# Solid dispersions of spironolactone by co-spray drying with Soluplus® and PVP

**Nizar Al-Zoubi[1], Wasfi Obeidat[2], Faten Odeh[1], Ahmad Al-Jaberi[1], Ioannis Nikolakakis[3]**

[1]Department of Pharmaceutical Sciences and Pharmaceutics, Faculty of Pharmacy, Applied Science University, Amman, Jordan nizoubi@yahoo.com [2]Department of Pharmaceutical Technology, Jordan University of Science and Technology, Irbid, Jordan, [3]School of Pharmacy, Faculty of Health Sciences, Aristotle University of Thessaloniki, 54124, Greece yannikos@pharm.auth.gr

## INTRODUCTION

Solid dispersion is a formulation strategy employed to enhance the bioavailability of highly lipophilic poorly-soluble drugs (Van den Mooter, 2012). Recently, an increased interest has been shown for the development of new drug carriers of enhanced solubilizing power and for the application of ternary solid dispersions, in which in addition to drug, two carriers are used in suitable proportions. This allows tailoring of the solid dispersion to obtain desirable product characteristics. Spironolactone (SP) is an established drug in the treatment of heart failure and hypertension which due to poor water-solubility, exhibits incomplete oral bioavailability (Clarke et al., 1977). The aim of this study was to investigate the applicability of spray drying to prepare solid dispersions of spironolactone with Soluplus® and PVP K30 and evaluate the production yield and the physical and thermal properties of the spray dried products

## MATERIALS AND METHODS

### Materials

Spironolactone was kindly donated by JPM, Amman, Jordan. Soluplus® (polyethylene glycol–polyvinyl caprolactam–polyvinyl acetate grafted copolymer) and PVP (Kollidon® K30) kindly donated by BASF, Germany. Deionised water and absolute ethanol were the solvents for the spray dried solutions.

### Preparation of the spray dried powders

Hydro-ethanolic solutions of spironolactone, Soluplus® and PVP were spray dried with a Pulvis mini-spray dryer GA 32 (Yamato Scientific, Japan) under the following conditions: inlet air temperature 105 ºC, outlet air temperature 58-62 °C, air pressure 1 kg/cm$^2$, feed rate 12 ml/min, spray nozzle 406 µm. The collected spray dried products were weighed and production yield calculated as percentage of the total initial solid content in the spray dried liquid.

### Characterization of spray dried powders

*Thermal analyses*: Netzsch STA 409 PC, Germany simultaneous DSC and TG analyzer using ~3 mg samples in perforated aluminum pan heated to 250 ºC, at 10 ºC/min, under nitrogen atmosphere. Moisture content **(**MC) was determined from mass change seen in TG curve.

*Particle size*: Laser diffraction (Mastersizer 2000A, Malvern, UK).

*Particle surface morphology:* Field emission gun scanning electron microscopy (FEI Company Eindhoven, Holland).

### Experimental design and statistical analysis

A 3-component simplex centroid mixture design was used to study the influence of composition on the production yield ($Y_1$), moisture content ($Y_2$) median particle size ($Y_3$), and dissolution efficiency (Y4), by fitting Scheffé quadratic model (Equation 1) to the data

$$Y=b_1X_1+b_2X_2+b_3X_3+b_{12}X_1X_2+b_{13}X_1X_3+b_{23}X_2X_3 \quad \ldots \quad (1)$$

The experimental plan consisted of 7 experimental batches (one repetition, Table 1). Constraints were applied for the drug $X_1$>20% and the polymers $X_2$, $X_3$ <80%. The percent (% w/w) of SP, Soluplus® and PVP K30 were the experimental factors ($X_1$, $X_2$ and $X_3$, respectively).

| Batch | SP | SL | PVP | Yield (%) | MC (%) | Diam (µm) |
|---|---|---|---|---|---|---|
| SD1 | 100 | 0 | 0 | 39.9 | 4.3 | 20.9 |
| SD2 | 20 | 80 | 0 | 51.9 | 2.9 | 6.9 |
| SD3 | 20 | 0 | 80 | 61.4 | 9.2 | 6.7 |
| SD4 | 20 | 40 | 40 | 69.1 | 5.5 | 6.2 |
| SD5 | 60 | 40 | 0 | 64.4 | 3.3 | 5.2 |
| SD6 | 60 | 0 | 40 | 62.5 | 5.7 | 12.1 |
| SD7 | 46.7 | 26.7 | 26.7 | 71.8 | 4.6 | 5.4 |
| RM | 100 | 0 | 0 | - | 1.1 | 17.0 |

**Table 1. Experimental batches with production yield, moisture content and particle size**

## RESULTS

SEM microphotographs of raw drug (RM) and of batches of spray dried alone drug (SD1), co-spray dried with Soluplus (SD2) or PVP (SD3) at drug/polymer ratio 1:4 (corners in the experimental design triangle) are shown in Figure 1. The particles of raw drug are seen as agglomerates of small

particles and those of the spray dried drug alone as spherical agglomerates with rough, porous surface. Batches SD2 and SD3 show less agglomerated particles with spherical or shriveled shape and smooth surface.

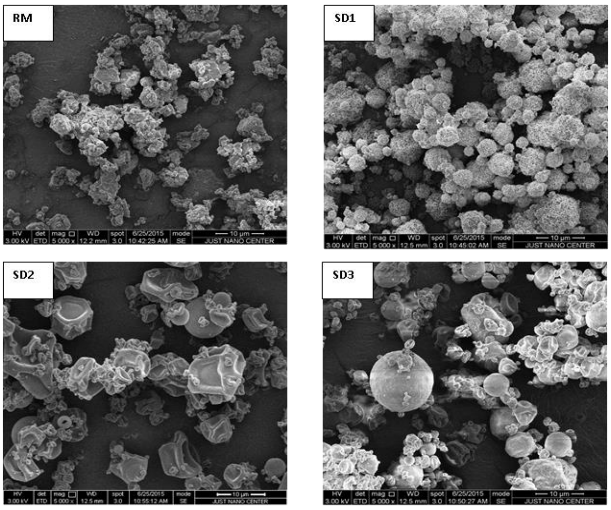


**Figure 1: SEM images of spironolactone raw material (RM) and spray dried batches SD1–SD3 (Table 1)**

Spray drying in lab-scale units usually results in incomplete recovery of solids due to sticking in the wall of the drying chamber and to the formation of fine particles escaping the aspirator. This is possibly the reason for the low yield of spray dried alone drug (SD1, Table 1). Higher yield between 61.4 and 71.8% is obtained when PVP is present and at low or mid Soluplus levels. The MC% for compositions with the more hydrophilic PVP is greater than 4.6% and for those with Soluplus is less than 5.5%.

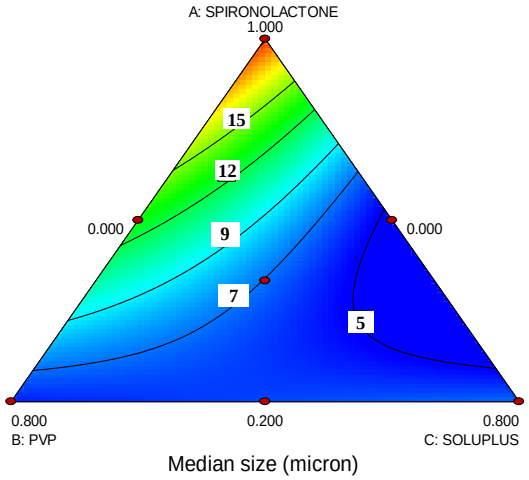


**Figure 2: Contour plots for median particle diameter**

Although the median particle diameter of spray dried product is mainly controlled by the size of the drying chamber and other parameters of the dryer, it appears from Table 1 and Figure 2 that it decreases with increasing polymer content. This can be attributed to the lower agglomeration as seen in Figure 1 (SD2, SD3).

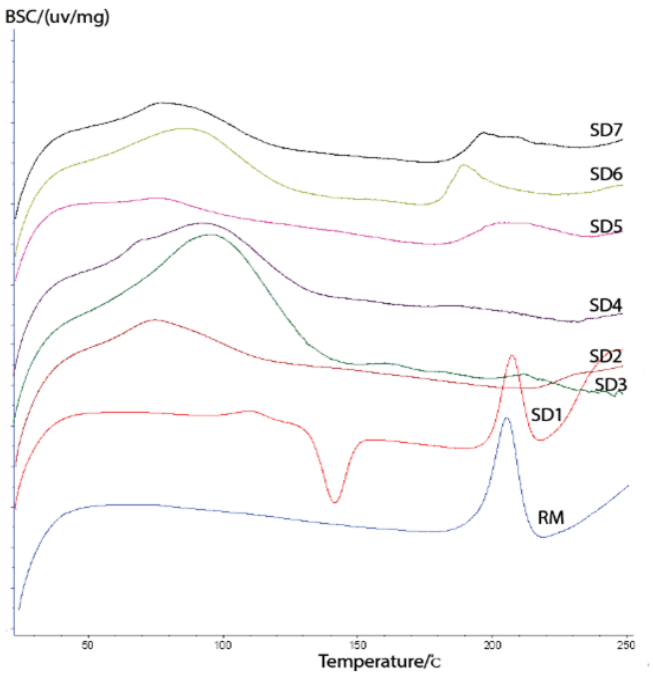


**Figure 3: DSC thermograms for co-spray dried products**

From the DSC thermograms in Figure 3 it can be seen that the raw drug shows one melting peak at 205.5 °C (Al-Hadiya et al., 2002) and the spray dried drug three events: a glass transition endotherm at 105.3 °C, due to amorphous SP content, an exothermic crystallization peak at 143.4 °C, and a melting peak at 205.5 °C., The thermograms of the co-spray dried products show a wide endotherm in the range 50-150 °C due to moisture evaporation. Co-spray dried batches SD5-SD7 with relatively low polymer content show an additional wide endotherm due to melting of recrystallized SP. There is no clear melting peak for the co-spray dried batches SD2-SD4 with higher polymer content, indicating absence of crystalline SP.

## CONCLUSION

Solid dispersions of amorphous SP can be successfully prepared using the novel copolymer Soluplus® and PVP with production yield between 39.9 and 71.8% and median particle diameter between 5.2 and 20.9 µm. Formulations with SP/Soluplus ratio 1/4 contain amorphous drug.

## REFERENCES


1. Van den Mooter, G. The use of amorphous solid dispersions: A formulation strategy to overcome poor solubility and dissolution rate. Drug Discovery Today: Technologies, 9(2), 79-85 (2012).
2. Clarke, J. M., et al. Factors influencing comparative bioavailability of spironolactone tablets. J. Pharm. Sci., 66(10), 1429-1432 (1977).
3. Al-Hadiya, et al. Spironolactone. Analytical Profiles of Drug Substances and Excipients, 29, 261-320 (2002).