ARB AND BIGUANIDE TAILORED BILAYER TABLET: AS POTENTIAL APPROACH IN EFFECTIVE THERAPEUTIC MANAGEMENT OF DIABETIC PATIENTS HAVING HYPERTENSION

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ABSTRACT

The aim of present study was to develop bilayer tablets of Irbesartan as immediate layer and Metformin hydrochloride as sustained release layer to treat hypertension in type II diabetic patients. Hypertension is also one of the complications of type II Diabetes. The bilayer tablets were formulated to reduce the polytherapy to monotherapy, thus improving patient compliance. The tablets were formulated using hydrophilic polymers such as HPMC K4M and HPMC K100M in varying ratios to retard the drug release for a period of 10 hours. The immediate release layer of Irbesartan was formulated using Sodium Starch Glycolate (2% and 4%). All the formulations were evaluated for physical characteristics, drug content, dissolution, release kinetics and stability studies. The stability studies indicated that the bilayer tablets were stable and do not show any significant changes in the physical characteristics, drug content and dissolution. The results obtained were found to be within the limits. Along with this all results shown promising outcomes in effective therapeutic management of type II diabetes with hypertension.1. INTRODUCTION

TABLETS

HISTORICAL BACKGROUND

Oral route is a most common route of administration; about 90 percent of drugs are administered via oral route for systemic effects. Among the drugs administered orally, solid dosage forms represent the preferred choice of class of product. Most common solid oral dosage forms are tablets and capsules. Tablets and capsules account

for well over half the total number and cost of all prescription issued. In December 1843, a patent was granted to the Englishman, William Brockedon, for a machine to compress powders to form compacts. The invention was first used to produce compacts of potassium bicarbonate and caught the imagination of a number of pharmaceutical companies. Later, Wellcome, in Britain was the first company to use the term tablets to describe the compressed dosage forms. [1]

What is tablet?

Tablets are solid preparations each containing a single dose of one or more active medicaments and usually obtained by compressing uniform volumes of particles. Tablets are intended for oral administration. Some are swallowed whole or after being chewed, some are dissolved or dispersed in water before being administered and some are retained in the mouth where the active medicament is liberated. Tablets are usually solid, right circular cylinders, the end of which are flat or convex and the edges of which may be bevelled. They may exist in other shapes like triangular, rectangular, etc. They may have lines or break-marks and may bear a symbol or other markings. Tablets may be coated or uncoated. They are sufficiently hard to withstand handling without crumbling or breaking.[2]

The British Pharmacopoeia defines tablet as, circular in shape with either flat or convex faces and prepared by compressing the medicament or mixture of medicaments usually with the added excipients, such as diluents, binders, disintegrants, glidants, lubricants, substance capable of modifying the preparation in the digestive tract, colouring matter authorised by the competent authority and flavouring substances.

ADVANTAGES OF TABLET MEDICATION [3]

➢ They are the unit dosage form and offer the greatest capabilities of all oral dosageforms for the greatest dose precision and least content variability.

➢ Low cost of among all oral dosage forms.

➢ They are lightest and most compact dosage forms.

➢ They are easiest and cheapest to package and ship.

➢ Product identification requires no additional processing steps when employing an embossed or monogrammed punch face.

➢ Provides greatest ease of swallowing with the least tendency for hang up above the stomach, especially when coated, provided the tablet disintegration is not excessively rapid.

➢ They lend themselves to certain special release profile products e.g. enteric coated or delayed release profiles.

➢ Easy large scale production than other oral dosage forms.

➢ They have the best combined properties of chemical, mechanical and microbiological stability among all the oral dosage forms.

➢ The emergency supplies of the drug can be conveniently carried by the patient.

DISADVANTAGES OF TABLET MEDICATION [3]

➢ Some drugs have resistance for compression into dense compacts, owing to their amorphous nature or flocculent, low density properties.

➢ Drugs with bitter taste, objectionable odour, sensitivity towards oxygen or hygroscopic nature may require encapsulation/entrapment prior to compression, or coating of tablets is required.

➢ Elderly, ill and children could have problem in swallowing the tablets.

TYPES OF TABLETS [4]

Tablets are divided into classes based on their route of administration and their function.

1.TABLETS ADMINISTERED ORALLY

A. Compressed tablets

- Sugar coated tablets
- Film coated tablets
- Enteric coated tablets
- Chewable tablets
- Controlled release tablets

B. Multiple Compressed Tablets

- Layered tablets
- Press coated tablets

2.TABLETS ADMINISTERED IN ORAL CAVITY

A. Buccal and sublingual tablets

B. Lozenges and Troches

C. Dental cones

3.TABLETS ADMINISTERED VIA OTHER ROUTES

A. Implants

B. Compressed suppositories or inserts

4.TABLETS ADMINISTERED IN SOLUTION FORM

A. Effervescent tablets

B. Dispensing tablets

C. Hypodermic tablets

D. Tablet triturates

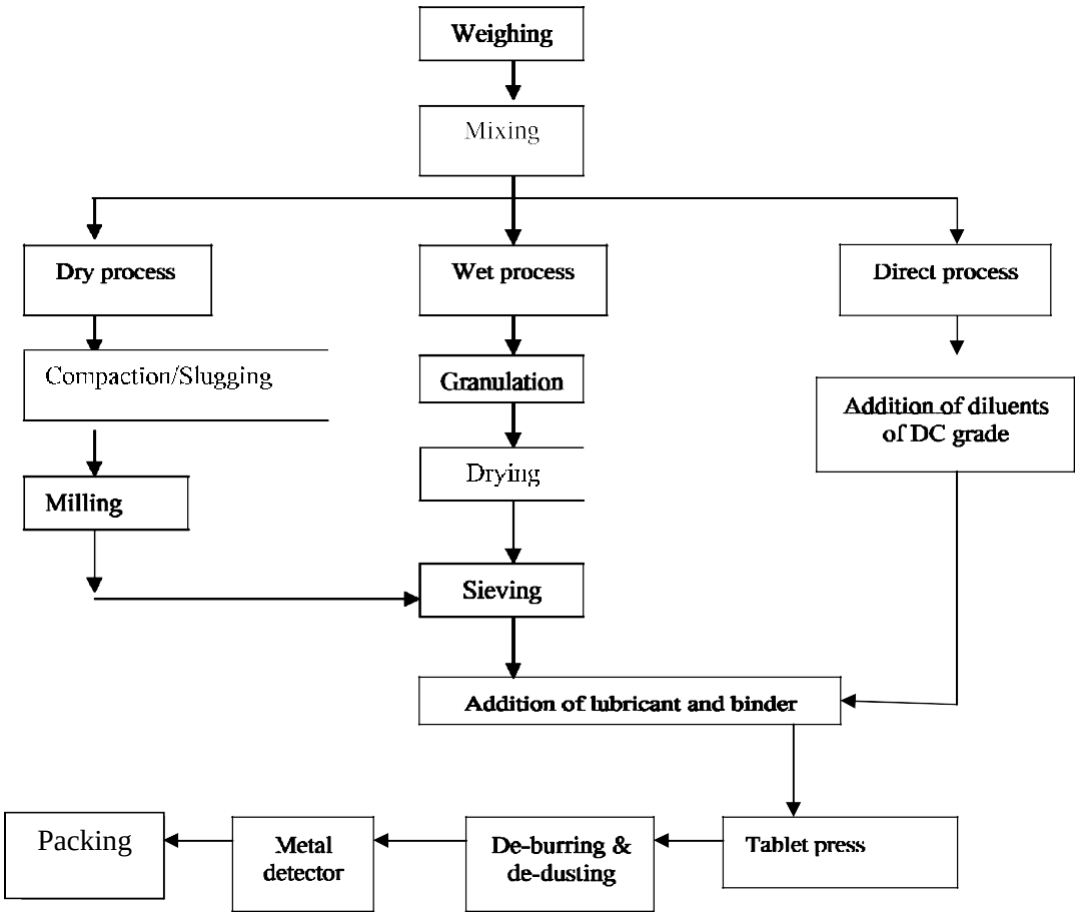
METHOD OF PREPRATION OF GRANULES FOR TABLETS [4]

1.Wet granulation

2.Dry granulation

3.Direct compression

FLOWCHART FOR DIFFERENT METHODS FOR TABLET GRANULATIONPREPARATION



MULTILAYER TABLETS [5]

Multilayer tablets are tablets made by compressing several different granulations fed into a die in succession, one on top of another, in layers. Each layer comes from a separate feed frame with individual weight control. Rotary tablet presses can be set up for two or three layers. More are possible but the design becomes very special. Ideally, a slight compression of each layer and individual layer ejection permits weight checking for control purposes.

Advantages of Multilayer Tablets

1.Incompatible substances can be separated by formulating them in separate layers as a two-layer tablet or separating the two layers by a third layer of an inert substance as a barrier between the two.

2.Two layer tablets may be designed for sustained release; one layer for immediate release of the drug and the second layer for extended release, thus maintaining a prolonged blood level.

3.Layers may be coloured differently to identify the product.

VARIOUS TECHNIQUES FOR A BILAYER TABLET [6]

The techniques are as follows

01. OROS® push pull technology
02. L-OROS tm technology
03. EN SO TROL technology
04. DUROS technology
05. DUREDAS™ technology

01. OROS® push pull technology

This system consists of mainly two or three layers which among one or more layer are essential of the drug and other layer consist of push layer. The drug layer mainly consists of drug along with two or more different ingredients. The drug layer consists of poorly soluble drug. There is further addition of suspending agent and osmotic agent. A semi permeable layer surrounds the tablet core.

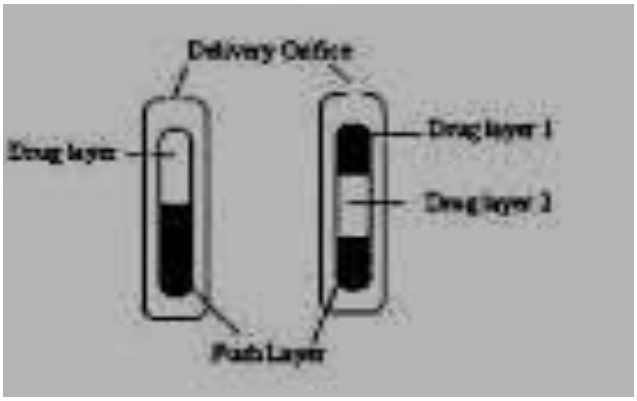


Fig. 1: Bilayer and Trilayer OROS push pull technology

02. 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, then with a osmotic push layer and then a semi permeable layer membrane drilled with an external orifice.

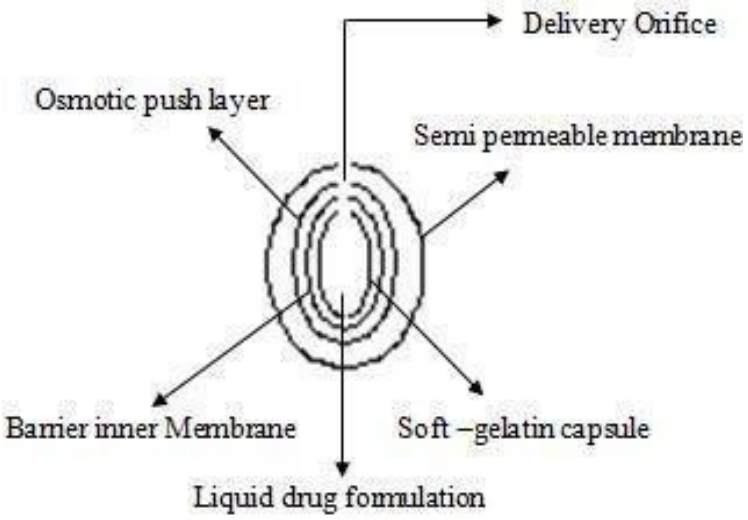


Fig. 2: L-OROS tm technology

03. EN SO TROL technology

Solubility enhancement of an order of magnitude or to create optimized dosage form Shire laboratory used an integrated approach to drug delivery focusing on identification and incorporation of the polymer that enhances the controlled release technologies.

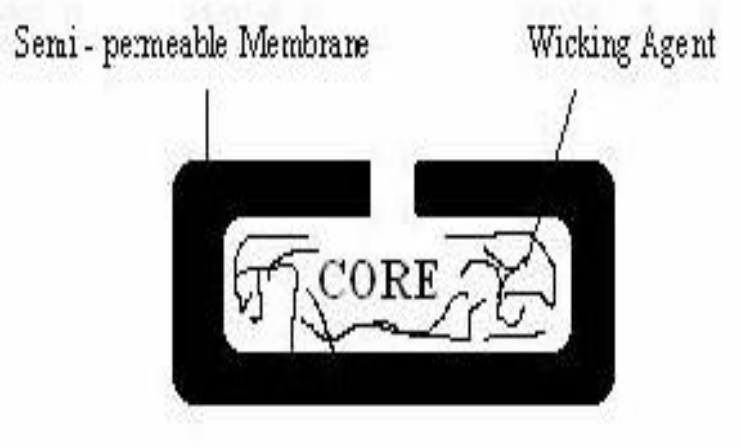


Fig. 3: EN SO TROL technology

04. DUROS technology

The system consists of an outer cylindrical titanium alloy reservoir. The 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 release minute quantity of concentrated form in continuous and consistent form over months or years.

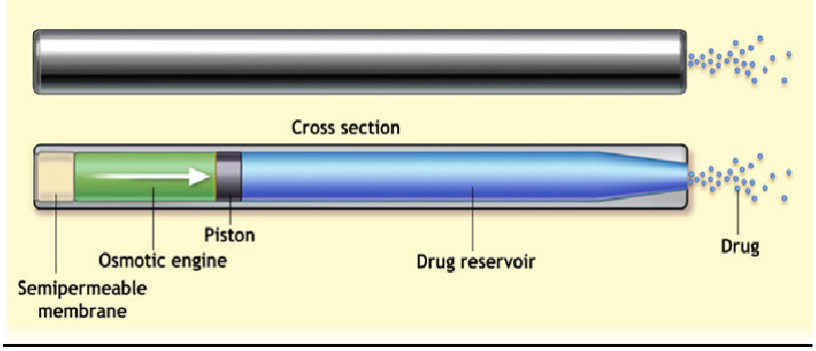


Fig. 4: DUROS technology

05. DUREDAS™ technology

It is a bilayer tablet which can provide immediate or sustained release of two drugs or different release rate of the same drug in one dosage form. The tabletting 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.

Fig. 5: DUREDAS Technology

Benefits offered by the DUREDAS™ technology includes:

✓ 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 onetablet.

✓ Unit dose, tablet presentation

The DUREDAS™ system can be easily manipulated to allow incorporation of two controlled release formulation in the bilayer. 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 granule is compressed first 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 DUREDAS™ technology is the production of controlled release dosage forms where by two drugs are incorporated into the different layers and drug release of each is controlled to maximise the therapeutic effect of the combination. Again both immediate and controlled release combinations of two drugs are possible.

PRECAUTIONS TO BE TAKEN TO GET GOOD BILAYER TABLETS [5]

For good-quality tablets with sharp definition between the layers, special care must be taken as follows:

1.Dusty fines must be limited. Fines smaller than 100 mesh should be kept at a minimum.

2.Maximum granule size should be less than 16 mesh for a smooth, uniform scrape-off at the die.

3.Materials that smear, chalk, or coat on the die table must be avoided to obtain clean scrape-off and uncontaminated layers.

4.Low moisture is essential if incompatibles are used.

5.Weak granules that break down easily must be avoided. Excessive amounts of lubrication especially metallic stearates should be avoided for better adhesion of the layers.

6.Formulation of multilayer tablets is more demanding than that of single layer tablets. For this reason, selection of additives is critical.

IMMEDIATE RELEASE TABLETS

Immediate release dosage forms are those for which ≥ 85% of the labelled amount dissolves within in 30 minutes. For immediate release tablets, the only barrier to drug release is simple disintegration or erosion stage which is generally accomplished in less than one hour. To enhance dissolution and hence bioavailability of any drug for immediate release tablets, disintegration is one of the important process.[7] Disintegrants are substances or mixture of substances added to the drug formulation that facilitates the breakup or disintegration of tablets or capsule content into smaller particles that dissolves more rapidly than in the absence of disintegrants. Superdisintegrants are generally used at a low level in the solid dosage form, typically 1-10% by weight relative to the total weight of the dosage unit. Few superdisintegrants are available commercially as Croscaramellose sodium, Crospovidone and Sodium starch glycolate.

Tablets for immediate release often consist of filler, a binder, lubricants and disintegrants. In many cases, the disintegration time of solid dosage forms is too long to provide appropriate therapeutic effect. To improve the disintegration time, so-called disintegrants are used. The most accepted mechanisms of their action are wicking, swelling, and deformation recovery and particle repulsion.[8] Together, these phenomena create a disintegrating force within the matrix. In the past, non-modified disintegrants were used to accelerate disintegration, that is, alginates, starches, ambrelite resins, cellulosic materials, pectines and others. Today, a fast working superdisintegrant is chemically modified, typically by cross linking the organic chains of a polymeric molecule. Three classes of superdisintegrants are commonly used. Modified cellulose (Croscaramellose Sodium - Ac-Di-Sol®, Vivasol®), crosslinked polyvinyl-l pyrrolidone (Polyplasdone® XL-10) and modified starch (Sodium Starch Glycolate – Primojel®,Explotab®)

CONTROLLED DRUG DELIVERY SYSTEMS[9]

In the past, many of the terms used to refer to therapeutic systems of controlled and sustained release have used in an inconsistent and confusing manner. Although descriptive terms such as “timed release” and “prolonged release” give excellent manufacturing identification, they can be confusing to health care practitioners.

Sustained release constitutes any dosage form that provides medication over an extended period of time. Controlled release however denotes that the system is able to provide some actual therapeutic control, whether this is of temporal nature, spatial nature or both. In other words, the system attempts to control drug concentrations in the target tissue. This correctly suggests that there are sustained release systems that cannot be considered as a controlled release systems.

In general, the goal of a sustained release dosage form is to maintain therapeutic blood or tissue levels of the drug for an extended period. This is usually accomplished by attempting to obtain zero order release from the dosage form. Zero order release constitutes drug release from the dosage form that is independent of the amount of the drug in the delivery system (i.e., a constant release rate).

Sustained release generally do not attain this type of release and usually try to mimic zero order release providing drug in a slow first order fashion (i.e., concentration dependent).

Systems that are designated as prolonged release can be considered as attempts at achieving sustained release delivery. ***Repeat action tablets*** are a method of sustained release in which multiple doses of a drug are contained within the dosage form and each dose is released at a periodic interval. ***Delayed release systems***, in contrast, may not be sustaining, since often the function of these dosage forms is to maintain the drug within the dosage form for some time before release. Commonly the release rate is not altered and does not result in sustained delivery once drug release has begun. Enteric coated tablets are example of this type of dosage form.

Controlled release, although resulting in a zero order delivery system, may also incorporate methods to promote localization of the drug at an active site. In some cases, a controlled release system will not be sustaining, but will be concerned strictly with localization of the drug. Site- specific systems and targeted delivery systems are the descriptive terms used to denote this type of delivery control.

GENERAL PRINCIPLE OF CONTROLLED RELEASE SYSTEMS

The idea of providing an exact amount of drug at the site of action for a precise time period is usually approximated by most systems. This approximation is achieved by creating a constant concentration in the body or an organ over an extended period of time; in other words, the amount of drug entering the system is equivalent to the amount removed from the system. All forms of metabolism and excretion are included in the removal process: urinary excretion, entero hepatic recycling, sweats, faecal and so on. Since for most of the drugs these elimination processes are first order, it can be said that at certain blood level, the drug will have specific rate of elimination. This idea is to deliver drug at the exact rate for an extended period. This is represented mathematically as

Rate in = Rate out = K_{elim} X C_d X V_d

Where, C_d is the desired drug level, V_d is the volume of distribution and K_{elim} is the rate of drug elimination from the body. Often such exacting delivery proves to be difficult to achieve administration routes other than intravenous infusion. Non invasive routes (e.g., oral) are obviously preferred.

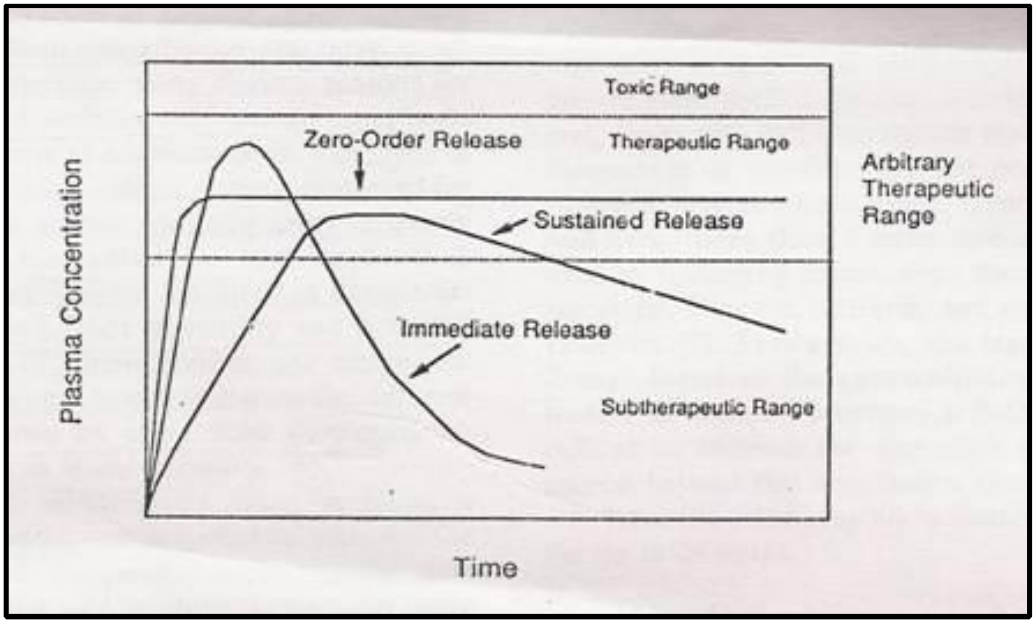


Fig. 6: Drug level versus time profile showing differences between zero order controlled release, slow first order sustained release, and release from a conventional tablet orcapsule.

Figure 6 shows comparative blood level profiles obtained from administration of conventional, controlled and sustained release dosage forms. The conventional tablet or capsule provides a single and transient burst of drug. A pharmacological effect is seen as long as the amount of drug is within the therapeutic range. Problems occur when peak concentration is above or below this range, especially for drugs with narrow therapeutic windows.

The slow first order release obtained by sustained release preparation is generally achieved by slowing the release

of drug from a dosage form. In some cases this is accomplished by a continuous release process; however system that release small bursts of drug over a prolonged period can mimic the continuous system.

SUSTAINED RELEASE (SR) DRUG DELIVERY SYSTEMS [4]

Sustained release drug delivery systems can be defined as any dosage form that prolongs the therapeutic activity of the drug by continuously releasing medication over an extended period of time. In absence of suitable clinical evidence of this therapeutic effect it can be defined as any dosage form that gives prolongation of the drug levels in the blood. The major advantage of this category is that, in addition to the convenience of reduced frequency administration, it provides levels that are devoid of the peak and valley effect.

By providing smooth plasma level of drug over longer period of time, sustained release drug delivery technology can minimize side effects, improve efficacy and by enabling once daily dosing – maximize patient compliance.

ADVANTAGES

Sustained release products offer many potential benefits over conventional dosage formulations e.g,

1.Sustained blood levels

- For drugs with relatively short half lives, the use of sustained release productsmay maintain therapeutic concentrations over prolonged periods.

2.Dosage frequency reduction

- Minimize or eliminate local side effects.
- Minimize or eliminate systemic side effects.
- Obtain less potentation or reduction in drug activity with chronic use.
- Minimize drug accumulation with chronic dosing.

3.Improve patient compliance

- A reduction in the number of daily doses offered by sustained release productshas the potential to improve compliance.

4.Improve efficiency in treatment

- Improve control of condition i.e., reduced fluctuation in drug levels
- Improve bioavailability of some drugs.
- Make use of special effects. Eg., sustained release of aspirin for morning reliefof arthritis by dosing before bedtime.

5.Economy i.e. reduction in health care costs

- The average cost of treatment over an extended time period may be less, with less frequency of dosing, enhanced therapeutic benefits and reduced side effects.
- The time required for health care professional to dispense and administer the drug and monitor patient is also reduced.

DISADVANTAGES

1.Sustained release products contain a higher drug load and thus any loss of integrity of the release characteristics of the dosage form has potential problems.

2.The larger size of sustained release products may cause difficulties in ingestion or transit through the gut.

3.Sustained release products may cause decreased systemic bioavailability in comparison to conventional dosage forms, which may be due to incomplete release, increased first pass metabolism, increased instability, insufficient residence time for complete release, site specific absorption, pH dependent stability etc.

4.Possibility of dose dumping due to food, physiologic or formulation variables or chewing or grinding of oral formulations by the patient and thus increased risk of toxicity.

RELEASE MECHANISM FOR SUSTAINED AND CONTROLLED RELEASEPRODUCTS [10, 11]

Based on the release mechanism these are classified as follows

- ❖ Diffusion controlled products
- ❖ Dissolution controlled products
- ❖ Erosion products
- ❖ Osmotic pump systems
- ❖ Ion exchange resins

01. Diffusion controlled products

In these systems, there is a water soluble polymer, which controls the flow of water and the subsequent release of dissolved drug from the dosage form. Diffusion occurs when a drug passes through the polymer that forms the controlled release device. The diffusion can occur through the pores in the polymer matrix or by passing between polymer chains. These are broadly classified into two categories.

A. Reservoir devices

B. Matrix devices

The basic mechanisms of drug release from these two systems are fundamentally different.

A. Reservoir Devices

In this system a water insoluble polymeric material encases a core of drug. Drug will partition into the membranes and exchange with the fluid surrounding the particles or tablet.

The active ingredient is released to the surrounding environment by diffusion process through the rate limiting membrane. In the reservoir systems the drug delivery rateremains fairly constant.

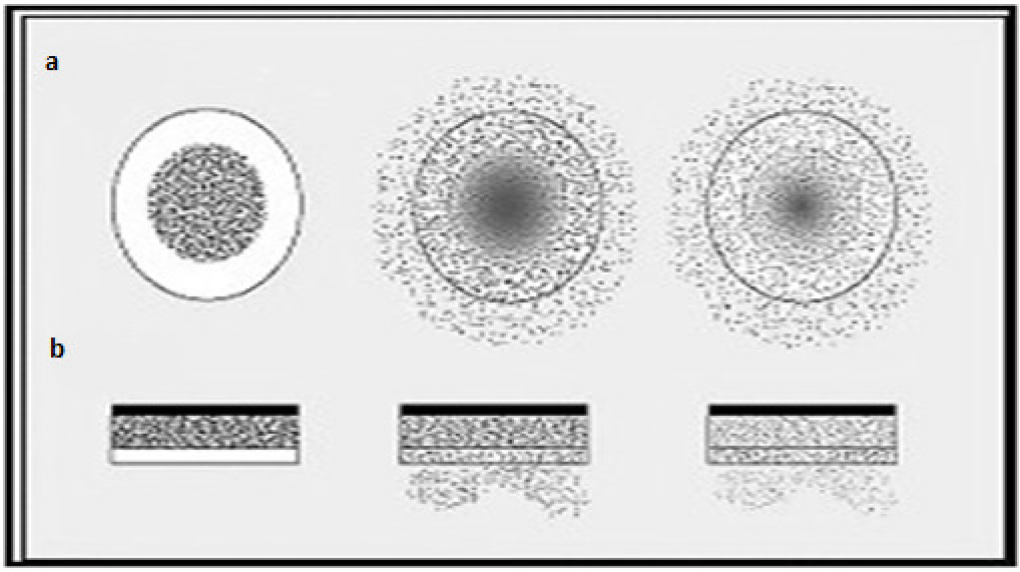


Fig. 7: Drug delivery from typical reservoir devices: (a) Implantable or oralsystems and (b) Transdermal systems

B. Matrix Devices

In the matrix device the drug or active ingredient is dispersed in polymer matrix to form a homogenous system known as matrix system. Diffusion occurs when the drug passes from the polymeric matrix into the external environment. As the release continuous, its rate normally decreases with the system, since the active ingredient has progressively longer distance to travel and therefore requires a long diffusion time to release.

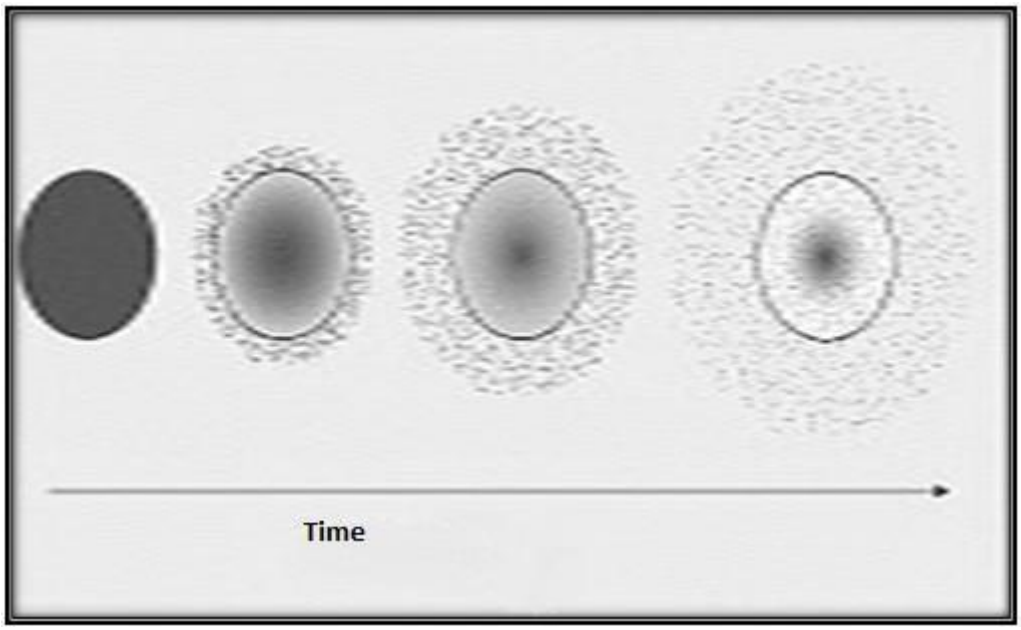


Fig. 8: Drug delivery from a typical matrix drug delivery system

2. LITERATURE REVIEW

REVIEW FOR BILAYER TABLETS

1) Ramana G et al. [12] formulated and evaluated the sustained release bilayer tablets of Ambroxol hydrochloride. The tablets were prepared by direct compression technique using sodium starch glycolate as super disintegrant for fast release layer and CR grade polymers such as HPMC K4M , Ethyl cellulose independently and also in combinations. The formulation containing Drug: HPMC: EC at the ratio of 1:0.5:30% exhibited an initial burst effect followed by sustained release over a period of 12 hours. The dissolution data of various formulations were fitted into Higuchi and Peppas models, which are linear with Higuchi's plot and "n" values obtained from Peppas were within 0.45 to 0.89 indicate the mechanism of drug release diffusion coupled with erosion.

2) Brijesh Patel et al. [13] designed and evaluated Mucoadhesive controlled release oral bilayer tablets of Indomethacin. Solid dispersion of Indomethacin was prepared using PEG 6000 to improve the solubility of Indomethacin. Bilayer tablets were prepared using direct compression technique employing Ac-Di-Sol as superdisintegrant for immediate release layer and Carbapol 934 LR, HPC for sustained release layer. The polymers were used alone or in combinations. By varying the concentrations of polymers several batches were formulated. The batch containing the mixture of Carbapol 934 LR and HPC in the ratio of 1:1 showed a better drug release than individual formulation containing Carbapol 934 LR and HPC. The drug release kinetics was studied and it was found that the drug was released from the formulation by diffusion.

3) Deelip Derle et al. [14] formulated and evaluated buccoadhesive bilayer tablets of Propranolol hydrochloride. The tablets were prepared by direct compression method. Bioadhesive polymers such as sodium alginate and Carbapol 971P were used and ethyl cellulose was used as an impermeable backing layer. The tablets were prepared in two steps, initially the drug polymer mixture was compressed after that the backing layer of ethyl cellulose was placed over the compact and then compressed into bilayer tablets. Tablets containing sodium alginate and Carbapol 971P in the ratio of 5:1 showed the maximum percentage of *in vitro* release without disintegration for 12 hours. The mechanism of drug release was found to follow zero-order kinetics.

4) Nagaraju R et al. [15] formulated and evaluated bilayer sustained release tablets of Salbutamol and Theophylline. Wet granulation technique was employed for preparation of granules. PVP K30 in Isopropyl alcohol was used as a binder. Various polymers such as HPMC K4M, HPMC K100M, Xanthan gum, Ethyl cellulose and HPMC-P were studied. HPMC-P and HPMC K4M were found to be best in controlling the release.

5) Ashish A Pahade et al. [16] designed and developed bilayer sustained release tablets of Isosorbide mononitrate. Wet granulation technique was employed for preparing granules using PVP K30 as binder. The immediate release granules were prepared using Croscaramellose Sodium as superdisintegrant. Hydrophilic and hydrophobic matrix material such as HPMC K4M and Polyox WSR 303 was used for preparing sustained release layer. The influence of hydrophilic and hydrophobic polymer and granulation technique was studied. By varying the concentrations of HPMC K4M four formulations of bilayer tablets were prepared. The formulation containing HPMC K4M at a concentration of 19.33% w/w was selected as the optimized batch as it showed better *in vitro* release profile compared to other batches. Similarly by varying the concentration of hydrophobic polymer Polyox WSR 303 three batches of bilayer tablets were prepared. The formulation containing 15% w/w showed better *in vitro* release

profile and thus it was optimized for further studies.

6) Bhavesh Shiyani et al. [17] formulated and evaluated bilayer tablets of Metoclopramide hydrochloride (MTH) and Ibuprofen (IB). MTH was formulated as immediate release layer by using various disintegrants like Ac-Di-Sol, Polyplasdone XL, Explotab, Agar and Gellan Gum. The formulation containing Ac-Di-Sol was optimized for preparing Bilayer tablets. Sustained release layer of IB was formulated using hydrophilic matrix HPMC K4M, buffering agent sodium bicarbonate and PVP K30. By increasing the concentrations of HPMC K4M and PVP K30 the release was reduced. By inclusion of buffering agent sodium bicarbonate the release was increased as well as there is reduction in gastric irritation as IB is a weak acid. The drug release mechanism was found to be Quasi-Fickiandiffusion.

7) Narendra C et al. [18] studied the optimization of bilayer floating tablets of Metoprolol Succinate. A 2^3 factorial design was used for optimizing the formulation with respect to polymer-drug (X1), polymer-polymer (X2) and different viscosity grades of s polymer ratio(x3) as independent variables. Four dependent variables are percentage of drug release at 8 hours, t50%, diffusion coefficient and floating time. X1 and X2 significantly affected the floating time and release properties, but the effect of different viscosity gradesof HPMC K4M and HPMC K100M was not significant.

8) Vinoth kumar G et al. [19] formulated and evaluated bilayer tablets of Cefixime trihydrate and Dicloxacillin sodium. Wet granulation technique was used to formulate granules for both the layers. Cefixime trihydrate was formulated as immediate release layer using Croscaramellose sodium as superdisintegrant. Sustained release layer of Dicloxacillin sodium was formulated by varying the concentrations of HPMC K4M and HPMC K100M. Nine batches of bilayer tablets were prepared. All the formulations were compared with the innovator product in respect to all tablet properties such as hardness, friability, disintegration time and dissolution. The percentage drug release of formulation F5 showed drug release comparable to the innovator product disintegration time and drug release and thus it was optimized and kept for further studies.

9) Gohel MC et al. [20] fabricated and evaluated bilayer tablets containing conventional Paracetamol and modified release Diclofenac sodium. A 2^3 full factorial design was adopted using the amount of polyethylene glycol, microcrystalline cellulose and Crospovidone as independent variables for fabricating Paracetamol tablets. Diclofenac sodium tablets were prepared using varying concentrations of HPMC K4M as matrixing agent. The results of analysis of variance showed that the friability of Paracetamol was distinctly influenced by the formulation variables. Diclofenac sodium layer was optimized by comparing the formulation with the innovator product. The optimized layers were finally compressed into bilayer tablets. The tablets were subjected for drug release mechanism. It was found out that the bilayer tablets followed Korsmeyer-Peppas model.

10) Naeem MA et al. [21] developed and evaluated controlled release bilayer tablets containing microencapsulated Tramadol and Acetaminophen. Microencapsulation based phase separation technique using medium viscosity ethyl cellulose was employed to formulate separate Microparticles for extending the release of both drugs. The Microparticles of both the drugs were prepared separately and were used for formulating the bilayer tablets. The optimized batches were subjected for studying the release mechanism. The release kinetics was followed by Higuchi model with a good R^2 value. The tablets were subjected to accelerated stability studies for 3 months.

11) Nirmal J et al. [22] studied the formulation and evaluation of bilayer tablets of Atorvastatin calcium and Nicotinic acid. Atorvastatin calcium was formulated as

immediate release layer using Croscaramellose sodium as superdisintegrant. Nicotinic acid was formulated as sustained release layer using HPMC K100M in varying concentration.

12) Remya PN et al. [23] studied the formulation and evaluation of bilayer tablets of Ibuprofen and Methocarbamol. Wet granulation technique was employed for preparing granules using PVP K 30 as binder. The bilayer tablets were film coated using Advantia prime clear film coat material. Nine batches of bilayer tablets were prepared. The *in vitro* release of the bilayer tablets were compared with the innovator and the release kinetics of formulation 8 were taken as optimized formulation due to its higher dissolution rate and complied all other parameters with the official specifications.

13) Jadhav RT et al. [24] formulated and evaluated bilayer tablets of Piracetam and Vinpocetine. Wet granulation technique was employed for formulation of both layers. PVP K 30 was used as binder for preparing Piracetam granules and maize starch was used as binder for preparing Vinpocetine granules. Sodium starch glycolate was used as superdisintegrant. Bilayer tablets were optimized based on the disintegration time and comparison of the dissolution profile with the innovator product.

14) Hiremath JG et al. [25] studied the preparation and physicochemical characterization of Simvastatin loaded Mucoadhesive bilayer tablets. Tablets were prepared by direct compression technique by using mucoadhesive polymers such as Carbapol 934, HPMC and PVP in varying concentrations. Ethyl cellulose was used as backing membrane layer because of its water impermeable nature. The core layer was composed of drug and polymer in varying concentrations. To the backing layer Carbapol 934 and PVP K 32 was added to avoid premature cracking. FTIR and DSC were done to study the compatibility of the drug and excipients. F3 and F9 formulations were selected as optimized batch. F3 was selected for *in vitro* permeation studies based on its maximum drug release F9 formulation was selected based on the *in vitro* drug release, swelling index and good bioadhesive strength. The optimized batches were subjected to drug release kinetics.

15) Ajit S Kulkarni et al. [26] prepared the floating bilayer tablets of Diltiazem hydrochloride and Lovastatin. Direct compression technique was employed for preparing bilayer tablets. Lovastatin was formulated as immediate release layer using sodium starch glycolate as super disintegrant and Diltiazem hydrochloride was formulated as sustained release layer comprising of HPMC K4M and Xanthan gum as the release retarding polymers. Sodium bicarbonate was used as a gas generating agent. All the formulations released the Lovastatin within 30 minutes. HPMC K4M and Xanthan gum sustained the release for 12 hours.

16) Ziyaur Rahaman et al. [27] developed the bilayer floating tablets of Captopril using direct compression technique. The floating layer was formulated with various HPMC grades (K4M, K15M and K100M) and effervescent mixture of citric acid and sodium bicarbonate. The sustained release layer comprised of Captopril and various polymers such as HPMC K15M, PVP K30 and Carbapol 934P alone or in varying combination with the drug. Final formulation released approximately 95% of drug in 24 hours, while the floating time was 10 min and the tablet remained floatable throughout the studies. Placebo formulation containing barium suIRBhate in the release layer administered to human volunteers for *in vivo* X-ray studies showed the BFT had significantly increased the gastricresidence time.

17) **Ankarao A et al.** [28] prepared the Buccoadhesive bilayer tablets of Metoprolol tartrate. Core tablet of Metoprolol tartrate was prepared by direct compression technique using HPMC K4M, SCMC and Carbapol 934 as bioadhesive polymers to impart mucoadhesion and ethyl cellulose to act as an impermeable backing layer. Six formulations containing the bioadhesive polymers were prepared. The formulation F2 and F5 were optimized and obeyed zero order release kinetics with Non-Fickian diffusion.

18) **Ankarao A et al.** [29] studied the formulation and evaluation of Buccoadhesive Bilayer tablets of Carvedilol. Direct compression was employed for preparing core tablets using HPMC K4M, SCMC, and Carbapol 934 as bio-adhesive polymer to impart mucoadhesion. Ethyl cellulose was used as impermeable backing membrane. The formulations containing HPMC and SCMC were optimized based on the buccoadhesive property and release characteristics.

REVIEW FOR METFORMIN HYDROCHLORIDE

19) **Bagyalakshmi J et al.** [30] developed a bilayer formulation containing Metformin hydrochloride and Glipizide. Metformin hydrochloride was formulated as sustained release layer using varying grades of HPMC (K4M, K15M, and K100M). Glipizide was formulated as immediate release layer. Due to the poor solubility of Glipizide, Solid dispersion technique using sodium starch glycolate was employed using Kneading method to improve the solubility of glipizide. The solid dispersion system was characterised by

FT-IR and *in vitro* dissolution studies. Both the layers were optimized separately the optimized batches were then finally compressed into bilayer tablets.

20) **Kotta Kranthi Kumar et al.** [31] designed, developed and characterized sustained release of Metformin and Gliclazide bilayer tablets. Wet granulation technique was employed using various grades of HPMC for preparing granules. Trail batch of Metformin hydrochloride containing HPMC K100M and trail batch of Gliclazide containing HPMC K15M was optimized for preparing bilayer tablets. The tablets were compared with the innovator product.

21) **Rajendran NN et al.** [32] formulated and evaluated sustained release bilayer tablets of Metformin hydrochloride and Pioglitazone hydrochloride. Pioglitazone HCl was formulated as immediate release layer by direct compression method using sodium starch glycolate and Croscaramellose sodium. Sustained release layer of Metformin hydrochloride was formulated by wet granulation technique using different viscosity grades of HPMC (K4M & K100M). The immediate release layer containing varying super disintegrants was compressed separately and they were compared with the innovator product. The formulation containing sodium starch glycolate (5%) was optimized as it matched with the burst release of the innovator product. The sustained release layer was formulated by varying the concentration of HPMC K4M and HPMC K100M. The formulated tablet was compared with the innovator. The concentration of HPMC K100M (8.82%) and HPMC K4M (4.70%) was optimized as it showed the comparable release profile with the innovator. The optimized formulations were finally compressed intobilayer tablets and were studied for drug release kinetics.

22) **Ramesh et al.** [33] formulated and evaluated bilayer sustained release tablets of Metformin hydrochloride and Pioglitazone. Dry granulation technique was employed for formulation of immediate release layer using Croscaramellose sodium in varying proportions. Sustained release layer granules were formulated by wet

granulation technique using bio-adhesive polymers such as Sodium carboxy methyl cellulose and various grades of HPMC (K4M & K15M). The tablets were optimized separately and the optimized batches were finally compressed into bilayer tablets. The bilayer tablets gave a bimodal release indicating the immediate release followed by sustained release. The optimized batch was subjected to release kinetics to study the release mechanism.

23) **Durga Prasad Pattanayak et al.** [34] designed bilayer formulation of Metformin hydrochloride and Glimepiride. Glimepiride was formulated as immediate release layer and was optimized separately. Metformin was formulated as sustained release layer. Two different matrix formulations were developed, one matrix layer with hydrophilic swellable layer such as HPMC and another matrix layer with hydrophobic layer such as PEO. The sustained release profile of HPMC matrix system was better than PEO matrix system. Thus it was optimized and compared with the innovator product. The optimized formulations were finally compressed into bilayer tablets. The tablets were subjected to study the drug release mechanisms. The formulation exhibited zero order kinetics and followed Non-Fickian transport.

24) **Yamsani Madhusudan Rao et al.** [35] studied the formulation and release characteristic of a bilayer matrix tablet containing Glimepride immediate release component and Metformin hydrochloride as sustained release component. Immediate release layer was formulated by direct compression using sodium starch glycolate as super disintegrant. Sustained release layer was formulated in 5 batches by wet granulation technique using HPMC K4M, SCMC as matrix forming polymer and PVP K 30 as binder. Batch 5 containing a mixture of Hydrophilic polymers in the ratio of 7.05:26.4% released the drug in the controlled manner and thus optimized and evaluated for further studies.

25) **Madhabhai Manordas Patel et al.** [36] designed and developed bilayer gastro retentive tablets containing Metformin hydrochloride and Glipizide for the treatment of Type II diabetes. Direct compression was employed for formulating both the layers. Metformin hydrochloride was formulated as sustained release layer using various grades of HPMC. Glipizide was formulated as immediate release layer using various superdisintegrants i.e. Croscaramellose Sodium, Crospovidone and sodium starch glycolate. Sodium starch glycolate (5%) was optimized as superdisintegrant for immediate release layer based on faster disintegration time. 3^2 full factorial designs were used to optimize sustained release formulations of Metformin hydrochloride. The ratio of polymer blend (X1) and content of gas generating agents (X2) was chosen as independent variables. Among the different grades of HPMC investigated, the viscosity of the polymer affects the drug release. From the results we can conclude that prepared bilayer tablets showed desirable release profile, good floating and sustained effect in stomach.

26) **Saptarshi Dutta et al.** [37] studied the formulation and evaluation of Metformin hydrochloride sustained release matrix tablets. Dry granulation technique was employed using various grades of HPMC (K4M & K100M). The formulation containing HPMC K100M alone showed release profile comparable to the marketed product for a period of 12 hours and thus it was optimized. The optimized formulations were studied for drug release kinetics which showed that the formulation released the drug by diffusion. The tablets were kept for accelerated stability studies.

27) **Senthilkumar KL et al.** [38] formulated, developed and evaluated Metformin hydrochloride sustained release tablets. Wet granulation technique was employed for formulation of tablets by using various grades of HPMC (K4M & K100M) as release retarding polymers and PVP K 30 as binder. The formulation containing 13% HPMCK100 was optimized as it fulfilled the requirements for a sustained release tablets.

28) Jayaprakash S et al. [39] studied the formulation and evaluation of bilayer tablets of Metformin hydrochloride. Direct compression technique was employed for formulation of bilayer tablets using sodium starch glycolate and Crospovidone as super disintegrant for immediate release layer and HPMC K4M as release retardant polymer for sustained release layer. Formulation containing HPMC K4M, SCMC as binder for sustained release layer was optimized. Immediate release layer containing Crospovidone and sodium starch glycolate in combination was optimized. The optimized formulation was finally compressed into bilayer tablets and its drug release mechanism was studied and was found out that it followed swelling mediated diffusion. The formulations were kept for accelerated stability studies for a period of 3 months.

29) Manju Nagpal et al. [40] formulated and evaluated of Metformin Oro-dispersible tablets. Direct compression method using super disintegrant approach, effervescent approach and sublimation approach was used for formulation of tablets. Formulation prepared by effervescent approach showed improved disintegration time and dissolution profile and thus it was taken as an optimized batch.

30) Prameela Rani A et al. [41] studied the formulation and evaluation of Orodispersible Metformin tablets. A comparative study on Isphagula husk and Crospovidone as superdisintegrants. Direct compression technique using superdisintegrants was used for the formulation. The batch prepared using Isphagula husk (8%) was taken as an optimized formulation as it showed rapid disintegration time, hardness and good dissolution profile.

31) Sunil Kumar et al.[42] formulated and evaluated of extended release Metformin tablets. Wet granulation technique was employed for the formulation of extended release tablets using HPMC K100M as polymer and stearic acid and IPA as binder agent. Seven batches of formulations were prepared. Batch 7 was taken as an optimized batch as it showed better release profile compared to other batches. The optimized batch was kept for accelerated studies for a period of 3 months.

32) Kamlesh J Wadher et al.[43] formulated and evaluated of sustained release matrix tablets of Metformin hydrochloride using pH dependent and pH independent methacrylate polymers. Direct compression technique was employed for formulation of tablets using pH dependent (Eudragit L-100 and S-100) and pH independent (Eudragit RIRBO and RSPO) polymer combinations. Various formulations were prepared using the polymers alone or in combination. Formulation containing Eudragit S-100 and Eudragit RIRBO in the ratio of 0.3:0.7 w/w gave a sustained release pattern.

33) Margret Chandira et al.[44] studied the formulation and evaluation of extended release tablets containing Metformin hydrochloride. Wet granulation technique was employed for the formulation of tablets using HPMC K100M and Carbapol 71 G in combinations. Ten batches of formulations were prepared using the above polymers. Batch 10 showed the release profile comparable with the innovator product. The optimized formulation was kept for accelerated stability studies.

34) Ashok Kumar A et al. [45] formulated and evaluated Mucoadhesive microcapsules of Metformin hydrochloride with Gum Karaya. The microcapsules were prepared with a coat of alginate and Gum Karaya by employing Ionotropic Gelation process and Emulsification Ionotropic Gelation process. The microcapsules prepared by Emulsification Ionotropic Gelation process was found to be spherical which showed slow and extended release overa period of time. Drug release was diffusion controlled and followed zero- order kinetics.

35) **Lian-Dong Hu et al.** [46] prepared and evaluated sustained release Metformin hydrochloride pellets. Centrifugal granulation was used to prepare pellets. The influence of surface modification by talc, the effects of Eudragit types and ratios, as well as the correlation between in vitro release and in vivo absorption were investigated in detail. The blend was coated with Eudragit L30D-55 and Eudragit NE30D at 7% or 10% level. The coated pellets showed good release profile. The absorption site specificity of Metformin hydrochloride in the intestine, three dissolution media, 0.1 N HCl, distilled water and phosphate buffer (pH 6.8) was used and the release was studied.

REVIEW FOR IRBESARTAN

36) **Doddayya Hiremath et al.** [47] designed and characterized of bilayer controlled release matrix tablets of Irbesartan. Direct compression technique was employed for formulating bilayer tablet. Irbesartan was formulated as immediate release as well as sustained release layer. Immediate release layer was formulated using Sodium starch glycolate as super disintegrant. Sustained release layer was formulated using polymers such as Xanthan gum and Gum Karaya in varying proportions. Immediate release layer containing Sodium starch glycolate (6%) was optimized. Sustained release layer containing polymer in equal proportions was optimized for final preparation of bilayer tablets. The optimized formulations were subjected to study the drug release mechanisms. The tablets showed zero order release Kinetics and Non-Fickian diffusion.

37) **Varma MM et al.** [48] studied the formulation and evaluation of Irbesartan matrix tablets for controlled release. Tablets were prepared by direct compression technique using Carbapol 934P and HPMC K100M as polymers. 11 formulations were prepared totallyand all the batches showed the release profile for a period of 24 hours.

38) **Ramya Chakrahari et al.** [49] formulated and evaluated of sustained release matrix tablets of Irbesartan. Wet granulation technique was employed using different polymers such as HPMC, Ethyl cellulose and Xanthan gum. Nine formulations were prepared. The formulation containing HPMC was optimized as it released the drugs for a period of 10 hours. The drug followed zero order release and non-Fickian transport. The optimized tablets were kept for accelerated stability studies.

39) **Prajapati BG et al.** [50] studied the formulation and *in vitro* evaluation of once daily sustained release matrix tablets of Irbesartan. Direct compression technique was employed using polymers HPMC K4M, HPMC K200M, Eudragit RSPO. 8 batches were prepared by varying the polymer concentrations. Batch 4 containing HPMC K4M, HPMC K200M, Eudragit RSPO was optimized based on the release profile as it sustained the release for a period of 24 hours.

40) **Mohanthy BR et al.** [51] developed and optimized Irbesartan tablets. Direct compression technique was employed using sodium starch glycolate as super disintegrant. Totally 8 formulations were prepared. Formulation 8 was selected as optimized batch as the release profile was comparable with the innovator product. The optimized tablets were kept for accelerated stability studies.

41) **Rajesh Gollapudi et al.** [52] formulated and evaluated sustained release matrix tablets of Irbesartan. Direct compression method was followed for preparing tablets using Eudragit RIRBO, RSPO and Ethyl cellulose individually or in combination. The formulations containing Eudragit RIRBO and RSPO were optimized based on the *in vitro* release profile and f2 factor. Mathematical analysis of the release kinetics indicated that drug release mechanism was Fickian diffusion.

42) **Suhas M Kakade et al.** [53] studied the formulation and evaluation of mouth dissolving tablets of Irbesartan. Direct compression technique was employed for preparing tablets using super disintegrants like Polyplasdone XL 10, Croscaramellose sodium and Explotab in different concentrations. The tablets were optimized based on the disintegration time. Polyplasdone XL 10 has faster disintegration time compared to the other two superdisintegrants.

43) **Mohd Azharuddin et al.** [54] formulated and evaluated controlled release matrix tablets of antihypertensive drug using natural and synthetic hydrophilic polymers. Direct compression technique was employed for preparing tablets using HPMC K4M and Xanthan gum. The polymers were used alone or in combinations for the formulation of tablets. Nine batches were prepared and the 9th batch containing the polymers in equal proportions was optimized as it sustained the release for a period of 24 hours.

44) **Lingaraj S Danki et al.** [55] developed and evaluated gastro retentive drug delivery system of Irbesartan. Wet granulation technique was used for formulating the tablets by employing polymers like HPMC K4M, HPMC K 15M, Carbapol 934P and sodium alginate at different drug to polymer ratios with and without gas generating like sodium bicarbonate and citric acid. Various formulations were prepared using the polymers and gas generating agents. The formulation containing HPMC K4M as polymer and gas generating agent in the ratio of 1:1 showed shorter floating lag time, good swelling property and good release profile. The optimized formulation was subjected to further short time stability studies.

45) **Vijaya Muthumanikandar R et al.** [56] developed and evaluated Buccoadhesive tablets of Irbesartan. Wet granulation technique was employed for formulation of tablets using Carbapol 934P, HPC, sodium alginate and SCMC as bioadhesive polymer. The formulation containing Carbapol and HPC in the ratio of 30%:20% was optimized based on its adequate bioadhesiveness, swelling properties and release profile. The optimized formulation was studied for drug release kinetics. The formulation followed first order release kinetics. The optimized formulation was sealed in aluminium packing and kept for accelerated stability studies for a period of 3 months.

46) **Suman A et al.** [57] studied the formulation and *in vitro* evaluation of Irbesartan floating tablets. Effervescent technique was used for formulating granules using varying grades of HPMC(K4M, K15M & K100) and using gas generating agent.12 formulations were prepared using the varying grades of HPMC. The formulation containing HPMC K100 (12%w/w of drug) and sodium bicarbonate (9%) showed rapid floating time, higher swelling and better release profile compared to the other formulations containing HPMC K4M and HPMC K15M. The optimized formulation was subjected to release kinetics.

47) **Reeta Rani Thakur et al.** [58] studied the formulation evaluation and optimization of mouth dissolving tablets of Irbesartan. Direct compression technique was employed for the formulation of tablets using sodium starch glycolate as Super disintegrant and sodium bicarbonate and citric acid as effervescent agents. Nearly ten formulations (A-J) were formulated and evaluated for precompression and post compression parameters and it was concluded that formulation C satisfied the criteria in all aspects and thus it was optimized.

48) **Pavithra TK et al.** [59] formulated and evaluated hydrogel based oral controlled drug delivery system of antihypertensive drug. Tablets were prepared by wet granulation technique. Simplex lattice design was used to develop the matrix tablets and evaluate the relationship and influence of different content levels of HPMC, Eudragit RSPO, Eudragit RIRBO and ethyl cellulose in order to achieve zero order release of drug. The

combination of HPMC with Eudragit sustained the release for a period of 8 hours. The tablets were then studied for drug release kinetics.

49) Permender Rathee et al. [60] studied the stability indicating UV- Spectrophotometric methods for simultaneous determination of Irbesartan and Hydrochlorothiazide in pharmaceuticals. Two new stability indicating methods have been described for simultaneous assay of Irbesartan and Hydrochlorothiazide in bulk and tablet formulation using 0.1N HCl as solvent. Method A is based on simultaneous equation and Method B is based on Q absorbance ratio method. Both the methods have been developed and validated. Both the methods provide good sensitivity comparable to that achieved in sophisticated techniques such as HPLC. Thus these methods can be used routinely for determination of bulk sample and tablets.

50) Rudy Bonfilio et al. [61] studied Irbesartan dissolution testing for drug release evaluation pharmaceutical capsules using HPLC and UV Spectrophotometry. A 2^4 factorial design was carried out to optimize dissolution condition and phosphate buffer pH
6.8 as dissolution medium and stirring speed of 50rpm. Spectra of Irbesartan was built in the range of 400 to 200nm using 1cm quartz cuvettes. The maximum peak was obtained at205nm.

3.AIM AND PLAN OF WORK

AIM OF THE PROJECT WORK

01. The main objective of the present study is to develop bilayer tablets containing Irbesartan for immediate release and Metformin hydrochloride for sustained release for diabetic patients having hypertension.

02. To provide effective, safe and stable pharmaceutical oral formulation containing an Antihypertensive drug Irbesartan as immediate release layer and oral hypoglycemic drug Metformin hydrochloride as sustained release layer for effective treatment of hypertensionin patients having Type-II diabetes mellitus.

PLAN OF WORK

- Preformulation studies.
- Physical and Chemical compatibility studies.
- Calibration curve.
- Pre compression studies of the drug and blends of Irbesartan.
- Formulation of Immediate release (IR) tablets.
- Post compression studies of IR tablets for physical parameters like uniformity ofweight, thickness, diameter, hardness and friability.
- Determination of drug content of IR tablets.
- Disintegration studies of IR tablets.
- *In vitro* dissolution study of IR tablets.
- Pre compression studies of the drug and blends of Metformin hydrochloride.
- Formulation of sustained release (SR) tablets.

- Post compression studies of SR tablets for physical parameters like uniformity ofweight, thickness, diameter, hardness and friability.
- Determination of drug content of SR tablets.
- *In vitro* dissolution study of SR tablets.
- Formulation of bilayer tablets from the optimized batches of IR and SR layer.
- Post compression studies of bilayer tablets for physical parameters like uniformity ofweight, thickness, diameter, hardness and friability.
- Determination of drug content by simultaneous equation method.
- *In vitro* dissolution study of bilayer tablets.
- Evaluation of release kinetics of optimized bilayer formulation.
- Determination of stability of bilayer tablets as per ICH guidelines.

4.ATIONALE

RATIONALE FOR SELECTION OF AT_1 BLOCKER (IRBESARTAN)

Irbesartan is a competitive antagonist to Angiotensinogen II and devoid of partial agonistic activity and 10,000 times more selective for AT_1 than AT_2 receptors.[62] Pharmacologically AT_1 antagonist differs from ACE inhibitors in the following ways. AT_1 antagonists do not interfere with the degradation of bradykinin and other ACE substrates thus there is no rise in level or potentation of bradykinin. AT_1 antagonist results in more complete inhibition of AT_1 receptor activation than ACE inhibitors. ACE inhibitor associated cough is not seen in AT_1 antagonist and angioedema is rare.[63] All of these makeAT_1 antagonists better over ACE inhibitors.

RATIONALE FOR SELECTION OF METFORMIN HYDROCHLORIDE FORTYPE II DIABETES [64]

Metformin is Antihypergylcemic, not a hypoglycemic. It does not cause insulin release from pancreas and generally does not cause hypoglycemia even in large doses. Metformin reduces glucose levels primarily by decreasing hepatic glucose production and by increasing insulin action in muscle and fat. Metformin given alone improves glycemic control and lipid concentrations in patients who respond poorly to diet or to sulfonylurea alone. Metformin has minimal side effects and a safer drug to treat diabetes.

RATIONALE FOR SELECTION OF IRBESARTAN AND METFORMIN HYDROCHLORIDEFOR FORMULATING BILAYER TABLETS

Most patients with type II diabetes have a prior history of cardiovascular complications and hypertension accounts for 75% in patients with type II diabetes.[66] Patients with other complications have to take more number of drugs. In order to reduce the polytherapy to monotherapy in patients with hypertension and type II diabetes and to improve patient compliance bilayer tablets were selected where two drugs can be given in combination. One such attempt was the formulation of bilayer tablets of Irbesartan and Metformin hydrochloride.PROFILES DISEASE PROFILE

DIABETES MELLITUS

Definition

Diabetes mellitus is not a single disease entity but rather a group of metabolic disorders sharing a common underlying feature of hyperglycemia. Hyperglycemia in diabetes results from defects in insulin secretion, insulin action, or most commonly both. DM consists of a group of disorders characterized by hyperglycemia; altered metabolism of lipids, carbohydrates, and proteins; and an increased risk of complications from vascular disease.[64] The chronic hyperglycemia and attendant metabolic dysregulation may be associated with secondary damage in multiple organ systems, especially the kidneys, eyes, nerves and blood vessels.

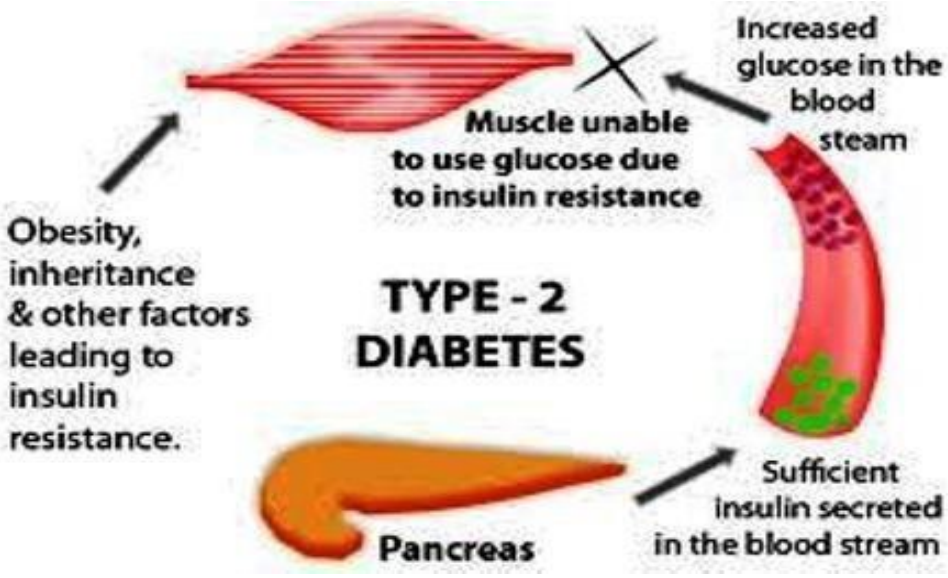


Fig. 9: Complications of Type II diabetes

Epidemiology [64]

The incidence of diabetes varies widely throughout the world. In the U.S., 5–10% of all diabetic patients have type 1 DM, with an incidence of 18/100,000 inhabitants/year. The vast majority of diabetic patients (~90% in the U.S.) have type 2DM. Incidence rates of type 2 DM increase with age, with a mean rate of about 440/100,000/year by the sixth decade in males in the U.S. According to American

Diabetes Association, Diabetes affects over 20 million children and adults, or 7% of the total population in the United States are unaware that they have hyperglycemia. Approximately 1.5 million new cases are diagnosed each year in the United States, and diabetes is the leading cause of end stage renal disease, adult onset blindness and non traumatic lower extremity amputations. 6 million people in the USA have Type 2 diabetes; India has a whopping 30 million and more people who are diabetics. According to a WHO estimate released in 1998, India will have the maximum number of diabetics in the world by 2025.

Classification [65]

1) Type 1 Diabetes Mellitus or Insulin Dependent Diabetes Mellitus
2) Type 2 Diabetes Mellitus or Non-Insulin Dependent Diabetes Mellitus
3) Type 3 Diabetes Mellitus (due to drugs such as Glucocorticoids, Thiazide diuretics, Protease inhibitors used to treat HIV, Diazoxide, Growth hormone etc.)
4) Type 4 Diabetes mellitus or Gestational Diabetes Mellitus**.**

Pathogenesis of Type 2 Diabetes Mellitus

Type 2 diabetes is a prototypic multi factorial complex disease. Environmental factors, such as a sedentary life style and dietary habits, and genetic components affect the risk of developing DM. [66] These factors are more clearly defined for type 2 DM. Obesity is a major risk factor, and 80–90% of type 2 DM subjects in the U.S. are obese. Studies also support a strong genetic basis for type 2 DM. Mutations in glucokinase cause the autosomal dominant disorder MODY2; these patients have an increased glycemic threshold for insulin release that results in persistent mild hyperglycemia. Other single-gene mutations cause the other types of MODY, including those affecting pancreatic transcription factors. [64]

Obesity and insulin resistance [66]

Insulin resistance is defined as the failure of the target tissues to respond normally to insulin. It leads to decreased uptake of glucose in muscle, reduced glycolysis and fatty acid oxidation in the liver, and an inability to suppress hepatic gluconeogenesis.

The epidemiologic association of obesity with Type 2 diabetes has recognised for decades, with visceral obesity observed in greater than 80% of patients. Obesity has profound effects on sensitivity of tissues on insulin and as a consequence, on systemic glucose homeostasis. Insulin resistance is present even in simple obesity unaccompanied by hyperglycemia, indicating a fundamental abnormality of insulin in state of fat excess. The risk of diabetes increases as the body mass index increases. It is not the absolute amount but also the distribution of body fat that has effect on insulin sensitivity: central obesity (abdominal fat) is more likely to be linked with insulin resistance than are peripheral fat depots.

β -Cell Dysfunction

In type 2 diabetes, β cells seemingly exhaust their capacity to adapt to the long term demands of peripheral insulin resistance. In states of insulin resistance like obesity, insulin secretion is initially higher for each level of glucose than in controls. This hyperinsulinemic state is a compensation for peripheral resistance and can often maintain normal plasma glucose for years. Eventually, however, β cells compensation becomes inadequate and there is a progression of hyperglycemia. The observation is that not all the obese individuals with insulin resistance develop overt diabetes suggests that an intrinsic predisposition to β cell failure must also exist.

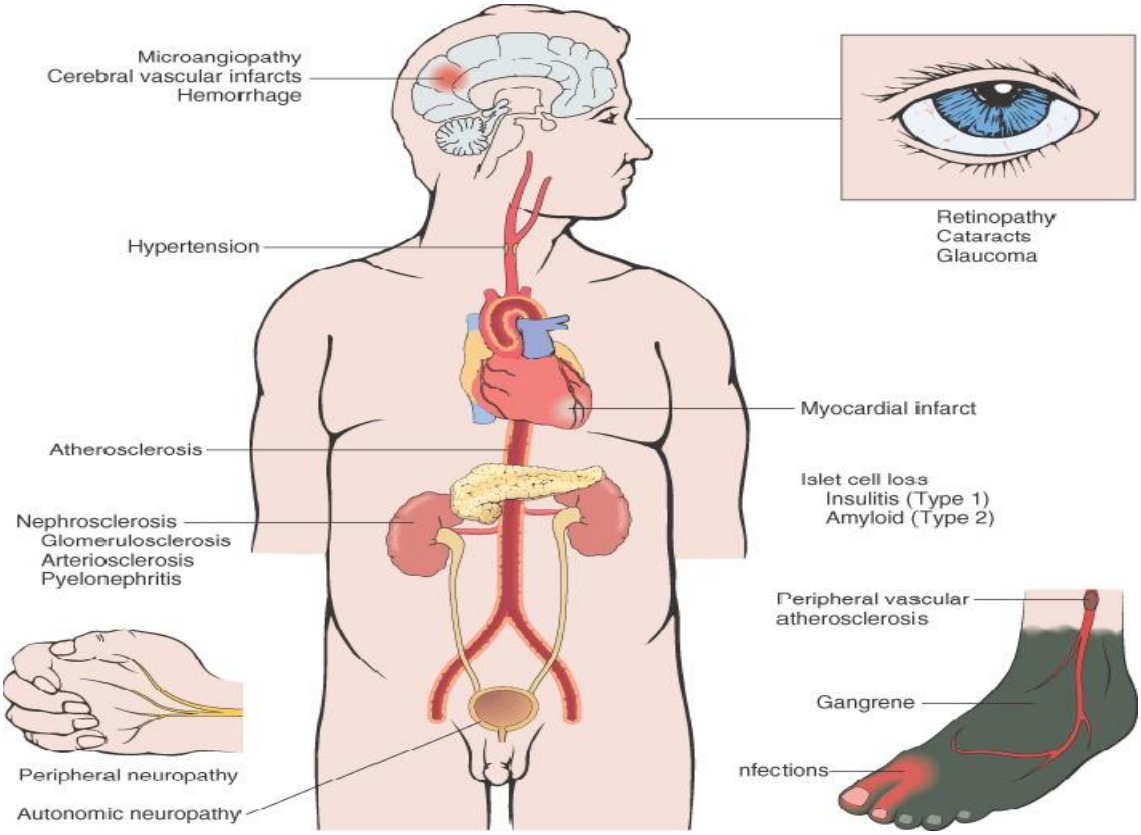


Fig. 10: Long-term complications of Diabetes

Morphology of diabetes and its late complications

Pathologic findings in the pancreas are variable and not necessarily dramatic. The important morphologic changes are related to many late systemic complications of diabetes.

1.Pancreas: Lesions in the pancreas are inconstant and rarely of diagnostic value. Distinctive changes are more commonly associated with type 1 than with type 2 diabetes. One or more of the following alterations may be present.

- Reduction in the number and size of islets.
- Leukocytic infiltrates in the islets.
- Subtle reduction in islet cell mass in Type 2 diabetes
- Amyloid deposition within islets in Type 2 diabetes
- An increase in the number and size of islets

2.Diabetes Macrovascular disease: Diabetes exacts a heavy toll on the vascular system. Endothelial dysfunction which predisposes to atherosclerosis and other cardiovascular morbidities is widespread in diabetes, as a consequence of the deleterious effect of persistent hyperglycemia and insulin resistance on the vascular compartment. Myocardial infarction caused by atherosclerosis of the coronary arteries, is the most common cause of death in diabetes.

3.Hyaline arteriosclerosis

4.Diabetic Microangiopathy

5.Diabetic Nephropathy

6.Renal atherosclerosis and arteriosclerosis

7.Pyelonephritis

8.Diabetic ocular complications

9.Diabetic Neuropathy

Clinical features of diabetes mellitus [67, 68]

➢ Polyuria, polydipsia, and polyphagia

➢ Weight loss and irreducible fatigue.

➢ Blurred vision

➢ Decreased sensation or numbness in the hands and feet

➢ Dry, itchy skin

➢ Frequent bladder and vaginal infections

➢ male impotence (erectile dysfunction)

➢ slow healing of cuts or sores

➢ Family history of diabetes (i.e., parent or sibling with type 2 diabetes)

➢ Obesity (BMI _ 25 kg/m2)

➢ Habitual physical inactivity

➢ Race/ethnicity (e.g., African American, Hispanic American, NativeAmerican, Asian American, Pacific Islander)

➢ Previously identified IFG or IGT

➢ History of GDM or delivery of baby >4 kg (>9 lb)

➢ Hypertension (blood pressure ≥140/90 mmHg)

➢ HDL cholesterol level ≤ 35 mg/dL (0.90 mmol/L) and/or a triglycerideLevel ≥250 mg/dL (2.82 mmol/L)

➢ Polycystic ovary syndrome or Acanthosis nigracans

➢ History of vascular disease

Unfortunately, many people with type 2 diabetes go undiagnosed for several years and are not diagnosed until they go to the doctor with symptoms or complications of diabetes.

Diagnosis

Blood glucose values are normally maintained in a very narrow range, usually
70 to 120 mg/dL. The diagnosis of diabetes is established by noting elevation of bloodglucose by any of the three criteria.

i. A random glucose concentration greater than 200mg/dL, with classical signs andsymptoms.

ii. A fasting glucose concentration greater than 126mg/dL on more than one occasion. iii.An abnormal oral glucose tolerance test (OGTT), in which the glucose
concentration is greater than 200mg/dL 2hours after a standard carbohydrate load

Treatment and Management [62]

The main goal of diabetes management is to maintain blood glucose levels within the normal range as much as possible. Weight control, diet, and exercise are all important components of management. The most important and main treatment for type 2 diabetes is nutritional.

✓Weight reduction and exercise

✓Treatment with insulin analogues (for Type I diabetes)

✓Treatment with oral hypoglycaemic agents (for Type II diabetes)

There are several types of oral diabetes medications, also called oralhypoglycemics, which work to lower blood glucose:

❖ **Sulfonylureas:** This family of medications includes Gliclazide, Glimepiride, and Glyburide. These medications are widely recommended for type 2 diabetes and work by stimulating the pancreas to release insulin. However, these medications don't work for type 1 diabetes.

❖ **Biguanides:** This medications include Metformin and work to improve insulin sensitivity and to reduce the glucose produced by the liver.

❖ **Acarbose:** This type of medication prolongs the absorption of carbohydrates after a meal. For these pills to work, they must be taken with or after a meal.

❖ **Thiazolidinediones:** This family of medications includes Pioglitazone and Rosiglitazone and they work to improve insulin sensitivity.

❖ **Meglitinides:** This family of medications includes Repaglinide and Nateglinide. They lower postprandial (after meals) glucose levels by stimulating the pancreas torelease insulin.

❖ **Dipeptidyl peptidase-4 inhibitors:** This class of medications includes Sitagliptin and saxagliptin. They heIRB improve insulin release from the pancreas and decrease liver release of glucose.

❖ **GIRB-1 analogs:** This class of medications includes Liraglutide, which is a synthetic form of the hormone GIRB-1. It heIRBs the body release insulin when blood sugar levels are high, and also reduces the release of sugar from the liver. Itis taken as a daily injection under the skin.

Disease Profile Hypertension [69, 70]

Hypertension is defined as sustained elevation of systemic arterial blood pressure. Blood pressure is the force, which the blood put against the walls of arteries as it flows through them. Arteries are the blood vessels that carry oxygenated blood from the heart to the body's tissues.

BP = Cardiac output X **Peripheral resistance**

CLASSIFICATION

1.Primary hypertension

They also called as essential or idiopathic hypertension, affects 90% to 95% of hypertensive individuals.

2.Secondary hypertension

It is caused by altered hemodynamics associated with primary disease, such as renal disease. Although many diseases cause secondary hypertension, this forms of hypertension accounts of 5% to 8% of cases.

3.Isolated hypertension

It is elevated systolic blood pressure accompanied by normal diastolic blood pressure (below 90mmHg). It is the manifestation of increased cardiac output or rigidity ofaorta or both.

RISK FACTORS

➢FOR PRIMARY HYPERTENSION

- Family history
- Advancing age
- Race (most common in blacks)
- Obesity
- Tobacco use
- High intake of sodium or saturated fat
- Excessive alcohol consumption
- Sedentary lifestyle, stress.

➢FOR SECONDARY HYPERTENSION

- Excessive Renin
- Mineral deficiencies (calcium, potassium& magnesium)
- Diabetes mellitus
- Coarctation of the aorta
- Renal artery disease or parenchymal disease
- Brain tumor, quadriplegia, head injury
- Pheochromocytoma, Cushing's syndrome, Hyperaldosteronism
- Thyroid, pituitary or parathyroid dysfunction
- Hormonal contraceptive, cocaine, sympathetic stimulants, MAO inhibitorstaken with tyramine, oestrogen replacement therapy, NSAID's
- Pregnancy

PATHOPHYSIOLOGY

Arterial blood pressure is a product of total peripheral resistance and cardiac output. Cardiac output is increased by conditions that increase heart rate or stroke volume, or both. Peripheral resistance is increased by factors that increase blood viscosity or reduce the lumen size of vessels.

Several mechanisms may lead to hypertension, including

✓ Changes in the arteriolar bed causing increased peripheral vascular resistance

✓ Abnormally increases tone in the sympathetic nervous system that originates in thevasomotor system centres, causing increased peripheral vascular resistance.

✓ Increased blood volume resulting from renal or hormonal dysfunction

✓ Arteriolar thickening caused by genetic factors, leading to increased peripheralvascular resistance.

✓ Abnormal renin release, resulting in the formation of Angiotensin II, whichconstricts the arteriole and increased blood volume.

Prolonged hypertension increases the workload of the heart as resistance to left ventricular ejection increases. To increase contractile force, the left ventricle hypertrophies, raising the oxygen demand and workload of the heart. The pathophysiology of secondary hypertension is related to the underlying disease.

- ❖ Stroke
- ❖ Myocardial infarction
- ❖ Heart failure
- ❖ Arrhythmias
- ❖ Retinopathy
- ❖ Encephalopathy
- ❖ Renal failure

SIGNS AND SYMPTOMS [63]

i. Generally produces no symptoms

ii. Occipital headache

iii. Epistaxis possibility due to vascular environment

iv. Bruits

v. Dizziness, confusion, fatigue

vi. Blurry vision

vii. Nocturia

viii. Edema

DIAGNOSTIC TEST RESULTS

- ♦ Serial blood pressure measurements show elevation
- ♦ Urine analysis shows protein, casts, red blood cells or white blood cells suggesting renal disease; presence of catecholamines associated with pheochromocytoma; or glucose, suggesting diabetes
- ♦ Blood chemistry reveals elevated blood urea nitrogen and serum creatinine levels suggestive of renal disease or hypokalemia indicating adrenal dysfunction.
- ♦ Excretory urography may reveal renal atrophy, indicating chronic renal disease.
- ♦ Electrocardiography detects left ventricular hypertrophy or ischemia.
- ♦ Chest X-rays shows cardiomegaly.
- ♦ Echocardiography reveals left ventricular hypertrophy.

TREATMENT

1.Lifestyle modifications to reduce risk factors

2.Treatment of underlying cause

3.Treatment with antihypertensive agents [62]

The various agents used are

01. ACE inhibitors

Captopril, Enalapril, Lisinopril, Perindopril, Ramipril.

02. Angiotensin (AT_1) Antagonists

Irbesartan, candesartan, Irbesartan, Olmesartan

03. Calcium channel blockers

Verapamil, Diltiazem, Nifedipine, Felodipine, Amlodipine, Nitrendipine,Lacidipine

04. Diuretics

i) Thiazides : Hydrochlorothiazide, chlorthalidone, Indapamide

ii) High ceiling : Furosemide

iii)Potassium sparing : Spironolactone, Triamterene, Amiloride

05. β **Adrenergic Blockers**

Propranalol, Metoprolol, Atenolol

06. B +α **Adrenergic Blockers**

Labetolol, Carvedilol

07. α **Adrenergic Blockers**

Prazosin, Terazosin, Doxazosin, Phentolamine, Phenoxybenzamine

08. Central sympatholytics

Clonidine, Methyldopa

09. Vasodilators

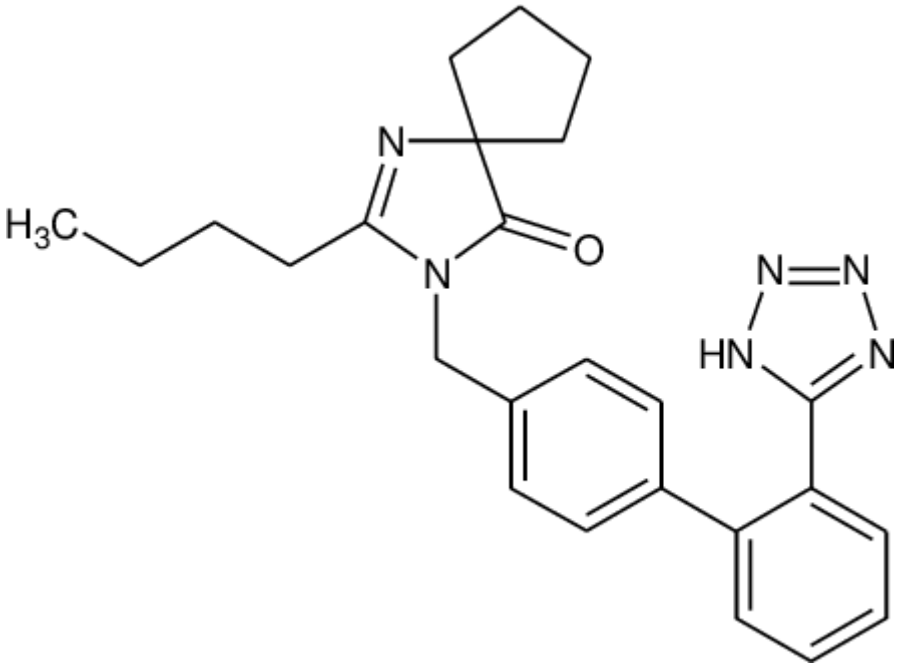
i) Arteriolar : Hydralazine, Minoxidil, Diazoxide

ii) Arteriolar + Venous: Sodium Nitroprusside.

DRUG PROFILE

IRBESARTAN [71, 72]

Chemical structure



Chemical Name	:	2-butyl-3-[p-(o-1H-tetrazol-5- ylphenyl)benzyl]-1,3-diazaspiro[4.4]non-1-en-4-one
Molecular Formula.	:	$C_{25}H_{28}N_6O$
Molecular Weight	:	465.0
Description Solubility	:	A white to off- white crystalline powder.
	:	Poorly soluble in water, soluble in alcohols, slightly soluble in commonorganic solvents such as Acetonitrile and methyl ethyl ketone. [73]

Mechanism of Action

Irbesartan is the first of a class of antihypertensive agents called Angiotensin II (AG II) receptor antagonists. prevents angiotensin II binding to the AT1 receptor in tissues like vascular smooth muscle and the adrenal gland.7,8 Irbesartan and its active metabolite bind the AT1 receptor with 8500 times more affinity than they bind to the AT2 receptor.7,8 Irbesartan's prevention of angiotensin II binding causes vascular smooth muscle relaxation and prevents the secretion of aldosterone, lowering blood pressure.7,8

Angiotensin II would otherwise bind to the AT1 receptor, inducing vasoconstriction and aldosterone secretion, raising blood pressure

Pharmacokinetics [62]

Absorption	:	Absorbed well orally but undergoes substantialfirst pass metabolism.
Bioavailability	:	Approximately 33%
Half life	:	The terminal $t_{1/2}$ of Irbesartan is 2.5 hours and that of E-3174(active metabolite) is 6-9 hours.
Plasma Protein binding	:	99.7%, primarily to albumin.
Volume of distribution	:	34 L [Irbesartan], 12 L [active metabolite].
Metabolism	:	The metabolism of Irbesartan to E -3174 andto inactive metabolites is mediated by CYP2C9 and CYP3A4.
Excretion	:	4% is excreted in unchanged form, 6% of active Metabolite is excreted in urine. Biliary excretion Contributes to the elimination of Irbesartan and its metabolites.

Therapeutic Indications

1.Treatment of hypertension - given alone or in combination with other antihypertensiveagents.

2.Nephropathy in Type 2 Diabetic patients.

Route/Dosage

1.Hypertension:

Adults: **PO** Initial dose: 50 mg once/day; 25 mg once/day if volume depleted or history ofhepatic impairment. Maintenance: 25 to 100 mg/day.

2.Nephropathy in Type 2 Diabetes:

Adults: **PO** Initial dose: 50 mg once daily; the dose may be increased to 100 mg once dailybased on BP response.

Contraindications: Hypersensitivity to Irbesartan.

Adverse effects **:** Dizziness, insomnia, nasal congestion, diarrhoea, dyspepsia, sinusitis,muscle cramps, myalgia, back pain, leg pain.

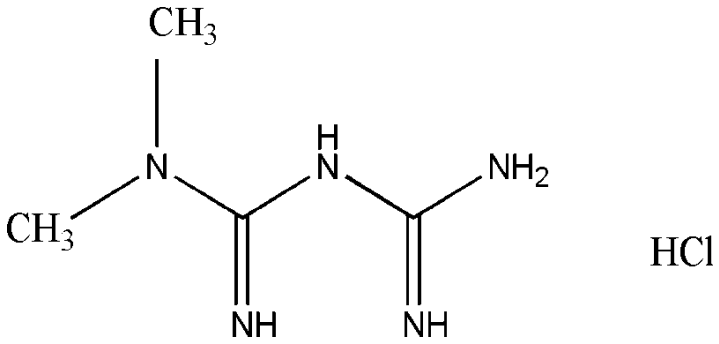
Drug interactions

01. Irbesartan may increase levels of blood potassium which can lead to serious heart problems (arrhythmias). Therefore, concomitant use of other substances that increase blood potassium-such as potassium-sparing diuretics (for example, spironolactone , triamterene, and amiloride), potassium supplements, or salt substitutes containing potassium, may lead to dangerous increases in serum potassium.

02. Combining Irbesartan or other ARBs with Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) in patients who are elderly, volume-depleted (including those on diuretic therapy), or with poor kidney function may result in reduced kidney function, including kidney failure. These effects usually are reversible. The antihypertensive effect of Irbesartan may be reduced by aspirin and other NSAIDs such as ibuprofen, indomethacin and naproxen.

METFORMIN HYDROCHLORIDE [74, 75]

Chemical structure



Chemical Name : 1,1 Dimethylbiguanide monohydrochloride

Molecular Formula : $C_4H_{11}N_5$.Hcl

Molecular Weight : 165.62

Description : A white, hygroscopic, crystalline powder.

Solubility : Freely soluble in water, soluble in ethanol, practicallyinsoluble in chloroform and ether.

Mechanism of Action

The mechanism of action of Metformin hydrochloride is different from other classes of oral antihyperglycemic agents. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. These effects are mediated by the initial activation by Metformin of AMP-activated protein kinase (AMPK), a liver enzyme that plays an important role in insulin signalling, whole body energy balance, and the metabolism of glucose and fats. Activation of AMPK is required for Metformin's inhibitory effect on the production of glucose by liver cells. Increased peripheral utilization of glucose may be due to improved insulin binding to insulin receptors. AMPK probably also plays a role, as Metformin administration increases AMPK activity in skeletal muscle. AMPK is known to cause GLUT4 deployment to the plasma membrane, resulting in insulin independent glucose uptake.

Pharmacokinetics [62]

Absorption : Metformin is absorbed mainly from the small intestine.
Bioavailability : 50 to 60% under fasting conditions.
Half life : ~2 hours.
Plasma protein binding : The drug is stable, does not bind to plasma proteins.Metabolism : It is not metabolized.
Excretion : Excreted unchanged in the urine.

Therapeutic indications

01. For use as an adjunct to diet and exercise to improve glycemic control in adult patients (18 years and older) with type 2 diabetes.
02. Prediabetes.
03. Polycystic ovary syndrome.
04. Gestational diabetes.

Route/Dosage

The maximum recommended daily dose of Metformin is 2.5 g divided into threedoses with meals.

Contraindications

Renal disease or dysfunction as suggested by serum Creatinine > 1.5 mg/dL in males or > 1.4 mg/dL in females or abnormal Ccr; conditions which predispose to renal dysfunction (eg, cardiovascular collapse, acute MI, septicaemia); in patients undergoing radiologic studies involving parenteral administration of iodinated contrast material (potential to acutely alter renal function); acute or chronic metabolic acidosis, including diabetic ketoacidosis.

Adverse effects

Unpleasant/metallic taste, Diarrhea, nausea, vomiting, abdominal bloating, flatulence,anorexia, Lactic acidosis, subnormal vitamin B_{12} levels.

Drug interactions

1.Alcohol: Potentiates effect of Metformin on lactate metabolism.

2.Cationic Drugs (eg, Amiloride, Digoxin, Quinidine): May increase Metformin serum concentration by competing for tubular secretion.

3.Cimetidine: Increases Metformin serum concentration.

4.Furosemide: May increase Metformin serum concentration; Metformin may reduce furosemide serum concentration.

5.Iodinated Contrast Material: May cause acute renal failure and has been associated with lactic acidosis in patients receiving Metformin.

6.Nifedipine: Increases Metformin serum concentration.

EXCIPIENT PROFILELACTOSE [76]

1.Nonproprietary Names

BP: Lactose, PhEur: Lactose Monohydrate, USP-NF: Lactose monohydrate

2.Synonyms

CapsuLac; GranuLac; Lactochem; Lactosum monohydricum Monohydrate;Pharmatose; PrismaLac; SacheLac; SorboLac; SpheroLac; SuperTab 30GR; Tablettose.

3.Chemical Name

O-β-D-Galactopyranosyl-(1, 4)-α-D-glucopyranose monohydrate

4.Empirical Formula

$C_{12}H_{22}O_{11}.H_2O$

5.Molecular Weight

360.31

6.Functional Category

Dry powder inhaler carrier, lyophilization aid, tablet binder, tablet and capsule diluents, tablet and capsule filler.

7.Description

The stable crystalline forms of lactose are α-lactose monohydrate, β-lactose anhydrous and stable α-lactose anhydrous. Lactose occurs as white to off-white crystalline particles or powder. Lactose is odorless and slightly sweet-tasting, α-lactose is approximately 20% as sweet as sucrose, while β-lactose is 40% as sweet.

8.Solubility

Practically insoluble in chloroform, ethanol and ether. Soluble in water.

9.Applications

Lactose is widely used as filler and diluent in tablets and capsules. Lactose is also used as a diluent in dry-powder inhalation; Lactose is also used in the manufacture of dry powder formulations for use as aqueous film-coating solutions or suspensions. Lactose is also used in combination with sucrose (approximately 1:3) to prepare sugar-coating solutions.

HYDROXYPROPYLMETHYL CELLULOSE [76]

1.Nonproprietary Names

BP:Hypromellose, JP: Hypromellose, PhEur: Hypromellose, USP: Hypromellose

2.Synonyms

Benecel MHPC; E464; Hydroxy propyl methylcellulose;HPMC; hypromellosum; Methocel; methycellulose propylene glycol ether; methyl hydroxypropylcellulose; Metolose; MHPC; Pharmacoat; Tylopur; Tylose.

3.Chemical Name

Cellulose hydroxypropyl methyl ether

4.Molecular Weight

Molecular weight is approximately 10000–1500000.

5.Functional Category

Bio-adhesive material, coating agent, controlled-release agent, emulsifying agent,film-forming agent, suspending agent, sustained-release agent and tablet binder.

6.Description

Hypromellose is an odourless and tasteless, white or creamy-white fibrous orgranular powder.

7.Solubility

Soluble in cold water, forming a viscous colloidal solution; practically insoluble inhot water, chloroform, ethanol (95%) and ether.

8.Incompatibilities

Hypromellose is incompatible with some oxidizing agents.

9.Applications

Hypromellose is widely used in oral, ophthalmic, nasal, and topical pharmaceutical formulations. It is primarily used as a tablet binder, in film-coating and as a matrix for use in extended release tablet formulations. Concentrations between 2-5% w/w may be used as a binder in either wet or dry granulation processes. High-viscosity grades may be used to retard the release of drugs from a matrix at levels of 10–80% w/w in tablets and

capsules. Hypromellose is also used in liquid oral dosage forms as a suspending and/or thickening agent at concentrations ranging from 0.25–5.0%.

ETHYLCELLULOSE [76]

1.Nonproprietary Names

BP: Ethylcellulose, PhEur: Ethylcellulose, USP-NF: Ethylcellulose

2.Synonyms

Aquacoat ECD; Aqualon; Ashacel; E462; Ethocel; ethylcellulosum; Surelease.

3.Chemical Name

Cellulose ethyl ether

4.Empirical Formula and Molecular Weight

Ethylcellulose is partially ethoxylated. Ethylcellulose with complete ethoxyl substitution (DS = 3) is $C_{12}H_{23}O_6(C_{12}H_{22}O_5)_nC_{12}H_{23}O_5$ where n can vary to provide a wide variety of molecular weights.

5.Functional Category

Coating agent, tablet binder, tablet filler, viscosity increasing agent.

6.Description

Ethylcellulose is a tasteless, free-flowing, white to light tan-coloured powder.

7.Solubility

Ethylcellulose is practically insoluble in glycerin, propylene glycol, and water.

8.Incompatibilities

Incompatible with paraffin wax and microcrystalline wax.

9.Applications

Ethylcellulose is widely used in oral and topical pharmaceutical formulations. The main use of ethyl cellulose in oral formulations is as a hydrophobic coating agent for tablets and granules. Ethylcellulose coatings are used to modify the release of a drug, to mask an unpleasant taste, or to improve the stability of a formulation. High-viscosity grades of ethyl cellulose are used in drug microencapsulation. High-viscosity grades of ethyl cellulose are used in drug microencapsulation. Ethylcellulose has also been used as an agent for delivering therapeutic agents from oral (e.g. dental) appliances. In topical formulations, ethylcellulose is used as a thickening agent in creams, lotions, or gels, provided an appropriate solvent is used. Ethyl cellulose is additionally used in cosmetics and food products.

MICROCRYSTALLINE CELLULOSE [76]

1.Nonproprietary Names

BP: Microcrystalline Cellulose, JP: Microcrystalline Cellulose, PhEur: Cellulose, Microcrystaline, USP-NF: Microcrystalline Cellulose.

2.Synonyms

Avicel PH; Cellets; Celex; cellulose gel; hellulosum microcristallinum; CeIRBhere; Ceolus KG; crystalline cellulose; E460; Emcocel;Ethispheres; Fibrocel; MCC Sanaq; Pharmacel; Tabulose; Vivapur.

3.Chemical Name

Cellulose

4.Empirical Formula

$(C_6H_{10}O_5)_n$ where n = 220.

5.Functional Category

Tablet and capsule diluent, Adsorbent, tablet disintegrant, suspending agent.

6.Description

Microcrystalline cellulose is purified, partially depolymerised cellulose that occurs as a white, odorless, tasteless, crystalline powder composed of porous particles. It is commercially available in different particle sizes and moisture grades that have different properties and applications.

7.Solubility

Slightly soluble in 5% w/v sodium hydroxide solution; practically insoluble in water, dilute acids, and most organic solvents.

8.Incompatibilities

Microcrystalline cellulose is incompatible with strong oxidizing agents.

9.Applications

Microcrystalline cellulose is widely used in pharmaceuticals, primarily as a binder/diluent in oral tablet and capsule formulations where it is used in both wet-granulation and direct-compression processes. In addition to its use as binder/diluents, microcrystalline cellulose also has some lubricant and disintegrant properties that make it useful in tabletting.

STARCH [76]

1.Nonproprietary Names

BP: Maize starch, Potato starch, Rice Starch, Tapioca Starch, Wheat Starch JP: Corn Starch, Potato Starch Rice Starch, Wheat Starch, PhEur: Maize Starch, Pea Starch, Potato Starch, Rice Starch, Wheat Starch USP-NF: Corn Starch, Potato Starch, Tapioca Starch, Wheat Starch

2.Synonyms

Amido; amidon; amilo; amylum; C*PharmGel; Eurylon; fecule;Hylon; maydis amylum; Melojel; Meritena; oryzae amylum; Pearl;Perfectamyl; pisi amylum; Pure-Dent; Purity 21; Purity 826; solani amylum; tritici amylum.

3.Chemical Name

Starch

4.Empirical Formula

$(C_6H_{10}O_5)_n$ where n = 300–1000.

5.Functional Category

Tablet and capsule diluent, tablet and capsule disintegrant, tablet binder, thickening agent.

6.Description

Starch occurs as an odorless and tasteless, fine, white to off-white powder.

7.Solubility

Practically insoluble in cold ethanol (96%) and in cold water Starch becomes soluble in hot water at temperatures above the gelatinization temperature. Starches are partiallysoluble in dimethylsulfoxide and dimethylformamide.

8.Applications

Starch is a versatile excipient used primarily in oral solid-dosage formulations where it is utilized as a binder, diluent, and disintegrant. In tablet formulations, freshly prepared starch paste is used at a concentration of 3–20% w/w (usually 5–10%, depending on the starch type) as a binder for wet granulation. Starch is one of the most commonly used tablet disintegrants at concentrations of 3–25% w/w; a typical concentration is 15%. Starch has been investigated as an excipient in novel drug delivery systems for nasal and other site-specific delivery systems.

SODIUM STARCH GLYCOLATE [76]

1.Nonproprietary Names

BP: Sodium Starch Glycolate, PhEur: Sodium Starch Glycolate,USP-NF: SodiumStarch Glycolate.

2.Synonyms

Carboxy methyl starch, sodium salt; carboxy methyl amylum natricum; Explosol: Explotab; Glycolys; Primojel; starch carboxy methyl ether, sodium salt; Tablo; Vivastar P.

3.Chemical Name

Sodium carboxymethyl starch.

4.Functional Category

Tablet and capsule disintegrant.

5.Description

Sodium starch glycolate is a white or almost white free-flowing very hygroscopicpowder.

6.Solubility

Practically insoluble in methylene chloride. It gives a translucent suspension in water.

7.Applications

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 of about 4%. Disintegration occurs by rapid uptake of water followed by rapid and enormous swelling. Increasing the tablet compression pressure also appears to have no effect on disintegration time.

POVIDONE [76]

1.Nonproprietary Names

BP: Povidone, PhEur: Povidone, USP-NF: Povidone.

2.Synonyms

E1201;Kollidon; Plasdone; poly[1-(2-oxo-1-pyrrolidinyl)ethylene]; polyvidone;polyvinyIRByrrolidone; povidonum; Povipharm; PVP; 1- vinyl-2-pyrrolidinone polymer.

3.Chemical Name

1-Ethenyl-2-pyrrolidinone homopolymer

4.Empirical Formula

$(C_6H_9NO)_n$

5.Molecular Weight

2500–3,000,000

6.Functional Category

Disintegrant, dissolution enhancer, suspending agent, tablet binder.

7.Description

Povidone occurs as a fine, white to creamy-white colored, odourless or almost odorless, hygroscopic powder. Povidones with K-values equal to or lower than 30 are manufactured by spray-drying and occur as spheres. Povidone K-90 and higher K-valuepovidones are manufactured by drum drying and occur as plates.

8.Solubility

Freely soluble in acids, chloroform, ethanol (95%), ketones, methanol and water.

Practically insoluble in ether, hydrocarbons and mineral oil.

9.Applications

Povidone is used in a variety of pharmaceutical formulations primarily used in solid- dosage forms. In tabletting, Povidone solutions are used as binders in wet-granulation processes. It is also added to powder blends in the dry form and granulated *in situ* by the addition of water, alcohol, or hydro alcoholic solutions. Povidone is used as a solubilizer in oral and parenteral formulations, and has been shown to enhance dissolution of poorly soluble drugs from solid-dosage forms Povidone is also used as a suspending, stabilizing, or viscosity-increasing agent in a number of topical and oral suspensions and solutions.

MAGNESIUM STEARATE [76]

1.Nonproprietary Names

BP: Magnesium Stearate, JP: Magnesium Stearate, PhEur: Magnesium Stearate USP-NF: Magnesium Stearate.

2.Synonyms

Dibasic magnesium stearate; magnesium distearate; magnesia stearas; magnesium octadecanoate; octadecanoic acid, magnesium salt; stearic acid, magnesium salt; Synpro 90.

3.Chemical Name

Octadecanoic acid magnesium salt

4.Empirical Formula

$C_{36}H_{70}MgO_4$

5.Molecular Weight

591.24

6.Functional Category

Tablet and capsule lubricant.

7.Description

Magnesium stearate is a very fine, light white, impaIRBable powder of low bulk density, having a faint odour of stearic acid and a characteristic taste. The powder is greasy to the touch and readily adheres to the skin.

8.Incompatibilities

Incompatible with strong acids, alkalis, and iron salts.

9.Applications

Magnesium stearate is widely used in cosmetics, foods and pharmaceutical formulations. It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25% and 5.0% w/w. Magnesium stearate is hydrophobic and may retard the dissolution of a drug from a solid dosage form; the lowest possible concentration is therefore used in such formulations. It is also used in barrier creams.

TALC [76]

1.Nonproprietary Names

BP: Purified Talc, JP: Talc, PhEur: Talc, USP: Talc

2.Synonyms

Altalc; E553b; hydrous magnesium calcium silicate; hydrous magnesium silicate; Imperial; Luzenac Pharma; magnesium hydrogen metasilicate; Magsil smanthus; Magsil Star; powdered talc; purified French chalk; Purtalc; soapstone; steatite; Superiore; talcum.

3.Chemical Name

Talc

4.Empirical Formula

Talc is a purified, hydrated, magnesium silicate, approximating to the formula $Mg_6(Si_2O_5)_4\ (OH)_4$. It may contain small, variable amounts of aluminium silicate and iron.

5.Functional Category

Anticaking agent, glidant, tablet and capsule diluent; tablet and capsule lubricant.

6.Description

Talc is a very fine, white to greyish-white, odorless, impaIRBable, crystalline powder. Itadheres readily to the skin and is soft to the touch and free from grittiness.

7.Solubility

Practically insoluble in dilute acids and alkalis, organic solvents, and water.

8.Incompatibilities

Incompatible with quaternary ammonium compounds.

9.Applications

Talc was widely used in oral solid dosage formulations as a lubricant and diluent. It is widely used as a dissolution retardant in the development of controlled-release products. Talc is also used as a lubricant in tablet formulations in a novel powder coating for extended- release pellets and as an adsorbent. In topical preparations, talc is used as a dusting powder. Talc is additionally used to clarify liquids and is also used in cosmetics and food products, mainly for its lubricant properties.

ACETONE [76]

1.Nonproprietary Names

BP: Acetone, PhEur: Acetone, USP-NF: Acetone.

2.Synonyms

Acetonum; dimethylformaldehyde; dimethyl ketone; b-ketopropane; pyroacetic ether.

3.Chemical Name

2-Propanone

4.Empirical Formula

C_3H_6O

5.Molecular Weight

58.08

6.Functional Category

Solvent

7.Description

Acetone is a colorless, volatile, flammable, transparent liquid, with a sweetish odourand pungent sweetish taste.

8.Solubility

Soluble in water; freely soluble in ethanol (95%).

9.Incompatibilities

Acetone reacts violently with oxidizing agents, chlorinated solvents, and alkali mixtures. It reacts vigorously with suIRBhur dichloride, potassium t-butoxide and hexachloromelamine. Acetone should not be used as a solvent for iodine, as it forms a volatilecompound that is extremely irritating to the eyes.

10. Applications

Acetone is used as a solvent or co solvent in topical preparations, and as an aid in wet granulation. It has also been used when formulating tablets with water-sensitive active ingredients, or to solvate poorly water-soluble binders in a wet granulation process. Acetone has also been used in the formulation of microspheres to enhance drug release. Owing to its low boiling point, acetone has been used to extract thermolabile substances from crude drugs.

ISOPROPYL ALCOHOL [76]

1.Nonproprietary Names

BP: Isopropyl Alcohol, JP: Isopropanol, PhEur: Isopropyl Alcohol, USP: Isopropyl Alcohol

2.Synonyms

Alcohol isopropylicus; dimethyl carbinol; IPA; isopropanol; petrohol; 2-propanol;sec-propyl alcohol; rubbing alcohol.

3.Chemical Name

Propan-2-ol

4.Empirical Formula

C_3H_8O

5.Molecular Weight

60.1

6.Functional Category

Disinfectant, solvent.

7.Description

Isopropyl alcohol is a clear, colorless, mobile, volatile, flammable liquid with a characteristic, spirituous odour resembling that of a mixture of ethanol and acetone; it has a slightly bitter taste.

8.Solubility

Miscible with benzene, chloroform, ethanol (95%), ether, glycerin, and water.

9.Incompatibilities

Incompatible with oxidizing agents such as hydrogen peroxide and nitric acid, which cause decomposition.

10. Applications

Isopropyl alcohol (propan-2-ol) is used in cosmetics and pharmaceutical formulations, primarily as a solvent in topical formulations, Although it is used in lotions, the marked degreasing properties of isopropyl alcohol may limit its usefulness in preparations used repeatedly. Isopropyl alcohol is also used as a solvent both for tablet film-coating and fortablet granulation, where the isopropyl alcohol is subsequently removed by evaporation.

6.MATERIALS AND METHODS

Table 1:List of materials and their applications in formulation.

S.No	Name of the material	Manufacture/ Supplier	Use in formulation
1.	Metformin hydrochloride	Gift Sample, Cipla limited, Indore	Active ingredient
2.	Irbesartan	Gift Sample, Cipla limited,Indore	Active ingredient
3.	HPMC K4M	Samsung fine chemicals, Korea	Hydrophilic polymer
4	HPMC K100M	Samsung fine chemicals, Korea	Hydrophilic polymer
5.	Ethyl cellulose	Zhongbao chemicals, China	Non swellablepolymer
6.	Microcrystalline cellulose	Shree Chemicals, Bhopal	Diluent
7.	Lactose	SD Fine chemicals, Gujrat	Diluent
8.	Starch	SD Fine chemicals, Gujrat	Diluent
9.	Sodium starch glycolate	SD Fine chemicals, Gujrat	Superdisintegrant
10	Poly vinyl pyrrolidoneK30	Jiao Zuo Yuanhai Fine Chemicals Ltd., China	Binder
11.	Isopropyl alcohol	SD Fine chemicals, Gujrat	Solvent
12.	Acetone	SD Fine chemicals, Gujrat	Solvent
13.	Talc	S D fine chemicals, Mumbai	Glidant
14.	Magnesium stearate	Shreeji Pharma, Vadodara	Lubricant
15.	Tartrazine yellow	Neelikon food dyes & Chemicals, Mumbai, India	Colouring agent

Table 2: List of Equipments/Instruments used

S.No	Equpiments/ Instruments	Manufacture/ Supplier
1.	Electronic weighing balance	Contech-CA223, 2008
2.	Tray Drier	Chitra, Ahmedabad
3.	Hot Air Oven	Industrial heaters, Indore
4.	27 Station Rotary Compression Machine	Minipress, Karnavati, Ahmedabad
5.	27 Station Rotary Bilayer Compression Machine	Karnavati, Ahmedabad
6.	Vernier calliper	Mitutoyo, Japan
7.	Monsanto Hardness Tester	Erweka, Mumbai
8.	Friabilator	Electrolab, India
9.	pH Meter	Symchrony, India
10.	Sonicator	JJ enterprise, Indore
11.	Disintegration Apparatus	Veego, Mumbai
12.	Dissolution Apparatus	Electrolab-TDT-06L, 2009
13.	UV- Visible Spectrophotometer	Agilent technologies cary60, 2012
14.	Fourier Transform Infra Red Spectrophotometer	Agilent technologies cary 630, 2012
15.	Stability Chamber	Technico, India

METHODOLOGYPREFORMULATION STUDIES [77]

Preformulation study is the first step in the rational development of dosage forms of a drug substance. It can be defined as an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. The overall objective of preformulation studies is to generate information useful to the formulator in developing stable and bioavailable dosage forms that can be mass produced.

DRUG EXCIPIENT COMPATIBILITY STUDY

The drug and the excipients chosen for the formulation were screened for compatibility by physical methods and Fourier Transform Infrared (FTIR) spectroscopic studies.

Physical Compatibility Study [78]

The physical compatibility studies were conducted to provide valuable information to the formulator in selecting the appropriate excipients for the formulation. It was done by mixing the drugs and the excipients and kept at room temperature and at 40° C and 75% RH. Any change in color of the physical mixture was observed visually.

Chemical Compatibility study by FTIR [55, 79]

Infrared spectroscopy can be used to identify a compound and also to investigate the composition of a mixture. Pure drugs, polymers, excipients, drug excipient mixture and the optimized formulation were subjected to FTIR studies to investigate the Drug- excipient interactions. The IR spectra of the test samples were obtained by Pressed Pellet Technique using Potassium bromide.

PREPARATION OF BUFFER SOLUTIONS

Preparation of 0.1 N Hydrochloric Acid (1.2 pH) [73]

8.5 mL of the hydrochloric acid was taken and dissolved in water and made upto1000 mL to get 0.1 N hydrochloric acid.

Preparation of 0.02 M potassium dihydrogen phosphate [73]

27.218 g of potassium dihydrogen phosphate was dissolved in distilled water and the volume was made upto 1000 mL using distilled water.

Preparation of 0.02 M Sodium Hydroxide [73]

8 g of sodium hydroxide was dissolved in distilled water and made upto 1000 mL with distilled water.

Preparation of 6.8 pH phosphate buffer solution [73]

50 mL of 0.02 M Potassium dihydrogen phosphate was taken in a 200 mL volumetric flask. 22.4 mL of 0.02 M sodium hydroxide solution was added and mixed well then the volume was made upto 200 mL using distilled water.

CALIBRATION CURVE

For Metformin hydrochloride [80]

100 mg of drug was weighed and transferred to a 100 mL standard flask and made upto volume using 0.1 N HCl. 10 mL of the stock solution was pipetted out in a separate 100 mL standard flask and the volume was made up using 0.1 N HCl. From the resulting solution 2, 4, 6, 8 and 10 mL were pipetted out into separate 100 mL standard flasks and made upto volume using 0.1 N HCl to represent 2, 4, 6, 8 and 10 µg/mL of the drug. The absorbance of the solutions was measured at 233 nm taking 0.1 N HCl as blank using UV- Visible spectrophotometer. The same procedure was repeated using 6.8 pH phosphate buffer solution as solvent. The calibration curve was then plotted taking concentration (µg/mL) along X-axis and absorbance along Y- axis.

For Irbesartan [81]

100 mg of drug was weighed and transferred to a 100 mL standard flask and made upto volume using 0.1 N HCl. 10 mL of the stock solution was pipetted out in a separate 100 mL standard flask and the volume was made up using 0.1 N HCl. From the resulting solution 2, 4, 6, 8 and 10 mL were pipetted out into separate 100 mL standard flasks and made upto volume using 0.1 N HCl to represent 2, 4, 6, 8 and 10 µg/mL of the drug. The absorbance of the solutions was measured at 246 nm taking 0.1 N HCl as blank using UV- Visible spectrophotometer. The calibration curve was then plotted taking concentration (µg/mL) along X-axis and absorbance along Y- axis.

PRECOMPRESSION STUDIES OF DRUG AND BLENDFLOW PROPERTY MEASUREMENTS [77]

The flow properties of powders are critical for an efficient tabletting operation. A good flow of the powder or granulation to be compressed is necessary to assure efficient mixing and acceptable weight uniformity for the compressed tablets. The flow property measurements include Bulk Density, Tapped Density, Compressibility index, Hausner's ratio and Angle of Repose. The flow property measurements of drug and blends were determined to select the type of granulation technique to be carried out for the formulation.

A. BULK DENSITY (ρ_b) [81]

It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder into a measuring cylinder. This initial volume was called the bulk volume. From this the bulk density was calculated according to the formula mentioned below. It is expressed in g/mL and is given by

$\rho_b = \mathbf{M / V_b}$

Where, **M** and $\mathbf{V_b}$ are mass of powder and bulk volume of the powder respectively.

B. TAPPED DENSITY(ρ_t) [81]

It is the ratio of weight of the powder to the tapped volume of powder. The powder was introduced into a measuring cylinder with the aid of funnel and tapped for 500 times on a wooden surface at 2 sec interval and the volume attained was the tapped volume. It is expressed in g/mL and is given by

$\rho_t = \mathbf{M / V_t}$

Where, **M** and $\mathbf{V_t}$ are mass of powder and tapped volume of the powder respectively.

C. ANGLE OF REPOSE (θ) [81]

The flow properties were characterized in terms of Angle of repose, Carr's index and Hausner's ratio. For determination of Angle of Repose (θ), the drug and the blends were poured through the walls of a funnel, which was fixed at a position such that its lower tip was at a height of exactly 2.0 cm above a hard surface. The drug or the blends were poured till the time when upper tip of the pile surface touched the lower tip of the funnel. Angle of repose was calculated using following equation.

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

Where, **h** = height of pile in cm; **r** = radius of pile in cm

D. CARR'S INDEX (OR) % COMPRESSIBILITY [81]

It indicates powder flow properties. It is measured for determining the relative importance of interparticulate interactions. It is expressed in percentage and is given by

$$CI = \frac{\rho_t - \rho_b}{\rho_t} \times 100$$

Where, ρ_t and ρ_b are tapped density and bulk density respectively.

E. HAUSNER'S RATIO [81]

Hausner's ratio is an indirect index of ease of powder flow. It is calculated by thefollowing formula.

$$HR = \rho_t / \rho_b$$

Where, ρ_t and ρ_b are tapped density and bulk density respectively.

Table 3: Values of Angle of Repose, Compressibility Index and Hausner's Ratio [82]

Flow property	Angle of Repose (θ)	Compressibility Index (%)	Hausner's Ratio
Excellent	25-30	<10	1.00-1.11
Good	31-35	11-15	1.12-1.18
Fair	36-40	16-20	1.19-1.25
Passable	41-45	21-25	1.26-1.34
Poor	46-55	26-31	1.35-1.45
Very poor	56-65	32-37	1.46-1.59
Very Very poor	>65	>38	>1.60

7. ORMULATION DEVELOPMENT

Formulation of Immediate release granules of Irbesartan

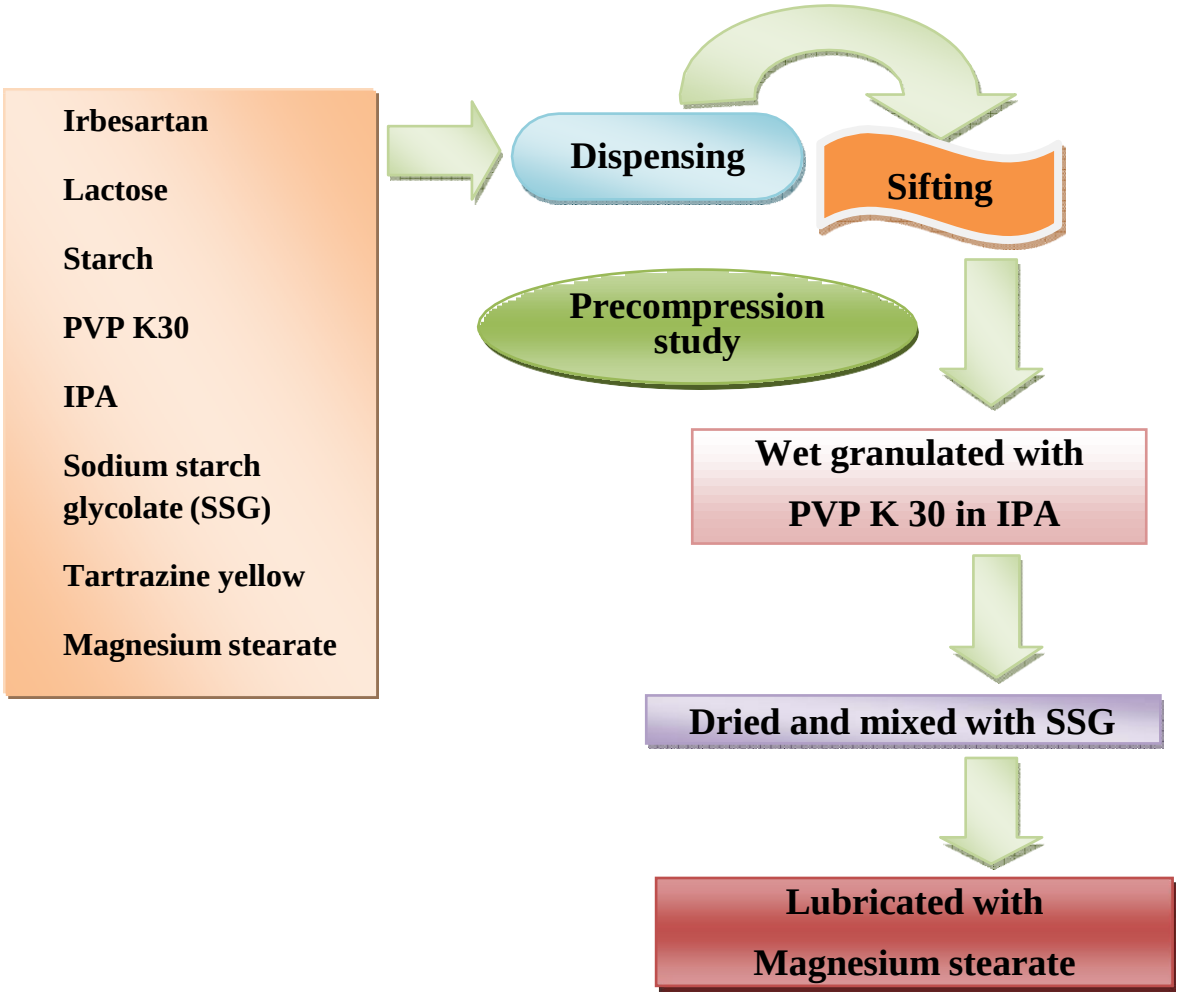
The immediate release granules of Irbesartan (IRB1 and IRB2) were prepared by wet granulation technique.[49] Sodium Starch Glycolate (SSG) was used as a super disintegrant in (2% and 4% concentrations) to improve dissolution of the drug. The granules were compressed by 27 station tablet compression machine using 11/32 inch (8.73mm) concave punches.

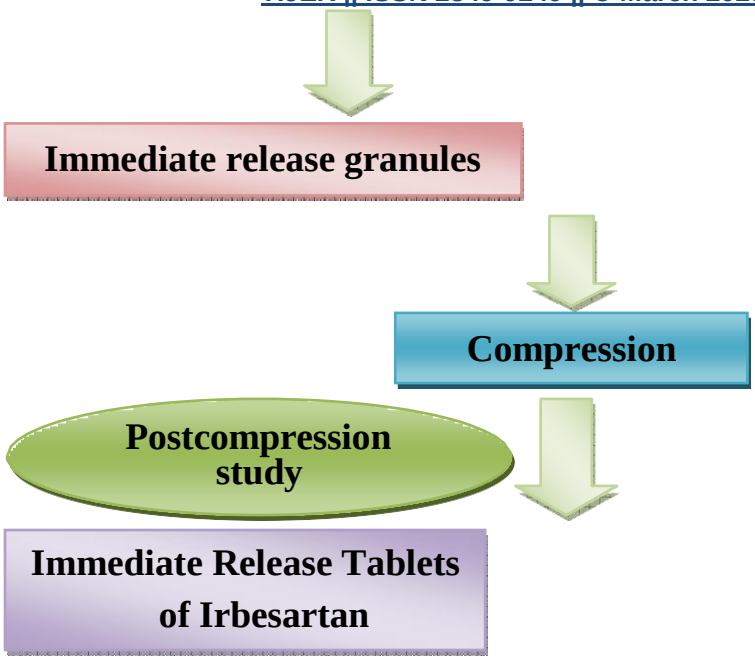
Table 4: Composition of immediate release granules

S.NO	INGREDIENTS	IRB1 (mg)	IRB2 (mg)
01.	Irbesartan	50	**50**
02.	Lactose	86.6	**82.0**
03.	Starch	69.0	**69.0**
04.	PVP K-30	4.6	**4.6**
05.	Isopropyl alcohol	q.s	**q.s**
06.	Sodium starch glycolate	4.6	**9.2**
07.	Magnesium stearate	4.6	**4.6**
08.	Tartrazine yellow	1.0	**1.0**
09.	Starch	10	**10**
Total weight		230.0	**230.0**

The immediate release tablet of Irbesartan was formulated and optimized. The optimized formulation was used for the final bilayer tablets.

Flowchart for formulation of Irbesartan immediate release (IR) tablets





Formulation of Sustained Release Granules of Metformin Hydrochloride

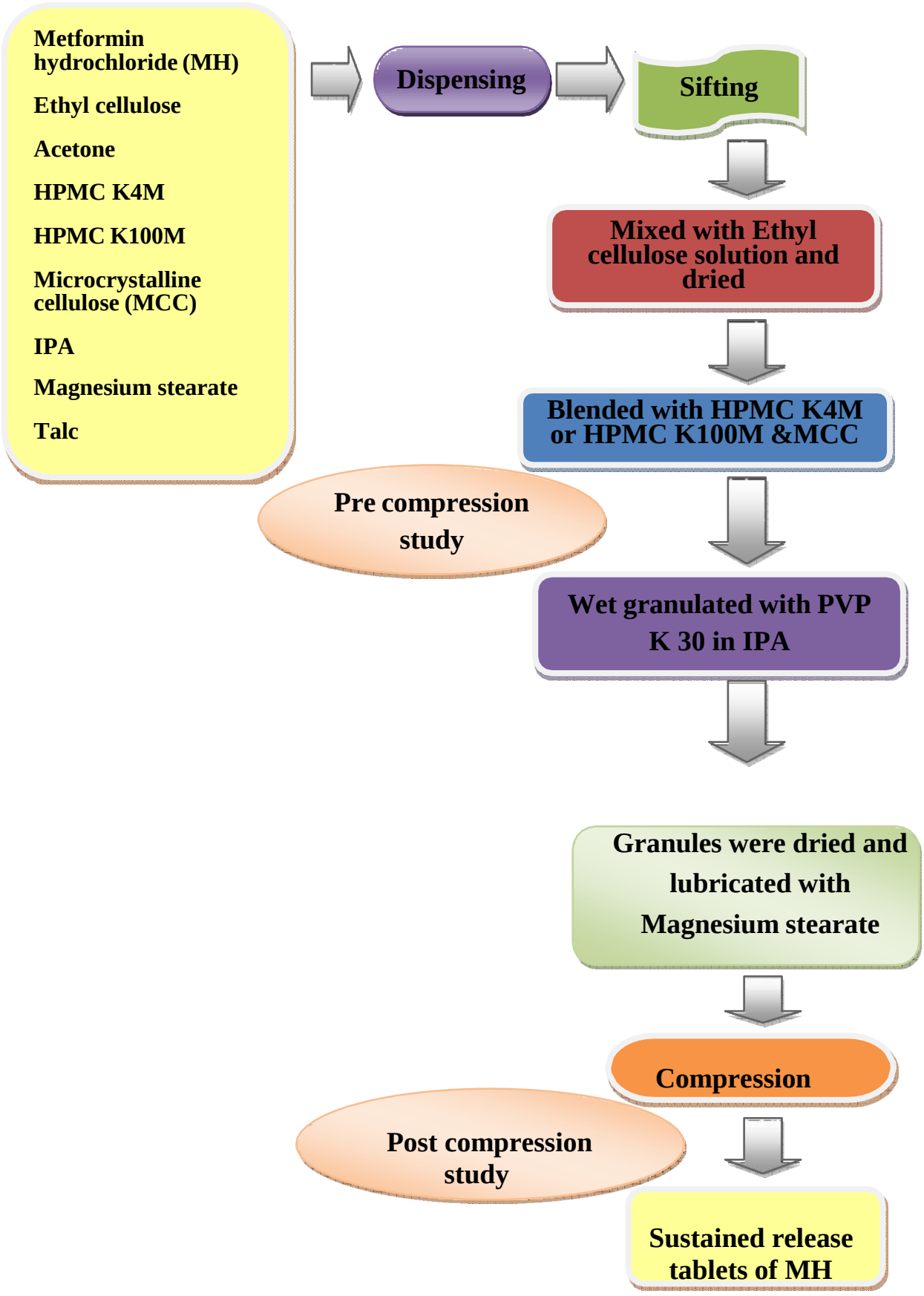
The sustained release granules were prepared by wet granulation technique. [32] Different polymers such as HPMC K4M, HPMC K100M and ethyl cellulose are used in different ratios. The tablets were compressed by 27 station tablet compression machine using 19 x 9 mm caplet shaped punches.

Table 5: Composition of sustained release Metformin hydrochloride tablets

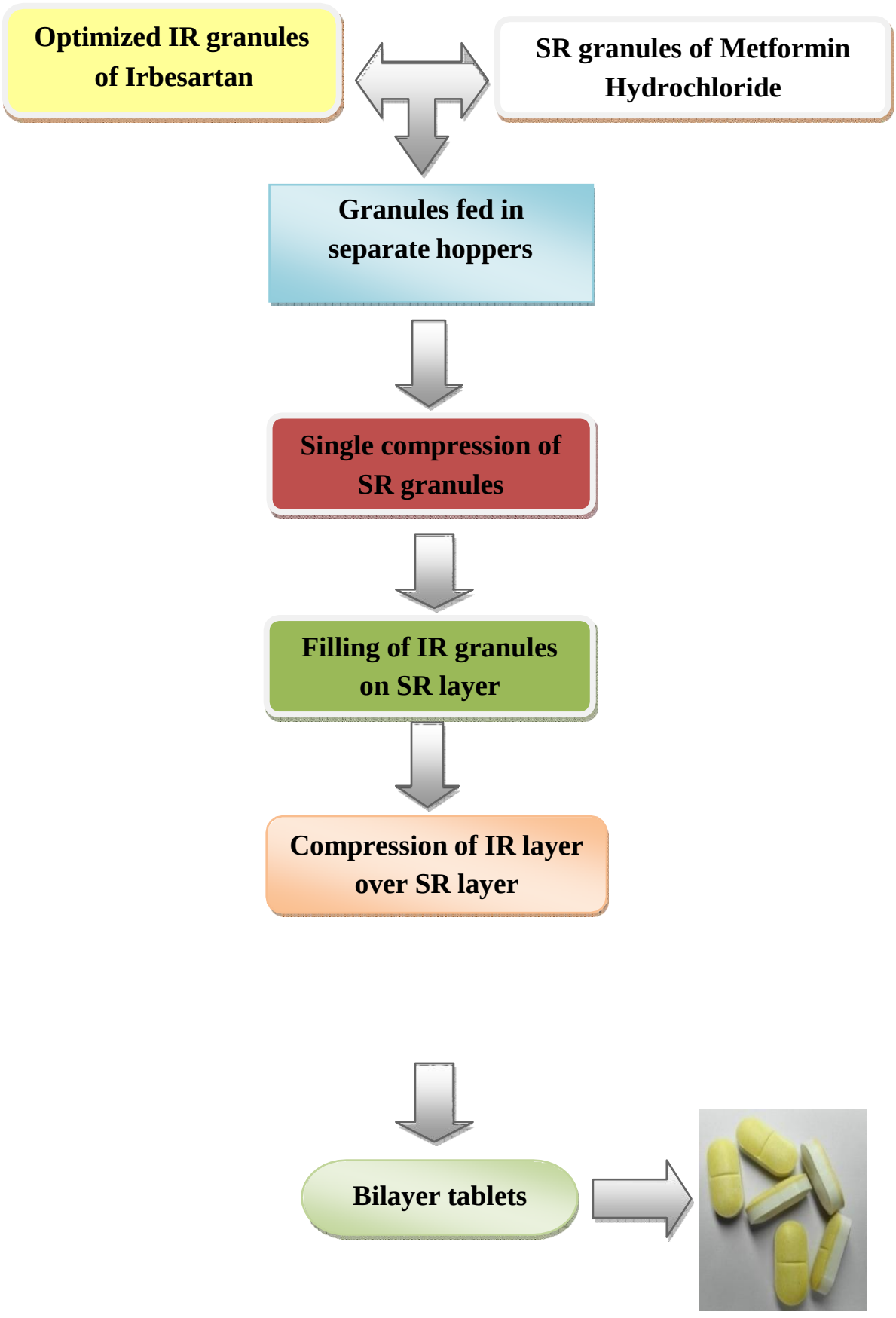
S.NO	INGREDIENTS	F1(mg)	F2(mg)	F3(mg)	F4(mg)	F5(mg)
01.	Metformin hydrochloride	500	500	500	500	**500**
02.	Ethyl cellulose	25	25	25	25	**25**
03.	Acetone	q.s	q.s	q.s	q.s	**q.s**
04.	HPMC K4M	200	-	50	100	**100**
05.	HPMC K100M	-	200	100	50	**100**
06.	Microcrystalline cellulose pH102	62.5	62.5	112.5	112.5	**62.5**
07.	PVP K-30	42.5	42.5	42.5	42.5	**42.5**
08.	Isopropyl alcohol	q.s	q.s	q.s	q.s	**q.s**
09.	Magnesium stearate	10	10	10	10	**10**
10.	Talc	10	10	10	10	**10**
Total weight		850	850	850	850	**850**

The optimized batch of sustained release Metformin hydrochloride tablets was then compressed with the optimized batch of immediate release tablets to get bilayer tablets.

Flowchart for formulation of Metformin Hydrochloride Sustained Release Tablets



Flowchart for bilayer tablets of Irbesartan and Metformin hydrochloride



POST COMPRESSION STUDIES

1.PHYSICAL PARAMETERS

A. General appearance

The general appearance of the tablets from each formulation batch was observed. The general appearance parameters are shape, colour, presence or absence of odour and taste. They were evaluated visually.

B. Uniformity of Weight [73]

Twenty tablets were selected at random and weighed individually. The average weight was also calculated. The average weight is determined. The individual weight was compared with the average weight.

Table 6: Uniformity of weight

S.No	Average weight of tablet	% Deviation
1	80 mg or less	10
2	More than 80 mg but less than 250 mg	7.5
3	250 mg or more	5

C. Thickness and diameter [73]

The thickness and diameter was measured to determine the uniformity of size and shape. Thickness and diameter of five tablets was measured using vernier caliper.

D. Hardness [73]

Hardness is defined as the force required for breaking a tablet at diametric compression test and it is termed as tablet crushing strength. Hardness of five tablets was determined using Monsanto hardness tester. It is expressed in Kg/cm^2.

E. Friability [73]

Friability of the prepared formulations was determined by using Roche friabilator. Pre-weighed sample of tablets was placed in the friability tester, which was then operated for 100 revolutions, tablets were dedusted and reweighed. The friability of the tablets was calculated using the formula mentioned below.

$$\% \text{ Friability} = \frac{\text{Initial weight of the tablets} - \text{Final weight of the tablets}}{\text{Initial weight of the tablets}} \times 100$$

2.DRUG CONTENT

I. FOR IR TABLETS CONTAINING IRBESARTAN [73]

Twenty tablets were selected randomly and ground. The powder equivalent to 50mg of Irbesartan was weighed, mixed with 5 mL of methanol and made upto 100 mL with

0.1 N HCl. The solution was filtered and 2 mL of the filtrate was diluted to 100 mL with

0.1 N HCl. The absorbance of the resulting solution was measured at 246 nm taking 0.1 NHCl as blank using

UV-visible Spectrophotometer.

FOR SR TABLETS CONTAINING METFORMIN HYDROCHLORIDE [73]

Twenty tablets were selected randomly and ground. The powder equivalent to 85 mg of Metformin hydrochloride was weighed, mixed with 5 mL of methanol and made upto 100 mL with 6.8 pH phosphate buffer solution. The solution was filtered and 2mL of the filtrate was diluted to 100 mL of 6.8 pH phosphate buffer solution. The absorbance of the resulting solution was measured at 233 nm taking 6.8 pH phosphate buffer solution as blank using UV-visible Spectrophotometer.

II. BILAYER TABLETS OF IRBESARTAN AND METFORMIN HYDROCHLORIDE (SIMULATANEOUS EQUATION METHOD) [83]

Simultaneous estimation of Irbesartan and Metformin hydrochloride was carried out using UV-Visible Spectrophotometer.

PROCEDURE

The following equations were used to determine the contents.

$$C_x = \frac{A_2 a_{y1} - A_1 a_{y2}}{A_{x2} a_{y1} - a_{x1} a_{y2}}$$

$$C_y = \frac{A_1 a_{x2} - A_2 a_{x1}}{A_{x2} a_{y1} - a_{x1} a_{y2}}$$

Where a_{x1} **and** a_{x2} = The absorptivity of drug X at λ_1 and λ_2 respectively. a_{y1} **and** a_{y2} **=** The absorptivity of drug Y at λ_1 and λ_2 respectively.A_1 **and** A_2 **=** The absorbance of sample at λ_1 and λ_2 respectively.

The ratios $\frac{A_1 / A_2}{a_{x1} / a_{x2}}$ **and** $\frac{a_{y1} / a_{y2}}{A_1 / A_2}$ should lie outside the range of 0.1 – 2.0 for the precise determination of X and Y drugs**.** This criteria is satisfied only when the λ_{max} of the two components is reasonably dissimilar and the components should not interact chemically.

Preparation of standard stock solution of Irbesartan

Irbesartan equivalent to 50 mg was accurately weighed. 50 mL of 0.1 N HCl was added and sonicated for 10 min. The volume was made upto 100 mL with 0.1 N HCl. 2 mL of the solution was diluted to 100 mL with 0.1 N HCl.

Preparation of standard stock solution of Metformin hydrochloride

Metformin hydrochloride equivalent to 50 mg was accurately weighed. 50 mL of 0.1 N HCl was added and sonicated for 10 min. The volume was made upto 100 mL with 0.1 N HCl. 2 mL of the solution was diluted to 100 mL with 0.1 N HCl.

Preparation of sample solution

Twenty tablets were accurately weighed and the average weight was calculated. The tablets were then ground to a fine powder. Powder equivalent to 100 mg of Metformin hydrochloride was weighed and transferred to a 100 mL standard flask. The powder was then dissolved in 0.1 N HCl and sonicated. The volume was made upto 100 mL with 0.1 N HCl. 2 mL of the solution was diluted to 100 mL with 0.1 N HCl. The absorbance of the resulting solution was measured at 246 nm and 233 nm respectively. The amount of both the drugs was determined.

3.*In vitro* disintegration studies for IR tablets [73]

The disintegration time was determined using disintegration test apparatus. The tablets were placed in each of the six tubes of the basket. The assembly was suspended in water maintained at a temperature of 37°C ± 2°C and the apparatus was switched on. The time taken to disintegrate the tablets completely was noted.

4.*In vitro* dissolution studiesFor IR tablets

The release of Irbesartan was determined using USP Type II (paddle) dissolution apparatus under sink condition. 900 mL of 0.1 N HCl was used as dissolution medium at a temperature of 37°C ± 0.5°C. The paddle was stirred at a speed of 100 rpm. The release studies were carried out for 30 min. The absorbance of the solution was measured at 246 nm taking 0.1 N HCl as blank using UV- Visible spectrophotometer.

For SR tablets

The release of Metformin hydrochloride was determined using USP Type II (paddle) dissolution apparatus under sink condition. 900 mL of 0.1 N HCl was used as dissolution medium for first two hours followed by 900 mL of pH 6.8 phosphate buffer solution for next eight hours maintained at a temperature of 37°C ± 0.5°C. The paddle was stirred at a speed of 100 rpm. The release studies were carried out for ten hours. The absorbance of the solution was measured at 233 nm taking respective buffer solutions as blank using UV- Visible spectrophotometer.

For Bilayer tablets

The release of bilayer tablets was determined using USP Type II (paddle) dissolution apparatus under sink condition. 900 mL of 0.1 N HCl was used as dissolution medium for first two hours followed by 900 mL of pH 6.8 phosphate buffer solution for next eight hours maintained at a temperature of 37°C ± 0.5°C. The paddle was stirred at a speed of 100 rpm. The release studies were carried out for ten hours. The absorbance of the solution as measured at 246 nm and 233 nm taking respective buffer solutions as blank using UV- Visible spectrophotometer.

5.*In vitro* release kinetics [84]

To study the *in vitro* release kinetics of the optimized bilayer tablets, data obtained from *in vitro* dissolution study

were plotted in various kinetic models.

i) Zero order equation

The zero order release kinetics can be obtained by plotting cumulative % drug released Vs Time (hours). It is ideal for the formulation to have release profile of zero order to achieve pharmacological prolonged action.

$$C = K_0 t$$

Where, K_0 = Zero order constant in Conc./ time

t = Time in hours

ii) First order equation

A graph was plotted with log % cumulative drug remaining Vs Time in hours.

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

C_0 = Initial drug concentration

K = First order constant

t = Time in hours.

iii)Higuchi kinetics

A graph was plotted with % cumulative drug released Vs Square root of time.

$$Q = Kt^{1/2}$$

K = Constant reflecting design variable system (Differential rate constant)

t = Time in hours.

The drug release rate is inversely proportional to the square root of time.

iv)Hixson and Crowell 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 Crowell erosion equation. A graph was plotted with cube root of % drug remaining Vs Time in hours.

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

Q_t = Amount of drug released at time t

Q_0 = Initial amount of drug

K_{HC} = Rate constant for Hixson Crowell equation

v) Korsmeyer – Peppas equation

To evaluate the mechanism of drug release, it was further plotted in Peppas equationas log cumulative % of drug released Vs log time.

$$M_t/M_\alpha = Kt^n$$

Where M_t/M_α = Fraction of drug released at time t

t = Release time

K = Kinetics constant (Incorporating structural and geometric characteristics ofthe formulation)

n = Diffusional exponent indicative of the mechanism of drug release.

Table 7: Diffusion exponent and solute release mechanism for cylindrical shape

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

vi) Stability Study [85]

Stability study of optimized bilayer tablets was carried out according to ICH guidelines. All the tablets were packed in blister and kept in a humidity chamber at 40° ± 2°C and 75% ± 5% RH for 3 months. Samples were withdrawn at monthly intervals and analyzed for uniformity of weight, thickness, hardness, friability, drug content and *in vitro* drug release.

8. RESULTS AND DISCUSSION

The present investigation was to formulate bilayer tablets for immediate release of Irbesartan and sustained release of Metformin hydrochloride to treat hypertension in Type II Diabetes Mellitus.

PREFORMULATION STUDIES

DRUG -EXCIPIENT COMPATIBILITY STUDY

The drug excipient study was conducted to reveal the excipient compatibility with the drug. The physical compatibility of drug and excipients are given in table 8

Table 8: Physical compatibility study of drug and Excipients

S.No	Drug + Excipient	Description and condition			
		Initial	Room temperature and 40°C/75% RH in days		
			10th	20th	30
01.	IRB	A white to off white crystalline powder	NC	NC	NC
02.	MH	A white, hygroscopic,crystalline powder.	NC	NC	NC
03.	IRB + MH	White almost crystallinePowder	NC	NC	NC
04.	Lactose	White to off –white crystalline Powder	NC	NC	NC
05.	Starch	White to off -white powder	NC	NC	NC

06.	PVP K30	White or creamy white hygroscopic powder	NC	NC	NC
07.	SSG	White or almost white free flowing very hygroscopicPowder	NC	NC	NC
08.	Tartrazine yellow	Yellow coloured crystalline Powder	NC	NC	NC
09.	Magnesiumstearate	White or almost whitecrystalline powder	NC	NC	NC
10.	HPMC K4M	White or creamy white powder	NC	NC	NC
11.	HPMC K100M	White or creamy white powder	NC	NC	NC
12.	Ethyl cellulose	Free- flowing, white coloured Powder	NC	NC	NC
13.	MCC pH 102	White crystalline powder	NC	NC	NC
14.	Talc	White or creamy white soft Powder	NC	NC	NC
15.	IRB + Lactose	White or crystalline powder	NC	NC	NC
16.	IRB + Starch	White or crystalline powder	NC	NC	NC
17.	IRB + PVP K 30	White or crystalline powder	NC	NC	NC
18.	IRB + SSG	Free flowing white crystalline Powder	NC	NC	NC
19.	IRB + TY	Free flowing yellow colour Powder	NC	NC	NC
20.	IRB + Magnesium Stearate	White, crystalline powder	NC	NC	NC
21.	MH +HPMCK4M	White, creamy white crystalline Powder	NC	NC	NC
22.	MH + HPMC K100M	White, creamy white crystalline Powder	NC	NC	NC
23.	MH + EC	White, almost white crystalline Powder	NC	NC	NC
24.	MH +MCC pH102	White, almost white crystalline Powder	NC	NC	NC
25.	MH+ PVP K30	White, creamy white crystalline Powder	NC	NC	NC
26.	MH + MagnesiumStearate	White crystalline powder	NC	NC	NC
27.	MH + Talc	White or creamy white powder	NC	NC	NC

NC – No Change

The physical compatibility was performed visually. The study reveals that the drug and the excipients were physically compatible with each other as there was no change of physical parameters. The excipients which were compatible with the drug were selected for the formulation.

Chemical Compatibility study

The possible interaction between the drugs and excipients used in the formulation wasstudied by FTIR spectroscopy. The results are given in the Figures

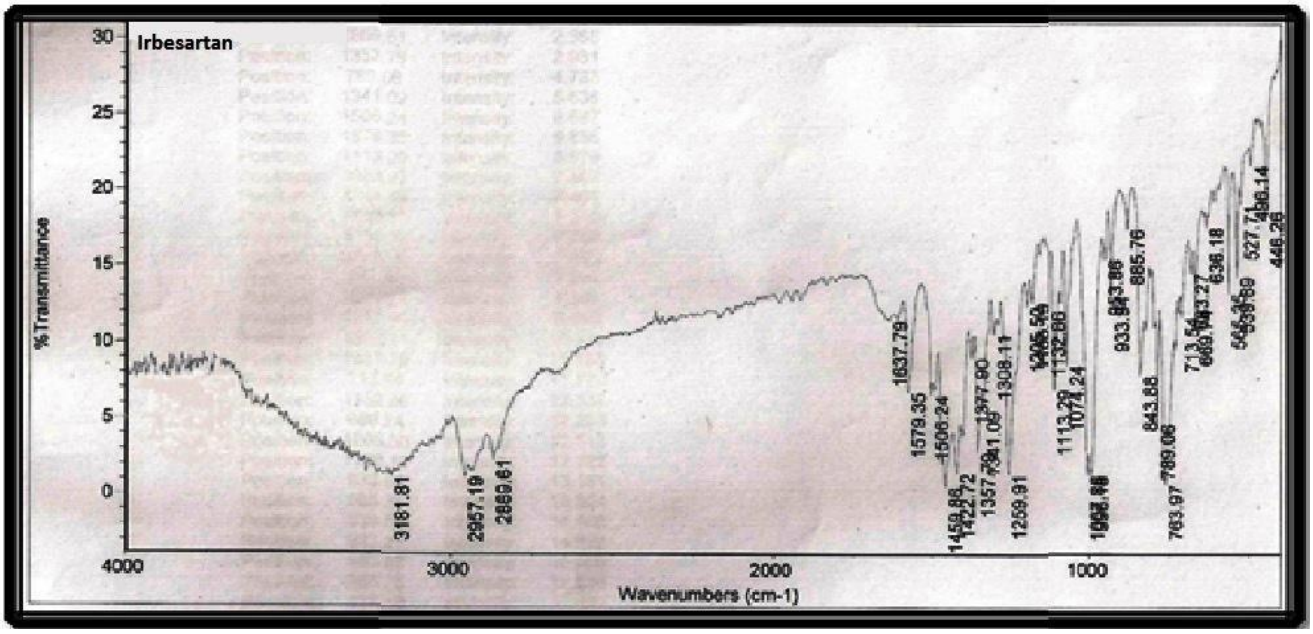


Fig. 11: FTIR of Irbesartan

Table 9: IR Spectral Interpretation of Irbesartan

S.No	Wave Number (cm^{-1})	Interpretation
01.	3181.81	C-H stretching vibrations (Aromatic)
02.	2957.19,2869.61	C-H stretching vibrations (Alkane)
03.	1637.79	C=C stretching vibrations
04.	1579.35	C-C stretching vibrations
05.	1459.86	C-H bending vibrations

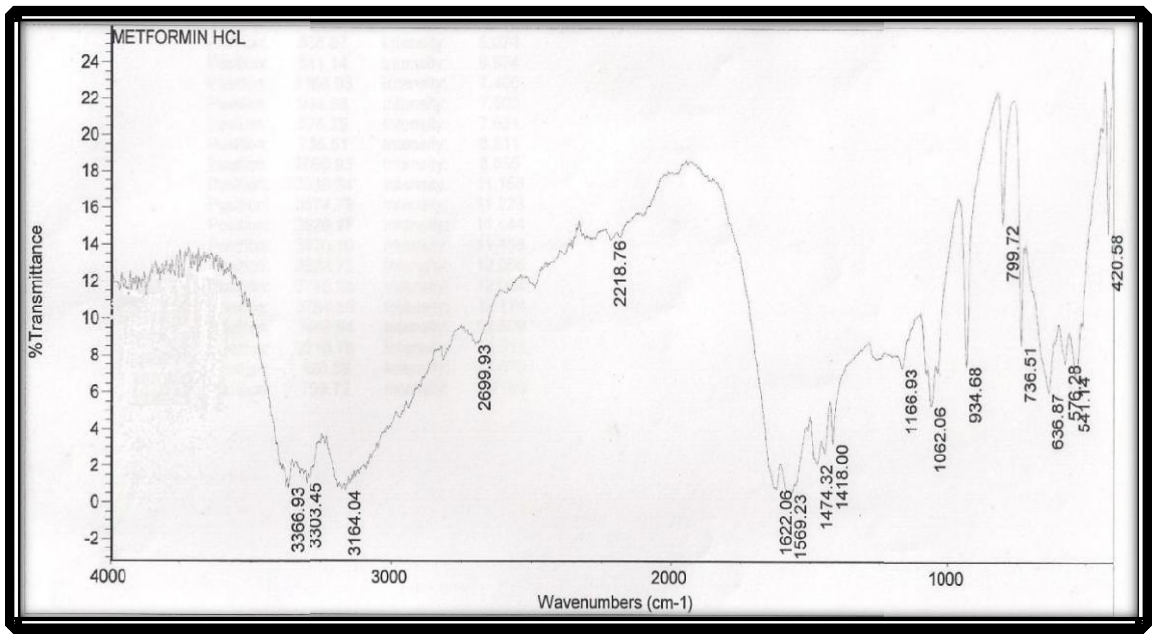


Fig. 12: FTIR of Metformin Hydrochloride

Table 10: IR Spectral Interpretation of Metformin Hydrochloride

S.No	Wave Number (cm^{-1})	Interpretation
01.	3366.93,3303.45	N-H stretching vibrations (1° amine)
02.	3164.04	N-H stretching vibrations (2° amine)
03.	2699.93	C-H stretching vibrations
04.	2218.76	C=N stretching vibrations
05.	1622.06	N-H bending vibrations

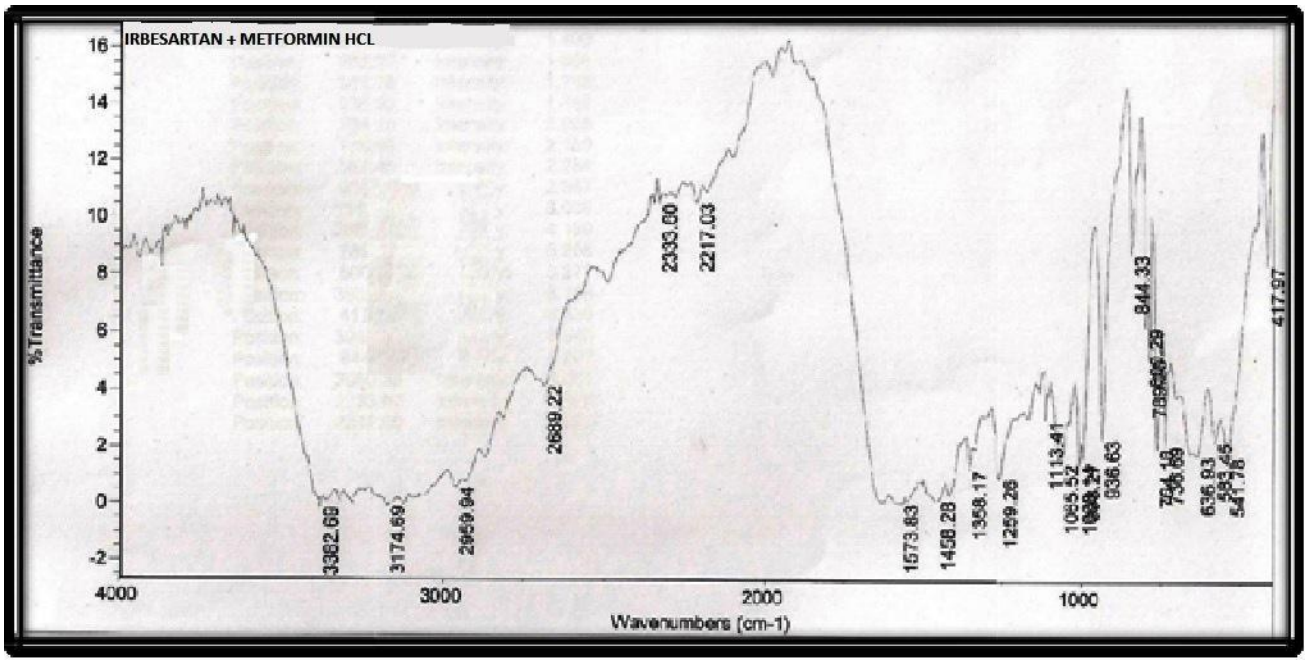


Fig. 13: FTIR of Irbesartan and Metformin Hydrochloride

Table 11: IR Spectral Interpretation of Irbesartan and Metformin HCl

S.No	Wave Number (cm^{-1})	Interpretation
01.	3382.69	N-H stretching vibrations
02.	3174.69	C-H stretching vibrations (Aromatic)
03.	2959.94	C-H stretching vibrations (Alkane)
04.	2217.03	C=N stretching vibrations
05.	1573.83	N-H bending vibrations

INFERENCE

The FTIR Hydrochloride showedpeak of Spectra for Irbesartan and Metformin no shiftand no disappearance of the characteristic peaks suggesting that there is no interaction between the two drugs.

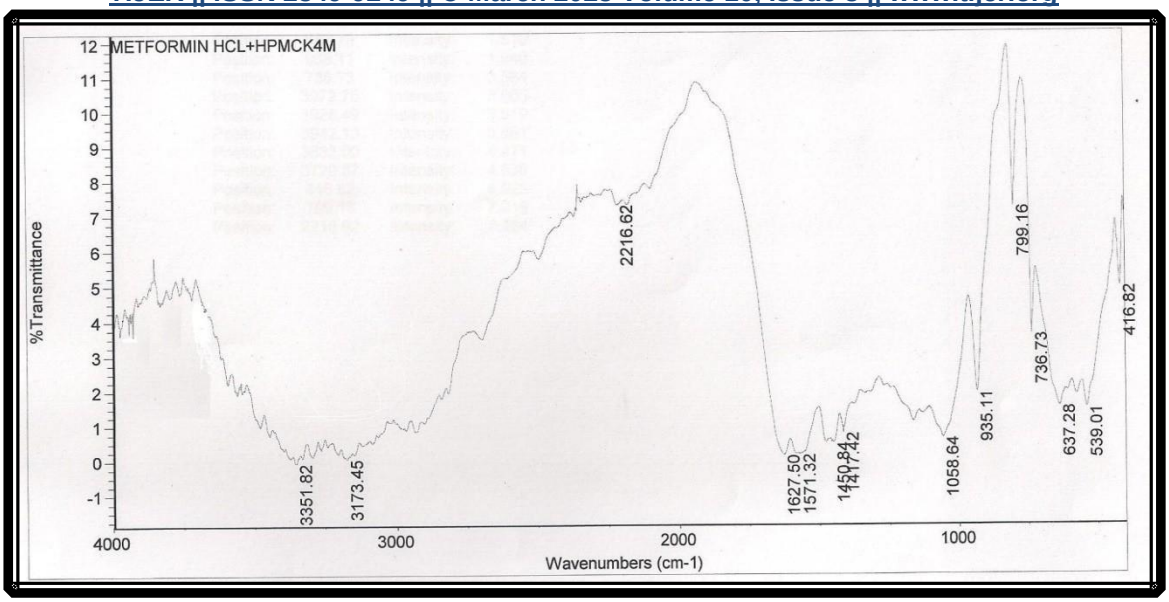


Fig. 14: FTIR Metformin Hydrochloride and HPMC K4M

Table 12: IR Spectral Interpretation of Metformin Hydrochloride + HPMC K4M

S.No	Wave Number (cm^{-1})	Interpretation
01.	3351.82	(2^{o} amine) N-H stretching vibrations
02.	3173.45	(1^{o} amine) N-H stretching vibrations
03.	2216.62	C=N stretching vibrations
04.	1627.50	N-H bending Vibrations

INFERENCE

The FTIR peak of Spectra for Metformin Hydrochloride and HPMC K4M showed no shift and no disappearance of the characteristic peaks suggesting that there isno interaction between the drug and the excipient.

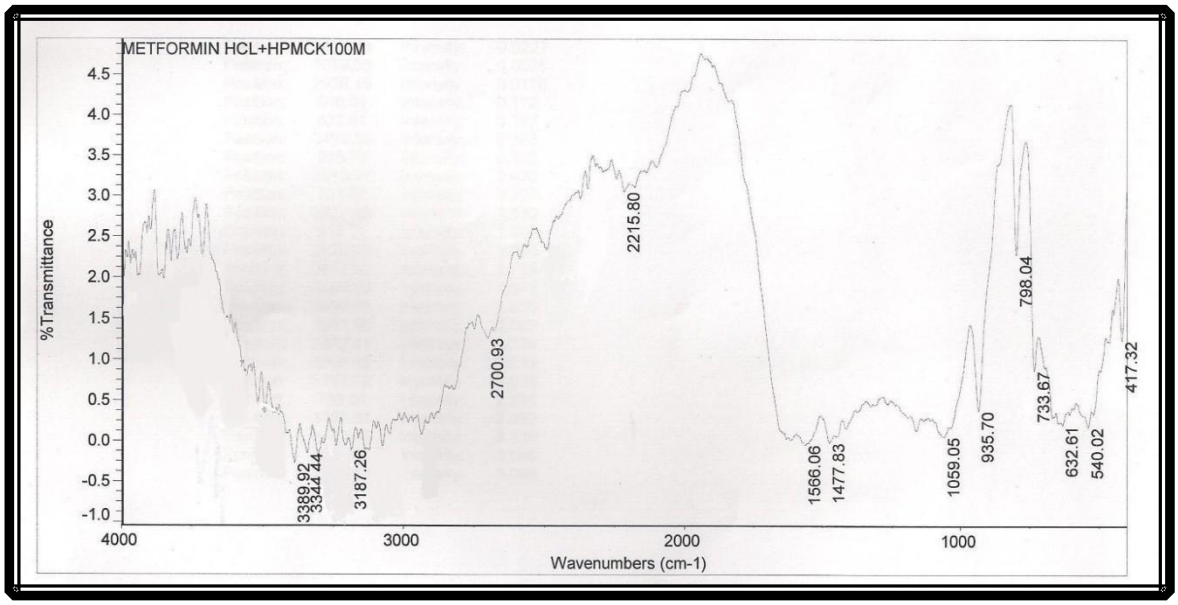


Fig. 15: FTIR of Metformin hydrochloride and HPMC K100M

Table 13: IR Spectral Interpretation of Metformin Hydrochloride + HPMC K100M

S.No	Wave Number (cm^{-1})	Interpretation
01.	3389.92, 3344.44	N-H stretching vibrations (1° amine)
02.	3187.26	N-H stretching vibrations (2° amine)
03.	2936.45	C-H stretching vibrations
04.	2215.80	C=N stretching vibrations
05.	1566.06	N-H bending vibrations

INFERENCE

The FTIR peak of Spectra for Metformin Hydrochloride and HPMC K100M showed no shift and no disappearance of the characteristic peaks suggesting that there is no interaction between the drug and the excipient.

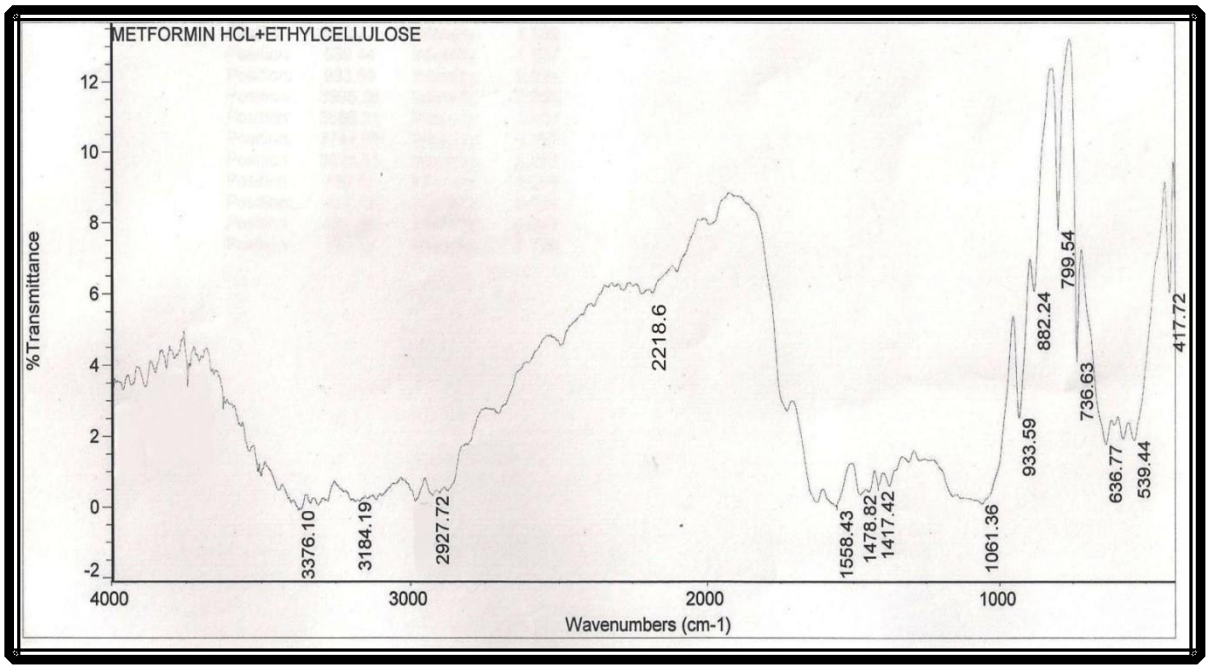


Fig. 16: FTIR of Metformin Hydrochloride and Ethyl Cellulose

Table 14: IR Spectral Interpretation of Metformin Hydrochloride + Ethyl Cellulose

S.No	Wave Number (cm^{-1})	Interpretation
01.	3376.10	(1° amine) N-H stretching vibrations
02.	3184.19	(2° amine) N-H stretching vibrations
03.	2927.72	C-H stretching vibrations
04	2218.76	C=N stretching vibrations
05.	1558.43	N-H bending vibrations

INFERENCE

The FTIR peak of Spectra for Metformin Hydrochloride and Ethylcellulose showed no shift and no disappearance of the characteristic peaks suggesting that there isno interaction between the drug and the excipient.

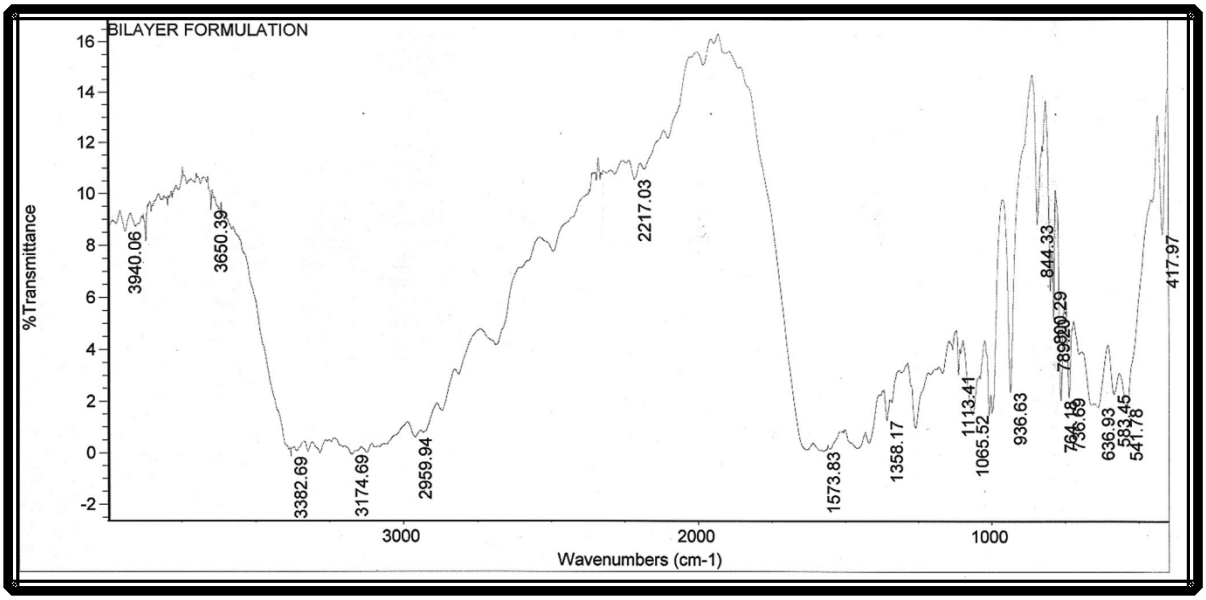


Fig. 17: FTIR of Bilayer Formulation

Table 15: IR Spectral Interpretation of Irbesartan and Metformin HCl

S.No	Wave Number (cm^{-1})	Interpretation
01.	3382.69	N-H stretching vibrations
02.	3174.69	C-H stretching vibrations (Aromatic)
03.	2959.94	C-H stretching vibrations (Alkane)
04.	2217.03	C=N stretching vibrations
05.	1573.83	N-H bending vibrations

INFERENCE

The FTIR peak of Spectra for final bilayer formulation showed no shift and no disappearance of the characteristic peaks suggesting that there is no interaction between the two drugs and also with the excipients in the final formulation.

CALIBRATION CURVE FOR IRBESARTAN

The calibration curve of Irbesartan is given in Table 16 and Fig 18.

Table 16: Data for calibration curve of Irbesartan in 0.1N HCl

Concentration (µg/mL)	Absorbance at λ_{246nm}
0	0.000
2	0.1430
4	0.2809
6	0.4301
8	0.5701
10	0.7020

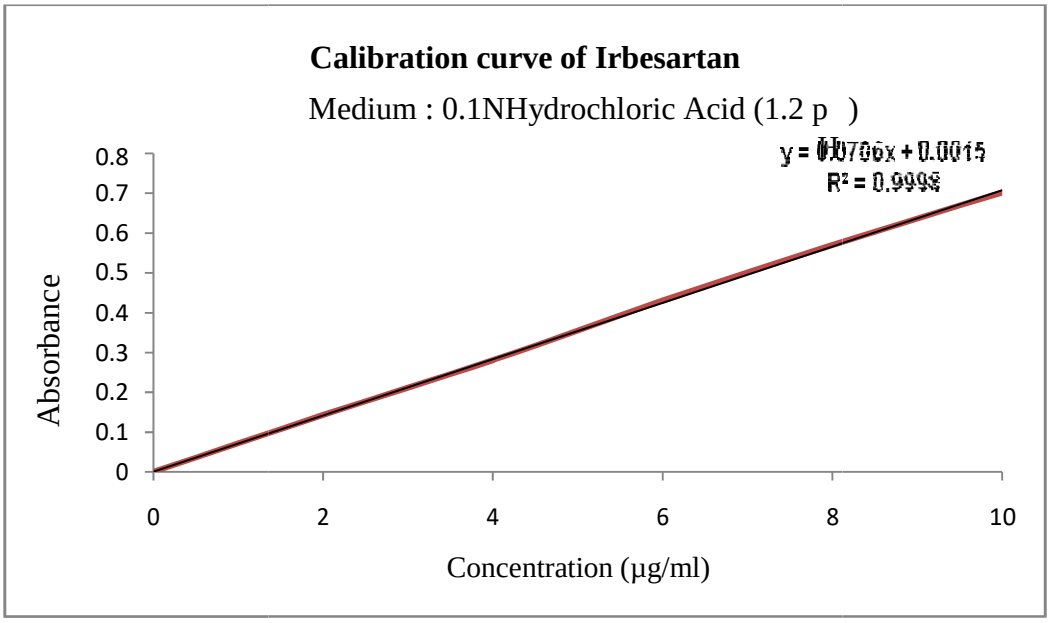


Fig. 18: Calibration Curve of Irbesartan in 0.1N HCl

It was found that the solution of Irbesartan in 0.1N HCl show linearity (R^2 = 0.9998) in absorbance at concentrations of 2 -10 (µg/mL) and obey Beer Lambert Law.

CALIBRATION CURVE FOR METFORMIN HYDROCHLORIDE

The calibration curve of Metformin hydrochloride in 0.1N HCl and 6.8 pHphosphate buffer is given in Table 17, 18 and Fig 19, 20.

Table 17: Data for calibration curve of Metformin hydrochloride in 0.1N HCl

Concentration (µg/mL)	Absorbance at λ_{233nm}
0	0.000
2	0.0668
4	0.1356
6	0.2009
8	0.2768
10	0.3402

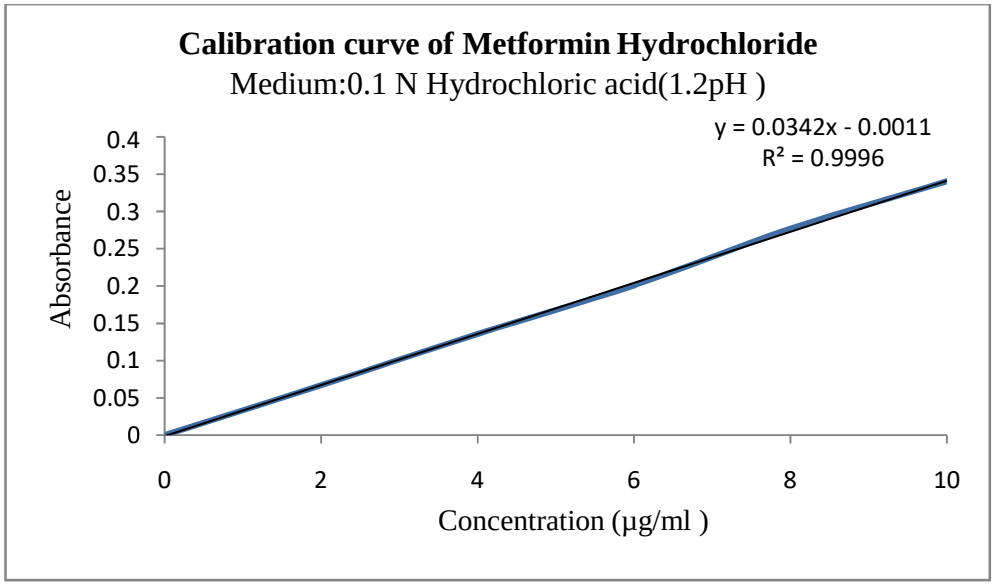


Fig. 19: Calibration curve of Metformin hydrochloride in 0.1 N HCl

It was found that the solution of Metformin hydrochloride in 0.1 N HCl show linearity (R^2 = 0.9996) in absorbance at concentrations of 2 -10 (µg/mL) and obey Beer Lambert Law.

Table 18: Data for calibration curve of Metformin hydrochloride in pH 6.8Phosphate Buffer

Concentration (µg/mL)	Absorbance at λ_{233nm}
0	0.000
2	0.1419
4	0.2845
6	0.4235
8	0.5818
10	0.7362

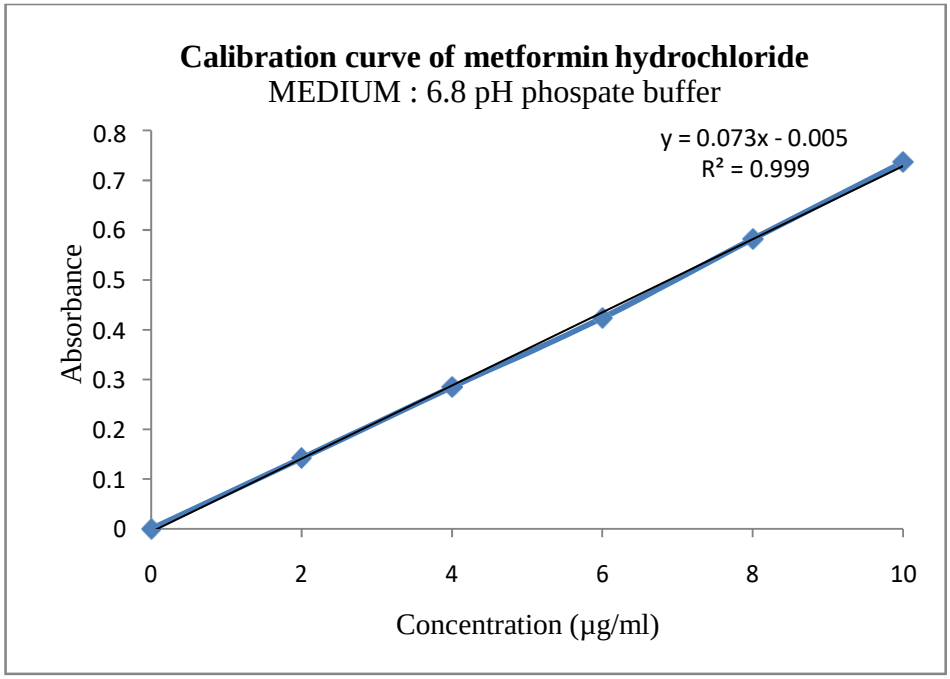


Fig. 20: Calibration curve of Metformin hydrochloride in 6.8 pH Phosphate Buffer

It was found that the solution of Metformin hydrochloride in 6.8 pH phosphate buffer show linearity (R^2 = 0.9996) in absorbance at concentrations of 2 -10 (µg/mL) and obey Beer Lambert Law.

FOR IR FORMULATION PRECOMPRESSION STUDY

The drug and the formulated blends were evaluated for precompression parameters. Theresults are given in Table 19.

Table 19: Precompression study of drug and formulated blends

Drug andblends	Bulk Density g/mL*	Tapped Density g/mL *	Compressibility index (%)*	Hausner's Ratio *	Angle of Repose (Degree)*
IRB	0.4203 ± 0.0095	0.5733 ± 0.0032	26.69 ±1.6348	1.36 ±0.0321	42.47 ± 0.0458
L1	0.5226 ± 0.0099	0.6427 ± 0.0079	18.69 ±0.5464	1.23 ±0.01	28.25 ± 0.0252
L2	0.5251 ± 0.0056	0.6288 ± 0.0261	16.36 ±4.2933	1.20 ±0.0651	29.56 ± 0.0208

*** Mean ± S.D (n = 3)**

The bulk density of the IR blends ranged from 0.5226 g/mL to 0.5251 g/mL and the tapped density ranged from 0.6288 g/mL to 0.6427 g/mL. The compressibility index of the IR blends ranged from 16.36% to 18.67% and Hausner's ratio ranged from

1.20 to 1.23. The angle of repose of the IR blends ranged from 28.25 to 29.56. The formulated blends show a fair compressibility index and poor flow.[82] So, wet granulation technique was used for preparing IR granules of Irbesartan.

The IR granules were evaluated for bulk density, tapped density, compressibility index, Hausner's ratio and Angle of Repose. The results are given in Table 20.

Table 20: Precompression study of immediate release granules

Formulation	Bulk Density g/mL *	Tapped Density g/mL *	Compressibility index (%)*	Hausner's Ratio *	Angle of Repose (Degree)*
L1	0.5522 ± 0.0041	0.6518 ± 0.0056	15.28 ± 0.3510	1.18 ± 0.0058	21.50 ± 0.0529
L2	0.5481 ± 0.0103	0.6503 ± 0.0065	15.31 ± 0.8995	1.19 ± 0.0173	21.48 ± 0.0265

*** Mean ± S.D (n = 3)**

The bulk density of the IR granules ranged from 0.5481 g/mL to 0.5522 g/mL and the tapped density of ranged from 0.6503 g/mL to 0.6518 g/mL. The compressibility index of the IR granules ranged from 15.28% to 15.31% and Hausner's ratio ranged from 1.18 to 1.19. The angle of repose of the IR granules ranged from 21.48 to 21.50. The granules showed good flow property.[82]

FORMULATION DEVELOPMENT

Preparation of IR tablets of Irbesartan

Wet granulation technique was employed for the formulation of IR granulesof Irbesartan.

The prepared tablets were easy to prepare and of uniform shape and size.

POST COMPRESSION STUDY FOR TABLETSUNIFORMITY OF WEIGHT

The uniformity of weight of the formulated tablets is given in Table 21.

Table 21: Uniformity of weight of the formulated tablets

Formulation	Uniformity of weight (mg) *
L1	230.50 ± 0.0004
L2	230.50 ± 0.0005

*** Mean ± S.D (n=20)**

The formulated tablets complies with the test for uniformity of weight.[73]

TABLET THICKNESS AND DIAMETER

The thickness and diameter of the formulated tablets is given in table 22.

Table 22: Thickness and Diameter of formulated tablets

Formulation	Thickness (mm) *	Diameter (mm) *
L1	3.290±0.014	8.769 ± 0.0088
L2	3.302±0.015	8.770 ± 0.0089

*** Mean ± S.D (n=5)**

The formulated tablets had uniform thickness and diameter.

HARDNESS

The hardness of the formulated tablets is given in table 23.

Table 23: Hardness of formulated tablets

Formulation	Hardness (Kg/cm^2) *
L1	3.10±0.22
L2	3.20±0.27

*** Mean ± S.D (n=5)**

All the formulated tablets showed sufficient mechanical strength to resist thetransportation.[79]

FRIABILITY

The friability of the formulated tablets is given in table 24.

Table 24: Friability of formulated tablets

Formulation	% Friability *
L1	0.086 ± 0.0040
L2	0.173 ± 0.0130

*** Mean ± S.D (n=3)**

The percentage friability of all the formulations were within the acceptable limits.[73]

DRUG CONTENT

The drug content of the IR tablets is given in the table 25 and fig.21.

Tabl 25: Drug content of formulated IR tablets

Formulation	% Drug Content *
L1	97.760 ± 0.260
L2	98.219 ± 0.804

*** Mean ± S.D (n=3)**

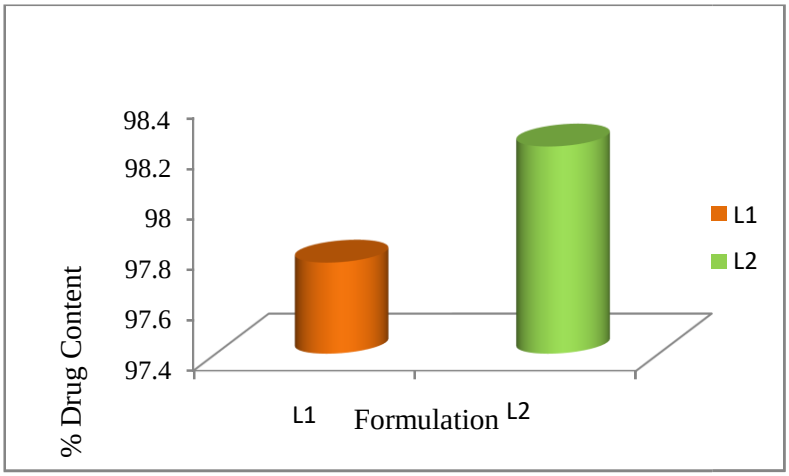


Fig. 21: Drug content of IR tablets

The drug content of the IR tablets was within Pharmacopoeial limits.[73]

DISINTEGRATION TIME

The disintegration time of the IR tablets is given in the table 26 and fig. 22.

Table 26: Disintegration time of IR tablets

Formulation	Disintegration time (minutes) *
L1	12’45’’ ± 0.4147
L2	4’52’’ ± 0.4493

*** Mean ± S.D (n=6)**

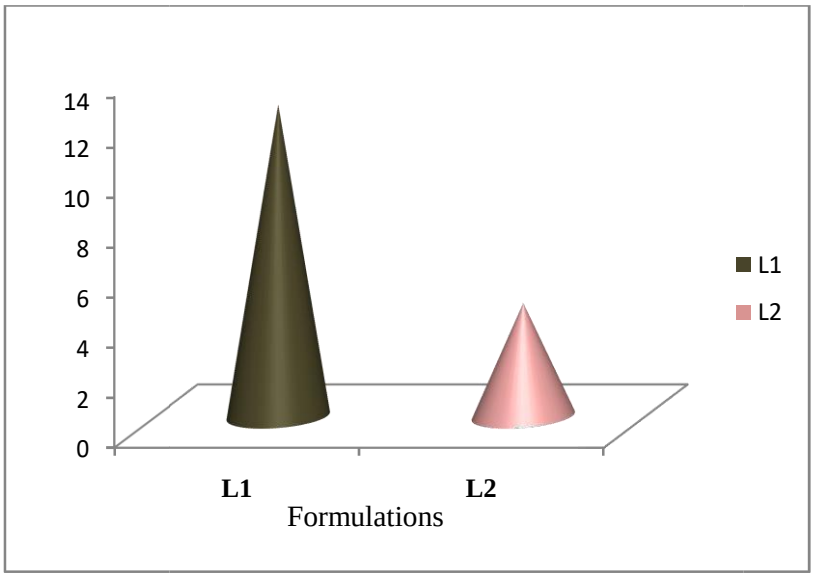


Fig. 22: Disintegration time of IR tablets

The disintegration time of the IR tablets ranged from 4’52” to 12’45”. The disintegration time of the IR tablets containing 4% sodium starch glycolate was foundto have faster disintegration time for IR tablets.[19]

IN VITRO DISSOLUTION STUDY

The *in vitro* dissolution of immediate release formulations of Irbesartan isgiven in table 27 and fig. 23.

Table 27: *In vitro* Dissolution study of Immediate release formulation of Irbesartan

Time (Minutes)	Cumulative % drug release *	
	L1	L2
0	0 ± 0.0000	0 ± 0.0000
10	91.34 ± 0.4812	89.35 ± 0.36
20	93.64 ± 0.2107	95.38 ± 0.40
30	95.80 ± 0.5568	98.45 ± 0.15
40	96.92 ± 0.0900	
50	98.03 ± 0.5300	
60	99.04 ± 0.1400	

*** Mean ± S.D (n=3)**

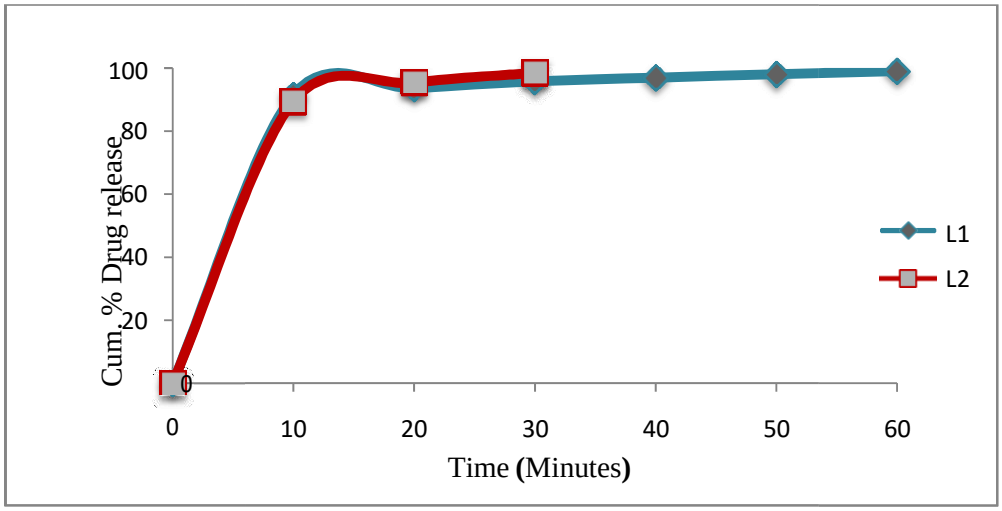


Fig. 23: In vitro Dissolution study of IR tablets of Irbesartan

The *in vitro* dissolution study of IR tablets showed that 4% concentration of SSG was found to be optimum for immediate release of Irbesartan. The 2 % concentration of SSG was found to be releasing the drug slowly when compared to 4 % SSG. The formulation containing 4 % of SSG showed drug release of 98.45% at the end of 30 min. Thereforetablets.[30] formulation L2 was optimized and selected for final bilayer

SR TABLETS

PRECOMPRESSION STUDY

The drug and the formulated blends of SR are evaluated for precompression parameters.The results are given in the table 28.

Table 28: Precompression study of drug and formulated blends

Drug and formulation Blend	Bulk densityg/mL *	Tapped densityg/mL *	Compressibility Index (%)*	Hausner's Ratio *	Angle of Repose (Degree)*
MH	0.5613 ± 0.0029	0.6763 ± 0.0086	17.00 ±0.8113	1.21 ±0.0153	42.37 ±0.0153
F1	0.4304 ± 0.0069	0.5462 ± 0.0094	21.19 ±0.6920	1.27 ±0.01	32.53 ±0.0153
F2	0.4309 ± 0.0070	0.5438 ± 0.0097	20.76 ±0.0656	1.26 ±0.0265	32.08 ±0.0300
F3	0.4276 ± 0.0044	0.5425 ± 0.017	21.18 ±0.1900	1.27 ±0.0265	32.01 ±0.0520
F4	0.4272 ± .0.0036	0.5397 ± 0.0058	20.84 ±0.0702	1.26 ±0.0208	32.55 ±0.0252
F5	0.4273 ± 0.0049	0.5462 ± 0.014	21.76 ±0.0600	1.28 ±0.0473	31.33 ± 0.0252

*** Mean ± S.D (n=3)**

The bulk density of the SR blends ranged from 0.4272 g/mL to 0.4309 g/mL and the tapped density ranged from 0.5397 g/mL to 0.5462 g/mL. The compressibility index of the SR blend ranged from 20.53 to 21.76 and Hausner's ratio ranged from 1.26 to 1.28. The angle of repose of the SR blend ranged from 31.33 to 32.55. The formulated blends showed poor flow property. Hence, wet granulation technique was used for preparation SR granules of Metformin hydrochloride.

The SR granules were evaluated for bulk density, tapped density, compressibility index, Hausner's ratio and Angle of Repose. The results are given in Table 29.

Table 29: Precompression study of sustained release granules

Formulation	Bulk densityg/mL *	Tapped densityg/mL *	Compressibility Index (%)*	Hausner's Ratio *	Angle of Repose (Degree) *
F1	0.4274 ± 0.0013	0.4773 ± 0.0123	10.44 ± 0.2476	1.12 ± 0.0252	25.49 ± 0.0200
F2	0.4225 ± 0.0015	0.4753 ± 0.0115	11.11 ± 0.0600	1.12 ± 0.0252	25.01 ± 0.0208
F3	0.4212 ± 0.0053	0.4793 ± 0.0131	12.12 ± 0.1200	1.14 ± 0.0416	24.30 ± 0.0361
F4	0.4252 ± 0.0040	0.4714 ± 0.0085	9.78 ± 0.0200	1.11 ± 0.0153	24.15 ± 0.0200
F5	0.4176 ± 0.0056	0.4792 ± 0.0062	12.85 ± 0.0500	1.15 ± 0.0208	23.20 ± 0.0153

*** Mean ± S.D (n=3)**

The bulk density of the SR granules ranged from 0.4176 g/mL to 0.4274 g/mL and the tapped density ranged from 0.4714 g/mL to 0.4793 g/mL. The compressibility index of the SR granules ranged from 9.80 to 12.85% and Hausner's ratio ranged from 1.11 to
1.15. The Angle of Repose of the SR granules ranged from 23.20 to 25.49. The formulated blend showed good flow property.[82]

FORMULATION DEVELOPMENT

Wet granulation technique was employed for the preparation of SR granulesof Metformin hydrochloride.

Five batches of SR granules were prepared by using hydrophilic polymers HPMC K4M and HPMC K100M in varying proportions. The formulations were compressed on a 27 station tablet compression machine using 19 x 9 mm caplet shaped punches.

POST COMPRESSION STUDYUNIFORMITY OF WEIGHT

The uniformity of weight for the formulated tablets is given in table 30.

Table 30: Uniformity of Weight

Formulation	Uniformity of weight (mg) *
F1	851.55 ± 0.0016
F2	851.10 ± 0.0018
F3	851.60 ± 0.0020
F4	850.65 ± 0.0015
F5	850.95 ± 0.0015

*** Mean ± S.D (n=20)**

The formulated tablet complies with the uniformity of weight.[73]

TABLET THICKNESS

The thickness of the formulated tablets is given in table 30.

Table 31: Thickness of formulated tablets

Formulation	Thickness (mm) *
F1	5.35 ± 0.0130
F2	5.34 ± 0.0150
F3	5.35 ± 0.0084
F4	5.33 ± 0.0084
F5	5.34 ± 0.0084

*** Mean ± S.D (n=5)**

The formulated tablets were uniform in thickness.

HARDNESS

The hardness of the formulated tablets is given in table 32.

Table 32: Hardness of formulated tablets

Formulation	Hardness Kg/cm^2 *
F1	4.0 ± 0.0447
F2	4.0 ± 0.0548
F3	4.0 ± 0.0447
F4	4.0 ± 0.0447
F5	4.0 ± 0.0548

*** Mean ± S.D (n=5)**

All the formulated tablets showed sufficient mechanical strength to resist thetransportation.[79]

FRIABILITY

The friability of the formulated tablets is given in table 33.

Table 33: Friability of formulated tablets

Formulation	Friability (%) *
F1	0.017 ± 0.0020
F2	0.023 ± 0.0020
F3	0.018 ± 0.0020
F4	0.020 ± 0.0050
F5	0.035 ± 0.0050

*** Mean ± S.D (n=3)**

The percentage friability of all formulations were within the acceptable limits.[73]

DRUG CONTENT

The drug content of the SR tablets is given in the table 34 and fig.24.

Table 34: Drug content of formulated SR tablets

Formulation	% Drug content *
F1	99.79± 0.0900
F2	98.86 ± 0.0800
F3	99.40 ± 0.0100
F4	99.03 ± 0.0902
F5	99.16 ± 0.2600

*** Mean ± S.D (n=3**

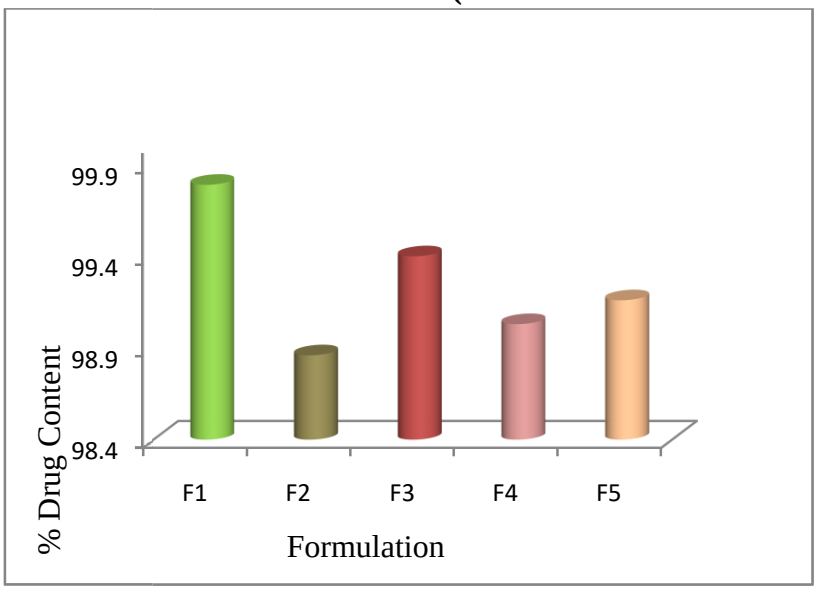


Fig. 24: Drug content of SR tablets

The drug content of the SR tablets were within the Pharmacopoeial limits.[73]

IN VITRO DISSOLUTION STUDY

The *in vitro* dissolution study of the formulated SR tablets is given in table 35 andfig.25.

Table 35: *In vitro* dissolution study of SR tablets

TIME (MIN)	Cum. % drug Release				
	F1 *	**F2 ***	**F3 ***	**F4 ***	**F5 ***
0	0 ± 0.0000	0 ± 0.0000	0 ± 0.0000	0 ± 0.0000	**0 ± 0.0000**
30	13.15 ± 0.0500	5.95 ± 0.1500	15.78 ± 0.0200	16.99 ± 0.0600	**15.15 ± 0.0500**
60	18.77 ± 0.1300	9.80 ± 0.1300	19.80 ± 0.0800	26.49 ± 0.1400	**25.10 ± 0.0500**
90	23.07 ± 0.0900	12.38 ± 0.1600	24.01 ± 0.7200	29.35 ± 0.1500	**31.58 ± 0.3400**
120	32.31 ± 0.2900	17.20 ± 0.1800	27.95 ± 0.1500	33.46 ± 0.4500	**36.37 ± 0.2100**
180	37.53 ± 0.5100	27.15 ± 0.3000	36.46 ± 0.1700	36.96 ± 0.1700	**45.29 ± 0.2100**
240	56.3 ± 0.2600	39.97 ± 0.0700	47.74 ± 0.1600	50.25 ± 0.4500	**54.55 ± 0.3500**
300	72.38 ± 0.2200	51.02 ± 0.0800	55.93 ± 0.1700	65.99 ± 0.1100	**60.12 ± 0.0800**
360	85.67 ± 0.2300	61.82 ± 0.2200	61.75 ± 0.0800	82.10 ± 0.5000	**66.20 ± 0.1500**
420	97.38 ± 0.4200	73.98 ± 0.0400	71.06 ± 0.4800	85.62 ± 0.1400	**73.60 ± 0.5000**
480		82.85 ± 0.2500	79.49 ± 0.3900	89.82 ± 0.3200	**82.80 ± 0.2700**
600		86.87 ± 0.0600	85.32 ± 0.1400	97.17 ± 0.1300	**92.25 ± 0.0500**

*** Mean ± S.D (n=3)**

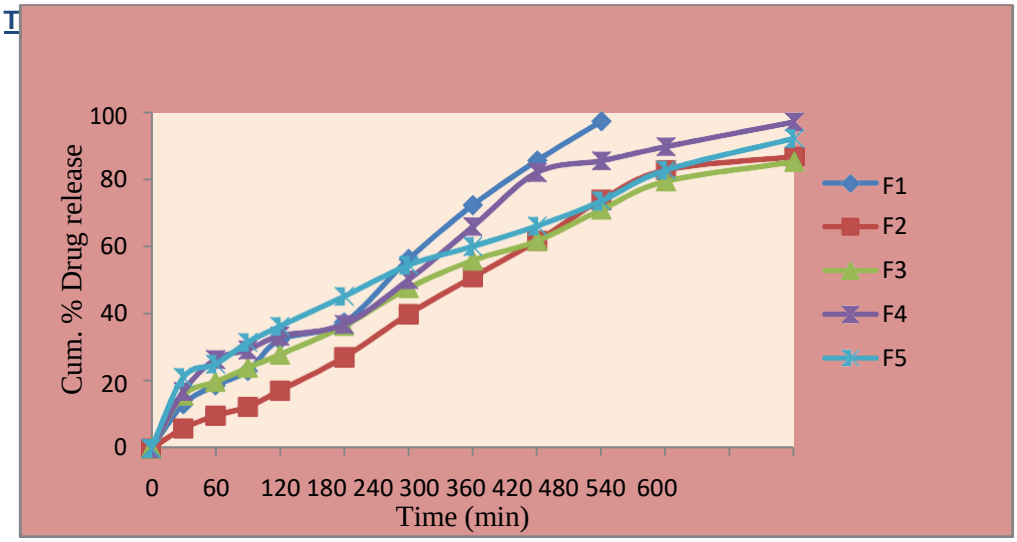


Fig. 25: In vitro dissolution study of SR tablets

The results of *in vitro* dissolution study of SR tablets showed that the formulation F1 containing Ethyl cellulose and HPMC K4M showed complete release in 7 hours. The formulation F2 containing Ethyl cellulose and HPMC K100M retarded the release as the concentration of Hydrophilic polymer was high. In formulations F3 and F4 containing ethyl cellulose, HPMC K4M and HPMC K100M in different proportions the release was retarded but did not meet the IP specifications. In formulation F5 containing Ethyl cellulose, HPMC K4M and HPMC K100M in 1:1 ratio, the release was sustained and it met the specifications as per IP.[73] Based on the release, formulation F5 was optimized for the final preparation of bilayer tablets.

FORMULATION DEVELOPMENT

PREPARATION OF BILAYER TABLETS

1.Optimized immediate layer of Irbesartan was prepared by wet granulation method.

2.Optimized sustained release layer of Metformin hydrochloride was prepared by wetgranulation method

The granules were compressed on 27 station bilayer tablet compressionmachine using 19 x 9 mm caplet shaped punches.

POST COMPRESSION STUDY OF BILAYER TABLETS

The compressed bilayer tablets were evaluated for following parametersand the values are given in table 36.

Table 36: Post Compression Study of Bilayer Tablets

Parameter	Result
Uniformity of weight (g) *	1.0814±0.0046
Thickness (mm) **	6.60±0.0055
Hardness (kg/cm^2) **	7.0 ± 0.0447
Friability (%) ***	0.14 ± 0.0200
Drug content (Simultaneous Estimation Method) ***	
i) Irbesartan (%)	97.36 ± 0.1400
ii) Metformin hydrochloride (%)	95.29 ± 0.2700

*** Mean ± S.D (n=20), ** Mean ± S.D (n=5), *** Mean ± S.D (n=3)**

IN VITRO DISSOLUTION STUDY

The *in vitro* dissolution of drugs in bilayer tablets is given in table 37, 38 and fig. 26 and 27.

Table 37: *In vitro* dissolution study of Irbesartan in bilayer tablets

Time (Min)	Cum. % Drug Release *
0	0.0 ± 0.0000
10	87.61 ± 0.2200
20	93.76 ± 0.3100
30	98.74 ± 0.1800

***Mean ± S.D (n=3)**

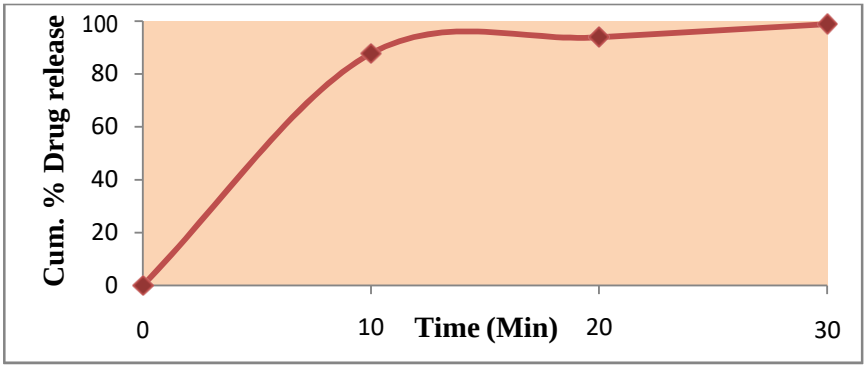


Fig. 26: In vitro Dissolution study of Irbesartan in bilayer tablets

Table 38: *In vitro* dissolution study of Metformin hydrochloride in bilayer tablets

Time (Min)	Cum.% Drug Release*
0	0.0 ± 0.0000
30	12.02 ± 0.0300
60	25.18 ± 0.1200
90	30.02 ± 0.0800
120	33.96 ± 0.1600
180	45.05 ± 0.0500
240	53.62 ± 0.3900
300	59.07 ± 0.7600
360	65.77 ± 0.6500
420	72.35 ± 0.3900
480	81.96 ± 0.1000
540	85.44 ± 0.5800
600	91.38 ± 0.1200

***Mean ± S.D (n=3)**

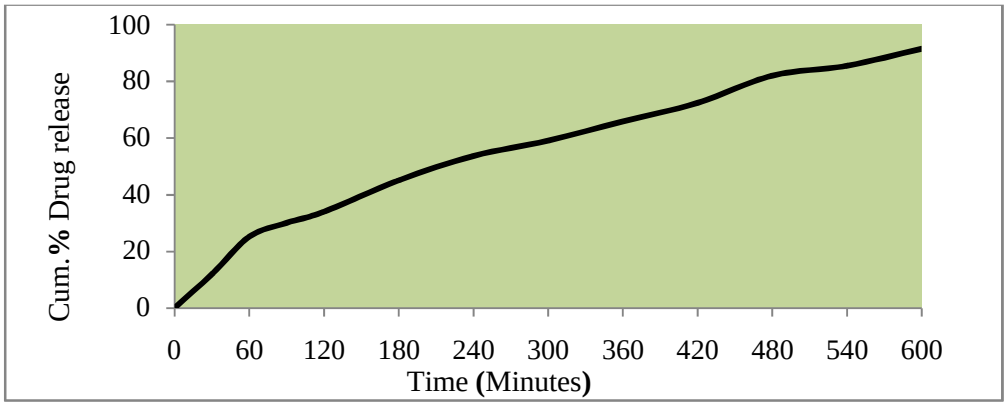


Fig. 27: In vitro Dissolution study of Metformin hydrochloride in bilayer tablets

The bilayer tablets showed release of 98.74% of Irbesartan in 30 min. the tablets released 25.18% of Metformin Hydrochloride in 1 hour, 45.05% of Metformin hydrochloride in 3 hours and 91.38% of Metformin hydrochloride at the end of 10 hours respectively. The drug release of the bilayer formulation was within the Pharmacopoeial limits.[73]

IN VITRO RELEASE KINETICS

The values obtained from *in vitro* dissolution of Metformin hydrochloride from bilayer tablets were fitted in various kinetics models. The results are given in table39 and fig. 28, 29, 30, 31, 32.

Table 39: *In vitro* release kinetics of bilayer tablets

Time (Hours)	% Cum Drug Release	% Cum Drug Remaining	Log % Cum Drug Remaining	Square root of time	Logtime	Log % cum drug release	Cube root of % drug remaining
0	0	100	2	0	∞	∞	4.6416
0.5	12.02	87.98	1.94438	0.7071	-0.3010	1.0799	4.4476
1	25.18	74.82	1.87402	1	0	1.4011	4.2138
1.5	30.02	69.98	1.84497	1.2247	0.1761	1.4774	4.1209
2	33.96	66.04	1.81981	1.4142	0.3010	1.5310	4.0421
3	45.05	54.95	1.73997	1.7321	0.4771	1.6537	3.8018
4	53.62	46.38	1.66633	2	0.6021	1.7293	3.5929
5	59.07	40.93	1.61204	2.2361	0.6990	1.7714	3.4463
6	65.77	34.23	1.53441	2.4495	0.7782	1.8180	3.2469
7	72.35	27.65	1.44169	2.6458	0.8451	1.8594	3.0239
8	81.96	18.04	1.25624	2.8284	0.9031	1.9136	2.6227
9	85.44	14.56	1.16316	3	0.9542	1.9317	2.4419
10	91.38	8.62	0.93551	3.1623	1	1.9609	2.0504

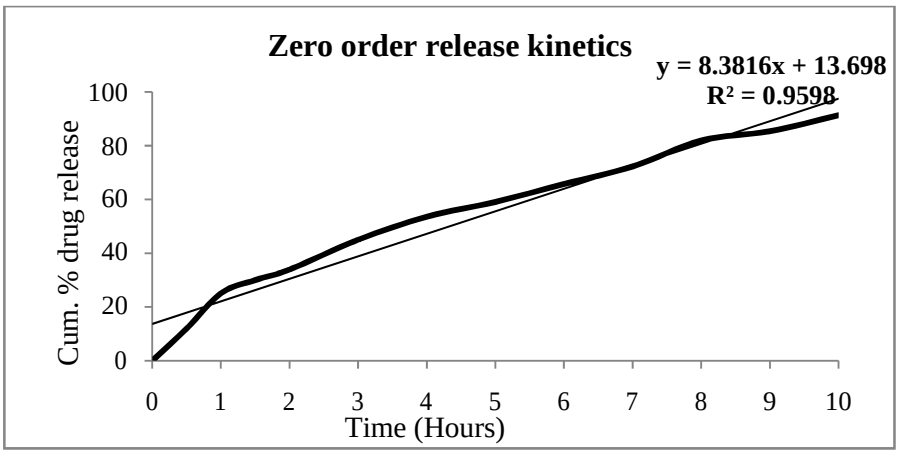


Fig. 28: Zero order release kinetics

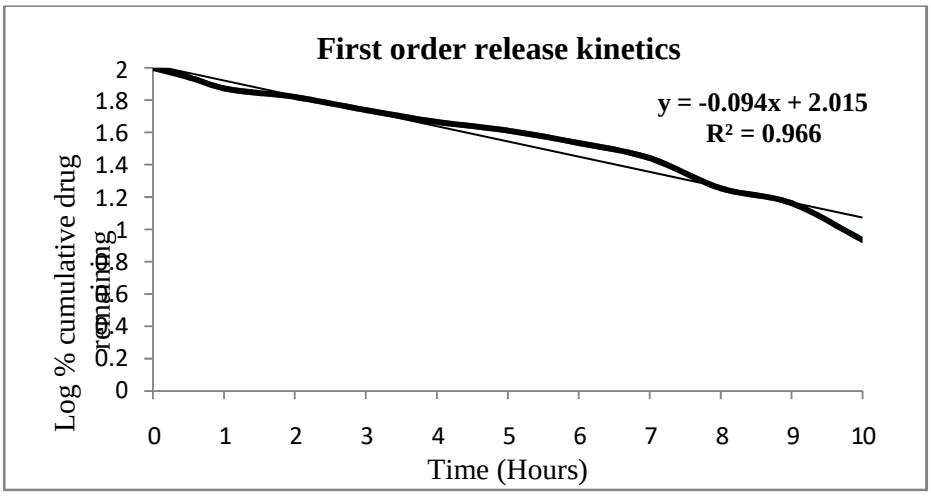


Fig. 29: First order release kinetics

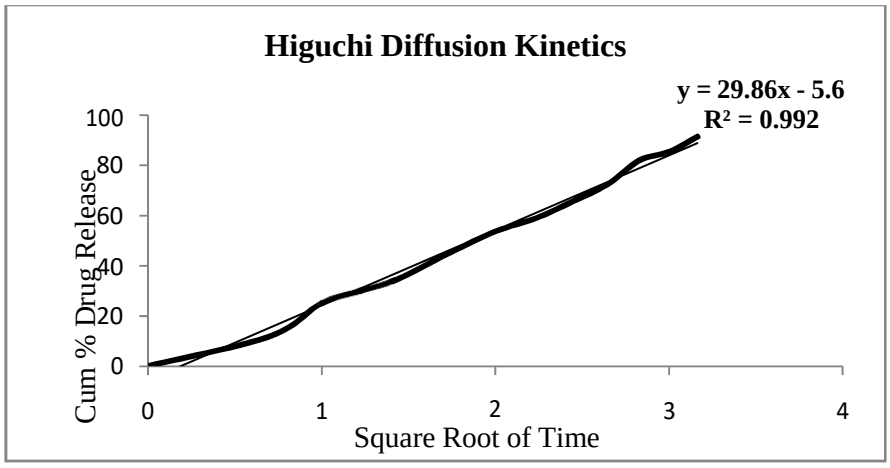


Fig. 30: Higuchi Diffusion Kinetics

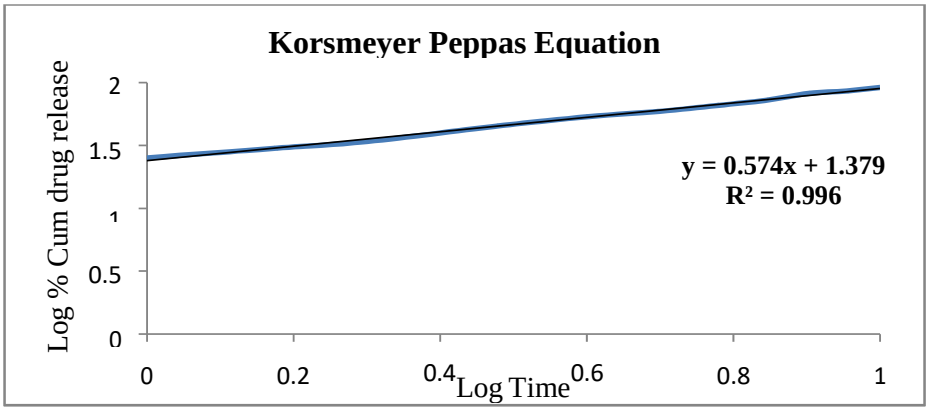


Fig. 31Korsmeyer Peppas Equation

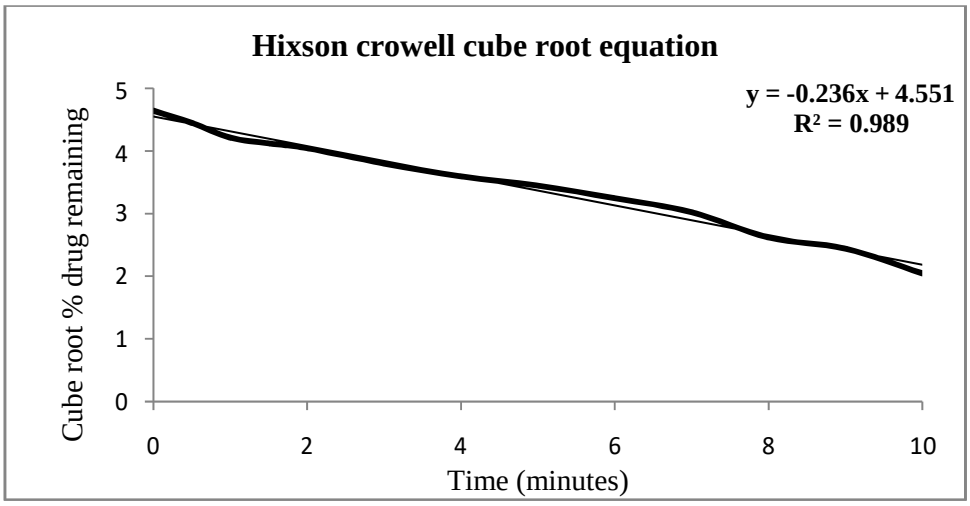


Fig. 32: Hixson Crowell cube root equation Determination of drug release mechanism of optimized bilayer tablets

➢ The order of release was found to be first order, in which R^2 value was close to 1.[84]

➢ The n value of Korsmeyer Peppas equation was found to be 0.574. The release followed anomalous (Non-Fickian) transport.[84]

➢ Swelling hydration of the polymer matrix, dissolution of the drug in the polymer matrix, diffusion of the drug through the polymer matrix and surface erosion of the matrix also play a role in the drug release. The results showed that the formulation followed first order release.

Stability Study

The optimized bilayer tablets were subjected to stability studies and theresults are given in Tables 40 and 41.

Table 40: Stability study of physical parameters of the optimized formulation

Parameters	Initial	1st month	2nd month	3rd month
Uniformity of weight (g)*	1.0814 ± 0.0046	1.0828 ± 0.0040	1.0828 ± 0.0026	1.0814 ± 0.0029
Thickness (mm)**	6.60 ± 0.0055	6.60 ± 0.0055	6.60 ± 0.0055	6.60 ± 0.0055
Hardness (kg/cm^2) **	7.0 ± 0.0447	7.0 ± 0.0447	7.0 ± 0.0447	7.0 ± 0.0447
Friability (%) ***	0.14 ± 0.02	0.12 ± 0.04	0.19 ± 0.0930	0.19 ± 0.0930

*** Mean ± S.D (n=20), ** Mean ± S.D (n=5), *** Mean ± S.D (n=3)**

Table 41: Assay and Dissolution profile of Bilayer tablets

Time interval (month)	Drug content (%) *		Cumulative % drug release *	
	Irbesartan	Metformin hydrochloride	Irbesartan (at the end of30 min)	Metformin hydrochloride(at the end of 10 hours)
Initial	97.36 ± 0.1400	95.29 ± 0.2700	98.74 ± 0.1800	91.38 ± 0.1200
1st month	98.20 ± 0.3000	95.35 ± 0.2500	98.82 ± 0.3200	91.17 ± 0.1900
2nd month	98.98 ± 0.2910	95.33 ± 0.2314	98.78 ± 0.3102	91.40 ± 0.1741
3rd month	99.46 ±0.3024	95.32± 0.2412	98.82 ± 0.3309	91.33 ± 0.1725

*** Mean ± S.D (n=3)**

9.SUMMARY AND CONCLUSION

The present study was aimed to develop bilayer tablets of Irbesartan as IR layer and Metformin hydrochloride as SR layer to treat hypertension in type II diabetic patients. Hypertension is also one of the complications of type II Diabetes. The bilayer tablets were formulated to reduce the polytherapy to monotherapy, thus improving patient compliance. The tablets were formulated using hydrophilic polymers such as HPMC K4M and HPMC K100M in varying ratios to retard the drug release for a period of 10 hours. The immediate release layer of Irbesartan was formulated using Sodium Starch Glycolate (2% and 4%).

All the formulations were evaluated for physical characteristics, drug content, dissolution, release kinetics and stability studies.

❖ The **Drug- excipient interaction** was investigated with FTIR spectroscopy. The study indicated that there was no interaction between the drugs and the excipients used in the formulations.

❖ The tablets were formulated by wet granulation technique because of the poor flow property of the drugs and blends.

❖ The formulated granules were evaluated for precompression studies which showed that the flow property was good.

❖ The formulated tablets were found to be within the limits with respect to uniformity of weight, hardness, thickness, diameter and friability.

❖ The **disintegration time** of IR tablets containing SSG 4% was found to be optimum.

❖ The **drug content** of the formulated IR tablets and SR tablets was found to be within the limits.

❖ Based on ***in vitro*** **dissolution studies**, formulations L2 was optimized and selected for final bilayer tablets.

❖ Five batches of SR formulations containing varying proportions of HPMC K4M and HPMC K100M were subjected to *in vitro* dissolution study. The formulation F5 met the IP specifications at the end of 1st hour, 3rd hour and the 10th hour. Thus the formulation F5 was optimized and selected for bilayer tablets.

❖ The optimized formulations of both IR and SR tablets were compressed intobilayer tablets.

❖ The **drug content** of the bilayer tablets were estimated by simultaneous estimation method and it was found

to be within the Pharmacopoeial limits.

❖ The ***in vitro*** **dissolution study** of the optimized bilayer tablets containing HPMC K4M and HPMC K100M in the 1:1 ratio retarded the release and met the IP specifications.

❖ The **release kinetics** of the optimized tablets showed that it follows first order release kinetics. The release of the drug from the matrix layer was depending on diffusion, swelling and erosion of the polymer.

❖ The **stability studies** indicated that the bilayer tablets were stable and do not show any significant changes in the physical characteristics, drug content and dissolution. The results obtained were found to be within the limits.

Future scope

❖ The *in vivo* studies have to be conducted and *in vitro - in vivo* correlation has to be done.

❖ Clinical studies could be carried out in healthy volunteers and Biopharmaceutical data has to be evaluated.

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