DRUG-EXCIPIENT COMPATIBILITY STUDIES FOR LOSARTAN POTASSIUM PULSATILE DOSAGE FORM

Y. Phani Krishna¹ & Y. A. Chowdary² & M. V. Basaveswara Rao³
¹Assistant Professor, ²Professor, ³Professor
¹Research Scholar, Krishna University,
¹Sir C. R. Reddy College of Pharmaceutical Sciences, Eluru, India.
²NRI College of Pharmacy, Pothavarappadu, India.
³KrishnaUniversity, Machilipatnam, India.

Received: July 12, 2018 Accepted: August 22, 2018

ABSTRACT
Losartan potassium is drug used for the treatment of hypertension. Cardiac diseases and respiratory diseases are mostly based on circadian rhythm. Time delayed drug delivery systems or pulsatile dosage forms plays important role in treating the diseases that depend on the circadian cycle. A target time such as 3, 4, 5, 6, 7, 8 hours can be fixed to release the drug and the dosage form can be manufactured such that it releases the drug at the required target time. Polymers like HPMC, Methyl cellulose, Ethyl cellulose and other gums like Acacia, Xanthan gum, Guar gum etc can be used alone or in combination to achieve the target. Drug-excipient compatibility plays pivotal role in pharmaceutical field. Ingredients that are incompatible with the drug cannot be used in the formulation. Various studies like HPLC, IR Spectrophotometric studies, and Accelerated stability studies can be carried out to find the compatibility between ingredients. Present paper discusses about the drug – excipient compatibility studies for the excipients with the drug that are used in the formulation of Losartan Potassium pulsatile dosage form.

Keywords: Pulsatile, Chronopharmacokinetics, time delayed, circadian rhythm, compatibility

I. INTRODUCTION
Drug-Excipient interaction studies¹ are used to maximize the stability of dosage form. Any physical and chemical interaction between drug and excipients² can affect the bioavailability and stability of drug. By performing drug-excipient compatibility studies we can know the possible reaction before formulating the final dosage form. Drug excipient compatibility studies can be performed using IR spectrophotometric studies, HPLC studies, accelerated stability studies, DSC etc. For the formulation of a Losartan potassium time delayed formulation, pre-formulation studies should be carried out, in which drug-excipient compatibility studies are a part. Various materials that are used in the formulation of the dosage form are mixed together with the drug and the compatibility of those ingredients with Losartan potassium is tested. Water and Methanol were used as the mobile phase in HPLC for carrying out drug-excipient compatibility or drug-excipient interaction³ studies. Initially standard graph of Losartan potassium is plotted using HPLC, and then the retention time of drug and other excipient mixture is compared to the retention time of the standard solution of drug. If the retention time varies between these chromatograms then there is a chance of incompatibility between the drug and the excipients that are used in the formulation. KBR pellet technique method is used in the IR spectrophotometric study. IR spectrogram of pure Losartan potassium is compared to the IR spectrogram of drug- excipient mixtures. Drug- Excipient interaction studies help in the better selection of excipients⁴ for the formulation of dosage form.

II. MATERIALS AND EQUIPMENT
Materials used in the study are Losartan potassium pure drug, Lactose, Starch, Hydroxy propyl methyl cellulose, magnesium stearate, talc, sodium alginate⁵. Equipments used in the study are mg sensitive weighing balance, stability chamber, Fourier transform infrared spectroscopy, High performance liquid chromatography.

III. MATERIALS AND EQUIPMENT EXPERIMENTAL METHODS
a) Procedure for preparation of drug excipient mixtures for compatibility study:
Losartan potassium and common pharmaceutical excipients such as diluents, binders, disintegrants, and lubricants were mixed in the ratio 1:1. 100 mg of Losartan potassium and 100 mg of excipient were mixed and taken in a 10 ml glass vials. The rubber closures were placed on the vials and were covered with aluminium foil. All the samples of drug-excipient blends were kept for 1-3 weeks at 40 ± 0.5°C/ 75 ± 1%
relative humidity in stability chamber. Then the samples were physically observed for (i) caking (ii) liquefaction (iii) discoloration (iv) odour (v) gel formation. After one week the samples were subjected for HPLC and FTIR studies to know the incompatibility between drug and excipients.

b) Preparation of mobile phase:
11 ml of HPLC grade water was mixed with 89 ml of HPC grade methanol. The solution was degassed in an ultrasonic water bath for 5 min and filtered through 0.45 µ filter under vacuum.

c) Preparation of standard solution:
10 mg of Losartan potassium was dissolved in mobile phase in 10 ml volumetric flask (A), and the solution was made up to the mark with mobile phase. The solution was sonicated for 5 min using digital ultra sonicator. 0.1 ml of above solution was diluted to 10 ml with mobile phase in another volumetric flask. This standard solution had a concentration of 10 µg of Losartan potassium/ml, (B). The solution was sonicated for 5 min. Chromatographic conditions that were maintained for carrying out the study are 1) drug- Losartan potassium, 2) Instrument- Schimadzu RPHPLC, 3) Mobile phase- Methanol: Water (89:11), 4) Column- C_{18}(250 mm x 4.6 mm, 5µ), 5) Wavelength- 230 nm, 6) Flow rate- 0.8 ml/min 7) Injection volume- 20 µl, 8) Run time- 5 min 9) Retention time- 2.8 min.

d) Preparation of drug-excipient solution for HPLC analysis:
20 mg of drug-excipient mixture were dissolved in q.s. 10 ml mobile phase. This solution was sonicated and 0.1 ml of this solution was diluted to 10 ml with mobile phase (approximately 10 µg/ml solution). This solution was used for HPLC analysis at 230 nm and the chromatograms were recorded.

e) FTIR analysis of drug-excipient mixture:
The drug-excipient compatibility study was carried out using FTIR method. In this technique a small amount of drug-excipient mixture was intimately mixed with about 100 times its weight of powdered potassium bromide, in small mortar and pestle. Mix it well to prepare a fine powder. This finely ground mixture is then passed under very high pressure (25,000 p sig) in evacuable die or hydraulic pellet press or minipress to form a small pellet (about 1-2 mm thick and 1 cm in diameter). The resulting pellet is transparent to IR radiation and is kept in the FTIR instrument to record the spectra.

IV. RESULTS AND DISCUSSION

a) Drug-excipient compatibility studies on Losartan potassium using HPLC
The prepared solutions having Losartan potassium with different pharmaceutical excipient mixture is measured with 0.8 ml / min flow rate at 230 nm using UV detector. The observed chromatograms are given below.

![Fig1: HPLC chromatogram of losartan potassium](image)

![Fig2: HPLC chromatogram of losartan potassium and lactose (1:1 mixture) stored at 40°C and 75% RH for one week](image)
Fig3: HPLC chromatogram of losartan potassium and starch (1:1 mixture) stored at 40°C and 75% RH for one week

Fig4: HPLC chromatogram of losartan potassium and HPMC (1:1 mixture) stored at 40°C and 75% RH for one week

Fig5: HPLC chromatogram of losartan potassium and magnesium stearate (1:1 mixture) stored at 40°C and 75% RH for one week

Fig6: HPLC chromatogram of losartan potassium and talc (1:1 mixture) stored at 40°C and 75% RH for one week
Fig7: HPLC chromatogram of losartan potassium and sodium alginate (1:1mixture) stored at 40°C and 75% RH for one week

Fig8: HPLC chromatogram of losartan potassium and sucrose (1:1mixture) stored at 40°C and 75% RH for one week

<table>
<thead>
<tr>
<th>S.NO</th>
<th>Sample</th>
<th>Retention time (in min) at 230 nm</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Losartan potassium</td>
<td>2.835</td>
</tr>
<tr>
<td>2.</td>
<td>Losartan potassium + Lactose</td>
<td>2.605</td>
</tr>
<tr>
<td>3.</td>
<td>Losartan potassium + Starch</td>
<td>2.676</td>
</tr>
<tr>
<td>4.</td>
<td>Losartan potassium + HPMC</td>
<td>2.558</td>
</tr>
<tr>
<td>5.</td>
<td>Losartan potassium + Magnesium stearate</td>
<td>2.568</td>
</tr>
<tr>
<td>6.</td>
<td>Losartan potassium + Talc</td>
<td>2.720</td>
</tr>
<tr>
<td>7.</td>
<td>Losartan potassium + Sodium alginate</td>
<td>2.594</td>
</tr>
<tr>
<td>8.</td>
<td>Losartan potassium + Sucrose</td>
<td>2.574</td>
</tr>
</tbody>
</table>

The retention time mentioned in table 1 was found to be nearly same in above chromatograms. So the drug is compatible with all the ingredients like lactose, starch, HPMC, Magnesium stearate, talc, sodium alginate and sucrose.

b) Drug-excipient compatibility studies on Losartan potassium using FTIR:

For Losartan potassium FTIR studies KBR pellets are prepared by using hydraulic pellet press. The resulting pellets are transparent to IR radiation. The observed spectras are given below.

Fig9: FTIR Spectra of Losartan potassium
Fig 10: FTIR spectra of Losartan potassium and lactose (1:1 mixture) stored at 40°C/75%RH for one week

Fig 11: FTIR spectra of losartan potassium and starch (1:1 mixture) stored at 40°C and 75%RH for one week

Fig 12: FTIR spectra of losartan potassium and HPMC (K05) (1:1 mixture) stored at 40°C and 75%RH for one week

Fig 13: FTIR spectra of losartan potassium and magnesium stearate (1:1 mixture) stored at 40°C and 75%RH for one week
From the above FTIR spectra, the characteristic peaks of drug such as OH stretching (3384.62 cm⁻¹), CH stretching Aliphatic (2954.33 cm⁻¹), CN stretching (1644.10 cm⁻¹), Al-CH in plane bending (1460.09 cm⁻¹), C-O or O-H stretching (1260.33 cm⁻¹), C-O-C ether linkage or C-C stretching (1014.38 cm⁻¹), C-Cl stretching (762.28 cm⁻¹) appeared for the Losartan potassium in all the spectra. So the drug is compatible with all the ingredients like lactose, starch, HPMC, Magnesium stearate, talc, sodium alginate and sucrose.

**V. CONCLUSION**

From the above HPLC results and FTIR results it is confirmed that the drug Losartan potassium is compatible with all the ingredients that were mentioned in the study. Any incompatibility with the ingredients mentioned above wouldn’t allow the usage of the above ingredients in the formulation and there would be requirement of change in the ingredients. Using above ingredients Losartan potassium time delayed drug delivery dosage form can be manufactured without affecting the therapeutic activity of the drug.

**REFERENCES**