INTRODUCTION
In addition to more conventional methods almost half of new molecular entities identified by pharmaceutical industry screening programs have paid to develop because of poor water solubility which makes their formulation difficult or even impossible. For tackling these problems, the nanotechnology has become one of the main applications in drug delivery. The nanotechnology based solution is a most advanced approach commercial to improve drug solubility and bioavailability. Nanotechnology is offering new ways to address these drug delivery challenges and is being applied in a wide range of health care settings. The poor water solubility has been attributed to almost half of the 150000 new molecular entities synthesized annually by pharmaceutical companies and is also claimed to reduce the performance of more than 10% of successfully marketed drugs. The drug olmesartan medoxomil has low bioavailability due to its poor aqueous solubility, in order to increase the oral bioavailability by reducing the size of particle in nano range for increasing aqueous solubility of drug ionic-gelation technique was selected for the preparation.

ABSTRACT
The drug olmesartan medoxomil bioavailability is only 26% due to its poor aqueous solubility. The purpose of this study is to improve aqueous solubility by nanotechnology of ionicgelation technique using chitosan as polymer and tripoly phosphate as cross linking agent. The nanoparticles of olmesartan medoxomil is formulated to increase oral bioavailability by preparing particles of nano size range with good zeta potential and SEM analysis of prepared particle is done to confirm the surface morphology of nanoparticles with free of clusters. The different formulation of olmesartan medoxomil nanoparticles were compressed into tablets and it complies with IP standard for tablet. In-vitro release study of all the formulation were done to confirms its enhancement of in-vitro bioavailability, when compare to marketed formulation-M of 93 ± 2.95% drug release at 60 minutes, formulation OLM-9 of nanoparticle has shown 99% at 20 minutes with particle size of 633 nm, which indicates 3 fold increase in the in-vitro dissolution rate of olmesartan medoxomil. The prepared particles were free from clusters and with good zeta potential.

KEYWORDS: olmesartan medoxomil, ionic gelation, SEM, bioavailability.

MATERIALS AND METHODS
Preformation studies
Melting point
A capillary tube was taken and it was filled with the help of Bunsen burner. Then this capillary tube which was filled with the drug was placed in a melting point viewer and degree at which the drug gets melted down was considered as the melting point of the drug.

Selection of analytical wave length and calibration of standard curve
A stock solution of 1 mg/ml of olmesartan medoxomil was prepared by dissolving 100 mg of drug in 100 ml of methanol and sonicated for few minutes. The stock solution was serially diluted to get 1 mcg/ml and λ max of the solution was found out by scanning from 200 to 400 nm.

Solubility study
Solubility of the drug is predicted by dissolving 1 gm of the drug in proportions of 1 ml, 10 ml, 30 ml and 100 ml of the proposed solvents. So according to the dilution or dissolving property the solubility was predicted by measuring the absorbance by using UV-Visible Spectroscopy method.

IR studies
Infrared spectra of drug and its inclusion complexes were recorded by
KBr pellet method using Fourier Transform Infrared Spectrophotometer. A baseline correction was made using dried potassium bromide and then spectra of dried mixtures of drug and inclusion complexes with potassium bromide were recorded. The samples were prepared by KBr pellet press method. The scanning range was 400 to 4000 cm\(^{-1}\).

**Preparation of olmesartan medoxomil nanoparticulate tablets**

The ionic gelation process is commonly used to prepare chitosan nanoparticles because it is very simple method. This process can be performed either by chemical or physical cross linking in the presence of counter ions to form hydrogel beads also called as gelispheres. The gelispheres are spherical cross linked hydrophilic polymeric entity capable of extensive gelation and swelling in simulated biological fluids and the release of drug through it controlled by polymer relaxations. The hydrogel beads are produced by dropping a drug loaded polymeric solution into the aqueous solution of polyvalent cations. The cations diffuse into the drug loaded polymeric drops, forming a three dimensional lattice of ionically cross linked moiety. However physically cross linked chitosan gels have been used in drug delivery system due to their enhanced biocompatibility compared to chemically cross linked chitosan. The biomolecules can also be loaded into these gelispheres under milled conditions to retain their three dimensional structure\(^5\).

**Characterization of nanoparticles**

Nanoparticles are characterized in the ways similar to those used for conventional particles such as appearance, color, odor, assay, impurities etc. The nanoparticle should be evaluated for their particle size, zeta potential, crystalline status, dissolution studies and \textit{in-vivo} studies.

**Particle size distribution**

It determines the physicochemical behavior of the formulation such as saturation, solubility, dissolution, velocity, physical stability, etc. When the particle size distribution is determined by photon correlation spectroscopy, laser diffraction and coulter counter multi sizer. The coulter counter multi sizer gives the absolute number of particles, in contrast to the LD method, which give only a relative size distribution. Where the particles should be less than 5 microns, as a higher particle size can lead to capillary blockade and embolism\(^6\).

**Zeta potential**

It indicates the stability of the particle for a stable particle stabilized by electrostatic repulsion with minimum \(\pm 30\) mv of zeta potential\(^6\).

**Evaluation of olmesartan medoxomil nanoparticulate tablets**

**Weight variation**

20 Tablets were selected randomly and weighed individually. The average weight of 20 tablets was calculated. Individual weights of the tablets were compared with the average weight.

**Hardness**

A tablet was placed between two anvils of the hardness tester, force was applied to the anvils, and the crushing strength that caused the tablet to break was recorded.

**Friability test**

10 tablets were weighed initially and placed in the friabilator, which was then operated at 25 RPM for 4 minutes or 100 revolutions, dropping the tablet a distance of 6 inches in each revolution. The \% friability was calculated

\[ \% \text{ Friability} = \frac{\text{Initial weight} - \text{final weight}}{\text{Initial weight}} \times 100 \]

**Drug content uniformity of tablet**

The prepared tablet was dissolved in methanol and its drug content was measured at 257nm after suitable dilution against blank of methanol using uv-visible spectrophotometer.

**Disintegration test**

The disintegration test is carried out using the disintegration tester which consists of a basket rack holding 6 plastic tubes, open at the top and bottom, the bottom of the tube is covered by a 10-mesh screen. The basket is immersed in a bath of water at 37°C.

**Dissolution study of olmesartan medoxomil**

Dissolution studies were carried out using USP 24 paddle dissolution instrument. 0.05 M phosphate buffer (pH 6.8) containing 1% sodium lauryl sulfate was used as the dissolution medium\(^6\).

**RESULTS AND DISCUSSIONS**

**Preformulation studies**

**Melting point**

Melting point was found to be 179\(^\circ\) C which confirms the identification of drug.

**Selection of analytical wave length and calibration of standard curve**

The diluted stock solution was scanned for maximum wavelength and it was found to be 257 nm, which was selected as the maximum wavelength for further studies.
Solubility study
Solubility of olmesartan medoxomil in different solvent was done, forms turbidity in water and ethanol, sparingly soluble in methanol and acetic acid.

IR spectra interpretation
The IR spectral interpretation shows that the spectra obtained from the formulation matches with original spectra of drug. Similarly characteristic peaks, for the polymers were also noticed in the formulation spectrum. There was no change of any characteristic peaks which confirms that the absence of chemical interaction between the drug and polymers.

Preparation of olmesartan medoxomil nanoparticle
OLM-nanoparticle was prepared using chitosan and sodium alginate as polymer, tripolyphosphate as cross linking agent and calcium chloride as stabilizer along with solvent of water and acetic acid by ionic gelation technique.

Particle size analysis of prepared nanoparticles
The OLM nanoparticles were analyzed by Malvern Zeta.Sizer after suitable dilution with water.

Table: 1 Particle size of olmesartan medoxomil nanoformulations

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Size (nm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OLM 1</td>
<td>1944</td>
</tr>
<tr>
<td>OLM 2</td>
<td>7690</td>
</tr>
<tr>
<td>OLM 3</td>
<td>1800</td>
</tr>
<tr>
<td>OLM 4</td>
<td>4240</td>
</tr>
<tr>
<td>OLM 5</td>
<td>940</td>
</tr>
<tr>
<td>OLM 6</td>
<td>849</td>
</tr>
<tr>
<td>OLM 7</td>
<td>1272</td>
</tr>
<tr>
<td>OLM 8</td>
<td>810</td>
</tr>
<tr>
<td>OLM 9</td>
<td>633</td>
</tr>
<tr>
<td>OLM 10</td>
<td>683</td>
</tr>
</tbody>
</table>

The particle size was found to be 633 nm for OLM 9 and 7690 nm for OLM 2 formulations respectively. Other formulations were between these size ranges. OLM 9 was selected for further studies due to its size of 633 nm and its surface charge of zeta potential was positive (15.7 mv) for OLM 9 formulation which indicates there was a uniform distribution of particles. So formulation OLM 9 was selected as best formulation because of its size and zeta potential.

Lyophilization to convert solid form of olmesartan medoxomil nanoparticle
The prepared nano suspension of OLM 9 were subjected to lyophilisation by using Lyodol freeze dryer and the temperature was maintained at - 40° C for 24 hours, which shows that the lyophilized nano particle powdered were free flowing, non sticky and free from aggregates while viewing through naked eye, which indicates the process used for formulation was good.

SEM study
Morphological studies of olmesartan medoxomil nanoparticles were conducted by SEM. The SEM images indicate that nano particles were within the nano range and with different shapes of particles without clusters.

Drug content
Lyophilized nano particles of olmesartan medoxomil OLM-9 were prepared as super saturated solution by dissolving excess of solute in methanol as solvent. This solution was filtered using whatmann filter paper and filtrate was analysed at 257 nm using UV spectroscopy after suitable dilution. The drug content was found to be 9.75 mg in 100mg of formulation and it was calculated for the equivalent dose of 20mg of olmesartan medoxomil in 205 mg of OLM-9 formulation.

Tablet punching
Tablets were punched using lyophilized nano formulation of Olmesartan medoxomil OLM-9 with HPMC-K10 as polymer and tale, magnesium stearate were excipients using 13mm punch and die.
Evaluation of olmesartan medoxomil nanoparticulate tablets

The prepared lyophilised nanoparticulate tablets of olmesartan medoxomil OLM-9 were evaluated for weight variation, appearance, friability, hardness, drug content uniformity, disintegration time and dissolution. The diameter of olmesartan medoxomil nanoparticulate tablet was found to be 13 mm. The thickness of olmesartan medoxomil nanoparticulate tablet was found to be 3.6 mm. The weight variation of tablet was found to be 300 ± 0.05mg. The appearance of tablet was regular, flat surface with an embossing breakline on one side and the other side is flatness. The friability of olmesartan medoxomil nanoparticulate tablet was noted as 0.95%. The average hardness of the tablet was found to be 5.1 kg ± 0.05, which was near to the IP limit. The above parameter for tablet formulation shows that the prepared lyophilized nanoparticulate tablets of olmesartan medoxomil comply within the IP limits.

Drug content uniformity of tablets

300 mg weight of OLM-9 tablet containing 19.56 ± 0.53 mg of olmesartan medoxomil which conforms suitability of method of preparation.

Disintegration test

The disintegration time of uncoated olmesartan medoxomil nanoparticulate OLM-9 of 6 tablets was within 12 minutes, which passes the test.

Dissolution study of olmesartan medoxomil

OLM-9 formulation and marketed formulation M were studied for its release character which was found to be 99% drug release at the end of 20 minutes for OLM-9 and 92.5% drug release for formulation M at the end of 60 minutes. The release study indicates that the formulation OLM-9 has shown higher amount of drug release when compared to marketed formulation with fast rate of release which shows that 3 fold increase in dissolution rate of lyophilized nano particles of olmesartan medoxomil by ionic gelation technique when compared to marketed formulation. This confirms the improvement of in vitro bioavailability of olmesartan medoxomil by ionic gelation techniques for nanoparticulate preparations.

Table: 2 Comparison of in vitro release profile of marketed formulation and olmesartan medoxomil nano particle (OLM-9) Tablets

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Marketed formulation (%)</th>
<th>OLM-9nano formulation (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>10.5 ± 2.54</td>
<td>42 ± 2.59</td>
</tr>
<tr>
<td>10</td>
<td>19.55 ± 2.58</td>
<td>75 ± 2.58</td>
</tr>
<tr>
<td>20</td>
<td>34.5 ± 2.56</td>
<td>99</td>
</tr>
<tr>
<td>30</td>
<td>69 ± 2.81</td>
<td>99</td>
</tr>
<tr>
<td>45</td>
<td>75 ± 2.59</td>
<td>99</td>
</tr>
<tr>
<td>50</td>
<td>84 ± 2.58</td>
<td>99</td>
</tr>
<tr>
<td>60</td>
<td>93 ± 2.95</td>
<td>99</td>
</tr>
</tbody>
</table>

CONCLUSION

The present study concludes that the drug olmesartan medoxomil in nanoparticulate drug delivery system of ionic-gelation technique yields nanosize of particles with good zeta potential and SEM analysis also confirms the surface morphology of nanoparticles with free of clusters. The formulation OLM-9 of olmesartan medoxomil nanoparticles were compressed into tablets and it complies with IP standard for tablet. In vitro release study of OLM-9 formulation confirms its enhancement of in vitro bioavailability by 3 fold, when compared to marketed formulation M.

ACKNOWLEDGEMENT:

The authors are thankful to Spansules Pharmatech Pvt Ltd, Hyderabad, for providing gift samples of olmesartan medoxomil for the study.

REFERENCES


Source of support: Nil, Conflict of interest: None Declared