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Cortisone Acetate Nano-particles Formation by Rapid Expansion of a Supercritical Solution in to a Liquid Solvent (Resolve Method): An operational Condition Optimization Study

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***Abstract*-A RESOLV (Rapid Expansion of Supercritical Solution in to A Liquid Solvent) process system has been developed to produce nano-particles with improved bioavailability. Jet receiving liquid conditions effects on the formed particles physical properties, is the main investigating subject at this study. Results showed that if the receiving liquid temperature adjusted at below 10° C, non-uniform and crystalline particles without any promoted solubility rate are obtained. The formed particles become finer and more uniform, when the jet receiving liquid temperature increases to about 40°C. Apart from the liquid temperature, using a surfactant such as Poly Ethylene Glycol (PEG) improves the particles properties. We proved that for a polymer molecular weight contrary to the concentration has more significant effect on the particles size and uniformity. Cortisone Acetate was used as the model solid component. A dilute supercritical mixture of Trifluoromethane (CHF3) in CO_2 (0.1 of Volume ratio.) was applied as the supercritical solvent in all runs.**

Key Words-Component- Supercritical Solution; Nano size Drugs; Protective Polymers; RESOLV

I. INTRODUCTION

Release process and the dissolution rate of a drug can be enhanced by reducing the particle size for the particulate solid drugs. Rapid expansion of supercritical solution is a popular method for producing nano size drugs. This method is specially recommended for producing the biologics, drugs and food material nano-particles because of the middle operational condition [1-7]. Using a liquid at the receiving end of the rapid expansion process (RESOLV), leads to a simple but significant modification on the RESS method that causes a considerable improving in physical properties of the produced nano powders. Spraying the supercritical solution into a high dense environment causes fine and uniform particles formation. So, the liquid condition such as temperature, density and presence of surfactants, can be definitely impressive on the resulted particles characteristics. CO2 which is an available, non-flame able and non-toxic gas, with middle supercritical point condition (72 bars and 31.1 °C) was used as the supercritical solvent [8-12]. Taking in to the CO_2 non-polarity, adding a polar co-solvent in to the supercritical CO_2 improves the solubility behavior for the polar and high molecular weight compounds processing [13]. CHF_3 with a mild critical condition (48.4 bars and 25.6 °C) was the applied supercritical co-solvent, in this work. Cortisone acetate is a white to practically white, odourless, crystalline, water insoluble powder which are readily absorbed from the gastrointestinal tract. Because of the low solubility it's bioavailability is very poor consequently [14-15]. Reducing the mean particles size causes results in the mean particle area and solubility increasing. The current study is concentrated on the effect of end receiving liquid temperature and the role of dissolving a degradable protective polymer (surfactant) in to the receiving liquid on the formed particles mean diameter. Impression of the surfactant molecular weight and concentration in the receiving liquid on the particles properties is also discussed at the present work.

II. MATERIALS AND METHOD

A. Material

Cortisone Acetate (Sina Daru , 99.99% purity) was used as the model component and CO_2 (Roham Gaz, 99.95%) was also applied as the solvent. Ethanol 99.8%, Sigma Aldrich) and Acetone (99.9%, Sigma Aldrich) were used in analytical grade form. Poly Ethylene Glycol (600, 3000 and 6000, Sigma Aldrich, Pure) was used as the water suspended surfactant.

B. Experimental Method

An RESS conventional apparatuses has been prepared for the current study [16-22]. See Fig. 1.

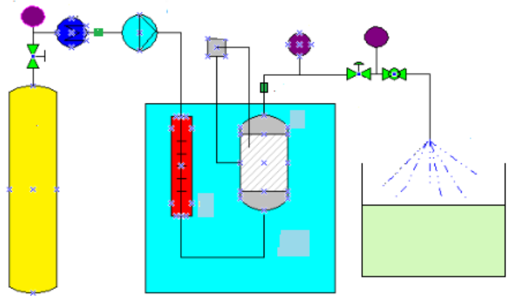

Figure 1. RESOLV Apparatuses

The solvent (CH_3-CO_2) mixture lows through a filter to a cooling system (F38-Me, Julabo), from the reservoir, in order to liquefy the gas solvent and compressed to the desired pressure by means of an HPLC pump (LC 6A, Shimadzu). After passing through a pre-heater coil, enters in to the extraction cell (16 cm; height and 7 mm; I.D., S.S.) which is loaded with the solid sample. Immediately after the extraction, supercritical solution passes through a micro-metering valve (S.S, Swagelok) and an expansion device (A stainless steel capillary, 5 mm; Length and 0.05 mm; I.D.) to a container which is filled with a uniform temperature liquid. For the all runs the extraction cell was adjusted on the 308 K (35 °C) and 200 bars. Spraying flow rate is constant and the same for all the runs.

C. Solubility

Test Solid component solubility in supercritical mixture was determined before starting the RESOLV tests. We obtained the Cortisone Acetate saturated mole fraction in CHF_3-CO2 supercritical mixture (0.1, Vol./Vol.) at seven different pressures (100-200 bars) and 35 K by a dynamic method. We also obtained the saturated solubility values at 40˚C and 45˚C in triplicate. Results showed, the supercritical solution is a good solvent for Cortisone Acetate ($Y=2.06 * 10^{-3}$) at 308 K and 200 bars. Y is the mole fraction of solute (Cortisone Acetate) in the supercritical mixture.

III. RESULTS AND DISCUSSION

RESOLV process was initially performed for seven different receiving liquid (pure water) temperatures, in order to anticipating the liquid temperature individual effect on the particles size. Using pure water as the expansion receiving environment in the seven different temperatures (273-383 K) showed that in the low temperatures (□ 293 K), large and separate solid nucleus are formed (100 nm□). This can be justified by liquid high density and the nano particles low surface activity in the low temperatures. Fig.2 shows that, increasing the temperature to 312 K resulted in the mean particles size gradual decreasing to about 75 nm.

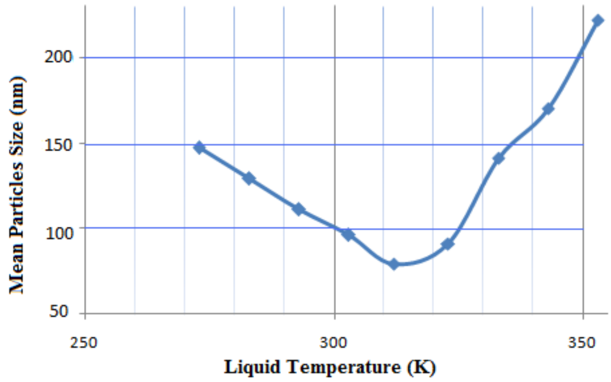

Figure 2. Liquid Temperature impact on the mean particle size

In higher temperatures results showed that the mean particles size change inversely with the temperature. Large particles formation in low receiving liquid temperature can be explained by temperature effect on super saturation factor (S) that affects on the nucleation rate inversely based on the equations (1) and (2) [22-27].

$$S = \frac{y_E(T_E, P_E)}{y^*(T, P)} \rangle 1 \quad (1)$$

$$I_f = \alpha[\frac{p}{kT}]^2[\frac{2\delta^{1/2}\upsilon}{(2\pi m)^{1/2}}]\exp[\frac{-16\pi}{3}(\frac{\delta}{kT})^3(\frac{\upsilon}{\ln S})^2] \quad (2)$$

I_f is nucleation rate and y_E and y are the concentrations of supercritical solution and the expanded fluid orderly. But in the high temperatures (312 K□), the initial appeared thin particles stick to each other and large clusters are formed (300 nm□). All the runs products were analyzed by PSD (Particle Size Distribution Test, Horiba; LA-90-V2).

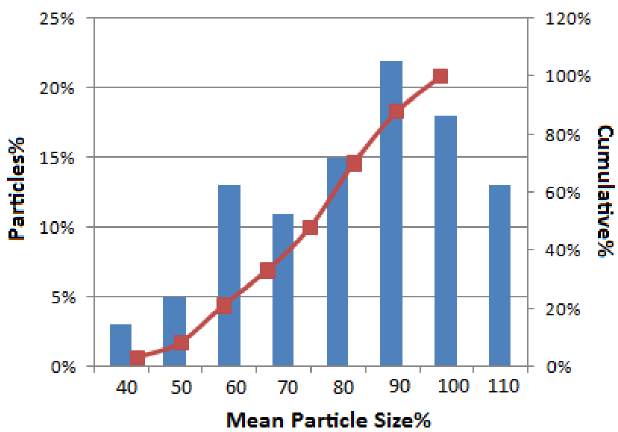

Figure 3. PSD test result for a particle with 87 nm diameter

Fig. 3 shows a sample of PSD test result for a particle with 87 nm diameter which produced by expansion into the pure water, at 302 K. After finding the optimum temperature, three different concentration of PEG solution were used as the receiving liquid and then PEG samples with the molecular weight of 3000 and 700 were also tested in the liquid solvent. After these observations, we used a surfactant solvent (Poly Ethylene Glycol + water) in different concentrations (25%, 50% and 75%) and molecular weights (700, 3000 and 6000) in 312 K. As seen at the Table I and II, particles size is very sensitive to the PEG molecular weight, as like as the PEG concentration. The PEG solution temperature was adjusted on 312 K, for the all runs.

TABLE I. SURFACTANT CONCENTRATION EFFECTS

(PEG MOLECULAR WEIGHT=6000)

Mean Particle Size(nm)	Polymer Concentration
61	25%
52	55%
46	75%

TABLE II. SURFACTANT MOLECULAR WEIGHT EFFECT

(PEG CONCENTRATION=75%)

Mean Particle Size(nm)	Polymer Concentration
30	6000
40	3000
46	700

A high molecular weight polymer makes a good covering in substance that prevents initial appeared nucleus. This result is naturally satisfies the obtain results for the different polymer concentration

IV. CONCLUSION

Receiving environment temperature and density have significant effects on the RESOLV products. Liquid density is directly affected by the temperature. Particle formation mechanism is governed by the solubility factor which is impressed by the expanding gas temperature. Based on the current investigations, the most appropriate liquid temperature, for the Cortisone Acetate-CO_2 system is about 300-320 K that is clearly a direct function of the liquid and solid model physic-chemical characteristics. Inserting a high molecular weight non-toxic polymer, as a surfactant, improves the particles uniformity and mean size. By using a concentrated polymer solution, nucleuses are well surrounded by the surfactants and minimum coalescence occurs.

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