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# Preparation of *Aprepitant* nanoparticles (efficient drug for coping with the effects of cancer treatment) by rapid expansion of supercritical solution with solid cosolvent (RESS-SC)

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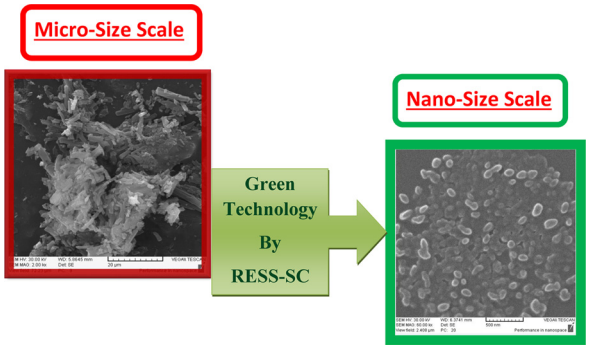
## GRAPHICAL ABSTRACT




## ARTICLE INFO

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## ABSTRACT

To improve dissolution properties of aprepitant (APR) as a poorly water-soluble drug, Rapid Expansion of Supercritical Solution with Solid Cosolvent (RESS-SC) was applied for the first time. Effects of four different parameters including temperature (308.2–338.2 K), pressure (15–33 MPa), spraying distance (1–10 cm) and nozzle diameter (150–450 μm) were investigated on the size and morphology of the precipitated nanoparticles. Also, equilibrium solubilities of APR in $CO_2$ and menthol were measured at different temperatures between 308.2 and 338.2 K and pressures in the range of 12–33 MPa using a static method. To characterize unprocessed and processed APRs, FTIR, DLS, SEM, XRD, DSC and dissolution rate were employed. The analyses revealed a great reduction in the size of the nanoparticles by RESS-SC (23 ± 1.6 nm, on average), as compared to the original particles of APR (25.6 μm, on average). Finally, the dissolution rate was enhanced by 8.2 folds following the RESS-SC process.

## 1. Introduction

For many years, chemotherapy has been applied as a cancer treatment. However, similar to an other drugs, it has been associated with side effects such as vomiting and nausea. Accordingly, aprepitant (APR) is used with other medications to help prevent nausea and vomiting caused by the cancer drug treatment. Aprepitantis have been also used alone to prevent the nausea and vomiting caused by surgery. It works

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**Nomenclature**

| | |
|---|---|
| $a_0$–$a_5$ | Adjustable parameters of model |
| *AARD* | Average absolute relative deviation |
| *a* | Empirical parameter |
| *A* | Surface area of solute |
| *b* | Empirical parameter |
| $f_1$ | Difference factor |
| $f_2$ | Similarity factor |
| *k* | Adjustable parameters of Reddy- Madras model |
| $k_w$ | Dissolution rate coefficient |
| *MSR* | Mean square regression |
| *MSE* | Mean square residual |
| $M_W$ | Molar mass, kg $mol^{-1}$ |
| *N* | Number of data points, dimensionless |
| *P* | Pressure |
| $P_{ref}$ | Reference pressure |
| *Q* | Number of independent variables in each equation |
| $R^2$ | Correlation coefficient |
| $R_j$ | Dissolved percentage of original sample |
| *SSE* | Error sum of squares |
| *SST* | Total sum of squares |
| *SSR* | Regression sum of squares |
| *T* | Temperature, K |
| $T_j$ | Dissolved percentage of processed sample |
| *y* | Mole fraction solubility |

*Greek symbols*

| | |
|---|---|
| ρ | Density, $kg.m^{-3}$ |
| $\gamma$ | Adjustable parameters of Reddy- Madras model |

*Subscripts*

| | |
|---|---|
| *1* | Solvent (SCF) |
| *2* | Solute (Drug) |
| *3* | Cosolvent (Menthol) |
| *c* | Critical property |
| *cal* | Calculated |
| *exp* | Experimental |
| *i,j,* | Component |

by blocking the action of neurokinin, a natural substance in the brain that causes nausea and vomiting [1,2]. APR is lipophilic and poorly soluble over the pH range 2–10. Aprepitant is a Biopharmaceutics Classification System (BCS) class IV drug, having low solubility and low permeability. It has been reported to have an aqueous solubility of 3–7 μg/mL in the pH range of 2–10 that is very low [3]. It is weakly basic with a pKa value of 9.78 [4]. Solubility of a drug in aqueous body fluid is an essential property and plays an important role in bioavailability of the drug after oral administration [5]. Low oral bioavailability of drugs can be attributed to one or a combination of the following factors: slow dissolution rate and poor solubility [3].

Because of APR poor solubility, it is difficult to follow conventional approaches to develop a formulation that will provide adequate systemic exposure to produce a therapeutic effect [6]. Various formulation strategies have been reported in the literature to enhance solubility, dissolution and bioavailability of poorly soluble compounds like APR [4], among which one can refer to the use of surfactants, particle size reduction, salt formation, cyclodextrin inclusion complexes, solid dispersions [4,7], pH adjustment, and the use of pro-drugs or incorporation of the drug in polymeric or lipid formulations [8]. The majority of these approaches have been used on a case-by-case basis depending on the physicochemical characteristics of the drug [7]. Recently in the pharmaceutical industry, reduction of the particle size has been used to improve its dissolution into the biological environment and blend active pharmaceutical ingredients (APIs) more uniformly with excipients. Conventional methods for reducing the particle size include mechanical approaches like crushing, grinding and milling, spray-drying, freeze-drying and recrystallization of solute particles from solutions using liquid anti-solvents [9–11]. Applying such methods leads to thermal and chemical degradation of products, consumption of large quantities organic solvent, broad particle size distribution, and solvent residue in particles [12].

Non-conventional methods for particle formation using supercrticial carbon dioxide ($SC-CO_2$) has been divided into three groups based on their role in the processing. In the first, second, and third groups, a supercritical fluid (SCF) is used as a solvent (e.g. rapid expansion of supercritical solution (RESS)), solute (e.g. particles form gas-saturated solutions (PGSS)), and anti-solvent (e.g. supercritical anti-solvent (SAS), Gas anti-solvent (GAS), aerosol solvent extraction system (ASES), and solution-enhanced dispersion by supercritical fluid (SEDS)), respectively. Non-conventional techniques have numerous advantages over the conventional ones, such as lower impurities in extracts and pollution to the environment, no solvent residues, and adjustability of solvent (selectivity by different pressures and temperatures). Among all the possible supercritical fluids, carbon dioxide has been largely used as a green solvent because it is nontoxic, nonflammable, nonpolluting, non-polar, non-explosive,easily removed from the extract and relatively cheap [13–17]. Among the methods mentioned for reducing the size of drug particles is rapid expansion of supercritical solution (RESS) that can improve properties of APIs; as it is capable of controlling particle morphology and polymorphic form of the drug substance by varying the RESS operating parameters. In this method, solute solubility of an API in supercritical $CO_2$ is firstly required to decide on appropriate micronization process. In order to achieve a high-enough solute solubility, RESS process is desirable as it needs no organic solvent. In this process, solid solute is firstly dissolved in a supercritical fluid. After reducing pressure through an expansion device, ultra-fine particles may be produced from the resultant low-pressure stream due to decreased solubility of the solute which ends up highly supersaturating the solute in the dense-gas medium. Therefore, this process allows to achieve extremely high supersaturations which are transmitted very quickly and homogeneously to the whole fluid, thus leading to the formation of small particles with narrow particle size distribution [18–20].

To the best of our knowledge, there was no report on production of APR nanoparticles using RESS-SC. The present work investigated experimentally studies dissolution rate improvement of APR using RESS-SC. For this purpose, firstly, solubility of APR in $CO_2$-menthol blend was measured experimentally and then correlated in wide ranges of temperature and pressure of 308.2–338.2 K and 12–33 MPa, respectively. Afterwards, Taguchi method was applied to investigate effects of extraction temperature, pressure, spray distance (the spray distance is distance of the tip of the nozzle to the surface of the glass slide) and nozzle diameter on APR particle size. Moreover, dissolution rates of processed and unprocessed particles were evaluated and compared to each other. The processed and unprocessed particles were characterized by Fourier Transform Infrared (FTIR) spectroscopy, Differential Scanning Calorimetry (DSC), X-ray Diffraction (XRD), Scanning Electron Microscopy (SEM), and Dynamic Light Scattering (DLS). The above-mentioned experiments allow us to examine capabilities of RESS-SC technique for producing APR drug nanoparticles.