FORMULATION AND EVALUATION OF SUSTAINED RELEASE BILAYER TABLETS OF GLIMEPIRIDE AND METFORMIN HCl

Dissertation work submitted to

THE TAMILNADU Dr. M.G.R.MEDICAL UNIVERSITY, CHENNAI.

In partial fulfillment of the requirements for the award of degree of

MASTER OF PHARMACY

IN

PHARMACEUTICS

BY

REG. NO: 26105111

Under the guidance of

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MAY-2012

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CERTIFICATE

This is to certify that the investigation in this thesis entitled **"Formulation and Evaluation of Sustained Release Bilayer Tablets of Glimepiride and Metformin HCl"** submitted to the Tamil Nadu Dr. M.G.R Medical University, Chennai, for the partial fulfillment of the award of degree of **Master of pharmacy** in **Pharmaceutics,** was carried out by **Regd. No. 26105111** in the Department of Pharmaceutics. **The Erode College of Pharmacy and Research Institute**, **Erode-638112**.

This work is original and has not been submitted in part or full to any other degree or diploma of this or any other university.

The Erode College of Pharmacy & Research Institute

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ENDORSEMENT BY THE PRINCIPAL

This is to certify that the investigation in this thesis entitled **"Formulation and Evaluation of Sustained Release Bilayer Tablets of Glimepiride and Metformin HCl",** submitted in partial fulfillment for the award of degree of **Master of Pharmacy** in **Pharmaceutics,** were carried out in the laboratories of The Erode College of Pharmacy & Research Institute by **Reg. No. 26105111** under the guidance of **Dr. V. Gasesan, M. Pharm., PhD., Professor** in the Department of Pharmaceutics, The Erode College of Pharmacy and Research Institute, Erode 638112.

DECLARATION

The research work embodied in this dissertation work entitled "**Formulation and Evaluation of Sustained Release Bilayer Tablets of Glimepiride and Metformin HCl"** was carried out by me in **Department of Pharmaceutics, The Erode College of Pharmacy & Research Institute, Erode**, under the direct supervision of **Dr. V. Ganesan, M. Pharm., PhD., Professor** Department of Pharmaceutics, The Erode College of Pharmacy & Research Institute, Erode – 638112.

This dissertation submitted to **The Tamil Nadu Dr. M. G. R. Medical University, Chennai**, as a partial fulfillment for the award of degree of Master of Pharmacy in Pharmaceutics during the academic year 2011 – 2012.

The work is original and has not been submitted in part or full for the award for any other Degree or Diploma of this or any other University.

Place: Erode.

Date: **Reg., No. 26105111**

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INDEX

LIST OF ABBREVATIONS

% -Percentage
Kg– Kilogram
Gm – Gram
Mg – Milligram
µg – Microgram
ml– Millilitre
°C – Centigrade
Nm –Nanometer
µl – Microliter
CI –Carr's Index
Mm – Millimetre
HPLC – High performance liquid chromatography
UV – Ultra-violet spectrophotometer
HPMC –Hydroxypropyl methyl cellulose
MCCP – Micro crystalline cellulose powder
SSG-Sodium starch glycholate
Mins– Minutes
RH – Relative humidity
USP – United states pharmacopoeia
NF – National formulary
BP –British pharmacopoeia
ICH – International conference on harmonisation
#- Mesh
SD – Standard deviation
Abs – Absorbance
IR – Immediate release
SR – Sustained release
Cm – Centimetre
Con – Concentration
F – Formulation

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INTRODUCTION

Usually conventional dosage form produce wide ranging fluctuation in drug concentration in the blood stream and tissues with consequent undesirable toxicity and poor efficiency. This factor such as repetitive dosing and unpredictable absorption led to the concept of controlled drug delivery systems. The goal in designing sustained or controlled delivery systems is to reduce the frequency of the dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required or providing uniform drug delivery. The primary objective of sustained release drug delivery is to ensure safety and to improve efficacy of drugs as well as patient compliance[1]. Bi-layer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances and also for sustained release tablet in which one layer is immediate release as initial dose and second layer is maintenance dose[2]. In the case of bi-layered tablets drug release can be rendered almost unidirectional if the drug can be incorporated in the upper non-adhesive layer its delivery occurs into the whole oral cavity.

BI-LAYER TABLETS[3]

Bilayer tablet is a unit compressed tablet dosage form intended for all oral administration. It comprises of two layers in which one layer is formulated as a conventional or immediate release part and another layer as modified release part or both of the former or later of the same or different drugs.

The goal in designing delayed release sustained or controlled delivery system is to:

Reduce the frequency of dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required, or providing uniform drug delivery.

- It would be a single dose for the duration of treatment whether it is for days or weeks, as with infection, or for the life time of the patient, as in hypertension or diabetes.
- It should deliver the active entity directly to the site of action, minimizing or eliminating side effects.
- This may necessitate delivery to specific receptors or to localization to cells or to specific areas of the body[4]

- The safety margin of high potency drug can be increase and the incidence of both local and systemic adverse side effects can be reduced in sensitive patient[5]

Advantages

- Decreased in dosing frequency
- Reduced peak to trough ratio of drug in systemic circulation.
- Reduced rate of rise of drug concentration in blood.
- Sustained & Consistent blood level with in the therapeutic window.
- Enhanced bioavailability
- Customized delivery profiles
- Reduced side effects
- Improved patient compliance

Quality and GMP-requirements:

- To produce a quality bi-layer tablet, in a validated and GMP-way, it is important that the selected press is capable of[6]
- Preventing capping and separation of the two individual layers that constitute the bi-layer tablet
- Providing sufficient tablet hardness
- Preventing cross-contamination between the two layers
- Producing a clear visual separation between the two layers
- High yield
- Accurate and individual weight control of the two layers is not so easily accomplished as this article aims to demonstrate.

Manufacturing aspect:

The manufacture of bi-layer tablets, produced by the sequential compaction of loose powder layers has recently become of increased interest within the pharmaceutical industry due to the tailored release profiles of active ingredients that may be obtained[7, 8] An observed disadvantage of the formulation however, is the predilection of the assemblies to fail at the interfacial boundary zone between the two adjacent layers.

Various Techniques:

OROS® push pull technology:

This system consist of mainly two or three layer among which the one or more layer are essential of the drug and other layer are consist of push layer (Fig.1). The drug layer mainly consists of drug along with two or more different agents. So this drug layer comprises of drug which is in poorly soluble form. There is further addition of suspending agent and osmotic agent. A semi permeable membrane surrounds the tablet core.

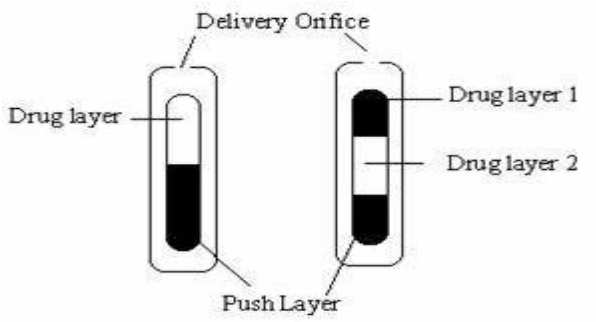


Fig1: Bilayer and trilayer OROS Push pull technology.

L-OROS tm technology:

This system used for the solubility issue Alza developed the L-OROS system where a lipid soft gel Product containing drug in a dissolved state is initially manufactured and then coated with a barrier membrane, than osmotic push layer and than a semi permeable membrane, drilled with an exit orifice (Fig.2).

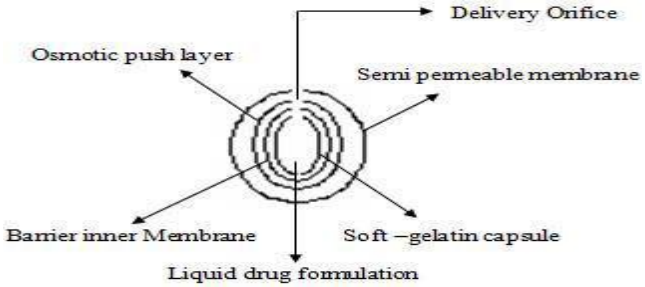


Fig 2: L–OROS tm technology.

EN SO TROL technology:

Solubility enhancement of an order of magnitude or to create optimized dosage form Shire laboratory use an integrated approach to drug delivery focusing on identification and incorporation of the identified enhancer into controlled release technologies[1].

DUROS technology:

The system consists from an outer cylindrical titanium alloy reservoir (Fig. 3).This reservoir has high impact strength and protects the drug molecules from enzymes. The DUROS technology is the miniature drug dispensing system that opposes like a miniature syringe and reglious minute quantity of concentrated form in continues and consistent from over months or Year.

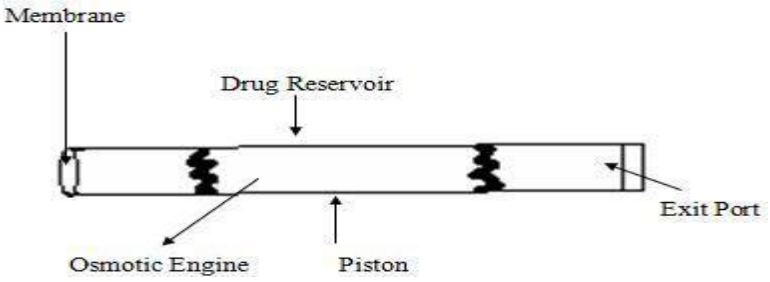


Fig 3: DUROS Technology

Elan drug technologies' Dual release drug delivery system:

DUREDAS™ Technology is a bilayer tablet which can provide immediate or sustained release of two drugs or different release rates of the same drug in one dosage form. The tab letting process can provide an immediate release granulate and a modified-release hydrophilic matrix complex as separate layers within the one tablet. The modified-release properties of the dosage form are provided by a combination of hydrophilic polymers.

Benefits offered by the DUREDAS™ technology include:

- Bilayer tabletting technology.
- Tailored release rate of two drug components.
- Capability of two different CR formulations combined.

- Capability for immediate release and modified release components in one tablet.
- Unit dose, tablet presentation.

The DUREDAS™ system can easily be manipulated to allow incorporation of two controlled release formulations in the bi-layer. Two different release rates can be achieved from each side. In this way greater prolongation of sustained release can be achieved. Typically an immediate release granulate is first compressed followed by the addition of a controlled release element which is compressed onto the initial tablet. This gives the characteristic bilayer effect to the final dosage form. A further extension of the DUREDAS™ technology is the production of controlled release combination dosage forms whereby two different drugs are incorporated into the different layers and drug release of each is controlled to maximize the therapeutic effect of the combination. Again both immediate release and controlled release combinations of the two drugs are possible. A number of combination products utilizing this technology approach have been evaluated. The DUREDAS™ technology was initially employed in the development of a number of OTC controlled release analgesics. In this case a rapid release of analgesic is necessary for a fast onset of therapeutic effect. Hence one layer of the tablets is formulated as immediate releases granulate. By contrast, the second layer of the tablet, through use of hydrophilic polymers, releases drug in a controlled manner. The controlled release is due to a combination of diffusion and erosion through the hydrophilic polymer matrix.

BI-LAYER TABLET PRESS

The XM 12 Bi-Layer Tablet Press features a retractable second layer feeder that permits automated first layer sampling at production speeds. The first layer sampling capability also offers a hardening feature, which the main compression station will automatically compress, the first layer tablet for in-process measurement. The two feeders are zero clearance and are configured with an integrated dust extraction manifold which cleans the die table and completely eliminates any potential for cross contamination. WipCon® solution available for potent for layer Tablet Press is a small-scale press which is ideal for product development scale-up, clinical trials and midrange production. The bi-layer execution, single-layer conversion kit and exchangeable turret

offer unprecedented flexibility. The XM 12 Bi-Layer Tablet Press offers a new standard in GMP with extreme accessibility to the compression zone and combinations of quick disconnects and smooth surfaces that permit fast cleaning and changeover.

The machine concept:

Advantages:

1. Flexible Concept
    - Bi-Layer execution with optional single-layer conversion kit
    - Exchangeable turret
    - Turret sizes for product development, scale-up, and mid-range production
    - Full production capability in a scale-up machine
    - Self-contained, fully portable design
2. Fast and Easy Changeover
    - Internal turret lift device for extreme simplicity in turret removal and installation
    - Clean compression zone with quick-disconnect design
3. Design Advantages
    - Small-scale bi-layer capability
    - Robust caster base permits full portability
    - Large touch screen flush mounted
    - Unique structural design eliminates vibration and noise
    - Zero clearance feeder for maximum yield and optimal layer separation
    - Retractable second layer feeder for automatic first layer sampling
4. Full instrumentation
    - Tamping force
    - Pre/Main compression force
    - Ejection force
5. Touch Screen Control
    - Press force control and single tablet rejection capability
    - Comprehensive data collection and analysis capability
    - Real time display and batch data documentation
6. Containment Solution
    - WipCon® solution available for potent products.

Applications of bi-layer for small scale:

The KORSCH XM 12 Bi-Layer Tablet Press is a small scale press which is ideal for product development, scale-up, Clinical trials, and midrange production. The bi-layer execution, single-layer conversion kit, and exchangeable turret Offer unprecedented flexibility. The XM 12 Bilayer tablet Press offers a new standard in GMP with extreme accessibility to the compression zone and combination of quick disconnects and smooths surfaces that permit fast cleaning and changeover. The machine features a 5 kN tamping station, 40 kN precompression station, 80 kN main compression station, and a unique structural design that eliminates vibration to the head piece and base frame. The result is an extreme reduction in the operating noise level. The XM 12 Bilayer tablet Press features a retractable second speeds. The first layer sampling capability also offers a hardening feature, in which the main compression station will automatically compress the first layer tablet for in-process measurement. The two feeders are zero clearance and are configured with an integrated dust extraction manifold, which cleans the die table and completely eliminates any potential for cross-contamination.

Properties:

- Free format graphic and statistical analysis to allow the export of many data formats.
- Reports can be automatically generated in a variety of data formats with and without an electronic signature.
- Charts can be dimensioned, comments added, formatted and exported before being processed in the MS Office world.
- Finger print recording during production. Overlay Technology allows safe and quick recognition of subsequent waveforms.
- Correlation Analysis to establish a “Knowledge Database” that serves to easily compare the properties of known and unknown ingredients. The database enables the user to correlate measuring values from the tableting process and derived and externally recorded quantities (e.g. tablet hardness, density, etc.).

- Compaction Analysis allows evaluations e.g. Heckel plot, energy, work of compression, contact time, compressibility.
- "Built-in" PAT function, i.e. the database is automatically filled with process data thereby helping to define and complete PAT requirement for Knowledge Space and Design Space.

XM 12 WipCon® development & analysis:

- Minimum space requirements, portable design
- Best cleaning / decontamination results for product specific demands
- Optimized glove port configuration
- All types of make/break connections possible
- High containment range for lab scale and medium size batches OEB 5 (1 μg/m³ > OEL >0.1 μg/m³) with RTP transfer system
- Medium containment range for small production batches OEB 4 (10 μg/m³ > OEL > 1 μg/m³) with split valve connections
- Connection to Wip tablet deduster on same containment level OEB 4 (10 μg/m³ > OEL >1 μg/m³)
- Negative pressure control and safe-change filter box attached or separate, depending on space availability.

Table 1: some examples for combination of drugs used as bilayer tablets

Combination of drugs	Reason
Metformin HCl + Pioglitazone	Reduce frequency of administration and improve patient compliance[11].
Diltiazem HCl + Lovastatin	Improve patient compliance and better disease management[12].
Metoprolol succinate + Amlodipine besylate	Lower doses of drug to reduce patient blood pressure; minimize dose dependent side effects and adverse reaction[13].
Solbutamol + Theophylline	Enhance patient compliance and prolonged bronchodilation[14].
Paracetamol + Diclofenac sodium	Reduce dose frequency and decrease incidence of GI side effects[15].
Tramadol + Acetaminophen	Prolonged release up to 12 hrs and improve patient compliance[16].

LITERATURE REVIEW

REVIEW OF BILAYER TABLET

Jagadeesh Singh SD et at., (2011)[9] reported that over the past 30 years as the expense and complications involved in marketing new drug entities have increased, with concomitant recognition of the therapeutic advantages of controlled drug delivery, greater attention has been focused on development of sustained or controlled release drug delivery systems. Bilayer tablet is new era for the successful development of controlled release formulation along with various features to provide a way of successful drug delivery system

Patel Mehul et al., (2010)[10] reported that several pharmaceutical companies are currently developing bi-layer tablets, for a variety of reason: patent extension, therapeutic, marketing tool name a few. To reduce capital investment, quite often existing but modified tablets presses are used to develop and produced such tablet.

Ramesh et al., (2010)[11] established metformin HCL SR 1000 mg and pioglitazone HCL 15 mg in the form of bi-layered sustained release matrix tablets and prepared using sodium carboxymethylcellulose and hydroxypropyl methylcellulose as bio-adhesive polymer and cross carmellose sodium to act as an impermeable backing layer. The formulation gave an immediate release effect followed by sustained release for 8 hrs. The stability studies of formulated product also comply with ICH guidelines.

Kulkarni et al., (2008)[12] developed bilayer floating tablet of ditiazem HCl and lovastatin. The tablet cosists of SSG as superdisintegrant for lovastatin in the IR layer and HPMC k4M and xanyhan gum as release retarding agents for diltiazem HCl in the controlled release layer. Sodium bicarbonate was used as the gas generating agent. Dicalcium phosphate was used as the channeling agent. The direct compression method was employed for preparation of the bilayer tablets. Various physicochemical parameters were evaluated for the prepared tablets.

Atram et al., (2009)[13] reported thatbilayer tablets of Amlodipin Besylate and Metoprolol Succinate were formulated for the management of hypertension. In the formulation of IR layer, SSG and pregelatinised tarch were used as superdisintegrant and was directly compressed. For SR portion, HPMC were used in granulation stage

and also extra granularly. In vitro drug release of the optimized formulation showed 9.96%, 35.56%, 52.12%, 90.46% release for Metoprolol Succinate in 1, 4, 8, 20 hrs respectively. However, Amlodipine Besylate released 98.28% at the end of 30 minutes.

Nagaraju R et al., (2009)[14] developed formulation and evaluation of bilayer sustained release tablets of salbutamol and theophylline**.** Salbutamol and theophylline are available in conventional dosage forms, administered four times a day, leading to saw tooth kinetics and resulting in ineffective therapy. The combination of these two drugs in a single dosage form will enhance the patient compliance and prolong bronchodilation. In-vitro dissolution studies were carried out for all the bi-layered tablets developed using USP dissolution apparatus type 2 (paddle). In-vitro dissolution studies were carried out for all the bi-layered tablets developed using USP dissolution apparatus type 2 (paddle).

Gohel MC et al., (2010)[15] investigated were to achieve immediate release of paracetamol and tailored release of diclofenac sodium from bi-layer tablets and were prepared by using hydroxypropyl methyl cellulose as a matrixing agent. The analysis showed that the friability of paracetamol was distinctly influenced by the formulation variables. The bi-layer tablets shown immediate release of Paracetamol and modified release of diclofenac.

Naeem MA et al., (2010)[16] developed bilayer tablet formulations of Tramadol HCl (TmH) and acetaminophen (AAP) microparticles Coacervation via temperature change was the encapsulated method used for the preparation of the microparticles, with ethyl cellulose (EC) of medium viscosity as the polymer for extending drug release. The physicochemical compatibility and stability of the tablets were determined by Fourier transform infrared spectroscopy (FTIR), x-ray diffractometry (XRD), differential scanning calorimetry DSC) and thermogravimetric analysis (TGA). Microencapsulated TmH and AAP can be developed into suitable bilayer tablets that are stable and capable of releasing the drugs over 12 h.

REVIEW OF DRUG & POLYMER

Yamsani Madhusudan Rao et al (2010)[17]., Reported that formulated Bilayer tablets provided immediate release of glimepiride and metformin HCl as sustained release over a period of 8 hours.The immediate release layer was prepared using sodium starch glycolate as super disintegrant and sustained release using HPMC K4M and sodium carboxy methyl cellulose as polymers and PVP K30 as binder. Formulations containing higher concentration of sodium starch glycolate and SCMC in IR and SR layer respectively were optimised for bilayer tablets.

Kumaresan C. et al., (2010)[18] developed once a daily fixed triple combination of antidiabetic drugs wherein Pioglitazone and glimepiride are as immediate release and metformin is as extended release indicated suitability for patient compliance and stability. The tablets were prepared using wet granulation, compression and drug coating technique. The best formula was selected by physical evaluation of tablets, comparative dissolution profiles and stability.

Durga Prasad Pattanayak et al., (2011)[19] reported that Bilayer matrix tablet containing 1mg glimepiride as immediate release and 502mg mg of metformin HCl as sustained release was designed and evaluated by using same analytical technique. HPMC and PEO were used as polymer to get the sustained release profile over a 24hrs. The best formula was selected by physical evaluation of tablets, comparative dissolution profiles and Pharmacokinetic studies of various formulations of metformin hydrochloride and glimepiride.

Sahu M et al., (2010)[20] Reported that the designed inlayered tablet of glimepiride as immediate release and metformin hydrochloride as sustained release indicated suitability for patient compliance. Inner core portion was designed using superdisintegrants for immediate release and outer cup portion was designed using polymers such as HPMC and PVP to modulate drug release.

J. Bagyalakshmi et al., (2011)[21] Reported that bilayer matrix tablet containing 500mg of metformin HCl as SR from one layer and 5mg glipizide as IR from another layer can be prepared by solid dispersion method. Solubility of glipizide was increased by solid

dispersion technique with sodium starch glycolate using kneading technique. Metformin was formulated using different grades of HPMC.

Manoranjan S et al., (2010)[22] Concluded that modified Inlayered tablet containing glimepiride as immediate release and metformin as sustained release was designed to improve oral therapeutic efficacy. Tablet compressing was done with core rod tooling where only one surface of core is exposed to outside and other drug is incorporated in cup portion. Common analytical method was developed for quantitative combined drug estimation.

N. N. Rajendran et al., (2011)[23] Concluded that Bilayer tablets of Metformin HCl and Pioglitazone HCl as an alternative to the conventional dosage form. Sustained layer of metformin were prepared by wet granulation method using different viscosity grade of HPMC as polymers and immediate release layer were prepared by direct compression using superdisintegrants such as SSG and Croscarmellose sodium. The result showed that combinations of polymers HPMC K100M and HPMCK4M in sustained layer can control the release of drug.

Kotta Kranthi Kumar et al., (2010)[24] Reported that Bilayer tablets of Metformin Hydrochloride and gliclazide was successfully formulated and evaluated. The investigation was aimed to the development of bilayered tablets of metformin hydrochloride and gliclazide as sustained release by using HPMC as retardant. The best formula was selected by physical evaluation of tablets, comparative dissolution profiles and similarity factor correlation studies of various formulations of metformin hydrochloride and gliclazide.

Laxmi Goswami et al., (2010)[25] Concluded that formulated floating bilayer tablets of metformin and pioglitazone remain buoyant over a period of 12-20 hours and released more than 80% of drug. The tablets were formulated by modified direct compression using polymers like HPMC, carbopol, PVP to facilitate immediate release of pioglitazone and sustained release of metformin and were subjected to various evaluation parameters including floating lag time, floating duration, drug content and spectrophotometric simultaneous estimation.

AR Mullaicharam et al., (2010)[26] Developed once daily sustained release matrix tablets of metoprolol tartrate with inlay hydrochlorthiazide tablet as immediate release.

Both the layers were prepared by wet granulation method. Five trial batches of sustained release granules were prepared using HPMC in various percentages and one optimum formulation was selected among them on basis of in vitro dissolution studies.

Chitra. P et al., (2011)[27] Formulated and optimized once daily sustained release inlay tablet of propranolol hydrochloride and hydrochlorthiazide.SR active ingredient is selected from higher dose and IR active ingredient is selected from lower dose. Tablets were evaluated for hardness, thickness, uniformity of weight, friability, content uniformity, in-vitro drug release. Optimized formulation could extend release of PRO for 24 hrs and HCTZ for 15 mins.

Tapan Kumar Pal et al., (2007)[28] Concluded that the study helped in finding optimum formulation of Metformin HCl with sustained drug release. Tablets were prepared by non-aqueous wet granulation method using HPMC K15M as matrix forming polymer. Drug release profile was formulated using response surface methodology. % of drug released in 1hr, 8 hrs and time to 50% drug release.

P. Jeyaprabha et al., (2010)[29] Prepared a modified release tablet of gliclazide by using different grades of hydroxypropyl cellulose. Release process involved erosion and diffusion mechanism. Among all the 9 formulations prepared, formulation F9 with GXF 15% cum EXF 12% had good release and highest f2 (56.9) value, therefore it was decided to comparable with innovator F1.

Chinam Niranjan patra et al., (2007)[30] developed a bilayer tablet of propranolol HCl using superdisintegrant SSG for the fast release layer and water immiscible polymers such as ethylcellulose, Eudragit RLPO and Eudragit RSPO for the sustaining layer. In vitro dissolution studies were carried out in a USP 24 apparatus I. The formulations gave an initial burst effect to provide the loading dose of the drug followed by sustained release for 12 h from the sustaining layer of matrix embedded tablets. In vitro dissolution kinetics followed the Higuchi model via a non-Fickian diffusion controlled release mechanism after the initial burst release.FT-IR studies revealed that there was no interaction between the drug and polymers used in the study. Statistical analysis (ANOVA) showed no significant difference in the cumulative amount of drug release after 15 min,but significant difference ($p < 0.05$) in the amount of drug released after 12 h from optimized formulations was observed.

Poonam S. Karekar et al., (2011)[31] Proposed spectrophotometric method for the estimation gliclazide in bulk and pharmaceutical dosage form. Wavelength maxima for gliclazide was found to be 229.5nm with molar absorptivity of 1.4962×10^4l/mol/cm. Beer's law was obeyed in the concentration range of 7-27 µg/ml. The limit of detection (LOD) and limit of quantification (LOQ) were found to be 0.31µg/ml and 0.92 µg/ml. Percentage recovery of drug for the proposed method ranged from 98.68-100.12% indicating no interference of the tablet excipients.

Tanbir Ahammad et al., (2011)[32] Prepared matrix tablets of gliclazide by direct compression and wet granulation process using Methocel K15M CR, studied effect of granulation process on drug release and found that wet granulation extend release more than that of direct compression technique.

Chauhan Pratik Navinchandra et al., (2011)[33] Developed mouth dissolving tablets of gliclazide using three super disintegrants hypromellose, crosspovidone and SSG at different concentrations with microcrystalline by direct compression. Among all the twelve formulations crosspovidone F6 emerged as overall best formulation due to its fast invitro dispersion when compared to other formulations and 97% drug release within 15 min.

Raja Rajeswari K et al., (2011)[34] Developed modified release hydrogel formulations of a poorly soluble drug, Gliclazide using a hydrophilic polymer HPMC in two grades i.e., HPMC 15cps and Methocel K4M. All six formulations were developed and evaluated for invitro drug release upto 16hrs and compared with that of marketed formulation. GMF VI was found to have similar release pattern proving to show controlled release following zero order release by anomalous diffusion.

S. Chandra et al., (2011)[35] Prepared fast dissolving tablets of gliclazide using solid dispersion and various concentrations of superdisintegrant agents like Ac-Di-Sol, Crospovidone, SSG by direct compression method. Among nine formulations, tablets of batch F6 containing Crospovidone and Avicel 102 showed super organoleptic properties along excellent invitro disintegration time and drug release as compare to other formulations.

Mahendra labana et al., (2011)[36] Designed modified release gliclazide by direct compression using HPMC as polymer, Dibasic calcium phosphate and maltodextrin as

binder. The prepared formulations were further evaluated for hardness, friability, drug content uniformity, in vitro dissolution time and short term stability and drug excipient interaction were studied.

Narendra Sharma et al., (2011)[37] Developed second derivative spectrophotometric method for determination of metformin hydrochloride in bulk and in tablet dosage form. The quantitative determination of the drug was carried out using the second derivative values measured at 233.8 nm. Calibration graph constructed at 233.8 nm was linear in concentration range of 4-20 μg/ml with correlation coefficient 0.9979. The method was validated as per ICH guidelines and can be used for determination of Metformin hydrochloride in tablet dosage form.

S A Patil et al., (2010)[38] Formulated solid dispersion of metformin hydrochloride using methocel K100M as carrier by solvent evaporation and co grinding method. Solid dispersion with 1:4 and 1:5 ratio of drug to polymer obtained by solvent evaporation and cogrinding were selected as best candidates suitable for prolonged release oral dosage form of metformin.

Dr K.L.Senthilkumar et al., (2011)[39] Formulated and evaluated metformin sustain release tablets using different polymers as release retarding agent and concluded that formulation of sustained release tablet of metformin containing 13% HPMC K100 with binder PVP K30 was found to be ideal or optimized formulation of sustained release tablets for 10 hour release as it fulfils all the requirements for sustained release tablet.

M. M. Varma et al., (2010)[40] Designed gastroretentive floating drug delivery system of metformin hydrochloride using HPMC K4M and carbopol 934P as polymers and sodium bicarbonate as gas generating agent by wet granulation method. Release of metformin HCl from the floating tablets formulated with HPMC and /carbopol was slow and spread over 12 h and depended on % of polymer in the tablet. Batch F4 (carbopol 934P 150 mg, sodium bicarbonate 50 mg) showed better sustained release than other formulations.

N. Aruna et al., (2011)[41] Formulated metformin HCl sustained release matrix tablet using Syzygium cumini as a release retarding agent which is antidiabetic in nature using various polymers HPMC K100M, Eudragit RLPO, Carbopol940, Ethyl cellulose by wet granulation method. Formulation containing HPMC K100M and ethyl cellulose showed

sustained drug release pattern upto 12 hrs which matched drug release pattern of innovator.

Sunil Kumar et al., (2011)[42] Designed extended release metformin tablet by wet granulation method using HPMC K100M as polymer, stearic acid and IPA as binder. The prepared formulations were further evaluated for hardness, friability, drug content uniformity, in vitro dissolution time and for in vitro drug release pattern in pH 6.8 phosphate buffer and short term stability and drug-excipient interaction were studied.

Manju Nagpal et al., (2011)[43] Developed oro-dispersible tablets of metformin by direct compression method using super disintegrants, effervescent and sublimation approach. Batch C4 prepared by effervescent approach was found to have the least disintegration time and maximum in vitro dissolution profile.

Margret Chandira et al., (2010)[44] Formulated extended release matrix tablet of metformin hydrochloride using different combinations of polymers HPMC K100M CR and carbopol 71 G by wet granulation method. Formulations F7, F9 and F10 containing HPMC K 100 M CR and Carbopol 71G in different concentration shows the extended drug release for up to 10 hrs, among these formulation, F10 is considered as optimized formulation because it shows similar drug release pattern with that of innovator.

Harrower AD et al., (2009)[45] Performed studies to assess the efficacy of various sulfonyl ureas in the management of diet failed NIDDM patients. The results showed that gliclazide is a potent hypoglycaemic agent having low incidence of side effects, few problems with hypoglycaemia and retains its efficacy longer than other sulfonylureas.

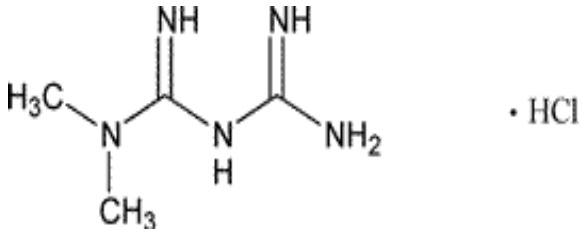
Pareek et al., (2010)[46] Evaluated efficacy and tolerability of metformin and gliclazide combination and found that addition of gliclazide to metformin is an effective treatment for inadequately controlled patients on sulfonyl urea or metformin alone and its combination achieves good glycemic control and improves lipid levels with better tolerability.

DRUG AND EXCIPIENTS PROFILE

METFORMIN HYDROCHLORIDE[47]:

Metformin is an oral antidiabetic drug in the biguanide class. It is the first-line drug of choice for the treatment of type 2 diabetes, in particular, in overweight and obese people and those with normal kidney function.

Chemical structure:



IUPAC name: N,N-dimethylimidodicarbonimidic diamide

Chemical formula: $C_4H_{11}N_5.HCl$

Molecular weight: 165.63 g/mol

Category: hypoglycemic

Dose: 0.5 to 3 g daily, in divided doses

PROPERTIES:

Description: white, crystalline powder hygroscopic

Solubility: freely soluble in water; slightly soluble in ethanol (95%); practically insoluble in acetone, chloroform, dichloromethane and ether.

Melting point: 222-226˚C

Storage: store in well closed container.

MECHANISM OF ACTION:

Metformin improves hyperglycaemia primarily by suppressing glucose production by the liver. Metformin activates AMP-activated protein kinase (AMPK), an

enzyme that plays an important role in insulin signalling, whole body energy balance, and the metabolism of glucose and fats. The mechanism by which biguanides increase the activity of AMPK remains uncertain; however, metformin increases the amount of cytosolic AMP. In addition to suppressing hepatic glucose production, Metformin increases insulin sensitivity, enhances peripheral glucose uptake (by phosphorylating GLUT-4 enhancer factor), increases fatty acid oxidation and decreases absorption of glucose from the gastrointestinal tract. Increased peripheral utilization of glucose may be due to improved insulin binding to insulin receptors.

Bioavailability **:** 50 to 60% under fasting conditions

Half life **:** 6.2 hours

Plasma protein binding **:** negligible

Volume of distribution **:** 300 – 1000 L

Metabolism **:** none.

Excretion **:** active renal tubular excretion.

CONTRAINDICATIONS

- Hypersensitivity to drug.
- Acute or chronic metabolic acidosis with or without coma.
- Underlying renal dysfunction.
- Heart failure requiring drug therapy.

ADMINISTRATION

- Administer with a meal.
- Make sure patient swallows extended release tablets whole without crushing or chewing.
- Don't administer extended release tablets to children.

DOSING INFORMATION

- Usual Adult Metformin Dose for Diabetes Mellitus Type II:
  500 mg orally twice a day (with the morning and evening meal)
- Extended Release:

500 to 2000 mg orally once a day (with the evening meal). Maximum daily dose is 2500 mg.

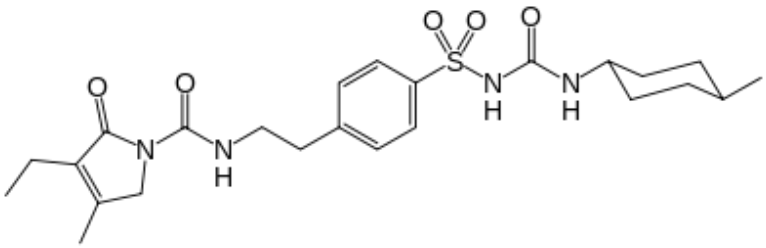
Adverse reactions

Diarrhoea, nausea, vomiting, abdominal bloating, abdominal cramping or pain, flatulence, anorexia.

GLIMEPIRIDE[48]:

It is a medium-to-long acting sulfonylurea anti-diabetic drug. It is sometimes classified as the first third-generation sulfonylurea,[1] and sometimes classified as second-generation

Structure:



Molecular weight: 490.617 g/mol

Molecular formula: $C_{24}H_{34}N_4O_5S$

Pharmacologic class: sulfonyl urea

Therapeutic class: hypoglycaemic

PROPERTIES:

Description: White, hydrophobic powder

Solubility: Practically insoluble in water, soluble in dimethylformamide, slightly soluble in methylene chloride, very slightly soluble in methanol.

Melting point: 181^0C

Storage: store in well closed container.

MECHANISM OF ACTION:

Like all sulfonylurea, Glimepiride acts as an insulin secretagogue. It lowers blood sugar by stimulating the release of insulin by pancreatic beta cells and by inducing increased activity of intracellular insulin receptors. Not all secondary sulfonylurea have the same risks of hypoglycaemia. Glibenclamide (glyburide) is associated with an incidence of hypoglycaemia of up to 20–30%, compared to 2% to 4% with Glimepiride. Glibenclamide also interferes with the normal homeostatic suppression of insulin secretion in reaction to hypoglycaemia, whereas Glimepiride does not have this property. Furthermore, glibenclamide diminishes the glucagon secretion in reaction to hypoglycaemia, whereas Glimepiride does not suppress this counter-regulatory reaction

Half life: **5** hours

Plasma protein binding : >99.5%, highly bound to plasma proteins

Metabolism: Extensively metabolized in the liver

Excretion: Metabolites and conjugates are eliminated primarily by the kidneys (60-70%) and also in the feces (10-20%).

Indications: Type 2 Diabetes Mellitus

Contraindications:

- Hypersensitivity to Glimepiride or other sulfonylurea
- Pregnancy

Adverse effects:

- Hypoglycaemia
- Gastrointestinal disturbance (reported)
- Skin reactions (rare)
- thrombocytopenia (rare)
- leukopenia
- haemolytic anaemia

SODIUM STARCH GLYCOLATE [49] :

Nonproprietary Names :

BP : Sodium Starch Glycollate

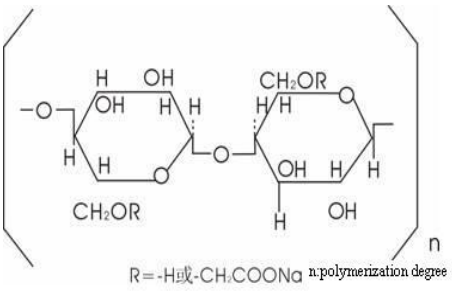
Ph Eur : Carboxymethylamylum natricum

USPNF : Sodium starch glycolate

Synonyms : Carboxymethyl starch, sodium salt; Explosol; Explotab; Glycolys; Primojel; starch carboxymethyl ether, sodium salt; Tablo; Vivastar P.

Chemical Name : Sodium carboxymethyl starch.

Structural Formula :



Molecular weight: $5\times10^5 - 1\times10^6$

Functional Category: Tablet and capsule disintegrant

Applications in pharmaceutical formulation or technology:

Sodium starch glycolate is widely used in oral pharmaceuticals as a disintegrant in capsule and tablet formulations. It is commonly used in tablets prepared by either direct compression or wet-granulation processes. The usual concentration employed in a formulation is between 2% and 8%, with the optimum concentration about 4%, although in many cases 2% is sufficient. Disintegration occurs by rapid uptake of water followed by rapid and enormous swelling.

Sodium starch glycolate has also been investigated for use as a suspending vehicle.

Description: Sodium starch glycolate is a white to off-white, odourless, tasteless, free-flowing powder.

Typical Properties: Acidity / alkalinity: pH 3.0–5.0 or pH 5.5–7.5 for a 3.3% w/v aqueous dispersion.

HYDROXY PROPYL METHYL CELLULOSE [50]:

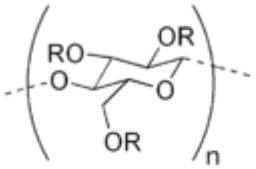
Nonproprietary Names:

BP: Hypromellose
JP: Hydroxypropylmethylcellulose
PhEur: Hypromellosum
USP: Hypromellose

Synonyms: Benecel MHPC; E464; hydroxypropyl methylcellulose; HPMC; Methocel; methylcellulose propylene glycol ether; methyl hydroxypropylcellulose; Metolose; Tylopur.

Chemical Name: Cellulose hydroxypropyl methyl ether

Structural Formula:



R = H or CH_3 or $CH_2CH(OH)CH_3$

Functional Category: Coating agent; film-former; rate-controlling polymer for sustained release; stabilizing agent; tablet binder; viscosity increasing agent.

Applications in pharmaceutical formulation or technology:

It is widely used in oral, ophthalmic and topical pharmaceutical formulations.

- Oral use - tablet binder, in film-coating, and as a matrix for use in Extended - release tablet formulations.

- Ophthalmic use - added as a thickening agent to vehicles for eye drops and artificial tear solutions.
- Topical use - emulsifier, suspending agent, and stabilizing agent in topical gels and ointments.

Description: Hypromellose is an odourless and tasteless, white or creamy white fibrous or granular powder.

Typical Properties: Acidity/alkalinity: pH = 5.5–8.0 for a 1% w/w aqueous solution.

Density (tapped): 0.557 g/cm^3

Density (true): 1.326 g/cm^3

Solubility: soluble in cold water, forming a viscous colloidal solution

XANTHAN GUM [51]:

Nonproprietary Names :

BP: Xanthan gum
PhEur: Xanthani gummi
USPNF: Xanthan gum

Synonyms: Corn sugar gum; E415; Keltrol; polysaccharide B-1459; Rhodigel; Vanzan NF; Xantural

Chemical Name: Xanthan gum.

Functional Category: Stabilizing agent; suspending agent; viscosity-increasing agent.

Applications in pharmaceutical formulation or technology:

Xanthan gum is widely used in oral and topical pharmaceutical formulations, cosmetics, and foods as a suspending and stabilizing agent.(3–5) It is also used as a thickening and emulsifying agent.

Description: Xanthan gum occurs as a cream- or white-colored, odorless, free-flowing, fine powder.

Typical properties: Acidity/alkalinity: pH = 6.0–8.0 for a 1% w/v aqueous solution. Melting point chars at 270˚C.
Solubility: practically insoluble in ethanol and ether; soluble in cold or warm water

MICRO CRYSTALLINE CELLULOSE [52] :

Nonproprietary Names:

BP: Microcrystalline cellulose
PhEur: Cellulosum microcristallinum
USPNF: Microcrystalline cellulose

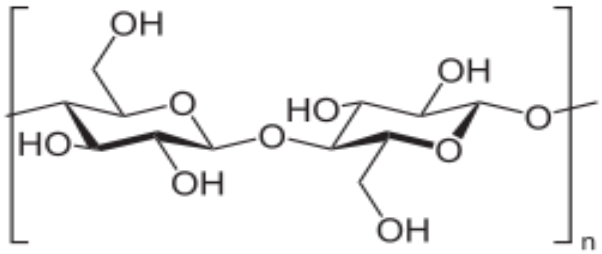
Synonyms: Avicel PH; Celex; cellulose gel; Celphere; Ceolus KG; crystalline cellulose; E460; Emcocel; Ethispheres; Fibrocel; Pharmacel; Tabulose; Vivapur.

Chemical Name: Cellulose

Empirical Formula: $(C_6H_{10}O_5)_n$

Molecular weight: approx. 36,000 where n is approx 220.

Structural Formula:



Functional Category: Adsorbent; suspending agent; tablet and capsule diluent; tablet disintegrant.

Applications in pharmaceutical formulation or technology:

Binder/diluent in oral tablet and capsule formulations where it is used in both wet-granulation and direct-compression processes

Description: Microcrystalline cellulose is a purified, partially depolymerized cellulose that occurs as a white, odorless, tasteless, crystalline powder composed of porous particles.

Typical Properties: Density (bulk) : 0.337 g/cm3
Density (tapped): 0.478 g/cm3
Density (true) : 1.512–1.668 g/cm3
Melting range : chars at 260–270˚C.
Solubility: slightly soluble in 5% w/v sodium hydroxide solution; practically insoluble in water, dilute acids, and most solvents

MAGESIUM STEARATE [53] :

Nonproprietary names:

BP/JP/USPF : Magnesium stearate.
Ph Eur : Magnesii stearas.

Synonyms: Magnesium octadecanoate; octadecanoic acid, magnesium salt; stearic acid, magnesium salt.

Chemical name: Octadecanoic acid magnesium salt.

Empirical formula: $C_{36}H_{70}MgO_4$

Molecular weight: 591.34

Structural formula: $[CH_3(CH_2)16COO]2Mg$

Functional Category:

USP: Tablet and capsule lubricant.
BP/EP: lubricant, pharmaceutical aid.
Others: Glidant, anti-adherent.

Applications in pharmaceutical formulation or technology:

Tablet and capsule lubricant, glidant or anti-adherent.

Description: Magnesium stearate is a very fine, light white, precipitated or milled, impalpable powder of low bulk density, having a faint odor of stearic acid and a characteristic taste.

Typical Properties: Density (bulk): 0.159 g/cm3

Density (tapped): 0.286 g/cm3

Density (true): 1.092 g/cm3

Melting range: 126–1308C (high purity magnesium stearate)

Solubility: Practically insoluble in ethanol, ether and water; slightly soluble in warm benzene and ethanol (95%).

TALC [54] :

Nonproprietary names:

BP : Purified talc

JP : Talc

PhEur : Talcum

USP : Talc

Synonyms: Altalc; E553b; hydrous magnesium calcium silicate; hydrous magnesium silicate; Luzenac Pharma; magnesium hydrogen metasilicate; Magsil Osmanthus; Magsil Star; powdered talc; purified French chalk; Purtalc; soapstone; steatite; Superiore.

Chemical name: Talc

Empirical Formula: $Mg_6(Si_2O_5)4(OH)4$

Molecular Weight: 379.3 g/mol

Functional Category: Anticaking agent; glidant; tablet and capsule diluent; tablet and capsule lubricant

Applications in pharmaceutical formulation or technology:

Talc was once widely used in oral solid dosage formulations as a lubricant and diluent. In topical preparations, talc is used as a dusting powder, although it should not be used to dust surgical gloves. Talc is additionally used to clarify liquids and is also used in cosmetics and food products, mainly for its lubricant properties.

Description: is a very fine, white to grayish-white, odorless, impalpable, unctuous, crystalline powder. It adheres readily to the skin and is soft to the touch and free from grittiness.

Typical properties: Acidity/alkalinity: pH 7–10 for a 20% w/v aqueous dispersion.
Solubility : Practically insoluble in dilute acids and alkalis, organic solvents, and water.

AIM AND PLAN OF WORK

Metformin is an oral antidiabetic biguanide drug for the treatment of type 2 diabetes, in particular, in overweight and obese people and those with normal kidney function. It is a class III high soluble, low permeable compound slowly and incompletely absorbed from the gastrointestinal tract and the absolute bioavailability of a single 500mg dose is reported to be 50%-60%. The compound also has relatively short plasma elimination half-life of 1.5 to 4.5 hrs, hence Metformin HCl has to be administered two or three times per day. Glimepiride is one of the third generation sulfonylurea drugs useful for control of diabetes. It maintains a more physiologic regulation of insulin secretion and the risk of hypoglycaemia is less than with other sulfonylurea. It's a white hydrophobic powder, practically insoluble in water; bioavailability is 100%, half-life is 5 hrs and available dose is generally 1mg or 2mg once a day. Glimepiride and Metformin simultaneously targets insulin resistance and insulin deficiency type II diabetes.

The aim is to develop a combination drug therapy for anti diabetic tablet formulation having different mechanism of action to complement each other and together effectively lower blood glucose level. The immediate release layer of Glimepiride is prepared by direct compression method using SSG as superdisintegrant with other excipients and sustained release layer of Metformin HCl are prepared by wet granulation method using HPMC and Xanthan Gum as polymer in different concentration with other excipients

PLAN OF WORK

1. To carry out brief literature review
2. Drug excipients compatibility studies by FT-IR
3. Formulation of granules for compression
4. Precompression evaluation
5. Formulation of Bilayer tablets
6. Postcompression evaluation
7. Pharmacokinetic study
8. Stability study

EXPERIMENTAL

MATERIALS USED:

Table 2 :

Name of the materials	Use in formulation	Manufacturers
Metformin HCl	Active ingredient	Arti Drugs Ltd.
Glimepiride	Active ingredient	Enaltec Labs Pvt. Ltd.
HPMC $K_{100}M$	Hydrophilic polymer	Shin_ETSU Chemicals Ltd.
Xanthan gum	Hydrophilic polymer	Shin_ETSU Chemicals Ltd.
Micro Crystalline Cellulose Avicel	Directly compressible diluents	Gujarat Microwax Pvt. Ltd.
Sodium Carboxy Methyl Cellulose	Hydrophilic polymer	Shin_ETSU Chemicals Ltd.
Iso propyl alcohol	Binder	Arti Drugs Ltd.
Sodium starch glycolate	Super disintegrants	Maruti chemicals ltd
Magnesium Stearate	Glidant	Vasa Pharmaceuticals Pvt Ltd
Talc	Lubricant	Gujarat Microwax Pvt. Ltd.
Col. Brilliant blue lake	Dye	Narmada Food and Drugs Ltd

INSTRUMENTS USED:

Table 3:

S. No.	Instrument	Manufacturer
1	Electronic Balance	Mettler Toledo, Mumbai
2	Rotary tablet Compression Machine (10 stages)	Cadmach, Ahmedabad
3	Hardness Tester	Electrolab, Mumbai
4	Friability Test Apparatus	Electrolab, Mumbai
5	Vernier calliper	Inox- somet, Japan
6	Dissolution apparatus.	Lab India. (USP XX III) (DTD – 06P), Mumbai
7	Double beam UV Spectrophotometer	Systronic corporation, Mumbai
8	FTIR Spectrophotometer	Shimadzu, Mumbai
10	Digital pH meter	Hanna instruments, Japan
11	Hot Air Oven	Kemi, Mumbai
12	Melting point apparatus.	Kemi, Mumbai
13	Bulk density apparatus.	Kemi, Mumbai

PREFORMULATION STUDIES:

Preformulation studies are the first step in the rational development of dosage form. It is an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. Preformulation investigations are designed to identify those physicochemical properties and excipients that may influence the formulation design, method of manufacture and pharmacokinetic-biopharmaceutical properties of the resulting product. Following are the test performed for the preformulation study.

Drug and Excipients compatibility studies[55, 56]:

Physical compatibility studies by FTIR:

The active ingredients and polymer (1:1) were mixed and taken in 2 ml glass vials and sealed. Then these glass vials were kept at room temperature and 40^0C/75%RH for about 1 month. The physical compatibility evaluation was performed in visual basis. The study implies that the drug, polymer and other excipients were physically compatible with each other as there was no change of physical description. The results have been shown in the Table 4.

Table 4: Drug–Excipients Physical compatibility studies

S.No	Drug + Excipients	Description at initial day	RT,40^0C/75%RH In days		
			10^{th}	20^{th}	30^{th}
1	MH	White, Crystalline powder	NC	NC	NC
2	GL	White, Crystalline powder	NC	NC	NC
3	XG	Creamy yellow crystalline powder	NC	NC	NC
4	HPMC $K_{100}M$	White, creamy crystalline powder	NC	NC	NC
5	SSG	White, free-flowing hygroscopic powder	NC	NC	NC
6	MCCP	White, crystalline powder	NC	NC	NC
7	Mg. Stearate	White, crystalline powder	NC	NC	NC
8	Talc	White or greyish white powder	NC	NC	NC
9	MH+GL	White, Crystalline powder	NC	NC	NC
10	MH+GL+XG	White, crystalline powder	NC	NC	NC
11	MH+GL+HPMC	White, crystalline powder	NC	NC	NC
12	MH+GL+SSG	White, crystalline powder	NC	NC	NC
13	MH+GL+All Exipients	White, crystalline powder	NC	NC	NC

MH-Metformin HCl, **GL**-Glimepiride, **XG**-Xanthan gum, **HPMC $K_{100}M$**-Hydroxy propyl methyl cellulose Grade, **SSG**-Sodium starch glycolate, **MCCP**-Microcrystalline cellulose powder

Chemical compatibility studies by FTIR:

IR spectra of drug and polymers and all super disintegrants alone and along with drug in KBr pellets at moderate scanning speed between 4000-400cm^{-1} was carried out using FTIR. The peak values and the possibility of functional groups shown in spectra (Table 4 & 5) were compared with standard values and shown below Fig 4 to 8.

Chemical compatibility studies by FT-IR:

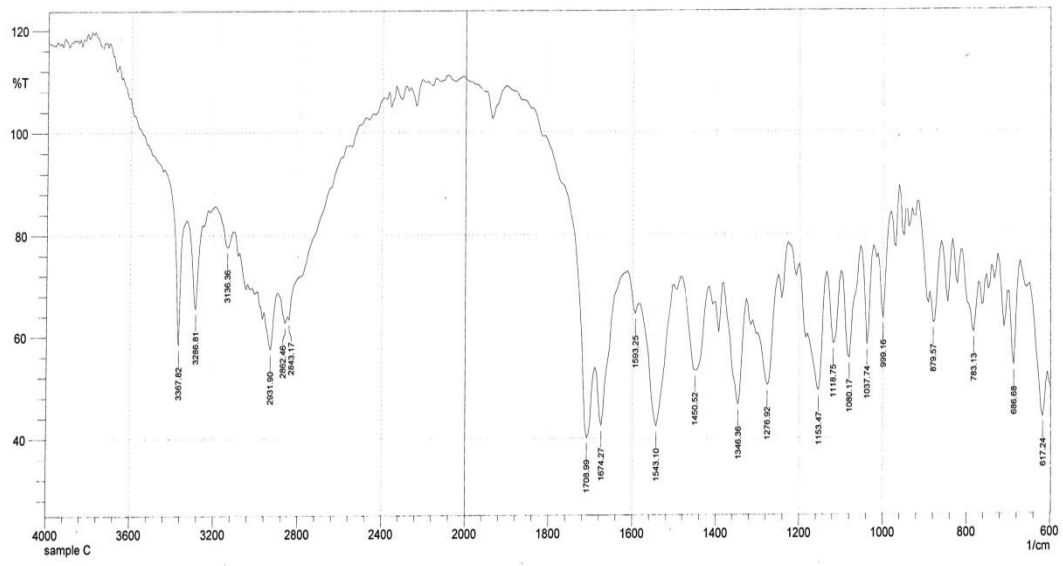


Fig 4: FT-IR spectra of Glimepiride

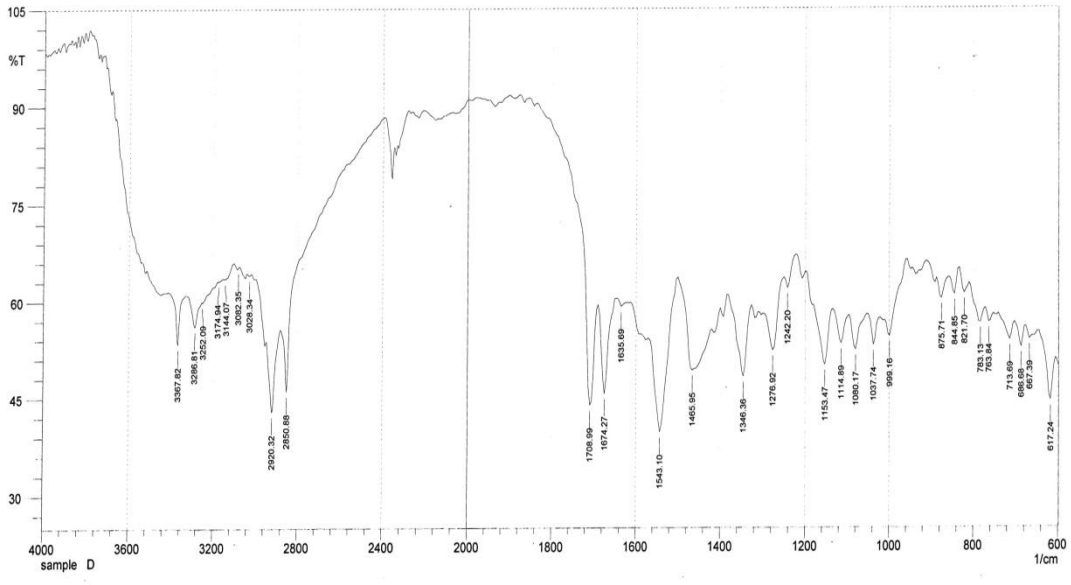


Fig 5: FT-IR spectra of Glimepiride + Sodium starch glycolate

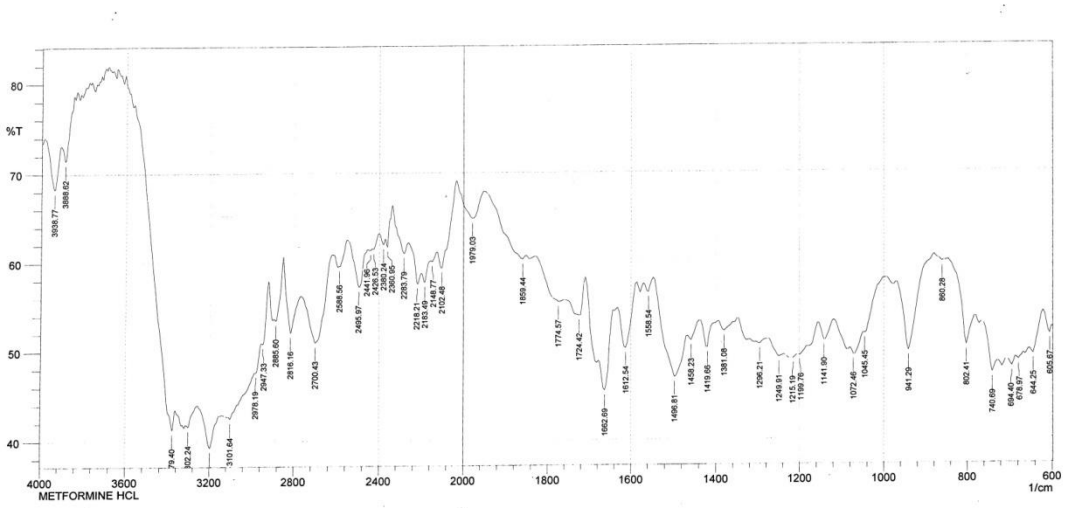


Fig 6: FT-IR spectra of Metformin HCl

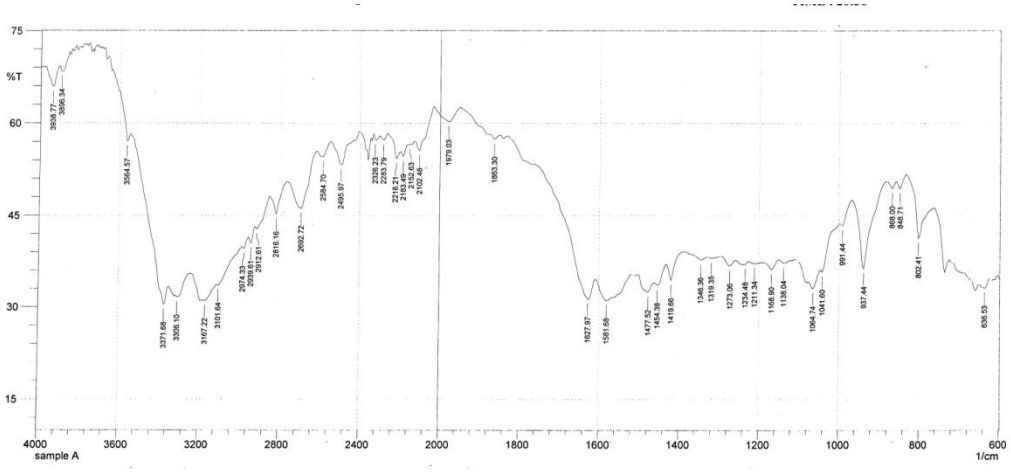


Fig 7: FT-IR spectra of Metformin HCl + HPMC

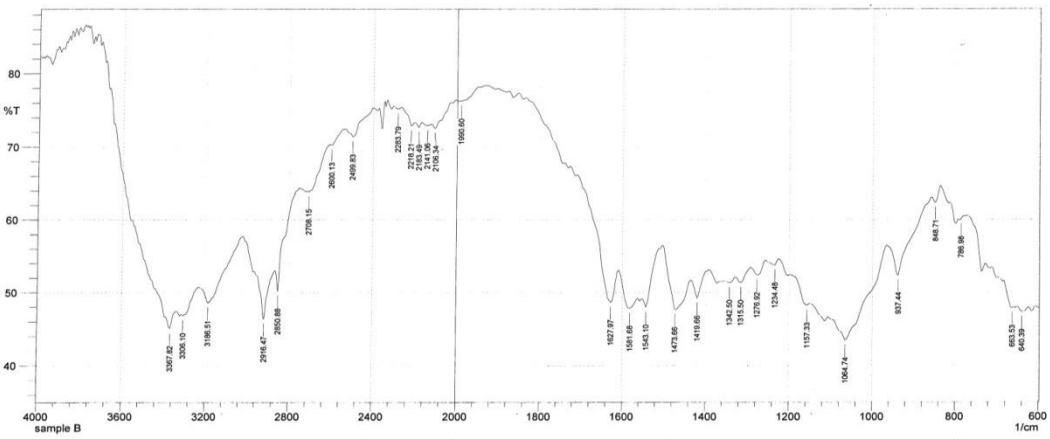


Fig 8: FT-IR spectra of Metformin HCl + Xanthan gum

Table 5: Interpretation of FT-IR spectra of Glimepiride

S. no	Functional group	Assessment peaks
1	N-H Amine	3367
2	C-H Aromatic	2931
3	C=O Amide	1708.17
4	C=C Aromatic	1543.10
5	Sulfoxides	1080

Table 6: Interpretation of FT-IR spectra of Metformin HCl

S. no	Functional group	Assessment peaks
1	C-H Alkanes	1458, 1381
2	C-H Strech	2885
3	N-H Amide	3200

Standard curve of Metformin HCl

100 mg of metformin HCl was dissolved in 100 ml of phosphate buffer pH 6.0 (stock solution). From the stock solution aliquots of 10, 20, 30, 40, 50 ml were pipetted out and made up to 100 ml with buffer. The absorbance of above solution was measured at 254 nm by UV spectrometer.

Correlation coefficient value indicates there is a linear correlation between concentration and absorbance. Metformin HCl obeys the beers law in concentration range of 10-100 µg/ml at 254 nm.

Table 7:

Concentration (µg/ml)	Absorbance
0	0
10	0.281
20	0.573
30	0.838
40	1.119
50	1.387

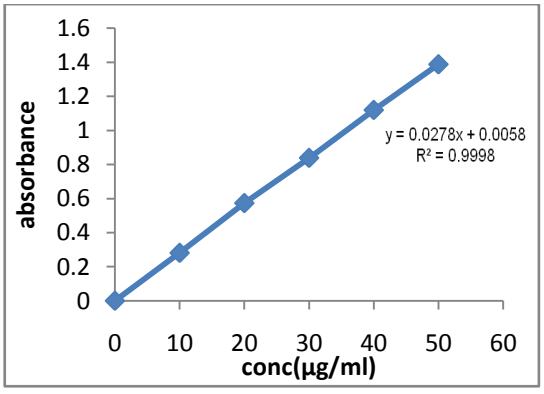


Fig 9: Calibration curve of Metformin HCl

Preparation of Bi layer tablets

Formula of immediate release Glimepiride:

Composition of the immediate release layer is given in Table 7. The final weight of the immediate release layer was fixed to 200 mg. An immediate release Glimepiride layer was prepared by direct compression. Accurately weighed quantity of Glimepiride, MCC and SSG were passed through sieve 40, mixed with brilliant blue lake which is passed from sieve 100. Add talc to above, rotate for 3 minutes at 20 rpm. Magnesium stearate was shifted through sieve 30 and blended with the final screened granules for 5 min at 20 rpm.

Table 8: Formula of immediate releasing layer

Ingredients	Quantity (mg)
Glimepiride	1
MCCP Avicel	188
SSG	6
Mg stearate	2
Talc	2
Brilliant blue lake	1
Total Weight of 1 tablet	200

Formula of sustained release Metformin HCl granules:

Compositions of different trial formulations for the sustained release layer are given in Table 8. Different batches of Metformin HCl sustained release layer (F_1 to F_6) were prepared with varying concentrations of different polymer by wet granulation method. Accurately weighed quantity of Metformin HCl, Micro Crystalline Cellulose, HPMC K100M, Sodium Carboxy Methyl Cellulose, Xanthan gum and talc were sieved using screen 22. The screened powders were then transferred into the rapid mixer granulator and mixed for 5 min. Binder solution of IPA were prepared. The dry mix was granulated by the above binder solution. Impeller was kept at 200 rpm. One to two minute binder addition and three min kneading without chopper was used to get desired granules. Drying of wet granules was carried out in rapid dryer (Retch rapid dryer, Germany) at temperature 50^0C and air flow at 60%. Final dried granules were passed through screen 20. Extra granular magnesium stearate was sifted through screen 40 and added to the above blend in blender and mixed for 3 min at 20 rpm.

Table 9: Formula of sustaining layer.

Ingredients	Quantity (mg)					
	F_1	**F_2**	**F_3**	**F_4**	**F_5**	**F_6**
Metformin HCl	504	504	504	504	504	504
Sodium Carboxy Methyl Cellulose	50	50	50	50	50	50
$HPMCK_{100}M$	-	-	-	150	200	250
Xanthan gum	150	200	250	-	-	-
MCC	120	70	20	120	70	20
Iso propyl alcohol	q.s	q.s	q.s	q.s	q.s	q.s
Talc	5	5	5	5	5	5
Magnesium stearate	20	20	20	20	20	20
Total wt	850	850	850	850	850	850

Pre compression Studies of granules [57, 58]:

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 (Table 12) and calculated according to the formula mentioned below. 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):

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 (Table 12). 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 (θ):

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

$$\theta = \tan^{-1} (h / r)$$

Where, θ - angle of repose.

h - height in cms

r - radius in cms.

The powder mixture was allowed to flow through the funnel fixed to a stand at definite height (h). The angle of repose was then calculated by measuring the height and radius of the heap of powder formed (Table 12). Care was taken to see that the powder particles slip and roll over each other through the sides of the funnel. Relationship between angle of repose and powder flow property.

Table 10: Angle of Repose as an Indication of Powder Flow Properties

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

4. Carr's index (or) % compressibility:

It indicates powder flow properties. It is expressed in percentage and is give

$$I = \frac{Dt - Db}{Dt} \times 100$$

Where, Dt - tapped density of the powder and

Db - bulk density of the powder.

Table 11: Relationship between % compressibility and flow ability

Percentage compressibility	Flow ability
5-12	Excellent
12-16	Good
18-21	Fair passable
23-35	Poor
33-38	Very poor
<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 (Table 12).

$$\text{Hausner's ratio} = \frac{Dt}{Db}$$

Where, Dt - tapped density, Db - bulk density.
Lower Hausner's ratio (<1.25) indicates better flow properties than higher ones (>1.25).

Table 12: Precompression study

S. no	Parameters	Formulation type	Formulation code					
			F1	F2	F3	F4	F5	F6
1	Angle of repose	Immediate Release layer	25.68	26.1	24.86	25.57	26.46	25.52
		Sustained Release layer	31.58	30.7	32.71	29.52	27.81	28.14
2	Bulk density (gm/cm^2)	Immediate Release layer	0.454	0.448	0.452	0.461	0.451	0.453
		Sustained Release layer	0.57	0.556	0.54	0.567	0.548	0.58
3	Tapped density (gm/cm^2)	Immediate Release layer	0.523	0.512	0.538	0.517	0.511	0.512
		Sustained Release layer	0.661	0.658	0.642	0.661	0.635	0.671
4	Hauser's ratio	Immediate Release layer	1.15	1.14	1.19	1.10	1.13	1.13
		Sustained Release layer	1.15	1.18	1.18	1.16	1.15	1.15
5	Compressibility index (%)	Immediate Release layer	13.19	12.5	15.98	9.80	11.74	12.10
		Sustained Release layer	13.76	15.50	15.62	14.22	13.70	13.43

COMPRESSION OF BILAYER TABLET:

Compression of bilayer tablets were done by using Cadmach double rotary bi-layer compression machine (Cadmach, Ahmedabad). The prepared granules of each layer were compressed using 19.00 × 9.00mm, 'D' tooling standard concave, flat faced modified capsule shaped punch. The hardness was kept between 9-12kp. Both the prepared granules came from two different hoppers to two different feed frames where they occupied the die cavity. The bottom or first layer of Metformin HCl was compressed first with lower pressure, which was then followed by filling of the die cavity by the second layer Glimepiride. The final compression was done only after both the granules occupied the die cavity one on top of the other. Both the layers were identified on the basis of colour since the immediate release layer had blue colour and the sustain release layer is white colour (Fig 10).

Table 13: Punches specification

S. no	Punch parameters	
1	Punch diamension	19 X 9 mm
2	Punch shape	Concave
3	Upper punch	Break line
4	Lower punch	Plane

Fig 10: Photograph of prepared bilayer tablets

POST COMPRESSION STUDIES OF TABLETS[61, 62]:

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 I.P. is shown in (Table 14). The tablet compression machine was suitably in tune to produce tablets of uniform weight.

Table 14: Weight Variation Specification as per IP

Average weight of tablet	Percent deviation
80 mg or less	±10
More than 80 mg but less than 250mg	±7.5
250 mg or more	±5

Thickness:

The thickness in millimeters was measured individually for 10 preweighed tablets by using vernier calipers. The average thickness was reported. Thickness may affect the hardness, disintegration time and dissolution rate (Table 15).

Hardness:

Tablet hardness was measured using electrolab hardness tester. The crushing strength of the 10 tablets with known weight and thickness of each was recorded in kilopond (kp) and the average hardness was reported. Tablets hardness was checked at the start and during the compression process to control an acceptable range of tablet hardness (Table 15).

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 (Table 15).

$$F = \frac{\text{Initial wt} - \text{Final wt}}{\text{Initial wt}} \times 100$$

Table 15: Post compression parameters

S. no	Parameters		Formulation					
			F1	F2	F3	F4	F5	F6
1	Weight variation (mg)		1060.5	1059.2	1051.9	1062.4	1055.8	1056.2
2	Thickness (mm)		6.63	6.69	6.70	6.78	6.71	6.70
3	Hardness (kg/cm^2)		10.1	9.8	10.2	10.4	9.9	10.1
4	Friability (%)		0.46	0.49	0.44	0.51	0.46	0.51
5	Content Uniformity (%)	IR	98.81	99.25	99.35	98.77	99.86	99.98
		SR	99.92	98.8	99.67	99.57	99.01	99.24

Drug content of bilayer tablet

For Metformin HCl

Preparation of phosphate buffer pH 6.0:

Weigh accurately about 6.8 gm of potassium dihydrogen orthophosphate in 1000 ml beaker, add sufficient water to dissolve and make up the volume with water. Adjust pH 6.0 with 1 M sodium hydroxide.

Standard preparation:

Weigh accurately about 50mg of Metformin HCl WS in 100ml volumetric flask, add 50ml of phosphate buffer pH-6 to dissolve with the aid of ultrasound and make volume 100ml with phosphate buffer pH-6. Transfer 1ml of this solution to 100ml volumetric flask and make volume 100ml with phosphate buffer pH-6.

Sample preparation:

Crush the content of 20 tablets to a fine powder and weigh equivalents to 50 mg of Metformin HCl to 100 ml volumetric flask, add 50 ml of phosphate buffer pH-6.0 to dissolve with the aid of ultrasound and make volume 100 ml with phosphate buffer pH-6.0. filter the solution through Whatman filter paper no.(1). Transfer 1 ml of this solution to 100 ml volumetric flask and make volume 100 ml with phosphate buffer pH-6.0.Measure the absorbance of standard and sample solution at about 254 nm using phosphate buffer pH-6.0 as a blank in the reference cell.

$$\text{Amount of MH} = \frac{\text{spl abs}}{\text{std abs}} \times \frac{\text{std wt}}{100} \times \frac{1}{100} \times \frac{100}{\text{spl wt}} \times \frac{\text{avg wt}}{1} \times \frac{\text{potency}}{100}$$

For Glimepiride:

Preparation of buffer:

Dissolve 1.5 gm of potassium dihydrogen phosphate in 500 ml of distilled water. Adjusted the pH with phosphoric acid.

Preparation of mobile phase:

Prepare a mixture of buffer and acetonitrile in the ratio of 800:200 respectively. Degas for 15 minutes and filter the mobile phase through 0.22 µ filter.

Diluents: 0.1 M Methanolic hydrochloride.

Chromatographic conditions:

Column : waters symmetry C_8 (100mm X 4.0 mm), 5 µ or Equivalent

Flow rate : 1.0 ml / minute

Wavelength : 276 nm

Injection volume : 20 µl

Column temperature : 40^0 C

Standard preparation:

Weigh accurately about 50 mg of Glimepiride WS to 100 ml volumetric flask, add 50 ml of diluent to dissolve with the aid of ultrasound and make volume with diluents. Transfer 10 ml of this solution to 50 ml volumetric flask and make volume with diluents.

Sample preparation:

Crush the content of 20 tablets to a fine powder and weigh accurately quantity of powder equivalent to about 5 avg weight(equivalent to 5 mg of glimepiride) of tablet to a 50 ml volumetric flask, add 25 ml of diluents to dissolve with the aid of ultrasound and make volume with diluents. Filter the solution through whatman filter paper no. 1.

$$\text{\% content uniformity} = \frac{\text{spl area}}{\text{std area}} \times \frac{\text{std wt}}{100\text{ ml}} \times \frac{10\text{ ml}}{50\text{ ml}} \times \frac{50\text{ ml}}{\text{spl wt}} \times \frac{\text{avg wt}}{100} \times \text{potency} \times \frac{100}{\text{L.C}}$$

***In-vitro* dissolution studies of bilayer tablet:**

Dissolution study of sustained release and immediate release of different tablet formulations were carried out separately.

Dissolution of sustained release tablet:

Preparation of phosphate buffer pH 6.0:

Weigh accurately about 6.8 gm of potassium dihydrogen orthophosphate in 1000 ml beaker, add sufficient water to dissolve and make up the volume with water. Adjust pH 6.0 with 1 M sodium hydroxide.

Dissolution conditions:

Apparatus	: USP Type II (Paddle type)
Medium	: 6.0 pH phosphate buffer
Rpm	: 50
Volume	: 900ml
Temp	: 37.5°C

Standard preparation:

Weigh accurately about 50mg of Metformin HCl WS in 100ml volumetric flask, add 50ml of dissolution medium to dissolve with the aid of ultrasound and make volume 100ml with dissolution medium. Transfer 2 ml of this solution to 100ml volumetric flask and make up volume with dissolution medium.

Procedure:

The study was carried out for 12 hours. 20 ml of samples were withdrawn at the time interval of 1, 2, 4, 6, 8, 10^{th} hour from the zone midway between the surface of the dissolution medium and top of the paddle, not less than 1 cm from the vessel wall. Filter through whatman filter paper no. 1. Transfer immediately 20 ml of dissolution medium to bowls to maintain the volume of medium. Transfer 2 ml of this filtrate to 100 ml volumetric flask and make volume with dissolution medium.Measure the absorbance of standard and sample solution at about 254 nm using dissolution medium as a blank in reference cell.

The percentage of Metformin HCl release was calculated using following formula.

$$\% \text{ of metformin} = \frac{\text{Spl. abs}}{\text{Std. abs}} \times \frac{\text{std wt}}{100\text{ ml}} \times \frac{2\text{ ml}}{100\text{ ml}} \times \frac{900\text{ ml}}{1} \times \frac{100\text{ ml}}{2\text{ ml}} \times \frac{1}{100} \times \text{potency} \times \frac{100}{\text{L.C}}$$

Dissolution of immediate release tablet:

Preparation of phosphate buffer pH 5.6:

Weigh accurately about 6.8 gm of potassium dihydrogen orthophosphate in 1000 ml beaker, add sufficient water to dissolve and make up the volume with water. Adjust pH 5.6 with 1 M sodium hudroxide.

Preparation of mobile phase:

Prepare a mixture of buffer and acetonitrile in the ratio of 800:200 respectively. Degas for 15 minutes and filter the mobile phase through 0.22 µ filter.

Diluents: 0.1 M Methanolic hydrochloride.

Dissolution conditions:

Apparatus: USP Type II (Paddle type)
Medium : 5.6 pH phosphate buffer
Rpm : 50
Volume : 900ml
Temp : 37.5°C

Chromatographic conditions:

Column : waters symmetry C_8 (100mm X 4.0 mm), 5 µ or Equivalent
Flow rate : 1.0 ml / minute
Wavelength : 276 nm
Injection volume : 20 µl
Column temperature : 40^0 C

Standard preparation:

Weigh accurately about 50 mg of Glimepiride WS to 100 ml volumetric flask, add 50 ml of diluents to dissolve with the aid of ultrasound and make volume with diluents. Transfer 10 ml of this solution to 100 ml volumetric flask and make volume with diluents. Further transfer 2 ml of this solution to 100 ml volumetric flask and make up volume with phosphate buffer pH 5.6.

Procedure:

Dissolution studies were carried out by USP paddle method Type II apparatus at 37± 0.50 ° c, taking 900ml of phosphate buffer pH 5.6 as a dissolution medium. Speed of rotation of paddle was set at 50rpm. Withdrawn 20 ml of solution from the zone

midway between the surface of the dissolution medium and top of the paddle, not less than 1 cm from the vessel wall. Filter through whatman filter no. (1). Samples were suitably diluted and analyzed. The percentage release was calculated.

$$\% \text{ of Metformin} = \frac{\text{spl. area}}{\text{std.area}} \times \frac{\text{std. wt}}{100\text{ ml}} \times \frac{10\text{ ml}}{100\text{ ml}} \times \frac{2\text{ ml}}{100\text{ ml}} \times \frac{900\text{ ml}}{1} \times \frac{1}{100} \times \text{potency} \times \frac{100}{\text{L.C}}$$

Table 16: *In-vitro* dissolution profile of formulation F1 to F6

Time	Formlulation type	Cumulative % of drug release					
		F1	**F2**	**F3**	**F4**	**F5**	**F6**
(Min)							
5	Immediate Release layer	54.79	57.15	56.67	56.40	56.15	57.26
10		71.12	71.10	70.88	73.24	68.66	72.43
20		89.46	89.73	90.03	92.02	89.62	90.27
30		99.06	99.33	99.00	101.55	100.93	99.80
(hours)							
1	Sustained Release layer	25.91	22.48	24.52	30.51	25.13	26.40
2		51.34	38.37	35.27	56.82	56.91	41.81
4		73.58	51.67	59.10	69.34	68.64	62.48
6		89.34	76.18	74.26	86.91	83.40	76.94
8		104.51	81.69	82.45	98.12	91.57	87.81
10			87.91	89.48		97.24	99.53

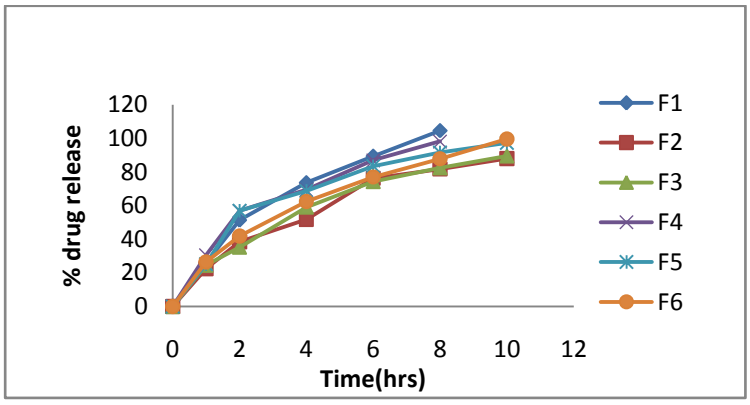


Fig 11: *In-vitro* drug release of Sustained Release layer of formulation F1 to F6

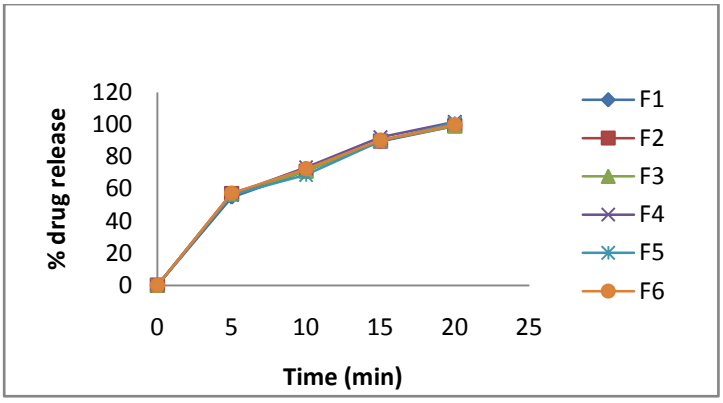


Fig 12: *In-vitro* drug release of Immediate Release layer of formulation F1 to F6

KINETIC ANALYSIS [63, 64.]

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.
5. Hixon and Crowell erosion equation – cube root of drug remaining Vs time in hrs

Zero order kinetics:

Zero order release would be predicted by the following equation: -

$$A_t = A_0 - K_0 t$$

Where,

A_t = Drug release at time 't'.

A_0 = Initial drug concentration.

K_0 = Zero - order rate constant (hr^{-1}).

When the data is plotted as cumulative percent drug release versus time, if the plot is linear then the data obeys Zero – order kinetics and its slope is equal to Zero order release constant K_0.

First Order Kinetics:

First – order release would be predicted by the following equation: -

$\text{Log } C = \log C_0 - Kt / 2.303$

Where,

C = Amount of drug remained at time‘t’.

C_0 = Initial amount of drug.

K = First – order rate constant (hr^{-1}).

When the data plotted as log cumulative percent drug remaining versus time, yields a straight line, indicating that the release follow first order kinetics. The constant ‘K_1’ can be obtained by multiplying 2.303 with the slope value.

Higuchi’s model:

Drug release from the matrix devices by diffusion has been described by following Higuchi’s classical diffusion equation: -

$Q = [D\varepsilon / \tau (2 A - \varepsilon Cs) Cst]^{½}$

Where,

Q = Amount of drug released at time‘t’.

D = Diffusion coefficient of the drug in the matrix.

A = Total amount of drug in unit volume of matrix.

Cs = the solubility of the drug in the matrix.

ε = Porosity of the matrix.

τ = Tortuosity.

t = Time (hrs) at which ‘q’ amount of drug is released.

Above equation may be simplified if one assumes that ‘D’, ‘Cs’ and ‘A’ are constant. Then equation becomes: -

$Q = Kt^{1/2}$

When the data is plotted according to equation i.e. cumulative drug release versus square root of time yields a straight line, indicating that the drug was released by diffusion mechanism. The slope is equal to 'K' (Higuchi's 1963).

Korsmeyer equation / Peppa's model:

To study the mechanism of drug release from the sustained-release matrix tablets of valsartan, the release data were also fitted to the well-known exponential equation (Korsmeyer equation/ peppa's law equation), which is often used to describe the drug release behavior from polymeric systems.

$M_t / M_\alpha = Kt^n$

Where,

M_t / M_α = the fraction of drug released at time't', K = Constant incorporating the structural and geometrical characteristics of the drug / polymer system, n = Diffusion exponent related to the mechanism of the release.

Above equation can be simplified by applying log on both sides, And we get: -

$$\text{Log } M_t / M_\alpha = \text{Log } K + n \text{ Log } t$$

Table 17: Description of diffusion mechanism

Diffusion exponent (n)	**Overall solute diffusion mechanism**
0.45	Fickian diffusion
0.45<n<0.89	Anomalous (non-Fickian) diffusion
0.89	Case-II transport
n >0.89	Super case-II transport

When the data is plotted as log of drug released versus log time, yields a straight line with a slope equal to 'n'. For Fickian release 'n' = 0.45 while for anomalous (non - Fickian) transport 'n' ranges between 0.45 and 1.0.

Hixson and crowell cuberoot erosion equation:

To evaluate the drug release with changes in the surface area and the diameter of particles, the data were plotted using the Hixson and cowell rate equation. The graph was plotted by cube root of % drug remaining Vs time in hours.

$$Q_0^{1/3}-Q_t^{1/3}=K_{HC}t$$

Where Q_t - amount of drug released in time t

Q_0 - initial amount of drug

K_{HC} - rate constant for Hixson crowell equation

Data obtained from in vitro release of metformin hydrochloride from the bilayer tablets were fitted in various kinetic models and results are tabulated in the Table No.

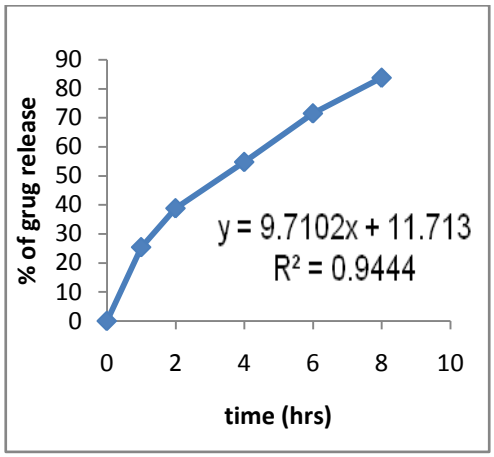


Fig 13: Zero order plot

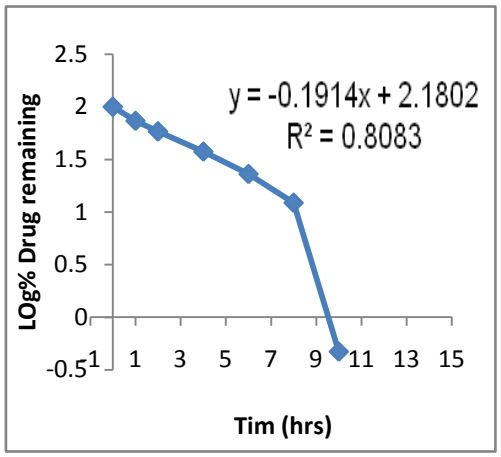


Fig 14: First order Plot

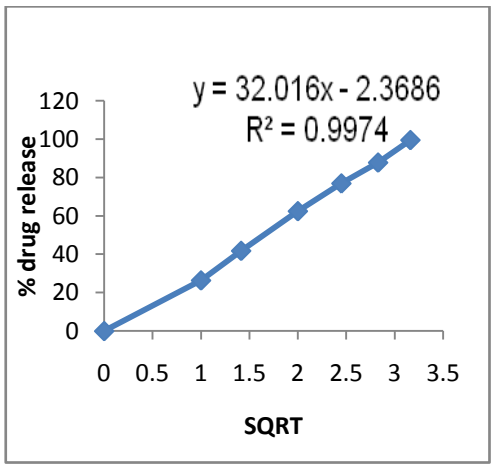


Fig 15: Higuchi plot

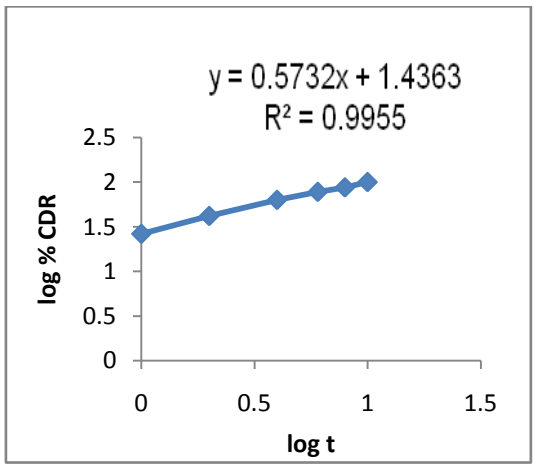


Fig 16: Korsmeyer -Peppas plot

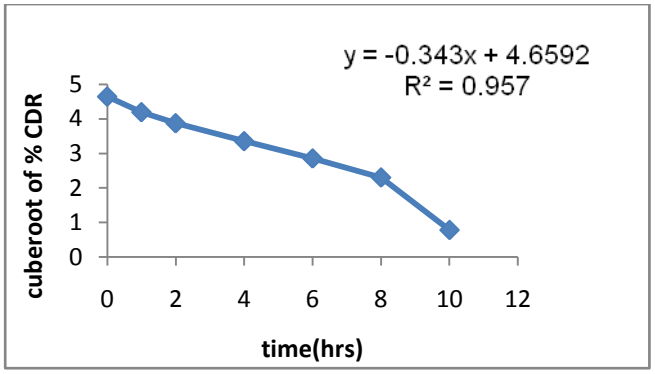


Fig 17: Hixson crowell cuberoot plot

Table 18: Results of kinetic study

Formulation code	Zero order (R^2)	First order (R^2)	Higuchi's kinetics (R^2)	Peppa's kinetics		Hixson Crowell's kinetics(R^2)
				R^2	N	
F1	0.932	0.995	0.988	0.972	0.648	0.991
F2	0.921	0.988	0.984	0.983	0.598	0.978
F3	0.922	0.998	0.991	0.990	0.585	0.990
F4	0.890	0.924	0.988	0.958	0.532	0.980
F5	0.849	0.979	0.971	0.911	0.544	0.980
F6	0.944	0.808	0.997	0.995	0.573	0.957

From the Table, it is proposed that the formulation follows zero order with regression value of 0.944. n value of Peppas equation was found to be 0.573. So the drug release follows non-fickian diffusion or anomalous release ($0.45<n<1$). Thus release was dependant both on drug diffusion and polymer relaxation. Based on the correlation coefficient obtained for higuchi's square root equation (0.997) and Hixson crowell cube root equation (0.957), drug release kinetics corresponds best to higuchi's model.

Thus the result shows that formulation follows zero order release kinetics. Drug release kinetics of this formulation corresponds best to higuchi's model. Drug release mechanism as per n value of korsmeyer peppas equation was found to be complex mechanism of swelling, diffusion and erosion.

STABILITY STUDIES: [65]

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under influence of a variety of environmental factors such as temperature, humidity and light, and enables recommended storage conditions, re-test periods and shelf-lives to be established.

ICH specifies the length of study and storage conditions:

Long term testing : $25^0C \pm 2^0C$ /60% RH ± 5% RH for 12 months.

Accelerated testing : $40^0C \pm 2^0C$ /75% RH ± 5% RH for 6 months.

The optimised bilayer tablets were subjected to stability studies and results were tabulated in following tables:

Procedure:

In the present study, stability studies were carried out at $40^0C \pm 2^0C$ for a specific time period up to 90 days for optimized formulation F6.

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.

Table 19: physiochemical data of stability studies

Parameters	**1st month**		**2nd month**		**3rd month**	
	25^0 C	**40°C**	**25^0 C**	**40°C**	**25^0 C**	**40°C**
Colour	No characteristic Changes					
Thickness						
Hardness						
Friability						

Table 20: Assay and dissolution profile of stability study

Intervals in months	**Drug**	**% drug content**		**Percentage cumulative release**	
		25^0 C	**40°C**	**25^0 C**	**40°C**
1st month	Metformin HCl	99.97	99.24	98.73	99.16
	Glimepiride	100.1	99.98	99.71	100.07
2nd month	Metformin HCl	98.86	97.25	98.45	98.56
	Glimepiride	99.29	100.2	100.02	99.61
3rd month	Metformin HCl	99.26	98.59	99.86	98.63
	Glimepiride	98.52	99.65	98.79	97.25

DISCUSSION

The study describes the formulation of both immediate and sustained release drug for increased therapeutic efficacy and patient convenience. The bilayer tablets were prepared by wet granulation method using IPA as a solvent which has been tried many times for the good release behaviour by taking various polymers. Unit formula was given in Table 8 & 9. Suitable formulation has been optimized. Tablet average weight is 1050mg, Thickness 6.7mm, Hardness 9-12kg/cm^2, Friability is 0.4% drug loss.

The physical compatibility evaluation was performed in visual basis. The study implies that the drug, polymer and other excipients were physically compatible with each other as there was no change of physical description. The results have been shown in the Table 4.The FT-IR spectrum of Glimepiride and Metformin HCl in formulation F6 was shown in the Figure 4 to 8 respectively. The spectra revealed the presents of peaks at 3367 cm^{-1} and 1458 cm^{-1} respectively (Table 5, 6) indicating that there was no interaction between drug and polymer used in the study.

The tablets of different formulations were subjected preformulation studies such as angle of repose, bulk density, tapped density, haussner's ratio, compressibility index and post compression parameters such as compressibility index, weight variation, thickness, hardness, friability and drug content. The results are shown in the Table no 12 & 15. All the formulation passes the test as per IP, 2007.

Figure 12 shows comparative percentage drug release of Glimepiride. The percentage in vitro drug release from formulations F1 to F6 ranged from 99.0% to 101.55% within 30 minutes. It's due to SSG as superdisintegrant in IR formulations. Figure 11 shows comparative percentage drug release of Metformin HCl. The percentage in vitro drug release from formulations F1 to F6 is shown in table 16. Complete release of drug occurred from the bilayer tablets within 10 hours.

The result suggested that various variables affecting the dissolution of the tablets. The optimization of the tablets was done based on experimental result such as its physiochemical parameters, dissolution and content uniformity. The tablets produced were stable and reliable. Formulation F6 shows better *in-vitro* drug release. So it is suggested that for highly water soluble drug like Metformin HCl, combination of different polymer can be used. The release data further indicated that combination of

SCMC and HPMC K 100M gives sustained release effect followed by the initially burst release effect due to the superdisintigrant SSG in immediate release layer.

The kinetics parameters of Metformin HCl release are shown in Table 18. It can be best expressed by Higuchi's and kosmeyer's peppas model (Fig: 15 & 16) as the plots showed high linearity and confirms diffusion mechanism (non fickian transport).

The stability study of the formulation F6 was done at 40^0c/75%RH for three months and it shows better stability of the product (Table 19 & 20).

CONCLUSION

The present work was aimed towards developing a bilayer tablets containing Glimepiride as immediate release and Metformin HCl as sustained release. The tablets were prepared using techniques of wet granulation and compression. The optimization of the tablets was done based on experimental result such as its physiochemical parameters, dissolution and content uniformity. The tablets produced were stable and reliable. The result suggested that various variables affecting the dissolution of the tablets. Formulation F6 shows better dissolution. So it is suggested that for highly water soluble drug like Metformin HCl, it is desirable to use combination of different polymer for sustained release layer and incorporation of superdisintegrant like SSG in immediate release layer. The release data further indicated that combination of SCMC and HPMC K 100M can give the sustained release effect followed by the initially burst release effect due to the superdisintegrant SSG in immediate release layer. HPMC K100M polymer controlled the release of Metformin HCl up to 10 hrs intended for once daily administration. The release data of in vitro study indicates that formulation follows zero order, Higuchi equation and diffusion takes place via non-fickian transport. Formulation F6 found to be stable at accelerated stability as per the ICH guidelines for a period of 3 months.

Finally it concluded that Glimepiride as immediate release and Metformin HCl as sustained release indicate promising potential of both drugs in the form of bilayer tablets an alternative to the conventional dosage form.

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