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FORMULATION AND ASSESSMENT COMBINATION OF SUSTAINED-RELEASE LOSARTAN POTASSIUM AND IMMEDIATE-RELEASE HYDROCHLOROTHIAZIDE

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ABSTRACT

The present study was aimed to develop bilayer tablets of Losartan potassium as Immediate Release layer and hydrochlorothiazide as Sustain 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 Losartan Potassium was formulated using Sodium Starch Glycolate (2% and 4%). 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 flowproperty 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 Immediate Release tablets containing SSG 4% was found to be optimum. The drug content of the formulated Immediate Release tablets and Sustain Release tablets was found to be within the limits. 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 ofthe 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 ofthe 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.

KEYWORDS*:* Losartan potassium, Hydrochlorothiazide, Ethyl cellulose, Microcrystalline cellulose, Lactose, Starch, Sodium starch glycolate.

INTRODUCTION

The majority of the time, uniform amounts of particles are compressed to create tablets, which are solid preparations that each contain a single dose of an active medication. Tablets are meant to be taken by mouth. Some are delivered whole or after chewing, some are dissolved or mixed with water before administration, and some are left in the mouth where the active medication is released. Tablets are typically solid, right circular cylinders with bevelled edges and flat or convex ends. Other shapes, such as triangles and rectangles, may also be present. They could be marked with lines or breakmarks, a symbol, or something else entirely. Coated or uncoated tablets are also possible. They are sufficiently tough to handle without breaking or crumbling.[1] The British Pharmacopoeia defines a tablet as having a circular shape, flat or convex faces, and being prepared by compressing a medication or combination of medications with excipients such as diluents, binders, disintegrants, glidants, lubricants, substances that can alter the preparation in the digestive tract, colorants approved by the appropriate authority, and flavoring agents.

Advantages of tablet medication

- They provide the best capabilities of all oral dosage forms for the most precise dosing and the least amount of content variability. They are the unit dosage form.
- All oral dose formulations have the lowest cost.
- These dose forms are the smallest and lightest.
- They are simple to package and transport at a reasonable price.
- When using a punch face that has been embossed or

monogrammed, product identification doesn't need any further processing processes.

- Provides the greatest ease of swallowing and the least likelihood for hang up above the stomach, especially when coated, provided that the tablet's quick disintegration is not excessive.
- They work well with products that have certain release profiles, like enteric coated or delayed release profiles.
- Manufacturing on a large scale is less complicated than with other oral dosageforms.
- They effectively combine mechanical, chemical, and other properties.

Disadvantages of tablet medication

Due to their amorphous form or flocculent, low-density qualities, several medications are resistant to compaction into dense compacts.

Drugs with an unpleasant taste, offensive odor, susceptibility to oxygen, or hygroscopic nature may need to be encapsulated or trapped before compression, or the tablets may need to be coated.

Children, the elderly, and those who are unwell may have difficulty ingesting the tablets.[2]

Immediate release tablets

85% of the amount shown on the label must dissolve within 30 minutes to be considered an immediate release dose form. The simple disintegration or erosion stage, which typically takes less than an hour to complete, is the only barrier to drug release for instant release tablets. Disintegration is one of the crucial processes for quick release tabl ets to improve medication solubility and, consequently, bioavailability.[3] Disintegra nts are compounds or mixtures of substances that are added to the medicine formulati on to help break down or disintegrate the contents of tablets or capsules into tiny parti cles that dissolve more quickly than they would otherwise. Superdisintegrants are normally employed at modest concentrations in dosage forms, approximately 1-10%byweight of the dosage units's total weight. Only a few superdisintegrants, such as sodium starch glycolate, crospovidone, and croscarmellose sodium, are commercially accessible. Filler, a binder, lubricants, and disintegrants are frequently found in tablets intended for quick release. Solid dose formulations frequently take too long to dissolve to provide the desired therapeutic impact. 'Disintegrants' are substances that speed up the disintegration process. The most widely acknowledged methods of their activity are particle repulsion, wicking, swelling, and deformation recovery.[4] These phenomena combine to provide a matrix-destabilizing force. In the past, non-modified disintegrants, such as alginates, starches, ambrelite resins, cellulosic materials, pectines, and others, were utilised to speed up disintegration. Today, a polymericmolecule's organic chains are often cross-linked to create a fast-acting superdisintegrant. There are typically three classes of superdisintegrants. They are modified cellulose, modified starch, and crosslinked polyvinyl pyrrolidone.

Controlled drug delivery systems

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.

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 = Kelim X Cd X Vd Where, Cd = Desired drug level

Vd = Volume of distribution and

Kelim= 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.

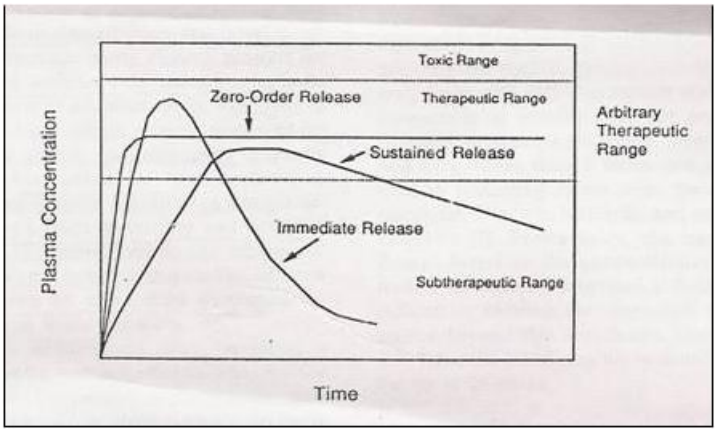

Fig. 1: Drug level versus time profile showing differences between zero order controlled release, slow first order sustained Release and Release from a conventional tablet or capsule.

Figure 1 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.[5]

Sustained release (sr) drug delivery systems

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 blood levels

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

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.

Improve patient compliance

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

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 relief of arthritis by dosing before bedtime.

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

- 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.
- The larger size of sustained release products may cause difficulties in ingestion or transit through the gut.
- 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.
- 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.[6]

Release mechanism for Sustained and Controlled releaseproducts

Based on the release mechanism these are classified as follows

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.

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 deliveryrate remains fairly constant.

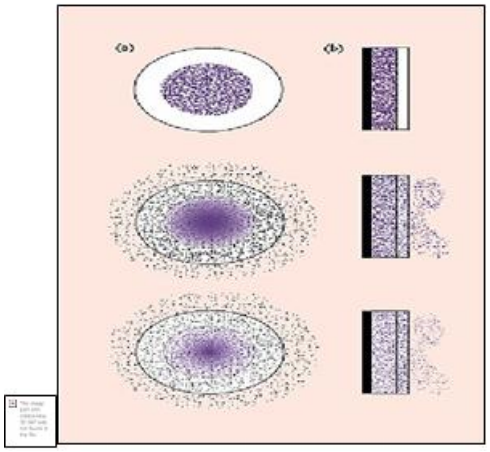

Fig. 2: Drug delivery from typical reservoir devices: (a) Implantable or oral systems and (b) Transdermal systems.

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.[7][8]

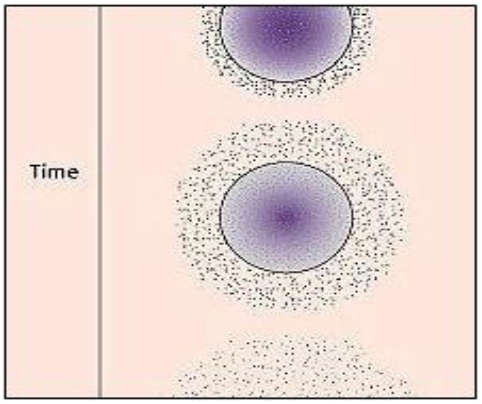

Fig. 3: Drug delivery from a typical matrix drug delivery system.

MATERIALS AND METHODS

Hydrochlorothiazide, Abhilash Chemicals, Tamilnadu, India, Active ingredient. Losartan potassium , Synergene Active Ing. (P) Ltd, Hyderabad, India, Active ingredient , Ethyl cellulose, Microcrystalline cellulose, Lactose, Starch, Sodium starch glycolate, Poly vinyl pyrrolidone K30, Isopropyl alcohol, Acetone, Talc, Magnesium stearate, Tartrazine yellow.

Methodology preformulation studies

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.[9]

Physical compatibility study

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 40^0 C and 75% RH. Any change in color of the physical mixture was observed visually.[10]

Chemical Compatibility study by FTIR
Pure drugs, polymers, excipients, drug excipient mixture and the optimized formulation were subjected to FTIR studies to investigate the Druge-xcipient interactions.[11][12]

Preparation of buffer solutions
Preparation of 0.1 N Hydrochloric Acid (1.2 pH) 8.5 mL of the hydrochloric acid was taken and dissolved in water and made upto 1000mL to get 0.1 N hydrochloric acid.

Materials and Methods
Preparation of 0.02 M potassium dihydrogen phosphate
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
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
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.[13]

Calibration curve
For hydrochlorothiazide
Weigh accurately 100 mg of hydrochlorothiazide transferred into two different 100 ml volumetric flask and dissolved in a small quantity of 1.2 & 7.4 pH buffer solutions separately. The required volume was made with the respective buffers to get the concentration of 1000 µg/ml. i.e. Stock solution-1. Pipette out 2 ml exactly from the stock solution-1 into another 100 ml volumetric flasks separately & make the volumewith respective buffers to get the concentration of 20 µg/ml. i.e. stock solution-2.[14]

For losartan potassium
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 205 nm taking N HCl as blank using UVVisible spectrophotometer. The calibration curve was then plotted taking concentration (µg/mL) along X-axis and absorbance along Y- axis.[15]

Precompression studies of drug and blend flow property measurements
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.[16]

Bulk density (ρb)
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
$\rho b = M / Vb$
Where, M and Vb are mass of powder and bulk volume of the powder respectively.

Tapped density(ρt)
It is the ratio of weight of the powder to the tapped volume of powder. The pwder 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
$\rho t = M / Vt$
Where, M and Vt are mass of powder and tapped volume of the powder respectively.

Angle of repose (θ)
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.
$\theta = \tan^{-1}(h/r)$ Where, h = height of pile in cm; r = radius of pile in cm

Carr's index (or) % compressibility
It indicates powder flow properties. It is measured for determining the relative importance of interparticulate interactions. It is expressed in percentage and is givenby
$CI = \frac{\rho t - \rho b}{Pt} \times 10$
Where, ρt and ρb are tapped density and bulk density respectively.

Hausner's ratio
Hausner's ratio is an indirect index of ease of powder flow. It is calculated by thefollowing formula.
$HR = \rho t / \rho b$
Where, ρt and ρb are tapped density and bulk density

respectively.[17]

Table 1: Values of Angle of Repose, Compressibility Index and Hausner's Ratio.

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

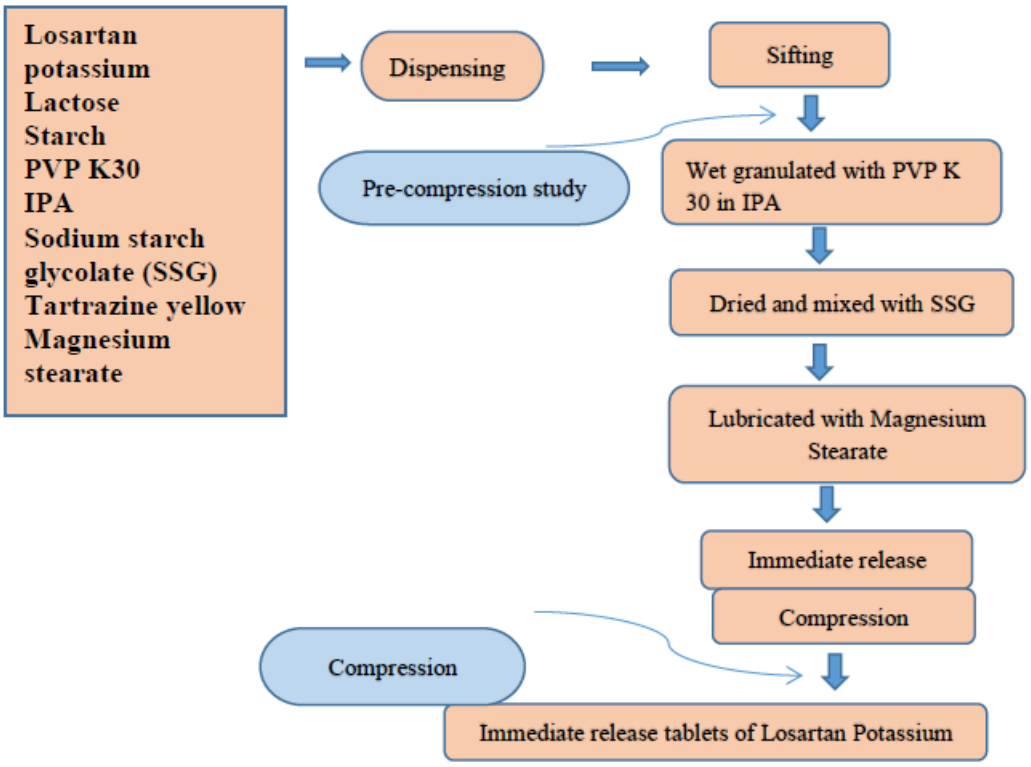

Fig. 4: Flowchat for formulation of Losartan potassium immediate release tablets.

Post compression studiesphysical parameters

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.

Uniformity of weight

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.

Thickness and Diameter

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

Hardness

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/cm2.

Friability

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.

% Friability = Initial weight of the tablets – Final weight of the tablets X 100

Initial weight of the tablets

Preparation of standard stock solution of losartan potassium

Losartan potassium 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 solutionwas diluted to 100 mL with 0.1 N HCl.

Preparation of standard stock solution of hydrochlorothiazide

The solution of 20 µg/ml of hydrochlorothiazide in 1.2 pH & 7.4 pH buffers was scanned in UV-spectrophotometer over the range between 200-400 nm against 1.2 pH & 7.4 pH buffers as blank respectively. The absorption spectra of hydrochlorothiazide showed only one strong absorption peak at 272 nm, which represent the maximum absorption (λ max) of the drug at respective buffers.[18]

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 205 nm and 233 nm respectively. The amount of both the drugs was determined.

***In vitro* release kinetics**

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 = K0t

Where, **K0 =** 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.

Log C = logC0 – Kt/2.303

Where, **C0 =** 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 = Kt1/2

Where, **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.

Q0 1/3 – Qt 1/3 = KHC X t

Where, **Qt =** Amount of drug released at time t

Q0 = Initial amount of drug

KHC = Rate constant for Hixson Crowell equation

Korsmeyer – Peppas equation

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

Mt/M**α** = Ktn

Where, **Mt/M**α **=** Fraction of drug released at time t

t = Release time

K= Kinetics constant (Incorporating structural and geometric characteristics of theformulation)

n = Diffusional exponent indicative of the mechanism of drug release.[19]

Table 2: 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

RESULTS AND DISCUSSION

The present investigation was to formulate bilayer tablets for immediate releaseof Losartan potassium 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. 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 studies

The possible interaction between the drugs and excipient used in the formulation was studied by FTIR spectroscopy.

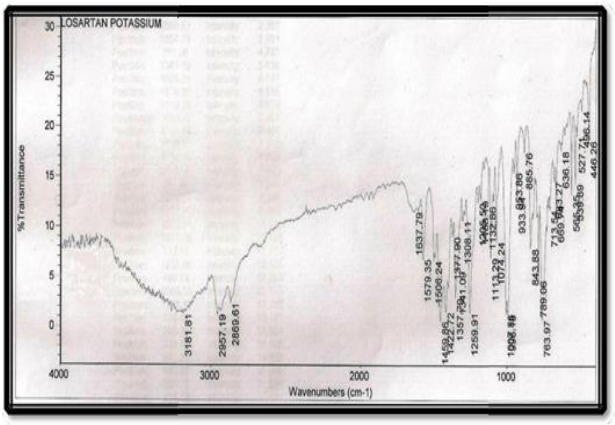

Fig. 5: FTIR of Losartan potassium.

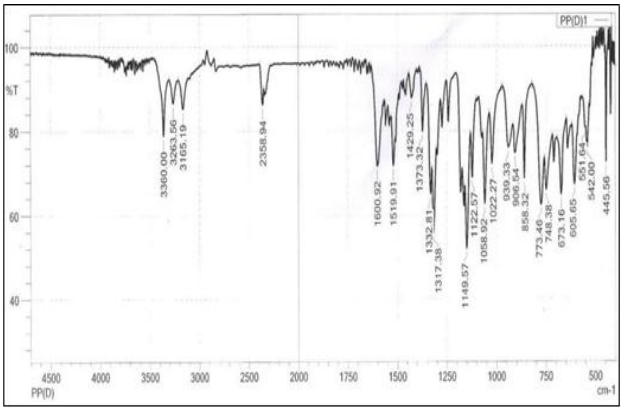

Figure 6: ATR spectra of Hydrochlorothiazide.

Calibration curve for losartan potassium

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

Table 3: Precompression study of immediate release granules.

Formulation	Bulk Densityg/mL *	Tapped Densityg/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

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 granulesranged 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]

Table 4: 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

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 0.4793g/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. Theformulated blend showed good flow property.[82]

In vitro dissolution study

The in vitro dissolution study of IR tablets showed that 4% concentration of SSG was found to be optimum for immediate release of Losartan potassium.

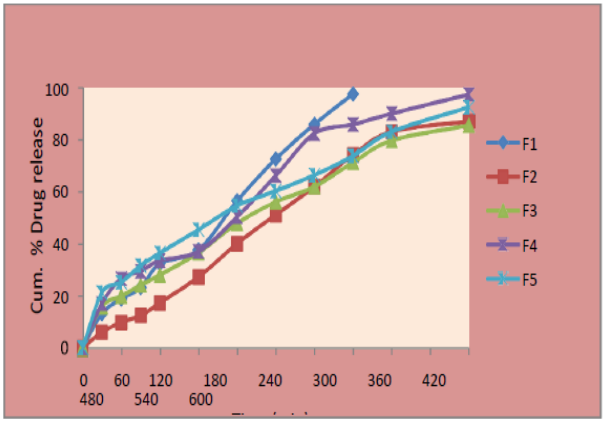

Fig. 7: In vitro dissolution study of sustain release tablets.

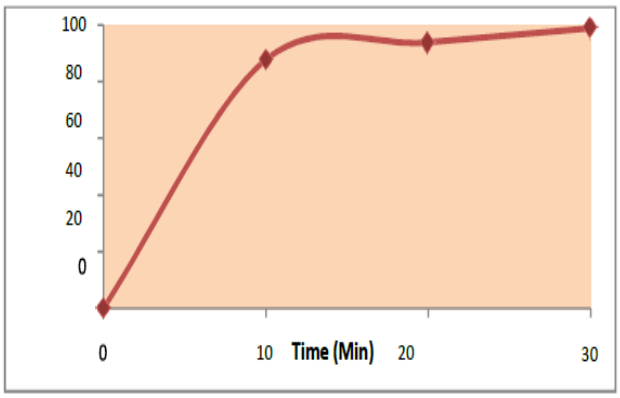

Fig. 8: In vitro Dissolution study of Losartan potassium in bilayer tablets.

Stability studies

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 40^0 ± 2^0C 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.[20]

CONCLUSION

The present study was aimed to develop bilayer tablets of Losartan potassium 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 Losartan Potassium 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 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 finalbilayer tablets.
- Five batches of sustain release formulations containing varying proportions of HPMC K4M and HPMC K100M were subjected to *in vitro* dissolution study. The formulationF5 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 into bilayer 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.

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