INTRODUCTION

Oral ingestion has been the most convenient and commonly employed route of drug delivery due to its ease of administration. The design of a modified release drug product is usually intended to optimize a therapeutic regimen by providing slow and continuous delivery over the entire dosing interval [1-3]. Bilayer tablets is the novel drug delivery system where a combination of two or more drugs in a single unit having different release profiles improves patient compliance; prolongs the drug action resulting in effective therapy along with better control of plasma drug levels. Bilayer tablets [4-6] can be the primary option to avoid chemical incompatibilities between active pharmaceutical ingredients by physical separation and to enable the development of different drug release profiles. Immediate release (IR) dosage forms are those for which ≥85% of the labeled amount dissolves within 30 min. Sustained-release (SR) 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. The approach decreases the pill burden on the patient. Treat different ailments in the same patient (co-morbidity) at the same time with only one tablet. Bilayer tablets also allow for synergistic combinations. These tablets will also provide elegance to the product.

The drug losartan potassium [7-9] was selected for IR layer. As the drug undergoes extensive first-pass metabolism (F=0.33) that can be overcome by formulating the drug as an IR layer because the entire drug releases in the region of the stomach and absorbs completely before entering into liver. The drug also has a biological half-life of 6-9 h that suits the drug for IR part. For SR layer, metformin hydrochloride layer (HCl) [10-12] is selected because of having large dose (500 mg) and t_{1/2} of around 2 h where frequent administration of drugs can be minimized. Hence, this work was aimed to release losartan potassium within 30 min and metformin HCl for a period of 10 h.

In this work, various natural polymers, namely, pectin, sweet potato starch, fenugreek gum, and ispaghula gum, were employed for the preparation of bilayer tablets. These polymers are natural origin, bio-processed, and biodegradable, whereas synthetic polymers derived from chemical reactions are found to be hard and are not biodegradable. These natural polymers have antioxidant and anti-aging properties compared to synthetic polymers. The natural polymer pectin that is extracted from orange peel has antioxidant, anti-diabetic, and reduces gastroesophageal reflux disease. Fenugreek gum has multiple uses such as treatment of obesity, hypertension, and reduction blood glucose levels. Ispaghula gum can be employed in the treatment of bladder problems and hypertension and can be employed for skin irritations. These polymers have super disintegrating properties (pectin, fenugreek gum, and ispaghula gum) as well as SR characteristics (xanthan gum and guar gum).

MATERIALS AND METHODS

Material

Losartan potassium was obtained as a gift sample from Hetero Labs, Hyderabad. Metformin HCl was obtained from Apogen Remedies, Bapatla. All the remaining chemicals used were of analytical grade.

Methods

Preparation of gums

Extraction of pectin

One hundred grams of orange peels were mixed with 500 ml water and 2.5 ml HCl. Boiled for 45 min and filtered. The filtrate was washed with 250 ml of boiled water. Later, it was cooled to 25°C. Extract was precipitated by adding 200 ml 95% ethanol. It was subjected to thorough stirring and left it for 30 min to allow pectin float on the surface. Extracted pectin was purified by washing with 200 ml of ethanol [13].

Extraction of sweet potato starch

The fresh sweet potato tubers were washed and peeled using a stainless steel knife. Peeled sweet potatoes were grinded and passed through a sieve of diameter 150 µm. The slurry was allowed to sediment for 3 h.
The supernatant liquid was then decanted and allowed to sediment. The sediment was treated with 0.1N NaOH to precipitate the protein content of starch. Extracted starch was air dried [14].

Extraction of fenugreek gum
One hundred grams of fenugreek seeds were coarsely grounded and 1500 ml of distilled water was added and then soaked for 12 h. Later, it boiled for 30 min with constant stirring. Then, it was passed through a muslin cloth, and filtrate was collected. Using a muslin cloth, the mucilage was separated and washed with acetone [15].

Extraction of ispaghula gum
Ispaghula seeds were taken in a beaker and to it, 10–20 times water was added and allowed to stand for 15 h. Solution was passed through a muslin cloth. Mucilage was precipitated with 3 volumes of 95% ethanol. Washed for 2 or 3 times with ethanol, and dried in an oven at 50°C [16,17].

Formulation of losartan potassium IR tablets
The IR granules of losartan potassium were prepared by wet granulation technique [18]. Fenugreek gum, sweet potato starch, and ispaghula gum were used as natural disintegrants. The composition of tablets was shown in Table 1.

Formulation of SR tablets metformin HCl
The SR granules of metformin hydrochloride were prepared by wet granulation technique. Guar gum, xanthan gum, and pectin were used as release retardants to control the drug release for a prolonged period of time [19]. The formulations of tablets were shown in Table 2.

Bilayer tablets of losartan potassium and metformin hydrochloride
Optimized IR granules of losartan potassium (L4) + SR granules of metformin hydrochloride were prepared. SR granules were fed in to separate hoppers of the bilayer tablet compression machine (Cadmach, Ahmedabad). Single compression of SR granules was done followed by the filling of IR granules on SR layer [20]. Finally, compression of IR layer over SR layer resulting in the formation of bilayer tablets.

Pre-formulation studies
Fourier transform infrared spectroscopy study was conducted to identify the purity of drug and test the compatibility of drug with excipients.

Evaluation of plane and bilayer tablets
Calibration curve
For losartan potassium
One hundred milligrams of drug were weighed and transferred to a 100 ml standard flask and made up to volume using 0.1 N HCl. Ten milliliters of stock solution were pipetted out in a separate 100 ml standard flask and volume was made up using 0.1 N HCl. From resulting solution, 2, 4, 6, 8, and 10 ml were pipetted out in a separate 100 ml standard flask and made up to volume using 0.1 N HCl to represent 2, 4, 6, 8, and 10 µg/ml of the drug. The absorbance of the solution was measured at 205 nm, taking 0.1 N HCl as blank using ultraviolet (UV)-visible spectrophotometer [21,22]. The calibration curve was then plotted, taking concentration (µg/ml) along X-axis and absorbance along Y-axis. It was shown in Fig. 1.

For metformin hydrochloride
One hundred milligrams of drug were weighed and transferred to a 100 ml standard flask and made up to volume using 0.1N HCl. Ten milliliters of the stock solution were pipetted out in separate 100 ml standard flasks and volume was made up to volume using a buffer. From the resulting solution, 2, 4, 6, 8, and 10 ml were pipetted out in a separate 100 ml standard flasks and made up to volume using 0.1N 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 a UV-visible spectrophotometer. The same procedure was repeated using a 6.8 phosphate buffer solution as a solvent. The calibration curve was then plotted, taking concentration (µg/ml) along X-axis and absorbance along Y-axis. It was shown in Fig. 2.

Uniformity of weight
Twenty tablets are randomly selected and weighed individually, then the average weight is calculated from the total weight of tablets.

### Table 1: Composition of IR tablets of losartan

| Ingredients          | L1 | L2 | L3 | L4 | L5 | L6 |
|----------------------|----|----|----|----|----|----|
| Losartan             | 50 mg | 50 mg | 50 mg | 50 mg | 50 mg | 50 mg |
| Potassium            |     |     |     |     |     |     |
| Lactose              | 80 mg | 75 mg | 80 mg | 75 mg | 80 mg | 75 mg |
| Starch               | 55 mg | 55 mg | 55 mg | 55 mg | 55 mg | 55 mg |
| PVP K 30             | 5 mg | 5 mg | 5 mg | 5 mg | 5 mg | 5 mg |
| Fenugreek gum        | 5 mg | 10 mg |     |     |     |     |
| Ispaghula gum        |     |     | 5 mg | 10 mg |     |     |
| Sweet potato gum     |     |     |     |     | 5 mg | 10 mg |
| Magnesium stearate   | 2.5 mg | 2.5 mg | 2.5 mg | 2.5 mg | 2.5 mg | 2.5 mg |
| talc                 | 2.5 mg | 2.5 mg | 2.5 mg | 2.5 mg | 2.5 mg | 2.5 mg |
| Total wt             | 200 mg | 200 mg | 200 mg | 200 mg | 200 mg | 200 mg |

IR: Immediate release

### Table 2: Composition of SR metformin hydrochloride tablets

| Ingredients            | F1  | F2  | F3  | F4  | F5  | F6  |
|------------------------|-----|-----|-----|-----|-----|-----|
| Metformin HCl          | 500 mg | 500 mg | 500 mg | 500 mg | 500 mg | 500 mg |
| Guar gum               | 100 mg | 150 mg | 200 mg |     |     |     |
| Xanthan gum            |     |     |     | 100 mg | 150 mg | 200 mg |
| Pectin                 |     |     |     |     |     |     |
| Lactose                | 160 mg | 110 mg | 60 mg | 160 mg | 110 mg | 60 mg |
| PVP K30                | 30 mg | 30 mg | 30 mg | 30 mg | 30 mg | 30 mg |
| Isopropyl alcohol      | q.s  | q.s  | q.s  | q.s  | q.s  | q.s  |
| Magnesium stearate     | 5 mg | 5 mg | 5 mg | 5 mg | 5 mg | 5 mg |
| Talc                   | 5 mg | 5 mg | 5 mg | 5 mg | 5 mg | 5 mg |
| Total wt               | 800 mg | 800 mg | 800 mg | 800 mg | 800 mg | 800 mg |

SR: Sustained release, HCl: Hydrochloride layer
Individual weights are compared with average weight. The percentage difference in weight variation should be within limits.

**Hardness test**
Five tablets were randomly selected from each formulation and the pressure at which each tablet crushed was recorded.

**Thickness**
Five tablets were randomly selected and thickness measured using Vernier Calipers.

**Friability**
Ten tablets were initially weighed and transferred into friabilator. The friabilator was operated at 25 rpm for 100 revolutions. The tablets were weighed and percentage friability was then calculated [23].

**Drug content**
Simultaneous estimation of both drugs was carried out using a UV-visible spectrophotometer.

Preparation of standard stock solution of losartan potassium: Losartan potassium equivalent to 50 mg was accurately weighed and 50 ml of 0.1 N HCl was added and sonicated for 10 min. The volume was made up to 100 ml with buffer and 2 ml of the solution was diluted with 100 ml 0.1 N HCl.

Preparation of standard stock solution of metformin hydrochloride: Metformin hydrochloride equivalent to 50 mg was taken and 50 ml of 0.1 N HCl was added and sonicated for 10 min. The volume was made up to 100 ml with buffer and 2 ml of the solution was diluted with 100 ml of 0.1 N HCl.

Preparation of sample solution: Twenty tablets were accurately weighed and then ground to a fine powder. One hundred milligrams of the powder were weighed and dissolved in 0.1 N HCl and then sonicated. The volume was made up to 100 ml with 0.1 N HCl. Two milligrams of the solution were diluted 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.

**Disintegration**
The disintegration test for IR tablet was performed by placing one tablet in each six tubes and to maintain temperature of disintegration media at 37°C and disintegrating time was noted.

**In-vitro dissolution**
*For IR tablets*
Dissolution studies of losartan potassium tablets were carried out using USP type II (paddle) dissolution apparatus, for a period of 30 min. Nine hundred milliliters of 0.1 N HCl were used as dissolution medium at a temperature of 37°C±0.5°C. The paddle was stirred at a
speed of 100 rpm [23]. The absorbance of the solution was measured at 205 nm, taking 0.1N HCl as a blank solution using a UV-visible spectrophotometer.

For SR tablets
Dissolution studies of metformin hydrochloride tablets were carried out using USP type II (paddle) dissolution apparatus. For the first 2 h, 900 ml of 0.1 N HCl was used as a dissolution medium followed by 900 ml of 6.8 phosphate buffer solution for the next 8 h at a temperature of 37°C±0.5°C. The paddle was stirred at a speed of 100 rpm. The absorbance of the solution was measured at 233 nm, taking pH 6.8 phosphate buffer as a blank solution using UV-visible spectrophotometer.

For bilayer tablets
The in-vitro dissolution was carried out using USP dissolution testing apparatus type II. The tablets were placed in 0.1 N HCl for the first 2 h and pH 6.8 phosphate buffer for the next 8 h. The apparatus was maintained at temperature 37°C and 50 rpm rotating speed was maintained. Five milliliters of aliquots were withdrawn and replaced with fresh dissolution medium maintained at the same temperature. Samples were analyzed using a UV spectrophotometer.

In vitro release kinetics
Data obtained from the in-vitro dissolution study of the optimized bilayer tablets were used to study in vitro release kinetics by plotting in various release rate kinetic models [23].

RESULTS AND DISCUSSION
The present study was to develop bilayer tablets containing losartan potassium for IR and metformin hydrochloride for SR for diabetic patients having hypertension and to provide effective, safe, and stable pharmaceutical formulation.

Different natural gums, namely, guar gum, xanthan gum, pectin, are used for SR [19] formulations. Fenugreek gum, ispaghula gum, and sweet potato gum are used as disintegrants [15] in IR formulation.

The selected polymers were evaluated for drug and excipient compatibility by performing Fourier-transform infrared studies. There were no interactions of drugs with excipients. The results were indicated in Figs. 3-6.

Preparation of IR tablets
Preliminary tablets were done by varying polymer content to study the influence of polymer on drug release.

The IR granules of losartan potassium with 2.5% and 5% concentrations of fenugreek gum, ispaghula gum, and sweet potato starch were formulated into six formulations L1-L6 which were given in Table 1. These tablets were subjected to weight variation, hardness friability, and disintegration, drug content. The values were shown in Table 3. The IR tablets disintegrated quickly due to the use of natural super disintegrants. All the four natural gums used decreases the disintegration time of tablet and can be effectively employed in fast dispersing tablets. As ispaghula gum affects the (decreases) disintegration time (by increasing the wetting) that depends upon pore size [24] of the inner surface of tablets. The gum acts as a natural super disintegrant due to its excellent swelling and wetting characteristics.

A comparison of percentage cumulative drug release of six IR Losartan potassium tablets is given in Fig. 7a. The formulation containing ispaghula gum 5% concentration exhibited superior drug release profile compared to remaining formulations. Hence, L4 formulation was selected to design bilayer tablets.

Preparation of SR tablets
The SR granules of metformin hydrochloride with varying concentrations of 12.55%, 18.75%, and 25% of guar gum, xanthan gum, and pectin were formulated into nine formulations F1-F9 which were given in Table 2. All the tablets formulated were within the specified limits. They have passed the official tests. Their values were shown in Table 4.

The results of in vitro dissolution study of metformin hydrochloride SR tablets using 0.1N HCl at first 2 h and 6.8 pH phosphate buffer for next 8 h showed that the formulation F1 showed complete release of

![Image](https://via.placeholder.com/150)

Fig. 3: Fourier-transform infrared of losartan potassium
98.69% of drug release at 7 h period of time, but it does not meet the IP specifications. In formulation F2 containing 150 mg guar gum showed SR drug release of 97.16% and met IP specifications. A comparison of percentage drug release of SR metformin hydrochloride formulations was depicted in Fig 7b. Based on the release, formulation F2 was selected for the final preparation of bilayer tablets. The remaining formulations were not selected for bilayer tablets since; those were not meeting the desired drug release standards.

**Bilayer tablet evaluation**

The compressed bilayer tablets were evaluated for uniformity of weight, thickness, hardness, friability, and drug content and the results are shown in Table 5. The results were within the specified limits.

**In-vitro dissolution**

The bilayer tablet showed the 98.73% release of losartan potassium in 30 min given in Fig. 15. The tablet released 31.42% of metformin
Fig. 6: Fourier-transform infrared of metformin and guar gum

Fig. 7: (a) Comparison of cumulative % drug release of six immediate release losartan potassium tablets (b) comparison of cumulative % drug release of SR tablets of metformin HCl

Table 3: Evaluation tests for IR losartan potassium tablets

| Formulation | Uniformity of weight (mg) (Mean±SD) (n=20) | Hardness (kg/cm²) (Mean±SD) (n=5) | %Friability (Mean±SD) (n=5) | %Drug content (Mean±SD) (n=5) | Disintegration time(min) (Mean±SD) (n=6) |
|-------------|------------------------------------------|-----------------------------------|-----------------------------|-------------------------------|----------------------------------------|
| L1          | 200.1±0.984                              | 2.98±0.31                         | 0.078±0.008                 | 96.81±0.93                    | 10                                     |
| L2          | 199.3±0.655                              | 3.15±0.25                         | 0.094±0.005                 | 98.33±0.103                   | 6                                      |
| L3          | 199.0±0.908                              | 3.11±0.48                         | 0.087±0.06                  | 97.31±0.54                    | 7                                      |
| L4          | 200.6±0.678                              | 3.24±0.16                         | 0.185±0.005                 | 99.21±0.117                   | 4                                      |
| L5          | 199.2±0.721                              | 2.94±0.39                         | 0.074±0.02                  | 98.23±0.738                   | 11                                     |
| L6          | 198.6±0.546                              | 3.08±0.51                         | 0.164±0.003                 | 97.21±0.217                   | 8                                      |

IR: Immediate release

hydrochloride in 2 h and 96.36% of metformin hydrochloride at the end of 10 h given in Fig. 8. The slow release of metformin HCl was due to the use of guar gum as SR polymer. Guar gum has exhibited sustained drug release characteristics due to the formation of a matrix around the surface of the tablet that undergoes drug diffusion, as reported earlier [19]. The drug release of bilayer formulation was within pharmacopoeial limits.

**In-vitro release kinetics**

The results obtained from *in vitro* dissolution studies were fitted in various kinetic models. The bilayer tablet followed zero-order release kinetics. The optimized formulation followed Fickian diffusion-based on *n*-value, as shown in Table 6. The rate of drug release is independent of the drug concentration in the formulation.
Table 4: Evaluation tests for metformin HCl SR tablet

| Formulation | Uniformity of weight (mg) (Mean±SD) (n=20) | Hardness (kg/cm²) (Mean±SD) (n=5) | %Friability (Mean±SD) (n=5) | Drug content (Mean±SD) (n=5) |
|-------------|--------------------------------------------|---------------------------------|---------------------------|-----------------------------|
| F1          | 797±0.96                                   | 4.08±0.013                      | 0.019                     | 98.69                       |
| F2          | 790±1.17                                   | 4.98±0.105                     | 0.021                     | 99.86                       |
| F3          | 797±0.68                                   | 4.12±0.009                     | 0.024                     | 99.51                       |
| F4          | 780±0.89                                   | 4.21±0.113                     | 0.029                     | 97.53                       |
| F5          | 799±0.91                                   | 4.10±0.005                     | 0.032                     | 97.79                       |
| F6          | 798±0.15                                   | 4.06±0.006                     | 0.030                     | 98.90                       |
| F7          | 796±1.12                                   | 4.18±0.004                     | 0.028                     | 99.83                       |
| F8          | 801±2.63                                   | 4.13±0.102                     | 0.025                     | 99.39                       |
| F9          | 798±3.18                                   | 4.16±0.132                     | 0.033                     | 98.73                       |

SR: Sustained release, HCl: Hydrochloride layer

Table 5: Evaluation tests for bilayer tablets

| Uniformity of weight (g) (Mean±SD) (n=20) | Thickness (mm) (Mean±SD) (n=5) | Hardness (kg/cm²) (Mean±SD) (n=5) | Friability % (Mean±SD) (n=5) | Disintegration time for IR layer (Mean±SD) (n=6) | Drug content (%) (Mean±SD) (n=5) |
|-------------------------------------------|--------------------------------|---------------------------------|---------------------------|-----------------------------------------------|-----------------------------|
| 1.061±0.0064                              | 5.98±0.0042                    | 7.0±0.0056                      | 0.16±0.0011               | 4 min 50 s                                   | Losartan potassium 96.63±0.1700 |
|                                           |                               |                                 |                           |                                              | Metformin 98.27±0.23          |

IR: Immediate release

Table 6: In vitro release kinetics of bilayer tablet

| Zero order (r) | First order (r) | Higuchi (r) | Peppas (r) | t_{50%} (h) | t_{90%} (h) | K (h⁻¹) |
|----------------|-----------------|------------|------------|-------------|-------------|---------|
| 0.986          | 0.885           | 0.975      | 0.978      | 5.023       | 9.041       | 8.529   |

CONCLUSION

The bilayer tablets designed for multiple drug therapy, that is, both diabetes and hypertension, can be effectively delivered using ispaghula gum and guar gum. The drugs losartan potassium and metformin HCl were delivered effectively by this approach.

ACKNOWLEDGMENTS

The authors are grateful to Apogen remedies Ltd. for providing gift samples of losartan.

AUTHORS’ CONTRIBUTIONS

The corresponding author has planned and designed the whole project. She was also involved in the preparation and communication of entire official article work. Author 2 was involved in experimental work.

CONFLICTS OF INTEREST

The author declares that there were no conflicts of interest.

AUTHORS’ FUNDING

The authors received no financial support for research, authorship, or publication of this article. However; they were thankful to Bapatla Education Society, Bapatla, for providing the necessary infrastructure facilities and chemicals.

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