopic analysis of Metformin hydrochloride

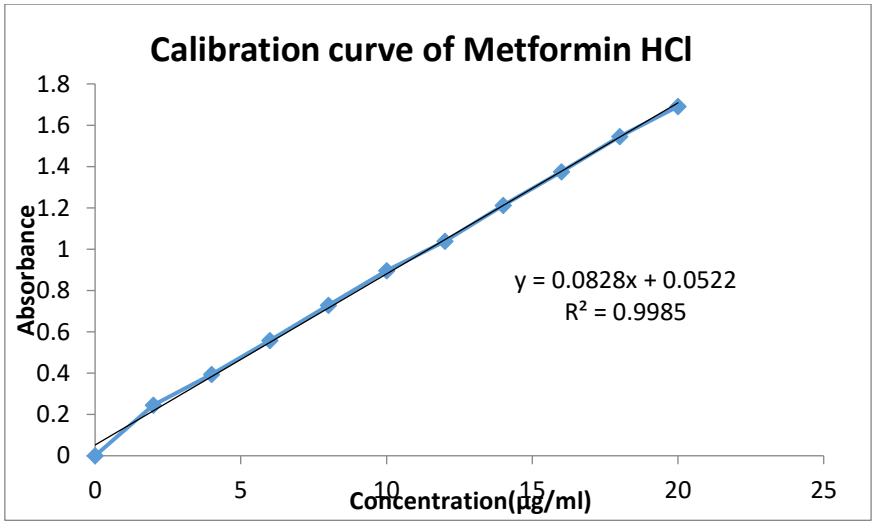

Figure no.2: Calibration curve of Metformin hydrochloride in 0.1 N Hydrochloric acid

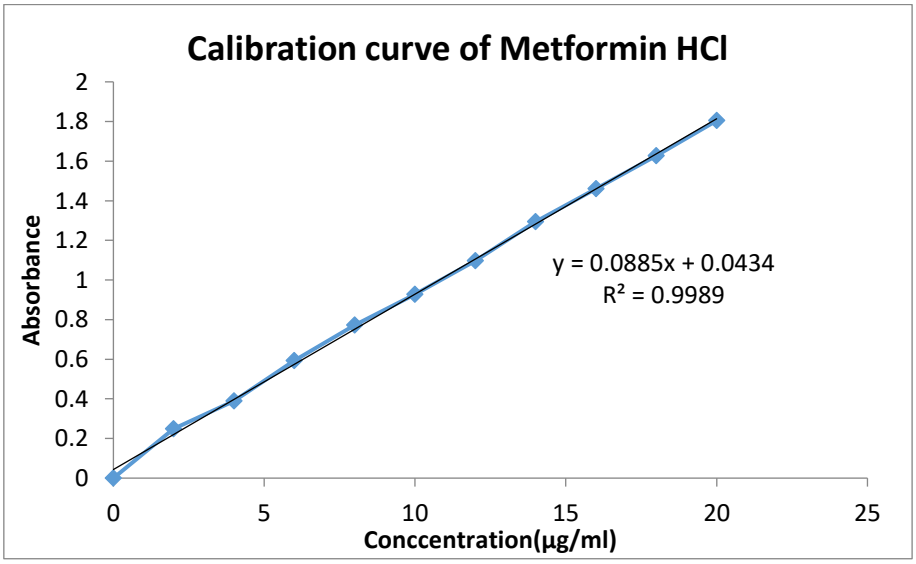

Figure no.3: Calibration curve of Metformin hydrochloride in phosphate buffer pH 6.8

Drug excipient compatibility studies using FTIR

The IR Spectra of both the drugs and the mixture of excipients are carried out using FTIR spectrometer (Perkin Elmer, Japan). The KBr disks were formed by taking Drug and KBr in a ratio of 1:100 respectively. Then this mixture was mixed well in mortar for three to five min. A very small amount of this mixture was uniformly spread and sandwich between the pellets and pressed using KBr pellet press at a pressure of 20,000 psi for 1 min. The pressure was then released and pellet was placed into the pellet holder. All the samples were scanned at the resolution of 4 cm^{-1} over the wave number region 4000-400 cm^{-1} using KBr disk method.

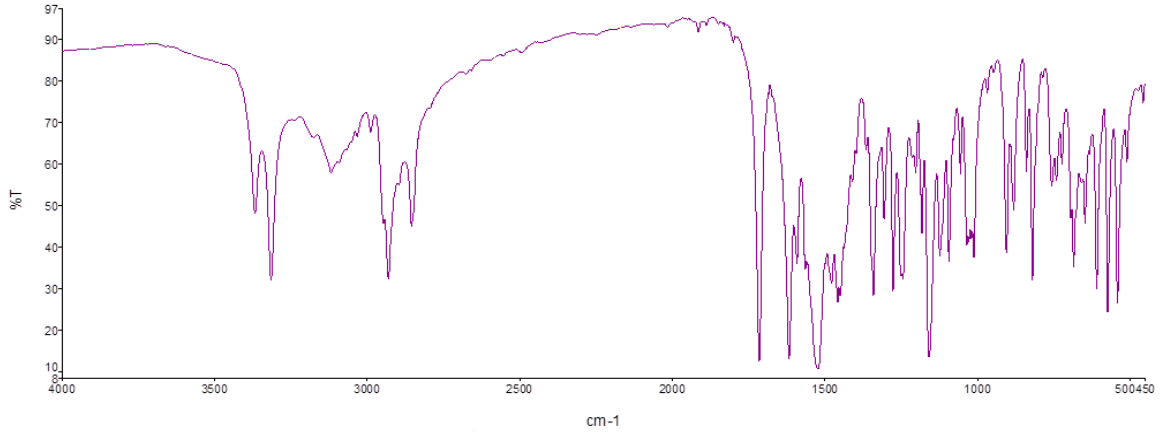

Figure no. 4: FTIR spectrum of Pure Glyburide

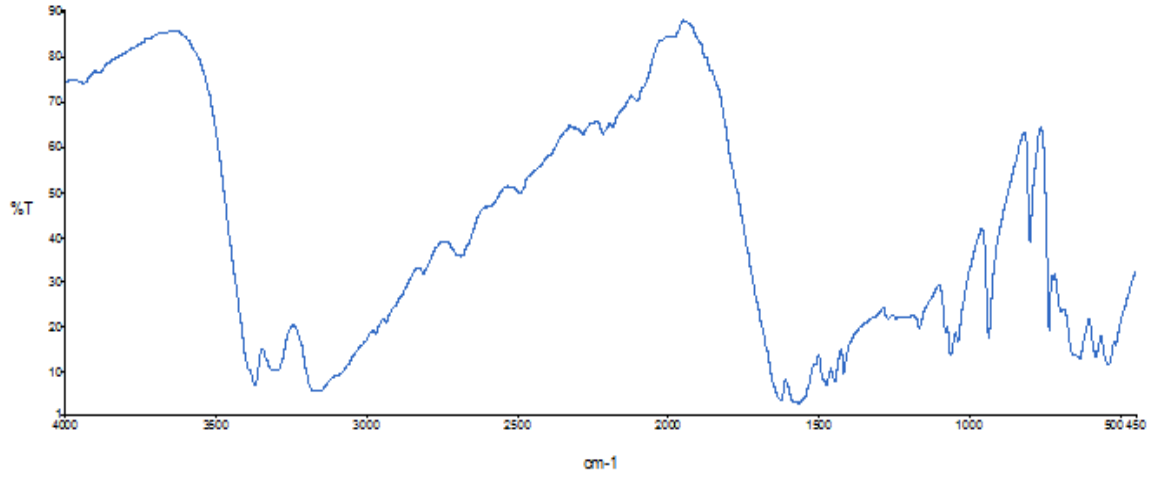

Figure no.5: FTIR spectrum of Metformin Hydrochloride

DSC studies

Differential scanning calorimetry was done for both drugs i.e. Glyburide and Metformin hydrochloride. The spectra showed endothermic peak at 169.11°C. (Figure no. 10.10) i.e. presence of Glyburide and thermal curve for Metformin hydrochloride exhibited a endothermal effect at 225.46^0c

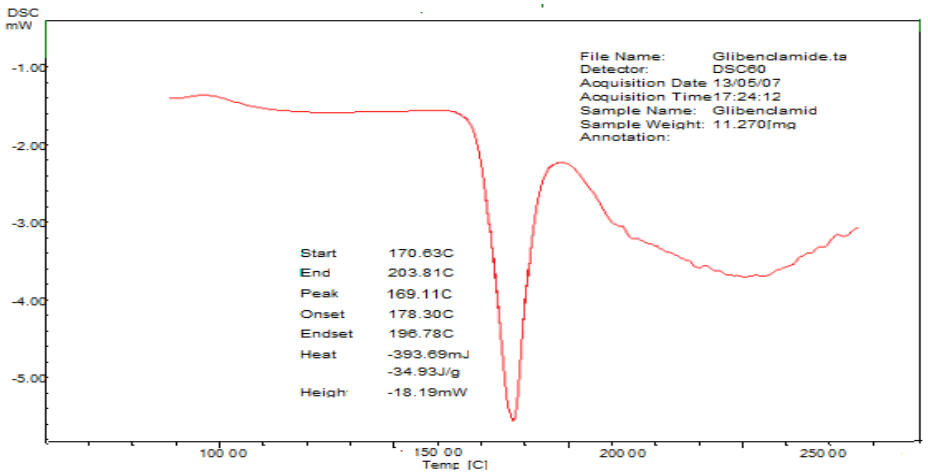

Figure no. 6: DSC curve of Pure Glyburide

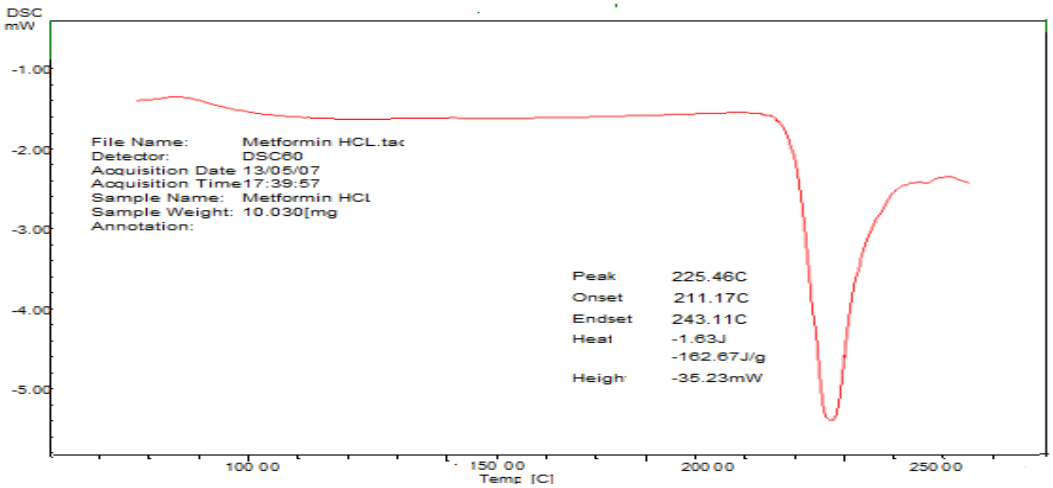

Figure no. 7: DSC thermogram for Metformin Hydrochloride

Evaluation of Inlay tablet

Table 7: Results for Evaluation Parameters for Inlay tablet

Batch code	Hardness(kg/cm^3)*	Thickness (mm)*	% Friability*	Weight variation (mg)*	Drug content* (Glyburide)	Drug content* (Metformin Hydrochloride)
Core tablet	3.5 ± .11	2.19 ± 0.03	0.20 ± 0.00	100 ± 0.01	97.28 ± 1.26	-
IT1	5.53 ± 0.05	5.89 ± 0.01	0.53 ± 0.00	751 ± 0.01	97.23 ± 0.80	96.65 ± 0.32
IT2	5.26 ± 0.10	5.82 ± 0.04	0.50 ± 0.02	750 ± 0.01	96.45 ± 1.27	98.21 ± 1.03
IT3	5.35 ± 0.05	5.82 ± 0.01	0.36 ± 0.01	750 ± 0.00	98.34 ± 0.34	97.07 ± 1.67

IT4	5.00 ± 0.08	5.9 ± 0.04	0.43 ± 0.05	749 ± 0.01	97.31 ± 0.58	95.08 ± 1.22
IT5	5.96 ± 0.1	5.87 ± 0.00	0.83 ± 0.01	751 ± 0.02	95.82 ± 1.36	97.28 ± 0.38
IT6	5.36 ± 0.08	5.9 ± 0.02	0.63 ± 0.02	751 ± 0.00	96.39 ± 0.80	95.08 ± 1.63
IT7	5.53 ± 0.11	5.83 ± 0.05	0.76 ± 0.03	750 ± 0.01	97.44 ± 1.72	96.65 ± 1.27
IT8	5.63 ± 0.07	5.83 ± 0.03	0.23 ± 0.04	750 ± 0.02	98.02 ± 0.84	95.81 ± 0.83
IT9	5.06 ± 0.06	5.79 ± 0.01	0.26 ± 0.01	749 ± 0.00	96.55 ± 0.58	96.23 ± 0.54

From the post compression parameters of inlay tablet, the hardness of tablet is between 5 – 5.96 kg/cm^2, the thickness of tablet is 5.9 mm for all batches, friability varies from 0.23 – 0.83%. The weight of tablets varies from ± 1%. All the values are in the range of specified limits. The drug content for Glyburide in inlay tablet varies from 96.55 – 98.34% and for Metformin Hydrochloride it is in the range of 95.08 – 98.21%.

Swelling Index Study of Sustained release cup portion of Inlay tablet

Table no.8: Result of Swelling Index study

Sr.no.	Batch	% Swelling index*
1.	IT1	55.21 ± 0.48
2.	IT2	59.89 ± 0.74
3.	IT3	70.13 ± 0.63
4.	IT4	68.84 ± 0.86
5.	IT5	76.12 ± 0.92
6.	IT6	81.23 ± 0.73
7.	IT7	71.03 ± 0.58
8.	IT8	74.31 ± 0.62
9.	IT9	82.68 ± 0.57

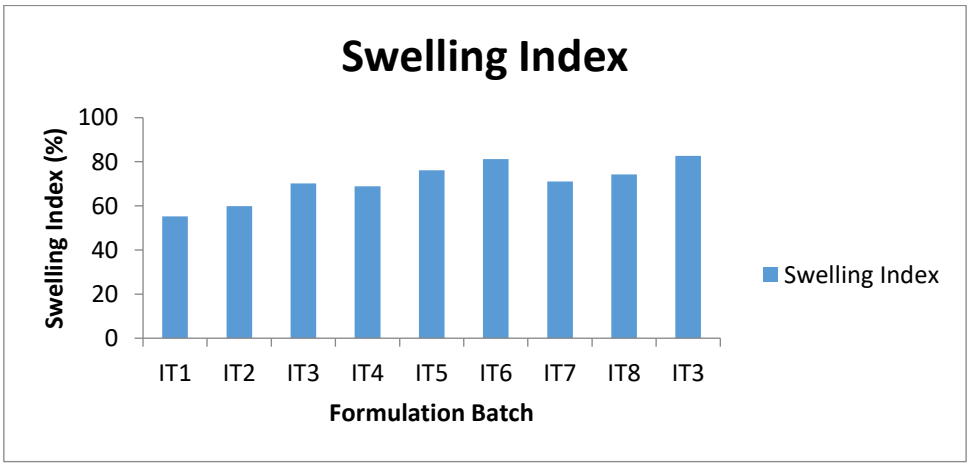

Figure no. 8: Comparison of % Swelling index of Sustained release cup portion

In vitro Dissolution studies

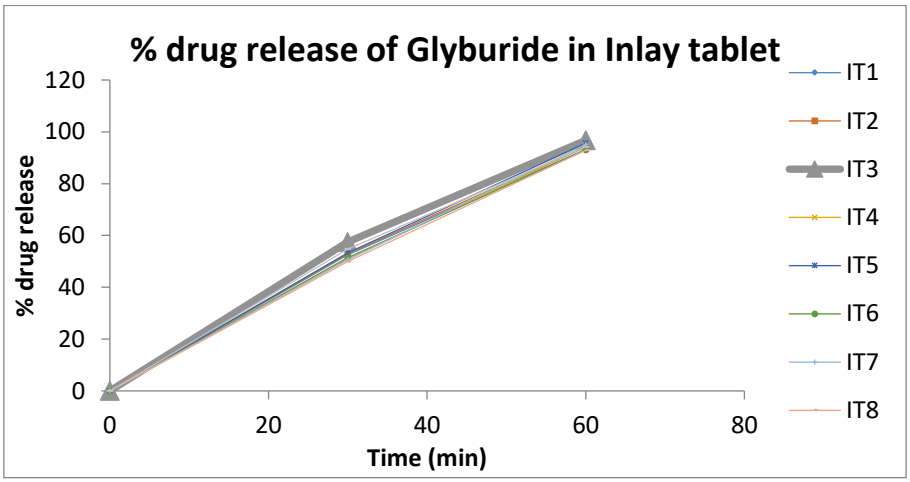

Figure no.9: %drug release of IR core tablet of Glyburide in inlay tablet.

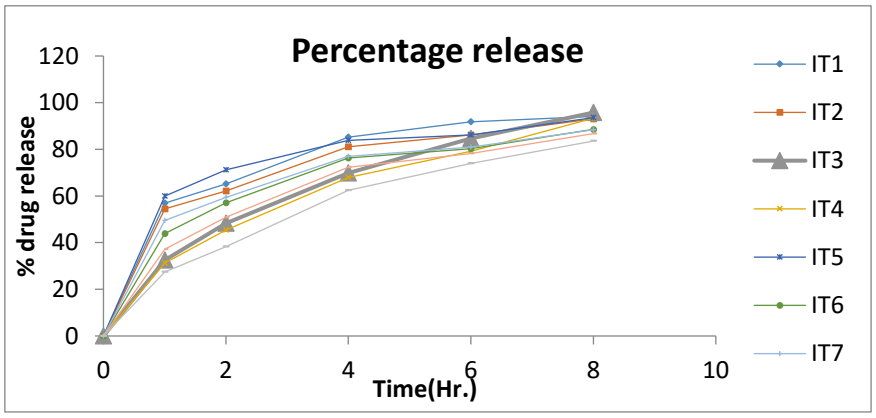

Figure no.10: % drug release of SR outer cup portion of Metformin Hydrochloride

The formulation IT3 showed better drug release up to 8 hours, which was achieved by optimum concentration ratio of HPMC K4M and HPMC K100. This releases the drug in a controlled rate at regular time intervals in appropriate concentrations as per the limits. Hence the formulation IT3 was selected for stability and further studies.

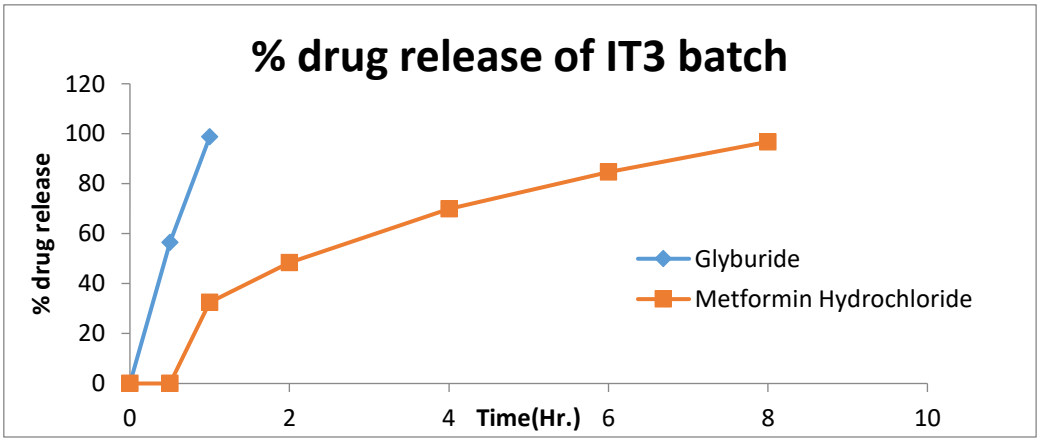

Figure no. 11: Percentage release of IT3 batch of Glyburide Immediate release core tablet and Metformin hydrochloride sustained release cup portion.

Stability Studies

Stability studies were conducted for the optimized batch (IT3). The stability study was performed at 40C ± 2˚C/75%RH ± 5%RH for 3 months. The tablets were analyzed for hardness, weight variation and *in-vitro* drug release, after a period of 90 days.

Table no. 9

Sr.no.	Tests	Limits	Initial results	1st month results	2nd month results
1.	Appearance	White color tablet with orange colored inlay tablet	Passes	Passes	Passes
2.	Average weight	± 1% from target weight	750	750	749
3.	Hardness	5 - 8 kg/cm^2	5.35	5.35	5.36
4.	Friability	± 1%	0.36	0.34	0.33

Table no. 10: Evaluation of in vitro dissolution of Inlay tablets of Stability Batch: IT3

Sr.no.	Tests	Limits	Initial results	1st month results	2nd month results
1.	Glyburide	NLT 85% of the labeled amount dissolved in 60 min.	96.7	95.6	95.1
2.	Metformin Hydrochloride				
	1st hour	Between 25-40%	32.49	32.21	32.17
	4th hour	Between 60-80%	69.88	67.47	67.73
	8th hour	NLT 85%	96.75	96.68	96.46

The tablets from batch IT3 was charged for stability at 40°C/75% RH for three months and the 3 months results was found to be satisfactory.]

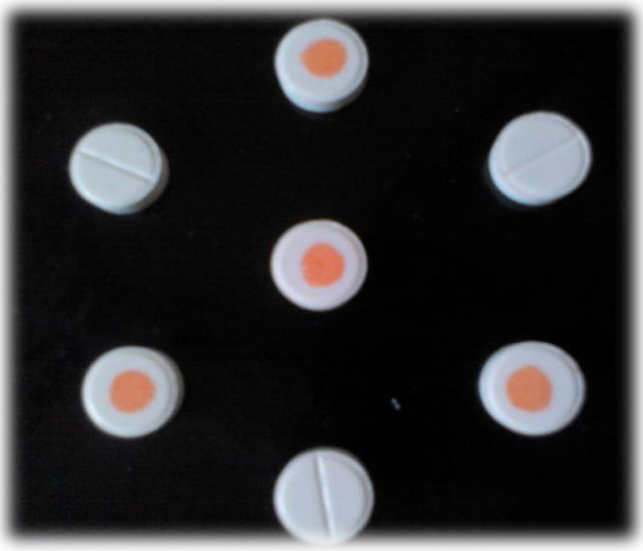

Figure no. 12:3 months' stability study of Inlay Tablets

Summary and conclusion

The present work involves the formulation development, optimization and in-vitro evaluation of inlay tablet containing Glyburide in the immediate release core tablet and Metformin Hydrochloride in sustained release cup portion. Superdisintegrants such as sodium starch glycolate, cross carmellose sodium and crospovidone used for immediate release core tablet of Glyburide and the hydrophilic matrix formers such as HPMC K4M, and HPMC K100 used for the sustained release cup portion of Metformin Hydrochloride. PVP K30 solution was used as binder for granulation of both the drugs. The wet granulation method was selected for the formulation of Glyburide immediate release tablet and Metformin Hydrochloride sustained release cup portion. From the preformulation studies, Pure drug and excipients characterization were carried out as well as drug-excipient compatibility studies were done by DSC and FTIR. From in vitro drug release pattern and from all evaluation parameters, Formulation IT3 was ideally suited to be sustained release formulation and was optimized.

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