Formulation Development of Porous Mannitol carrier: Improving the dissolution of poorly soluble drugs

Sharmila Shah, Roshan Bodhe, Ashish Gorle

ABSTRACT

Major challenges in the design of oral dosage forms are their low solubility and low bioavailability. Improving the dissolution of these oral dosage forms are one of the most challenging tasks for the formulation scientists as most of the drug candidates are highly lipophilic in nature. Telmisartan and Ezetimibe belong to the BCS class II, having high lipophilicity, poor water solubility and poor dissolution. The objective of this work was to improve the dissolution rate of poorly water soluble drugs by using porous carrier drug delivery system. Templating based spray drying methodology was used to prepare porous mannitol. Drug (Telmisartan, Ezetimibe) loaded porous mannitol carriers then characterized by P-XRD, DSC, SEM, BET surface area analysis and ATR-FTIR. ATR-FTIR studies showed complete removal of templating agent from carrier. P-XRD and DSC studies confirmed nano-confinement of drug in crystalline form. In vitro dissolution study results indicated that porous mannitol prepared using tartaric acid as templating agent showed significant improvement in dissolution rate than pure drugs and respective physical mixtures. These results suggest that, these porous carriers can be useful as drug carriers for improving the dissolution of lipophilic drugs.

Keywords: Templating agent, Spray drying, Mannitol, Surface area, Tartaric acid.

1. INTRODUCTION

Major challenges in the design of oral dosage forms are their low bioavailability. Poor solubility is one of the main causes of low bioavailability. More than 40% of newly developed drugs in the pharmaceutical industry are belong to class II and class IV of biopharmaceutical classification system (BCS). Improving the dissolution of these API is one of the most challenging tasks for the formulation scientists as most of the drug candidates originating from discovery are highly lipophilic in nature. In order to tackle problems related to solubility and dissolution, various approaches like micronization, nanosuspension, amorphous solid dispersion, cyclodextrin complexation, salt forms, solvates forms, mesoporous silica carriers have been explored till now. The above approaches also have some limitations like agglomeration after micronization, stability problems with nanosuspension, bulkiness of cyclodextrin complexes, Chances of phase transformation to crystalline state during processing and storage of amorphous solid dispersions.

Adsorption of drug on the silica materials to improve dissolution of poorly soluble drug is a novel approach. There is increasing interest in these potential carriers due to some of the interesting features such as large surface area, pore volume, controllable structural and textural parameters. However, these parameters may attribute to low bulk density, Hygroscopicity, and poor flow properties leading to issues in tabletting process. Further, this large pore volume and higher surface area may not be suitable to load low dose drugs as it may lead to problem in content uniformity. Therefore, the lack of down-stream process understanding of mesoporous silica to improve powder flow, compression and compaction properties while maximizing the dose, necessary for an oral dosage form was the driving force of this research.

Recently reported methodology to prepare porous lactose using template assisted spray drying technique. The surface area and pore size distribution were less as compared to mesoporous carriers. The authors reported improvement in
dissolution of few drugs like acetaminophen, indomethacin and nifedipine. However, the effect of hydrophobic carriers on the dissolution and effect of solid state transition of drug (that may possible during loading procedure) is not taken into consideration. Hence, the present work was designed to overcome the lacunae present in the literature available. In the present work mannitol was used as carrier material and modified to porous mannitol by using template assisted spray drying technique. The effect of various templating agents, concentrations and combinations on porosity and dissolution rate was evaluated using telmisartan and ezetimibe as model drugs. The hydrophobic drugs have the problem of poor dissolution performance and hence poor bioavailability. Among all approaches used for enhancement of dissolution of poorly water-soluble drugs, porous drug delivery system has gained a lot of attention in last two decades. Mesoporous silica carriers are one of the approach, but it has limitations of low water solubility, Hygroscopicity, compression issues during tableting. Hence, in the present study mannitol was converted to porous carrier that can overcome the above-mentioned issues.

Mannitol as core material and food grade acids and sugars as templating agents. Mannitol is water soluble, biodegradable, biocompatible and mostly used pharmaceutical diluent in solid oral dosage forms. Porous mannitol may offer potential carrier for poorly water-soluble drugs despite their much lower specific surface area and smaller pore volume compared with those of mesoporous silica.

Telmisartan and ezetimibe was selected as a model drug for this study due to their poor aqueous solubility and high lipophilic nature. Thus, making them suitable for the scope of this work.

**FORMULATION AND DEVELOPMENT**

**Method**

**Preparation of Porous Mannitol**

Required quantities of mannitol and templating agents (citric acid/tartaric acid) were taken and dissolved in specific quantity of Milli Q water, kept under stirring for 30 min. at room temperature to obtain clear solution. The clear solution was spray dried on spray dryer (JSL, Mumbai) with an inlet and outlet temperature of 140 °C and 60 °C respectively, aspirator rate of 1200 RPM, feed pump of specific RPM, and atomization pressure of 2kg/cm². The ethanol-soluble templating agent was removed from the mannitol structure by washing the spray-dried powder with sufficient amount of ethanol under continuous stirring for 24 h at room temperature, followed by vacuum filtration to recover the template-free mannitol. The practical yield of spray dried product was calculated by using following formula:

\[
\text{Practical yield (\%)} = \left( \frac{\text{Total weight obtained}}{\text{Total weight taken}} \right) \times 100
\]

**Drug loading**

Telmisartan was dissolved in mixture of dichloromethane and ethanol (1:1), while Ezetimibe solution was dissolved in acetone. The template free porous mannitol carrier was soaked in these solutions in RBF covered with parafilm with aluminum foil. The solvent was removed by using a rotary evaporator at 40°C temperature under vacuum. Finally, the product was dried in oven for few minutes to remove residual solvent. The percentage drug loading was calculated by using following formula.

\[
\% \text{ Drug loading} = \left( \frac{\text{Amount of drug in formulation}}{\text{Amount of formulation taken}} \right) \times 100
\]

**Determination of drug loading**

Accurately, weighed quantity (5mg) of drug loaded porous mannitol was dissolved in 10mL of methanol and sonicated for 30 minute. The resulting solution was filtered and the filtrates were scanned at (232 nm for Ezetimibe, 296 nm for Telmisartan using a 1 cm cell). The maximum absorbance was determined using UV-visible Spectrophotometer (UV 1700, Shimadzu, Japan) after appropriate dilutions in methanol. The above assay was done in triplicates.

**In vitro dissolution**

Preliminary dissolution studies were performed in USP type II dissolution tester (Electro lab-India, EDT-08Lx, Syringe pump (ESP: 124) and sample collector ESC: 12D) in different dissolution media Table: 1. Load the dissolution program as per parameter reported in table: 2, and allow to achieved the bath temperature 37°C, to determine the discriminating media using pure drugs. Then, the dissolutions of pure drugs, physical mixture and drug loaded porous mannitol was performed in selected dissolution media using parameters given in Table2. Here, physical mixture was prepared by triturating drugs with spray dried mannitol obtained after ethanol wash.

**Table: 1 Dissolution media for telmisartan and ezetimibe**

| Sr.No. | Dissolution media for telmisartan | Dissolution media for Ezetimibe |
|--------|----------------------------------|---------------------------------|
| 1      | Phosphate buffer (pH 7.5) (USP)   | 0.45%SLS in Acetate buffer pH 4.5 (USP) |
| 2      | Phosphate buffer saline (pH 7.4) | 1% SLS in water (IP)             |
| 3      | 0.3%SLS in phosphate buffer saline (pH 7.4) | 0.5% SLS in Water               |
| 4      | 0.2%SLS in phosphate buffer saline (pH 7.4) | 0.3% SLS in Water               |
| 5      | 0.3%SLS in phosphate buffer saline (pH 7.4) | 0.1N Hydrochloric acid (pH 1.2) |
| 6      | 0.1N Hydrochloric acid (pH 1.2) | -                               |
Dissolution Efficiency

The dissolution data obtained was treated to get percentage dissolution efficiency. The percentage DE was calculated at 15, 30, 60 and 120 minutes using the following formula for all the samples and compared. 

%DE = \left( \frac{\int_{t=0}^{t=15} \text{y} \, dt}{Y_{100}} \right) \times 100

Characterization methods

Scanning electron microscopy (SEM)

The morphology of the spray-dried mannitol before ethanol wash, after ethanol wash, drug loaded mannitol and physical mixture was examined by scanning electron microscope (SEM, JEOJ-JSM-IT100 and SEM JOEL-6360LV, Tokyo, Japan). A small amount of sample was placed on an SEM stub using double-sided adhesive tape and coated with gold at 20 mA for 2 minute using an auto fine coater (Ion sputter JFC 1600). After coating, the digital images of the samples at different resolution (2000 x, 4000 x, 8000 x, 10000 x) were obtained by the SEM with secondary electron detector with accelerating voltage 100 kV.

Specific surface area analysis

Specific surface areas of mannitol carrier before and after template removal were determined by using surface area analyzer (SMART SORB 92/93 Smart Instruments Co.(P) Ltd. Mumbai, India). Prior to measurements, weighed sample was regenerated by degassing to remove moisture and contamination. The regenerated sample was dipped in liquid nitrogen and the quantity of the adsorbed gas (70% Nitrogen + 30% Helium) was measured using thermal conductivity detector and then integrated using electronic circuit in terms of counts. The instrument was calibrated by injecting known quantity of nitrogen. The measured parameters were then used to calculate specific surface area of the sample by employing the adsorption theories of Brunauer, Emmett and Teller.

ATR- FTIR Spectroscopy

The chemical structure of Tartaric acid, spray dried mannitol before ethanol wash, after ethanol wash, pure drugs, physical mixtures and drug loaded porous mannitol samples were analysed on Spectrum Two Universal ATR sampling accessory (single reflection diamond) equipped with a LiTaO3 (Lithium tantalate) detector coupled with a PerkinElmer FTIR system. Each sample was placed on ATR sampling device and torque of 80N was applied and spectral scanning was taken in the wavelength region between 4000-700 cm/s with scan speed of 1 cm/s.

X-ray Powder diffraction (PXRD)

PXRD pattern of pure telmisartan, porous mannitol carrier, optimized telmisartan loaded mannitol and solvent precipitated telmisartan were recorded using (MAXima X XRD-7000, Shimadzu, Japan, X-ray diffractometer) operated at a voltage of 40 kV and current of 30 mA using Cu Kα radiation source (1.54 Å) passing through nickel filter with divergence slit (10), scatter slit (10) and receiving slit (0.3 mm) over the angular range (2θ) of 10 – 400 at a rate of 4° min⁻¹ in steps of 0.020 with step time of 0.3 second.

While, PXRD pattern of pure ezetimibe, porous mannitol carrier, optimized ezetimibe loaded mannitol and solvent precipitated ezetimibe were recorded using (PAnalytical Empyrean Netherlands, X-ray diffractometer ) operated at a voltage of 45 kV (current of 30 mAsing Cu Ka) radiation source (1.54 Å), divergence slit (1/4°), fixed mask (10mm), BBHD (BRAGG BRENTANO HD), anti-scatter slit 1° and receiving slit (0 mm) over the angular range (2θ) 5°-90° in step size (28) 0.0260 with scan step time 41.5650 seconds.

Differential scanning calorimetry (DSC)

Thermal analysis of pure drug loaded mannitol and solvent precipitated drugs were recorded on DSC colorimeter (DSC-60, Shimadzu Corporation, Kyoto, Japan).The accurately weighed sample (5 ± 2 mg) hermetically sealed in an aluminium pan (Sample sealer and crimper SSC-30 Shimadzu Corporation, Kyoto, Japan).The DSC runs were performed over a temperature range 25°C to 280°C, at heating rate 10°C/min under pure dry nitrogen flow of 50 ml/min using an empty aluminium pan as reference.

RESULTS AND DISCUSSION

UV-Spectral Analysis

The absorption maximum was found to be 296 nm for telmisartan and 232 nm for ezetimibe. Calibration curves of telmisartan and ezetimibe in methanol and different dissolution media are presented in (figure: 1), along with regression equations.

The linearity was observed in the range of 3μg/mL to 12μg/mL for telmisartan in methanol and 4μg/mL to 14μg/mL in 7.5 pH Phosphate buffer. In case of ezetimibe, the linearity was observed in the range of 3μg/mL to 18μg/mL in both methanol and 0.3% SLS in water.

Table 2: Dissolution parameters

| Sr.No. | Parameters          | Specification |
|--------|---------------------|---------------|
| 1      | Apparatus           | USP II        |
| 2      | RPM                 | 75            |
| 3      | Volume of media     | 900 mL        |
| 4      | Temperature         | 37°C±0.5°C    |
| 5      | Sampling volume     | 5 mL          |
| 6      | Weight of formulation | Equivalent to 5mg telmisartan and 10mg Ezetimibe |
Preparation of porous mannitol

The porous mannitol was prepared using different templating agents by spray drying. The preliminary experiments conducted to optimize the spray drying parameters showed that higher feed concentrations (20% w/v) and higher feed rates (> 20 rpm) leads to sticking of samples to the walls of spraying chamber (Table:3). This resulted in decrease in yield. Hence, the feed rate was fixed at 20 rpm and the feed concentration was optimized to 10%w/v. Similarly, increasing the concentration of templating acids above 2%w/w of carrier also produced sticky material with low yield. This may be due to decrease in the glass-transition temperatures of the amorphous spray-dried intermediate products with the use of templating acids with very low glass-transition temperatures.

When the sucrose was used with citric acid (1:1) as templating agent the yield is increased. This increase in yield was associated with increase in glass transition temperatures of spray dried intermediate products since sucrose increases the glass transition temperature of mixture. The ascorbic acid was oxidized during spray drying and product converted into yellow colour so this was not used in further process.

Table 3: Parameters for preparation of porous mannitol through spray drying

| Sr.N o. | Templating Agent | Mannitol: Template ratio | Water volume | Feed Rate (RPM) | Sticking | %Yield |
|---------|------------------|--------------------------|--------------|-----------------|----------|--------|
| 1       | -                | 10:0                     | 50           | 30              | More     | 40     |
| 2       | -                | 10:0                     | 100          | 30              | Less     | 47     |
| 3       | -                | 10:0                     | 100          | 20              | Less     | 65     |
| 4       | Citric acid     | 10:2                     | 50           | 20              | More     | 30     |
| 5       | Citric acid     | 10:2                     | 100          | 20              | Less     | 50     |
| 6       | Citric acid + Sucrose | 10:1:1                  | 100          | 20              | Less     | 70     |
Drug loading

The type of solvent, volume of solvent and soaking time will influence the drug loading into porous mannitol. Increase in the drug loading was seen with increase in soaking time from 12 h to 24 h and decrease in volume of solvent. Further, the solubility of drug in selected solvent also showed an effect on drug loading i.e. for ezetimibe more drug loading was obtained with acetone than ethanol. Drug loading was found to be decreased with increasing carrier ratio (Table: 4).

| Sr.no | Formulation name | Drug name | Drug: carrier ratio | % Loading |
|-------|------------------|-----------|---------------------|-----------|
| 1     | F1               | Telmisartan | 1:1                 | 45.73     |
| 2     | F2               | Telmisartan | 1:3                 | 30.56     |
| 3     | F3               | Telmisartan | 1:6                 | 15.71     |
| 4     | F4               | Telmisartan | 1:5                 | 10.22     |
| 5     | F5               | Ezetimibe   | 1:1                 | 46.06     |
| 6     | F6               | Ezetimibe   | 1:2                 | 31.72     |
| 7     | F7               | Ezetimibe   | 1:3                 | 15.21     |
| 8     | F8               | Ezetimibe   | 1:4                 | 14.11     |

In - vitro dissolution studies

Dissolution studies were performed in different media as per table no.4. Pure telmisartan showed complete drug release within 15 min from PBS pH 7.4 media with 0.1%, 0.2%, and 0.3% SLS and 1.2 pH hydrochloric acid media. Also, Ezetimibe showed complete drug release within 15 min from water with 1% and 0.5% SLS media and only 15% drug was released from 0.1N hydrochloric acid pH1.2 indicating these media cannot be used further to discriminate between pure drug and formulation. Hence, these are omitted and Phosphate buffer pH 7.5 for telmisartan and 0.3% SLS in water for ezetimibe were selected as discriminating dissolution media for conducting further dissolution studies.

As templating agent plays major role in the pores formation on mannitol, the selection was made based on dissolution studies of drug loaded porous mannitol prepared with different templating agents at 1:4 ratio of drug to carrier. Dissolution profiles of telmisartan and ezetimibe loaded mannitol prepared from different templating agents are shown in figure 2A and 2B respectively. From the figure it was evident that, the release of both drugs was higher from porous mannitol prepared using tartaric acid as templating agent. Hence, further studies were performed by taking porous mannitol prepared using tartaric acid as templating agent.

Further, similarity factor values also indicated all the three dissolution profiles were similar in for F1. Further to confirm that improved dissolution is due to loading into carrier, telmisartan was dissolved in the same solvent used for drug loading in the absence of carrier and precipitated drug was evaluated for dissolution. No significant changes were observed in dissolution of precipitated drug in comparison to pure telmisartan indicating, no solid state transition took place during drug loading and the improvement in dissolution was purely due to loading of telmisartan into the porous mannitol.
In case of ezetimibe, dissolution was more from drug loaded porous carriers compared to respective physical mixture and pure drug except F5 and F6 (1:1 and 1:2) showed lower % drug release from drug loaded carriers compared to their respective physical mixture and pure drug (Fig. 4 A-D). Precipitated ezetimibe also showed significantly lower dissolution compared to pure drug (Fig. 5 B) This may be due to conversion of ezetimibe to different form compared to pure drug during loading. Formulations containing mannitol in higher ratios i.e; F7 and F8 (1:4 and 1:6) showed significant improvement in dissolution rate. At higher carrier ratio the drug was incorporated into the pores which prevented conversion of ezetimibe to other form resulting in improvement of dissolution.

**Figure 3.** Dissolution of telmisartan formulations loaded in different ratio of drug to tartaric acid templated porous mannitol, respective physical mixtures and pure telmisartan in phosphate buffer pH 7.5, (n=3)

**Figure 4.** Dissolution of ezetimibe formulations loaded in different ratio of drug to tartaric acid templated porous mannitol, respective physical mixtures and pure ezetimibe in 0.3 % SLS in water, (n=3)
Figure 5 A and 5B shows comparison of dissolution profiles of telmisartan and ezetimibe from different drug to carrier ratios indicates that, the dissolution was improved with increasing carrier ratio from 1:1 to 1:4 and beyond 1:4 there was no significant improvement in dissolution for both drugs. Based on these 1:4 drug to carrier was found to be optimized and further characterized.

**Figure 5.** Dissolution of formulations prepared with different ratio of A) telmisartan to porous mannitol, B) Ezetimibe to porous mannitol, (n=3)

**Dissolution efficiency**

The increase in dissolution rate was further confirmed by comparing percentage dissolution efficiency of pure drug, physical mixtures and respective optimized formulations at 15, 30, 60 and 120 minutes (Fig.6) Dissolution efficiency of Optimized formulations (F3 and F7) were significantly higher compared to their respective pure drug and physical mixtures at all-time points.

**Figure 6.** Percentage dissolution efficiency of A) optimized telmisartan formulation (F3), respective physical mixture and pure telmisartan B) optimized ezetimibe formulation (F7), respective physical mixture and pure ezetimibe.

**Scanning electron microscopy (SEM)**

The unprocessed mannitol is cube shaped and nonporous (Fig.7A). The micrographs show some morphological changes for the mannitol powder, before (Fig.7 B) while, spray dried mannitol is spherical shaped and nonporous (Fig.7C), after templet removal by ethanol wash (Fig.7D). The surfaces of the spray-dried powders appeared to be nonporous, while more porosity appeared to be formed on the surface and also inside the ethanol washed mannitol. This increased surface area in after ethanol washed powder than before ethanol washed powder was further confirmed by using BET analysis.
Specific surface area analysis

The spray dried tartaric acid templated mannitol before ethanol washing have less BET surface area while after ethanol wash showed increase in surface area. Results of surface area analysis given in Table 5.

| Sr.No. | Description          | Surface Area (m²/gm) | Mean   | SD   | RSD  |
|-------|----------------------|----------------------|--------|------|------|
| 1     | Before ethanol wash  | 1.18 1.20 1.18       | 1.18   | 0.01 | 0.49 |
| 2     | After ethanol wash   | 3.43 3.42 3.43       | 3.43   | 0.01 | 0.34 |

ATR-FTIR Spectroscopy

The spectra of tartaric acid, spray-dried powders before and after ethanol wash are presented in figure 8. Absence of tartaric acid characteristic peaks at 1650 to 1750 cm⁻¹ (C=O stretching) in after ethanol wash powder (Fig 8C) compared to before wash carrier (Figure 8B) indicates complete removal of templating agent from porous mannitol.

The ATR-FTIR spectra of telmisartan plain drug, ezetimibe plain drug, their respective physical mixtures with carrier, ethanol washed carrier and respective optimized drug loaded formulations are depicted in figure 8 and 9. Telmisartan pure drug shows characteristic peaks of -NH, -CH, -C=O, C=C groups in IR region of 3057 cm⁻¹, 2967 cm⁻¹, 1697 cm⁻¹ and 1599 & 1458 cm⁻¹ respectively (Fig.9 P) While, ezetimibe plain drug shows characteristic peaks of -OH, -CH, C=O, - NH groups in IR region of 3240 to 3270 cm⁻¹, 2918 cm⁻¹, 1714 cm⁻¹, 1508 cm⁻¹ respectively (Fig.10 P). Presence of all the characteristic peaks of telmisartan (Fig.9 S) and ezetimibe (Fig.10 S) in drug loaded mannitol indicates absence of any interaction between the drug and carriers.
Figure 8: The ATR-FTIR spectra of A) Tartaric acid, spray dried mannitol, B) Before ethanol wash, C) After ethanol wash

Figure 9: The ATR-FTIR spectra of P) Telmisartan plain drug, Q) Physical mixture with after ethanol washed carrier, R) Ethanol washed carrier and, S) Telmisartan loaded formulation (F3)

Figure 10: The FTIR spectra of P) Ezetimibe plain drug, Q) Physical mixture with after washed carrier, R) Ethanol washed carriers and S) Ezetimibe loaded formulation (F7)
X-ray Powder diffraction (P-XRD)

The PXRD pattern of telmisartan formulation F3 (Fig.11R) have been compared with those of blank porous mannitol (Fig.11Q) pure telmisartan (Fig.11P), and telmisartan precipitates (Fig.11S) and ezetimibe formulations(Fig.12C), blank porous mannitol (Fig.12B), pure ezetimibe (Fig.12A) and ezetimibe precipitate (Fig.12 D).

These results suggested significant decrease in the peak intensities of the drug crystals in the PXRD patterns of the loaded mannitol (Fig: R and Fig: C). This may be due to deposition of drugs inside the nano confinements of porous mannitol.

PXRD pattern of precipitated telmisartan is similar to pure drug indicating no polymorphic changes. However, ezetimibe precipitate showed presence of mixture of form A and B which is reason for decrease in dissolution of precipitated ezetimibe as well as in lower carrier ratio formulations.

Figure 11: The PXRD spectra of  
P) Telmisartan plain drug,  
Q) Porous mannitol,  
R) Telmisartan loaded formulation (F3)  
S) Solvent precipitated telmisartan

Figure 12: The PXRD spectra of,  
A) Ezetimibe plain drug  
B) Porous mannitol,  
C) ezetimibe loaded formulation(F7),  
D) Precipitated ezetimibe.
**Differential scanning calorimetry (DSC)**

The DSC heating scans of loaded porous mannitol with telmisartan (Fig.13D) and ezetimibe (Fig.14D) were compared with those of pure crystalline drugs (Fig.13A, Fig.14A) and blank porous mannitol (Fig.13C and 14C). The thermograph of pure telmisartan, and porous mannitol showed an endothermic peak due to the melting of their crystalline structures at 269.7°C and 166.63°C, respectively. The DSC profiles of telmisartan loaded mannitol (F3) showed a shift to lower temperatures for the onset and the peak temperatures of the telmisartan melting process. This behavior can be linked with the confinement-induced melting-point depression phenomenon, stating that the melting peaks of crystalline solids appear at lower temperature when trapped in confined spaces. The extent of melting-point depression depends on the size of the crystals, which in turn is defined by the size of the pores in which they are confined. A melting-point depression from 269.7°C to 257.6°C was observed (Fig.13D) for deposited telmisartan crystals.

The thermographs of pure ezetimibe and porous mannitol carrier showed an endothermic peak due to the melting of their crystalline structures at 163.63°C and 166.17°C (Fig.14C). The ezetimibe loaded particles (F7) also showed endothermic peak due to the melting of crystalline structures at 166.75°C (Fig.14D) which has onset of peak at 163.9°C which is similar to onset of peak of pure ezetimibe. This clears that ezetimibe and porous mannitol carrier peaks are merged with each other.

**Figure 13.** The DSC spectra of A) Telmisartan pure drug, B) Telmisartan precipitate, C) Porous mannitol, D) Telmisartan loaded formulation (F3)

**Figure 14.** The DSC spectra of A) Ezetimibe pure drug, B) Ezetimibe precipitate, C) Porous mannitol, D) Ezetimibe loaded formulation (F7)
CONCLUSION

Template based spray drying methodology can be used to prepare porous mannitol. The feed rate and feed concentration affected the yield in spray drying process. The BET analysis confirmed the increase in surface area of mannitol carrier after washing out template using ethanol. In drug loading, the type of solvent, volume of solvent and soaking time affected the percentage drug loading. Out of all the templating agents and combinations, tartaric acid was found to be an effective templating agent at 1:4 ratio of drug to carrier. From the PXRD and DSC spectra it was found that the drugs were in crystalline from in porous mannitol and the reduced intensity of peaks in PXRD spectra concludes drug is in nano - confinements of porous mannitol. The drug loaded porous mannitol showed higher percentage CDR than pure drugs and respective physical mixtures. These results suggest that, mannitol porous carriers act as promising drug carriers for improving the dissolution rate of lipophilic drugs

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Ethics approval and consent to participate

Not Applicable.

Human and animal right

No animals/Humans were used for studies that are base of this research.

Consent for publication

Not applicable.

Conflict of interest

The authors confirmed that this article content has no conflict of interest.

REFERENCES

[1] Soniwala MM, Patel PR, Mansuri NS, Parikh RK, Gohel MC. Various approaches in dissolution enhancement of Rofecoxib. Indian journal of pharmaceutical sciences. 2005; 67(1):61-70.
[2] Gaur PK, Mishra S, Bajpai M. Formulation and evaluation of controlled-release of telmisartan microspheres: In vitro/in vivo study. Journal of food and drug analysis. 2014; 22(4):542-548.
[3] Patel J, Dhingani A, Garala K, Raval M, Sheth N. Design and development of solid nanoparticulate dosage forms of telmisartan for bioavailability enhancement by integration of experimental design and principal component analysis. Powder technology. 2014; 258:331-43.
[4] Kulkarni SA, Feng SS. Effects of surface modification on the delivery efficiency of biodegradable nanoparticles across the blood-brain barrier. Nanomedicine[Lond]. 2011; 6:377–394.
[5] Chauhan NN, Patel NV, Suthar SJ, Patel JK, Patel MP. Micronization of BCS Class-ll Drugs by Various Approaches for Solubility Enhancement-A Review. Research Journal of Pharmacy and Technology. 2012; 5(8):999-1005.
[6] Saffari M, Ebrahimi A, Langrish T. A novel formulation for solubility and content uniformity enhancement of poorly water-soluble drugs using highly-porous mannitol. European Journal of Pharmaceutical Sciences. 2016; 63:52-61.
[7] Sharma DK. Solubility enhancement strategies for poorly water-soluble drugs in solid dispersions: A review. Asian Journal of Pharmaceautics. 2016; (1):1-10.
[8] Pardi V, Chavan RB, Thipparpaboina R, Thatikonda S, Naidu VG, Shastri NR. Preparation, characterization, and cytotoxicity studies of niclosamide loaded mesoporous drug delivery systems. International journal of pharmaceutics. 2017; 528(1-2):202-214.
[9] Chavan RB, Jitkar V, Pardi V, Yadav B, Shastri NR. Inorganic Nano composites—A New Paradigm in Drug Delivery. InParticulate Technology for Delivery of Therapeutics 2017; 317-357. Springer, Singapore.
[10] Ebrahimi A, Saffari M, Langrish T. Improving the dissolution rate of hydrophobic drugs through encapsulation in porous lactose as a new biocompatible porous carrier. International journal of pharmaceutics. 2017 ; 521(1-2):204-213.
[11] Tan S, Ebrahimi A, Langrish T. Template-directed flower- like lactose with micro-meso-macroporous structure. Materials & Design. 2017 ; 117:178-84.
[12] Leung SS, Wong J, Guerra HV, Samnichik K, Prud’homme RK, Chan HK. Porous mannitol carrier for pulmonary delivery of cyclosporine A nanoparticles. The AAPS journal. 2017; 19(2):578-586.
[13] Peng T, Zhang X, Huang Y, Zhao Z, Liao Q, Xu J, Huang Z, Zhang J, Wu CY, Pan X, Wu C. Nanoporous mannitol carrier prepared by non-organic solvent spray drying technique to enhance the aerosolization performance for dry powder inhalation. Scientific reports. 2017; 7:46517.
[14] Littringer EM, Noisternig MF, Mescher A, Schrottner H, Walzel P, Griesser UJ, Urbantz ET. The morphology and various densities of spray dried mannitol. Powder technology. 2015; 246:193-200.
[15] Bodhe, R., Deshmukh, R., Gorle, A., Shinde, R. and Bodhe, P. Formulation, development and evaluation of carbamazepine extended release tablet: dissolution apparatus USP IV. World journal of pharmaceutical research, 2019; 8(9):1484-1504.
[16] Littringer EM, Mescher A, Schrottner H, Achelis L, Walzel P, Urbantz ET. Spray dried mannitol carrier particles with tailored surface properties – The influence of carrier surface roughness and shape. European journal of pharmaceutics and biopharmaceutics. 2012; 82(1):194-204.
[17] Saffari M, Ebrahimi A, Langrish T. A novel formulation for solubility and content uniformity enhancement of poorly water-soluble drugs using highly-porous mannitol. European Journal of Pharmaceutical Sciences. 2016; 83:52-61.
[18] Grigorov PI, Glasser BJ, Muzzio FJ. Formulation and manufacture of pharmaceuticals by fluidized-bed impregnation of active pharmaceutical ingredients onto porous carriers. AICHe Journal. 2013; 59(12):4538-52.
[19] Kawabata Y, Wada K, Nakatani M, Yamada S, Onoue S. Formulation design for poorly water-soluble drugs based on biopharmaceutics classification system: Basic approaches and practical applications. International Journal of Pharmaceutics 2011; 420(1):1-10.
[20] Saajani KT, Gajjar AK, Saajani JK. Drug solubility: importance and enhancement techniques. ISRN pharmacuetics. 2012 ; 1:1-10.