10. Summary and conclusions
SUMMARY

Spherical crystallization is a particle design technique, by which crystallization and agglomeration can be carried out simultaneously in one step. Moreover this modification of crystal habit also results in the modification of certain physicochemical properties as solubility, bioavailability and flowability of pharmaceutical ingredients. The flowability of drugs having poor flowability can be improved by imparting spherical shape to them. Prepared spherical agglomerates show increases in specific surface area which increases the dissolution rate and bioavailability. This method may also be used to increase the solubility of poor water soluble drug.

The present study was undertaken to develop spherical agglomerates of two BCS class II drugs Mebendazole and Lovastatin with a view to enhance their solubility, dissolution rate and flowability.

Mebendazole (MBZ) is practically insoluble in water. Only 10% of the MBZ is absorbed after oral administration. MBZ also shows poor flowability due to its needle shaped crystal habit and electrostatic charge.

Lovastatin (LVS) is also having poor water solubility. The oral bioavailability of lovastatin is approximately 5% and highly variable. Lovastatin shows poor flowing properties.

The present work describes the preparation of spherical agglomerates of both drugs by different techniques as follows:

I. Spherical agglomerates of MBZ were prepared using Quasi Emulsion Solvent Diffusion method

II. Spherical agglomerates of MBZ were prepared using modified SAXS method

III. Spherical agglomerates of MBZ were prepared using modified EPAS method

IV. Spherical agglomerates of LVS were prepared using solvent evaporation method
I. Preparation and characterization of spherical agglomerates of Mebendazole using Quasi-Emulsion Solvent Diffusion Method

- A quasi-emulsion solvent diffusion method was adopted for preparation of spherical agglomerates of MBZ using formic acid as a good solvent and water as a poor solvent. Glycerine was added to the solution of MBZ to increase the viscosity of the internal phase.

- Preliminary trials were taken to identify significant factors affecting formation of spherical agglomerates.

- A $3^3$ full factorial design was employed to study the effect of following independent variables at the three different levels on the characteristics of the product obtained. They are
  - Volume of formic acid (internal phase)
  - % v/v of glycerine in internal phase
  - Volume of water (external phase)

- Experimental trials were performed at all possible 27 combinations in triplicate and the resultant product obtained was evaluated for parameters: Volume Mean Diameter (VMD), Uniformity index, Hausner ratio, Carr’s index and amount of the drug dissolved in 60 minutes $C_{60}$.

- The process does not induce any chemical change in MBZ as evident from the comparison of FTIR spectra of the drug and the agglomerates prepared from the drug.

- Spherical agglomerates batches showed VMD greater than that of the drug indicating that formation of agglomerates had taken place.

- The agglomerates obtained were free flowing and spherical in shape as from scanning electron micrographs.

- All the batches of spherical agglomerates exhibit UI greater than 1.2 (maximum 1.29). Thus, PSD of spherical agglomerates may be described as nearly monodisperse.

- Spherical agglomerates showed improvements in the flowability and compressibility. It was concluded that spherical agglomerates with good flowability (low value of HR & %C) and with good dissolution (high value of
C$_{60}$ can be prepared by taking the low volume of internal phase & high % of glycerine in it as well as low volume of external phase.

- XRD indicates that MBZ get transformed to less crystalline form during spherical agglomeration process.
- No significant difference in DSC pattern of spherical agglomerates and pure MBZ suggests that the spherical agglomeration process did not induce interaction at the molecular level.
- The yield of various batches was found in the range of 65-70%.
- It is evident from the table that batch M7 has highest OD value. This can be called as the best batch amongst all 27 batches prepared.
- The checkpoint analysis showed no significant difference (p>0.05) was observed between calculated and experimental values of HR, %C and C$_{60}$ as shown in the checkpoint batches prepared which establishes the validity of the equation.

II. Preparation and characterization of spherical agglomerates of Mebendazole using modified SAXS method

- A modified SAXS method was adopted for preparation of spherical agglomerates of MBZ using formic acid as a good solvent and water as a poor solvent.
- Preliminary trials were taken for the preparation of spherical agglomerates of MBZ by employing two conditions viz. spraying along with sonication and spraying without sonication. The sonication was applied either continuous or pulsed manner.
- A 3$^2$ full factorial design was employed to study the effect of following two independent variables at three different levels on the characteristics of the product obtained. They are
  - Concentration of MBZ
  - Volume of water (external phase)
- Experimental trials were performed at all possible 9 combinations in triplicate and the resultant product obtained was evaluated for parameters: Volume Mean Diameter (VMD), Uniformity index, Hausner ratio, Carr’s index and amount of the drug dissolved in 60 minutes C$_{60}$. 
The process does not induce any chemical change in MBZ as evident from the comparison of FTIR spectra of the drug and the agglomerates prepared from the drug.

Spherical agglomerates batches also showed VMD greater than that of the drug indicating that formation of agglomerates had taken place.

The agglomerates obtained were free flowing and spherical in shape as from scanning electron micrographs.

All the batches of spherical agglomerates exhibit UI greater than 1.2 (maximum 1.67). Thus, PSD of spherical agglomerates may be described as nearly monodisperse.

Spherical agglomerates showed improvements in the flowability and compressibility. It was concluded that spherical agglomerates with good flowability (low value of HR & %C) and with good dissolution (high value of $C_{60}$) can be prepared by taking the low concentration of drug & high volume of external phase-water.

XRD indicates that MBZ get transformed to less crystalline form during spherical agglomeration process.

No significant difference in DSC pattern of spherical agglomerates and pure MBZ suggests that the spherical agglomeration process did not induce interaction at the molecular level.

The yield of various batches was found in the range of 65-70%. It is evident from the table that batch U6 has highest OD value. This can be called as the best batch amongst all 9 batches prepared.

The checkpoint analysis showed no significant difference ($p>0.05$) was observed between calculated and experimental values of HR, %C and $C_{60}$ as shown in the checkpoint batches prepared which establishes the validity of the equation.

### III. Preparation and characterization of spherical agglomerates of Mebendazole using modified EPAS method

A modified EPAS method was adopted for preparation of spherical agglomerates of MBZ using formic acid as a good solvent and water as a poor solvent.
Preliminary trials were taken for the preparation of spherical agglomerates of MBZ in which the effect of various variables were studied.

A $3^2$ full factorial design was employed to study the effect of following two independent variables at the three different levels on the characteristics of the product obtained. They are
- Concentration of MBZ
- Volume of water (external phase)

Experimental trials were performed at all possible 9 combinations in triplicate and the resultant product obtained was evaluated for following parameters: Volume Mean Diameter (VMD), Uniformity index, Hausner ratio, Carr’s index and amount of the drug dissolved in 60 minutes $C_{60}$.

The process does not induce any chemical change in MBZ as evident from the comparison of FTIR spectra of the drug and the agglomerates prepared from the drug.

Spherical agglomerates batches also showed VMD greater than that of the drug indicating that formation of agglomerates had taken place.

The agglomerates obtained were free flowing and spherical in shape as from scanning electron micrographs.

All the batches of spherical agglomerates exhibit UI greater than 1.2 (maximum 1.53). Thus, PSD of spherical agglomerates may be described as nearly monodisperse.

Spherical agglomerates showed improvements in the flowability and compressibility. It was concluded that spherical agglomerates with good flowability (low value of HR & %C) and with good dissolution (high value of $C_{60}$) can be prepared by taking the high concentration of drug & low volume of water.

XRD indicates that MBZ get transformed to less crystalline form during spherical agglomeration process.

No significant difference in DSC pattern of spherical agglomerates and pure MBZ suggests that the spherical agglomeration process did not induce interaction at the molecular level.
The yield of various batches was found in the range of 61-63%. It is evident from the table that batch E7 has highest OD value. This can be called as the best batch amongst all 9 batches prepared.

The checkpoint analysis showed no significant difference (p>0.05) was observed between calculated and experimental values of HR, %C and C<sub>60</sub> as shown in the checkpoint batches prepared which establishes the validity of the equation.

The following table shows the comparison of MBZ and its prepared spherical agglomerates by the above three different methods.

<table>
<thead>
<tr>
<th></th>
<th>% YIELD</th>
<th>HR</th>
<th>%C</th>
<th>C&lt;sub&gt;60&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>MBZ</td>
<td>-----</td>
<td>1.60±0.01</td>
<td>37.5±0.40</td>
<td>50.50±0.40</td>
</tr>
<tr>
<td>ESD produced MBZ</td>
<td>65±3 to 70±4</td>
<td>1.08±0.00 to 1.50±0.01</td>
<td>07.41±0.00 to 33.33±0.45</td>
<td>56.12±0.80 to 68.83±0.60</td>
</tr>
<tr>
<td>SAXS produced MBZ</td>
<td>64±3 to 70±3</td>
<td>1.25±0.00 to 1.50±0.02</td>
<td>20±0.00 to 33.33±0.45</td>
<td>59.3±0.2 to 74.1±0.6</td>
</tr>
<tr>
<td>EPAS produced MBZ</td>
<td>61±2 to 64±3</td>
<td>1.28±0.00 to 1.45±0.02</td>
<td>21.88±0.00 to 31.03±0.02</td>
<td>60.2±0.01 to 71.5±0.03</td>
</tr>
</tbody>
</table>

In GCMS report of formic acid 500 PPM, no sharp peak was observed. So, it was difficult to compare the GCMS report of formic acid with spherical agglomerates of batch M7, U6 and E7. The concentration of formic acid used in the processes was less than 5000 ppm. Besides this, formic acid is also present in the food materials in high concentration. So, the formic acid used here is not having any toxicity due to residual effect on the product.
IV. Preparation and characterization of spherical agglomerates of Lovastatin using solvent evaporation method

- Preliminary trials were taken for the preparation of spherical agglomerates of LVS using dichloromethane as a good solvent and water as a poor solvent.
- Here, seven variables were identified which may influence the product characteristics. They are concentration of drug, volume of dichloromethane, volume of water, rate of addition of drug solution, stirring time, concentration of PVA and stirring speed. Plackett Burman design (screening design) was employed to identify significant factors. From the results of total eight runs, it was found that concentration of drug, volume of water (external phase), stirring speed and stirring time influenced the product characteristics.
- A $2^4$ full factorial design was employed to study the influence of these four independent variables on the dependent variables Hausner ratio, Carr’s index and $C_{60}$ (% drug dissolved in 60 minutes). Four independent variables were taken at two levels.
- The process does not induce any chemical change in LVS as evident from the comparison of FTIR spectra of the drug and the agglomerates prepared from the drug.
- Spherical agglomerates batches also showed VMD greater than that of the drug indicating that formation of agglomerates had taken place.
- The agglomerates obtained were free flowing and spherical in shape as from scanning electron micrographs. All the batches of spherical agglomerates exhibit UI greater than 1.2 (maximum 1.79). Thus, PSD of spherical agglomerates may be described as nearly monodisperse.
- Spherical agglomerates showed improvements in the flowability and compressibility. It was concluded that spherical agglomerates with good flowability (low value of HR & %C) and with good dissolution (high value of $C_{60}$) can be prepared by taking the lower concentration of drug and higher concentration of PVA.
- XRD indicates that LVS get transformed to less crystalline form during spherical agglomeration process.
No significant difference in DSC pattern of spherical agglomerates and pure LVS suggests that the spherical agglomeration process did not induce interaction at the molecular level.

The yield of various batches was found in the range of 54-69%. It is evident from the table that batch L4 has highest OD value. This can be called as the best batch amongst all 16 batches prepared.

The checkpoint analysis showed no significant difference (p>0.05) was observed between calculated and experimental values of HR, %C and C60 as shown in the checkpoint batches prepared which establishes the validity of the equation.

**CHARACTERISTICS OF LVS AND ITS SPHERICAL AGGLOMERATES**

<table>
<thead>
<tr>
<th>% YIELD</th>
<th>HR</th>
<th>%C</th>
<th>C60</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVS</td>
<td>1.43±0.01</td>
<td>30±0.1</td>
<td>25.10±0.20</td>
</tr>
<tr>
<td>Solvent evaporation produced LVS</td>
<td>1.1±0.06 to 1.35±0.04</td>
<td>9.09±0.6 to 25.93±0.7</td>
<td>25.5±0.63 to 47.4±0.62</td>
</tr>
</tbody>
</table>

Spherical agglomerates of batch L4 showed 61.45 PPM of DCM as from GCMS report which is very lower than the limit of DCM (500 PPM).

**CONCLUSION**

The spherical agglomerates of MBZ and LVS prepared by the different methods showed improvement in the various properties like flowability, compressibility, dissolution etc. The developed methods can be used for a wide range of drug molecules which shows poor flowability, poor compressibility and poor solubility. The method can be used as a last step in the bulk drug manufacturing to modify the properties of the various drug molecules.