Organic solvent free microparticles from a novel melt dispersion method.

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Introduction

Residual volatile organic compounds (VOC) in microencapsulated products have raised serious concerns (Bitz and Doelker, 1995) and have motivated the development of VOC-free processes, such as particles from gas saturated solutions, rapid expansion of supercritical solutions (Jung and Perrut, 2001), and various melt congealing processes (Kowarski et al., 1964; Cusimano and Becker, 1968; Boswell and Scribner, 1973; Jozwiakowski et al., 1990). The technique in focus is commonly known as "melt dispersion" or "hot melt encapsulation" and involves the emulsification of a molten wax in aqueous or oil phase to obtain microdroplets. The cooling of such an emulsion transforms the emulsified droplets into microparticles. If an active substance is dispersed in the molten phase, it solidifies in the droplet matrix and therefore can be employed in controlled release applications. The initial attempts to emulsify molten wax into oil phase have yielded fairly wide particle size distribution ($Q_{3,48}$ < 420µm) (Kowarski et al., 1964), which was eventually improved to the mean diameter of 141µm (Adeyeye and Price, 1991); similarly, the factors affecting the drug loading of microparticles have also been evaluated (Bodmeier, 1992a, b). Even though melt dispersion is a promising technique to obtain organic solvent free microparticles, its employment at the industrial scale is fairly limited. The transformation of microdroplets into microparticles has been identified as a factor, which not only limits the product quality but also affects the mode and scale of operation. We have therefore studied the feasibility of mixing the emulsion, inline with an external cooling water stream.

The angled injection of a secondary stream in the pipeline has been studied by various researchers for optimal mixing and reactions. Forney and co-workers have evaluated the design of jet injections for pipeline mixing, which provided the detailed measurement of jet trajectories (Forney and Lee, 1982), scaling laws (Sroka and Forney, 1989), Mathematical basis (Forney and Grey, 1990), design parameters (Forney et al., 1996), and the numerical simulations (Wang et al., 1999) of the inline mixing setups. The computational simulations by Wang et al. (1999) concluded that the mixing at arm angle greater than 90° produce large scale vortices near injection point. Moreover, the impact of jet on the side wall at higher velocities increases the risk of wall wearing. Hence the recommendation of right angled injection was adopted in the present work (Figure 1f). Experimental part of this work includes the evaluation of shortest mixing length as the function of continuous phase/cold water velocity ratios, which were then employed to produce drug loaded microparticles; moreover, the encapsulation efficiency and controlled release behaviour of the microparticles was studied. The computational part consists of the simulations by a commercial CFD code (Fluent) employing a low-re k-epsilon model for turbulence. The velocity profile of inlets at constant temperature was taken as a boundary condition.

Materials and Methods

The experimental setup (Figure 1) consists of three metering pumps, an Ultra-Turrax T25 with 25F-IL head (c), an emulsion outlet tube (d), and a T-junction (f). The Beeswax and α-Tocopherol (Sigma Aldrich) form the oil phase (a) and an aqueous solution of polyvinyl alcohol (Polysciences Inc.) and sodium laureth sulfate (Sigma Aldrich) is employed as continuous phase (b). The two phases (a and b) are pumped to the dispersion head 25F-IL (c) of the Ultra Turrax T25 at fixed flow rates for emulsification. The emulsion flows through the outlet tube (d) into the cold water stream

(e) in the form of a jet (f), where the molten wax droplets solidify to form microparticles. The microparticles thus formed are filtered, washed and dried for analysis.

	Set 1	*Set 2*
Continuous Phase	**100 vol%; 60 °C**	**95 vol% 60°C**
PVA	1 wt%	1 wt%
SLES	1 wt%	1 wt%
Fluorescent	Traces	-
Water	98 wt%	
Dispersed Phase	-	**5 vol% 65°C**
Beeswax	-	90 wt%
α-Tocopherol	-	10 wt%

Table 1 : Basic Set of Experiments

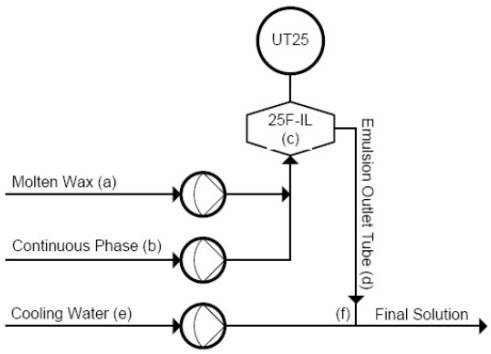


Figure 1: Experimental Setup

The experiments (Table 1) were conducted to investigate the optimum mixing length after mixing in the T-junction (Figure 1f) as a function of jet/cold water velocity ratio (Figure 2); effect of the emulsification speed in the mixing cell (Figure 1c). Also alpha-Tocopherol loaded microparticles were prepared as a model drug delivery system and characterized by the particle size distribution, encapsulation efficiency, and the release profile of active substance. The particle size distribution was analyzed by a Horiba LA-920 particle analyzer. Encapsulation efficiency and release profile of the alpha-Tocopherol was determined by high performance liquid chromatography (HPLC).

Results and Discussion

Previously, the diameter ratio of 0.01 to 0.25 has been the focus of research for fluid-fluid mixing in the T-junction, hence, the detailed work on the velocity ratio of two streams, diameter ratio of jet and main flow, mixing length and the empirical correlations is available in the literature (Maruyama et al., 1981; Forney et al., 1982; 1986; 1990; 1996; 1999). As the goal of present setup was to solidify the emulsion droplets, the upper limit of the diameter ratio (0.25) was employed. Hence, the optimum velocity ratio was first evaluated (Figure 2) and eventually employed in the second set of experiments to create drug loaded microparticles from the emulsified melt.

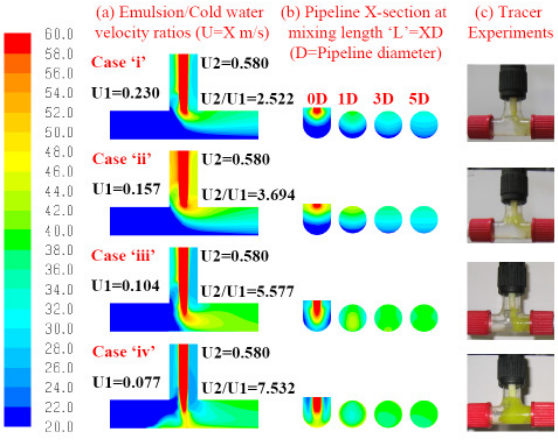


Figure 2: Heat and mass transfer for different velocity ratios

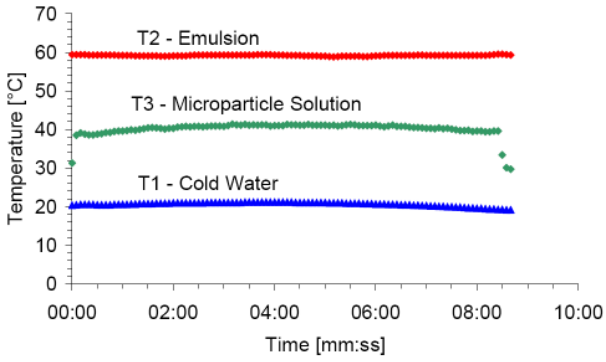
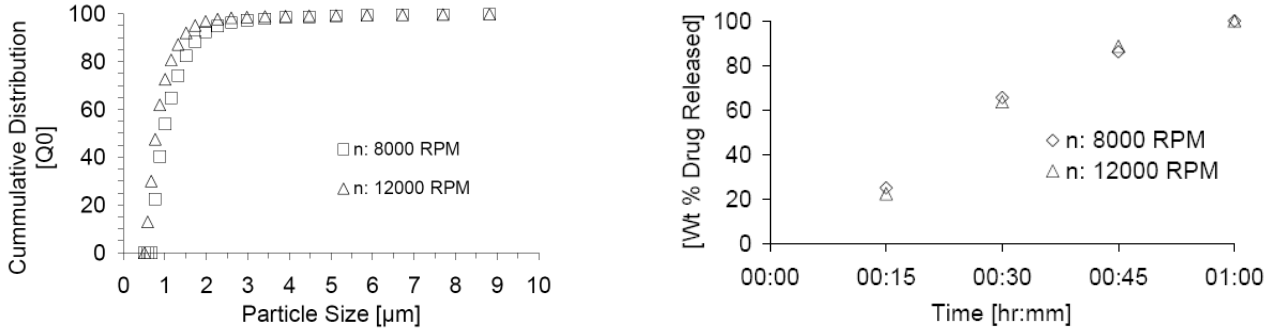


Figure 3: Microparticle formation due to continuous heat transfer in a T-junction

In the first set of experiments, the aqueous phase formed a jet stream and penetrated the cold water pipeline at a fixed velocity; a fluorescent tracer was added for optical evaluation of the mass transfer in the T-junction (Figure 2c). The case 'i' velocity ratio (2.52) was calculated by the

empirical relation given by Maruyama et al. (1981); it was observed that the jet (Figure 2a, case 'i') bent instantly at the injection point to form a parallel flow; and thus formed a layer on the upper wall of the pipeline; consequently, the two fluids did not mix optimally. The cross-sections of the pipeline at the length of 0, 1, 3 and 5 diameters (D: diameter of the pipeline) show the separation between the two streams because of insufficient radial mixing (Figure 2b, case 'i'), which results into relatively longer mixing length and hence, the non-optimal heat transfer. In the next experiment, the jet to pipe velocity ratio is increased to 3.69 by reducing the cold water velocity to 0.157 m/s. The resulting jet bent slightly after the injection point (Figure 2a, case 'ii'), which improved the radial distribution of the tracer. However, the parallel flow of the two streams was not eliminated due to insufficient penetration of the jet into the cold water stream. The temperature difference between the upper and lower wall of the pipeline (Figure 2b, case 'ii') showed little to no difference from the case 'i' and hence, the velocity ratio was still considered to be non-optimal

In case 'iii', the velocity of cold water stream was decreased to 0.104 m/s, hence, the velocity ratio increased to 5.57. The jet penetration in the cold water stream was now observed to be significantly better (Figure 2a, case 'iii'), that is, the jet bent at the pipeline axis and diffused in the cold water stream to result in the uniform tracer distribution; consequently, the tracer concentration (Figure 2c, case 'iii') was found to be uniform, which corresponded to the uniform temperature distribution in the respective CFD simulation (Figure 2b, case 'iii'). Thus, the required temperature drop was obtained in a mixing length of three pipeline diameters. The velocity ratio was further increased to 7.52 by changing the cold water velocity to 0.077 m/s; it was observed that the temperature distribution at three pipeline diameters was similar to that of case 'iii' (Figure2b, case 'iii' & 'iv'); however, the comparatively high velocity of the jet (Figure 2a, case 'iv') can damage the pipeline in continuous operation; therefore, the T-junction velocity ratios for emulsion systems are suggested to be 5.5±0.5. The mixing length 'L' is negligible as compared to the jet velocity (U2); therefore, it is concluded that the droplet size distribution does not change upon solidification and hence corresponds fully to the respective particle size distribution.



(a) Particle size distribution **(b) Release kinetics**

Figure 4: Drug Loaded Microparticles

In the second set of experiments, 10 wt % of alpha-Tocopherol was dissolved in molten beeswax, which was emulsified in the continuous phase at 8000 and 12000 RPM; the resulting emulsion was injected in the cold water stream (Figure 3) to solidify the emulsified droplets and thus alpha-Tocopherol loaded microparticles were formed (Figure 4a). The emulsion to cold water velocity ratio was kept constant at 5.5. The change in emulsification speed showed slight shift in the particle size distribution (Figure 4a); the increase in emulsification speed imparts a stronger impulse of energy in the system, which reduces the droplet size; hence the expected shift in particle size is observed. The change in emulsification speed did not seem to affect the encapsulation efficiency, which remained at 99 wt % for all experiments. The release kinetics of alpha-Tocopherol loaded

microparticles showed a sustained pattern (Figure 4b), which is typical of matrix structured drug formulations and did not seem to change the trend with the variation in the emulsification speed.

Conclusions

The experimental and computational evaluation of the fluid-fluid inline mixing length as a function of velocity ratio is presented, which was found to be 5.5 ± 0.5 for shortest possible mixing length. Moreover, a dissolved drug containing molten wax was emulsified in an aqueous phase; the injection of the resulting emulsion in the cold water stream produced microparticles, which can be employed as VOC-free drug delivery vehicles. Furthermore, the emulsification speed did not seem to have a significant affect on the release profile of the encapsulated drug. Also, lack of carrier-drug interactions led to the full recovery of encapsulated drug in one hour.

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