RESEARCH PAPER TITLE - FORMULATION AND EVALUATION OF SPHERICAL AGGLOMERATES OF CANDESARTAN CILEXETIL BY SOLVENT CHANGE METHOD

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Abstract
Candesartan cilexetil, exhibits poor water solubility, poor flowability and poor dissolution. Study was directed to improve the dissolution of Candesartan cilexetil. Spherical agglomerates containing Candesartan cilexetil was prepared by solvent change method. By using ternary phase diagram ratio of solvent addition was maintained. Drug was dissolved in methanol (good solvent), water (poor solvent), dichloromethane (bridging liquid) was used in the preparation. The produced drug particles were characterized by scanning electron microscopy (SEM), differential scanning calorimeter (DSC), x-ray diffraction (XRD) and Fourier transform infrared spectroscopy (FT-IR). In vitro dissolution study of prepared particle was carried out. It was found that dissolution profiles of batch B2 were increased. Further micromeritic properties were also increased. It was realized that appropriate amount of polymer addition along with highest speed will give better drug release.

Key words- Spherical agglomerates, DSC, SEM, XRD, FT-IR, in vitro dissolution, etc.

Introduction
In most of the formulations available in market drugs are directly used in the formulation as it is. However there are some other drugs that require modification in their physical, chemical and morphological characters. After changing such modification these drugs will become suitable to be used in the formulation.[1] Many of the drug in the market are come under BCS class 2 having poor solubility in water and less dissolution profile. Due to this problem effective concentration of drug is not achieved. To overcome these problems many solubility enhancement methods are used to increase the dissolution profile of drug.[3,4] Spherical agglomeration is one of the novel technique used to increase the solubility and dissolution rate of poorly soluble drugs. Spherical agglomeration process further helps to improve the flowability and compressibility of drug.[1,2]

Spherical agglomeration is multiple unit process in which crystallization, agglomeration and spheronization can be carried out simultaneously.[8] Formulated crystals can be called as spherical agglomerates. Spherical crystallization technique has been successfully utilized for improving of flowability and compressibility of drug. These technique may enable crystalline forms of a drug to be converted into different polymeric form having better bioavailability.[9]

Spherical agglomeration is a novel particle design method developed by Kawashima et.al. It is also come under particle engineering technique in which crystallization and agglomeration carried out simultaneously.[11] Many of the drugs administered by oral route because oral route administration is most convenient route for solid dosage forms. The basic requirement for commercial production of tablet is that material to be tabulated should have a good flowability, mechanical strength and compressibility. Hence it is necessary to evaluate and manipulate the above said properties. To impart these properties the drugs are subjected to particle design techniques such as spherical crystallization. Formulated agglomerates will improve the flowability and compressibility of drug which enables the direct tabletting of drug. It also minimizes the process in tabletting like mixing, granulation, drying and sieving etc. There are main four principle steps involved in the process of spherical crystallization like - 1) flocculation zone, 2) zero growth...
zone, 3) fast growth zone, 4) constant size zone.[11,12] Direct tabletting is preferred process for spherical agglomerates. It will minimize the cost of production and save time as compared to granule tabletting.

There are different methods of preparation of spherical agglomerates like
1) Solvent change method
2) Quasi emulsion solvent diffusion method
3) Ammonia diffusion method
4) Neutralization method
5) Traditional crystallization process
6) Crystallo-co-agglomeration

A saturated solution of drug in a good solvent is poured in bad solvent. The good solvent and poor solvent are freely miscible in each other.[2] In these method a third solvent bridging liquid is added in above mixture in small amount to induce and promote the formation of agglomerates. Depending upon the addition of amount of bridging liquid and speed of rotation the size of agglomerates vary. If speed of rotation in the formulation is increased then small size of agglomerates will formed and if speed will low particle size will be increased.[7,10] Also if less amount of bridging liquid is added in the mixture then large size particle are formed and if more amount of bridging liquid is added then small size particle will be formed. It is always necessary to maintain the ternary phase diagram ratio at the time of addition of three solvents.

Materials and methods
Candesartan cilexetil was obtained as a gift sample from Lupin Pharma, Aurangabad. Polyvinyl-Pyrrolidone K-30, dichloromethane and methanol were obtained from Research-Lab Fine Chemicals, Mumbai.

Preparation of spherical agglomerates of Candesartan cilexetil
Physical mixture of Candesartan cilexetil is prepared by dissolving 1 gm of drug in 50 ml of methanol then respective amount of PVP-K30 (as per batch) has been dissolved in 40 ml of water then first solution was poured into polymeric mixture given precipitate. These solutions are kept for stirring on mechanical stirrer for 1 hr. (as per respective rpm) during stirring 10 ml of dichloromethane (Bridging liquid) was added dropwise. Addition of Bridging liquid leads to formation of spherical agglomerates which were(after 1 hr) separated by filtration & dried at temperature for 24 hrs.

<table>
<thead>
<tr>
<th>Sr. no.</th>
<th>Batch no.</th>
<th>Candesartan cilexetil (gm)</th>
<th>PVP-K30 (gm)</th>
<th>Speed (rpm)</th>
<th>Drug:polymer</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>B1</td>
<td>1</td>
<td>3</td>
<td>600</td>
<td>1:3</td>
</tr>
<tr>
<td>2</td>
<td>B2</td>
<td>1</td>
<td>1</td>
<td>600</td>
<td>1:1</td>
</tr>
<tr>
<td>3</td>
<td>B3</td>
<td>1</td>
<td>3</td>
<td>400</td>
<td>1:3</td>
</tr>
<tr>
<td>4</td>
<td>B4</td>
<td>1</td>
<td>1</td>
<td>400</td>
<td>1:1</td>
</tr>
</tbody>
</table>

a. Determination of λ max
Stock solution of 100µg/ml was prepared by adding 10 mg of pure Candesartan cilexetil in 100 ml of solvent methanol. Stock solution (1 ml) was diluted to 10 ml of methanol to make 10µg/ml solution. This solution was filtered and scanned in UV spectrum at 200-400nm range. The maximum absorbance was recorded.

b. Percentage practical yield
Percentage practical yield (PY) was determined to measure the efficiency of method. This will also help in selection of appropriate method of production.

Practical yield (%) = "practical weight" /"theoretical weight" × 100

c. Determination of % drug content
Spherical agglomerates equivalent to 32 mg of Candesartan cilexetil were weighed accurately and dissolved in suitable quantity of solvent mixture methanol. The drug content was determined at 217 nm by UV spectrophotometer. Each sample analyzed in triplicate. The percent drug content was determined using the following equation:

% Drug content = (Practical drug content )/(Theoretical drug content ) × 100

d. Fourier transform infrared spectroscopy (FTIR):
FTIR has been used to assess the interaction between drug and carrier molecules in the solid state. Infrared spectra of agglomerated powder were obtained using FTIR spectrometer (FTIR Jasco 4100). About 2-4 mg of moisture free agglomerated sample was mixed with dry potassium bromide and FTIR spectra were obtained by KBr pellet method at 400-4000 cm-1 scanning range.
e. Powder X-ray diffraction:
To evaluate the crystallinity of Candesartan cilexetil the PXRD study was carried out by using X ray diffractometer. Powder X-ray diffraction patterns were recorded on Brucker D2 Phaser X-diffractometer.

f. Scanning Electron Microscopy (SEM):
SEM of Spherical agglomerates was carried out using JSM 6360, JEOL India Pvt. Ltd. to study the morphological characteristics of the optimized batch of agglomerates.

g. In-vitro dissolution studies of Prepared Spherical Agglomerates:
In-vitro dissolution studies of Spherical agglomerates of Candesartan cilexetil were carried out for 60 minutes using USP Dissolution test apparatus type II (Lab India DS8000, eight stages) at 50 rpm. Spherical agglomerates equivalent to 32 mg of Candesartan cilexetil was used for dissolution studies at 37±0.5°C in 900ml of pH 6.8 buffers as dissolution medium. Aliquots equal to 5 ml was withdrawn at regular time intervals (10, 20, 30, 40, 50, 60 mins), an equal volume of fresh dissolution medium was replaced to maintain the sink condition and aliquots were measured at 257 nm UV/Visible spectrophotometer. The dissolution studies were conducted in triplicate and the mean values were plotted versus time.[4]

Result and discussion
a. Physical and chemical parameters
- Color – white
- Odor – odorless
- Taste – tasteless
- State – white crystalline powder, fine powder. Etc.
- Solubility – freely soluble in methanol, dichloromethane, insoluble in water.
- Melting point- 174°C

b. Determination of $\lambda_{\text{max}}$ of Candesartan cilexetil
The standard solution of Candesartan cilexetil of concentration 10µg/ml showed maximum absorbance at the wavelength 217 nm.fig 1. Shows $\lambda_{\text{max}}$ of Candesartan cilexetil.[5]

c. Percentage practical yield
The results of percent practical yield studies are shown in table.2. The percent practical yield of the prepared spherical agglomerates by solvent change method is noted. It was found that solvent change method gives the practical yield in the range of 45 – 71%. The maximum yield was found 71.20% in batch B4 Batch.

table no.2. percentage practical yield of spherical agglomerates

<table>
<thead>
<tr>
<th>Sr .no.</th>
<th>Batch code</th>
<th>Percentage yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>B1</td>
<td>45.55</td>
</tr>
<tr>
<td>2</td>
<td>B2</td>
<td>65.41</td>
</tr>
<tr>
<td>3</td>
<td>B3</td>
<td>41.87</td>
</tr>
<tr>
<td>4</td>
<td>B4</td>
<td>71.20</td>
</tr>
</tbody>
</table>
d. Determination of % drug content

The drug content in spherical agglomerates by solvent change method was found to be maximum. Data is shown in table no.3. Drug content was found to be 60% - 85% suggesting solvent change method has good encapsulation of the drug.

<table>
<thead>
<tr>
<th>Sr.no.</th>
<th>Batch code</th>
<th>% Drug content</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>B1</td>
<td>69.23</td>
</tr>
<tr>
<td>2</td>
<td>B2</td>
<td>75.56</td>
</tr>
<tr>
<td>3</td>
<td>B3</td>
<td>64.35</td>
</tr>
<tr>
<td>4</td>
<td>B4</td>
<td>85.11</td>
</tr>
</tbody>
</table>

e. FTIR spectra of Candesartan cilexetil

The IR spectra of Candesartan cilexetil shows broad peak at 2866.67 cm\(^{-1}\) and 2938.98 cm\(^{-1}\). It belongs to the valance vibration of the C-H bonds in the CH and CH\(_2\) groups. It shows broad peak at 1753.94 cm\(^{-1}\) it belongs to the C-O str of carboxylic acid. Spectra of Candesartan cilexetil shows some peaks at 1611.23 cm\(^{-1}\) and 1472.32 cm\(^{-1}\) it shows presence of aromatic ring containing C-C str bonding. Some of the peaks are visualized at 1345 cm\(^{-1}\) to 1238 cm\(^{-1}\) it indicates that presence of carboxylic acid esters and ethers with C-O str bonding. Last peak is visualized at 1075.12 cm\(^{-1}\) it belongs to the primary and secondary amine. Fig.2 shows FTIR spectra of Candesartan cilexetil in the range of 4000 cm\(^{-1}\) to 400 cm\(^{-1}\).

![Fig. 2. FTIR spectra of Candesartan cilexetil](image)

The IR spectra of PVP-K30 (Fig. No.3) shows 2857.02 cm\(^{-1}\) (C-H stretching vibrations), 1609.31 cm\(^{-1}\) (C = O Carbonyl stretching), and 1238.08 cm\(^{-1}\) (C-N stretching vibrations).

The results revealed no considerable changes in the IR peaks of Candesartan cilexetil, when mixed with polymer PVP-K30. These observations indicated the compatibility of PVPK30 with Candesartan cilexetil. The FTIR spectrum of PVP-30 and Candesartan cilexetil is in Fig. No.3. IR spectra indicated no well-defined interaction between the drug and polymer.

![Fig. 3. FTIR spectra of Candesartan cilexetil and PVP-K30](image)
f. Powder X-ray diffraction study (XRD)

The presence of numerous distinct less diffused peaks in the X-Ray diffraction spectrum indicates that Candesartan cilexetil present as a crystalline material. Sharper diffraction peaks indicate more crystallize the drug. The powder XRD of Candesartan cilexetil is shown in Fig.no.4.

![XRD Graph of Candesartan Cilexetil](image)

**fig. no.4: XRD graph of candesartan cilexetil**

g. Scanning electron microscopy (SEM)

The optimized batch of spherical agglomerates of B1 to B4 was analyzed under optical microscopy. It shows spherical shaped agglomerates having good crystallinity as well as round and ball like shapes. The smallest particle visualized under SEM was near about size 201.69µm and the largest particle size was 445.23 µm. fig no.5,6,7,8. Indicates that images of spherical agglomerated batch B1 to B4 respectively.

![SEM Images of Spherical Agglomerates](image)

**fig no.5. SA batch B1**  
**fig no.6. SA batch B2**
**h. In-vitro dissolution studies of Prepared Spherical Agglomerates:**

The dissolution profile of prepared spherical agglomerates was shown in the table no.4. Dissolution profile of prepared agglomerates is compared with pure drug. Because of presence of polymer PVP k-30 dissolution of Candesartan cilexetil in the agglomerates which increases dissolution rate. The prepared batches of agglomerates in that Batch B2 and B4 shows dissolution rate up to 73.12% and 70.31% respectively.

<table>
<thead>
<tr>
<th>Sr. No</th>
<th>Time (min)</th>
<th>Pure drug</th>
<th>% Cumulative drug release</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>B1</td>
<td>B2</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>0.00±0.00</td>
<td>0.00±0.00</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>3.54±0.001</td>
<td>12.65±0.02</td>
</tr>
<tr>
<td>3</td>
<td>20</td>
<td>7.65±0.021</td>
<td>20.39±0.01</td>
</tr>
<tr>
<td>4</td>
<td>30</td>
<td>11.24±0.4</td>
<td>30.23±0.04</td>
</tr>
<tr>
<td>5</td>
<td>40</td>
<td>16.80±0.21</td>
<td>35.85±0.02</td>
</tr>
<tr>
<td>6</td>
<td>50</td>
<td>20.54±0.101</td>
<td>55.54±0.03</td>
</tr>
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</table>

**Conclusion**

Due to the poor water solubility of Candesartan cilexetil it exhibited only 20.45% dissolution rate in the 50 min. However in comparison the prepared batches of spherical agglomerates demonstrated increased dissolution rate as compared to the pure drug. Due to the incorporation of hydrophilic polymer all batches shows enhanced dissolution rate as well as solubility.[3,5,6]

From these above data it was found that batch B2 gives highest % cumulative drug release i.e.73.12%. & thus same batch was considered as optimized batch. Small particle size correlated for high dissolution rate.
Also there is a large effect on the addition amount of bridging liquid in the mixture. Rotation Speed in the process is also having great effect on the size of the particle. High speed process produces small sized particles or agglomerates which is having better dissolution result shown in batch B4.

Acknowledgement

I am thankful to my research guide Dr. Manoj Nitalikar for guiding me and encouraging me at every step of my research work. I am thankful to Lupin Pharm. Aurangabad and Research Lab-fine chemicals Mumbai for supplying drugs and excipient.

References


