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Resistant maltodextrin as a shell material for encapsulation of naringin: Production and physicochemical characterization

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ABSTRACT

Herein the potential of a relatively new water soluble fiber, resistant maltodextrin (RMD) to encapsulate grapefruit polyphenol, naringin, using spray drying was evaluated. Full factorial Design Of Experiments (DOE) for spray drying with two levels of fiber-naringin ratio and spray dryer inlet temperature was executed. Resulting powders were characterized with respect to particle size and morphology, crystallinity, thermal properties, moisture sorption and naringin aqueous solubility increase. A 60-80% encapsulation was achieved. Thermal and moisture sorption behaviors of these dispersions were found to be dominated by RMD. By varying fiber-naringin ratio and spray drying temperatures, naringin was able to disperse in amorphous form in RMD matrix, which led to 20-55% increase in aqueous solubility. Solubility enhancement was found to correlate positively with increasing fiber: naringin ratio and spray drying temperature due to multiple factors discussed in this study. In conclusion, fiber-polyphenol bicomponent nutraceutical was successfully developed based on a well-established encapsulation technology i.e. spray-drying.

1. Introduction

Resistant maltodextrin (RMD) is a randomly linked alpha-glucoside oligosaccharide with an average degree of polymerization of 10-15. It is a low glycemic index (10% that of maltodextrin) (Goda et al. 2006), undigestible fiber with almost 40% being fermented into short chain fatty acids (SCFA) (Fastinger et al. 2008). Most of the research work on RMD reported so far in the literature has focused on the nutritional benefits such as increase in *bifidobacterium spp*. populations in colon (LeFranc-Millot et al. 2012, Vester Boler et al. 2011, Fastinger et al. 2008), increased satiety (Guérin-Deremaux et al. 2011), and increase in fecal weight (Timm et al. 2013, Vester Boler et al. 2011) which facilitates treatment of idiopathic chronic constipation (Braquehais and Cava, 2011). However, we have only come across one recent report (Chen et al. 2013) on use of RMD as an encapsulating material using spray and freeze drying processes which mainly focuses on sensory and stability profiles. Also, there have also been no reports on the fundamental solid state properties of RMD which could enable its usage for wider applications.

Naringin (NN) is the most prominent bioflavonoid in grapefruit juice and is also responsible for its bitter taste that leads to low consumer acceptance (Drewnowski et al. 1997). In a clinical study by Jung et al. (2003), an intake of 600 mg of naringin every day for 8 weeks was reported to a decrease of total cholesterol and LDL by 14% and 17% respectively. The bioavailability of flavonoids is limited by factors such as susceptibility to oxidation, degradation in acidic pH, poor water solubility and aqueous dissolution rates (Sansone et al. 2009). Naringin exhibits low water solubility (Lauro et al. 2007) which has been hypothesized as the rate limiting step for its absorption in the body (Kanaze et al. 2006a). Hence, solubility enhancement may be one of the ways, if not the ultimate one, to improve

bioavailability. Despite demonstrated health benefits, the bitterness and poor water solubility limit its use in processed foods. Microencapsulation is a popular technique used to overcome these formulation challenges (Gharsallaoui et al., 2007). There are a few reports in the pharmaceutical literature for encapsulation of naringin such as production of microparticles for respiratory drug usage (Sansone et al. 2009) and gastroresistant microparticles (Lauro et al. 2007), both using spray drying. Kanaze et al. (2006 a,b) attempted encapsulation of naringin in polyvinylpyrrolidone (PVP) and polyethylene glycol (PEG) matrices, using solvent evaporation method. These reported works were conducted using pharmaceutical grade shell materials which cannot be applied for application in food industry. Only Ficarra et al. (2002) and Cui et al. (2012) have reported formation of inclusion complex of naringin in food grade β-cyclodextrin that improves its solubility significantly. However, the high cost of β-cyclodextrin is an impediment for its use for food product development. Although research in this area is in preliminary stages, results have shown a very strong radical scavenging antioxidant capacity of a fiber-polyphenol combination in the digestive system. In a recent work, Saura-Calixto (2011) has discussed the important role of indigestible fibers in carrying polyphenols to the colon, followed by metabolism of these polyphenols into health beneficial end products. The goal of current work was to investigate the potential of RMD as an encapsulating shell material for naringin using spray drying. The specific objective is to understand the influence of RMD: NN ratio in the formulation and spray drying inlet temperature, on properties related to solid state stability as well as solubility enhancement of encapsulated naringin.

2. Materials and methods

2.1. Materials

Naringin was purchased from Sigma Aldrich chemical company (St. Louis, MO, USA). Resistant maltodextrin (Promitor 85 ™) was obtained from Tate & Lyle Co. (Chicago, IL, USA). Ultrapure water was obtained from Millipore Milli-Q® Gradient A10 water system. Analytical grade ethanol was obtained from JT Baker (Center Valley, PA, USA).

2.2. Methods

2.2.1. Spray drying DOE and preparation of physical mixtures

A 2^2 full factorial study was conducted for spray drying with the following variables: RMD solution concentration and spray drying inlet temperatures. A total of four, 100 mL naringin (3% w/v) suspensions were prepared by slowly adding the polyphenol to a solution of RMD prepared in ultrapure water, accompanied by stirring with a magnetic bar at 1000 rpm for 20 minutes. The RMD solutions were prepared at two concentrations (20 and 40% w/v). Spray drying was conducted in an amber colored spray drying chamber since polyphenols are usually light sensitive (Fang and Bhandari, 2010) at temperatures of 155 and 180 °C using a nozzle of 0.7 mm diameter and constant feed flow rate of 3 mL/min. The full experimental design and assigned formulation codes in shown in Table 1. Only one trial was carried out per combination of RMD concentration and spray drying inlet temperature.

Naringin (3% w/v) suspensions in water (100 mL) without any added fiber were also spray dried at 155 °C and 180 °C (coded as NN-155 and NN-180) to be used as controls for selected characterization measurements. All final powders from the spray dryer were stored in screw capped amber colored bottles within a dry box. Two physical mixtures of the same ratios as the one used for spray drying, PM1 (93 RMD:7 NN) and PM2 (87 RMD:13 NN) were prepared by blending the weighed powders in a Turbula mixer (WAB, Switzerland) at 15 rpm for 20 min. The final mix was stored in a dry box maintained at 20% RH in amber colored glass bottles. The spray drying outlet temperatures were found to range from 95±3 and 110±4 °C for inlet temperatures of 155 and 180 °C respectively. There was minimal sticking of powder to the spray drying chamber surface and the chamber was easy to be cleaned, both of which are desirable aspects for an industrial scale process.e

Table 1. Spray drying full-factorial DOE

Formulations with 3% w/v naringin	Concentration of RMD in spray drying slurry (% w/v)	Spray drying inlet temperature (ºC)
A	20	155
B	20	180
C	40	155
D	40	180

2.2.2. Particle morphology and size distribution

The morphology of pure RMD, NN, physical mixtures as well as final spray dried formulations were observed under JEOL JSM-6700F Field Emission Scanning Electron Microscope (FESEM) (JEOL Ltd, Japan), operating at an accelerating voltage of 5kV under lower secondary electron imaging (LEI) mode. Each sample was dispersed onto a carbon adhesive-coated metal stubs and sputter coated with platinum for 1 min at 20 mA using Cressington 208 HR Sputter Coater (Cressington Scientific Instruments Inc., UK) prior to analysis.

The particle size distribution of spray dried formulations was determined using laser diffraction technique (Mastersizer 2000, Malvern Instruments Ltd., UK). The analysis was conducted in a dry mode (Scirocco dry dispersion unit, Malvern Instruments Ltd., UK) for these measurements. All samples were measured in triplicates at a feed pressure of 3 bars, which was finalized following pressure titration and a feed vibration rate of 50%. All samples were passed through a sieve with ball bearings in order to ensure breaking up of agglomerates and obtain reproducible results.

2.2.3. Encapsulation efficiency measurement

Encapsulation efficiency (EE) of naringin was defined in Eqn. 1 as:

$$EE = \frac{Experimental\ naringin\ content}{Theoretical\ naringin\ content} \quad \text{(Eq. 1)}$$

In general, HPLC is the preferred method for quantification studies. Herein Folin-Ciocalteu method which is based on UV-Vis spectrometry and a specific method for polyphenol estimation was chosen for quantification of naringin. Specifically for naringin, Lauro et al. (2007) have reported UV-Vis spectrometry to be as reliable as HPLC measurements. It was found that RMD showed an absorbance peak at 286 nm, interfering with that of narignin, thus preventing direct use of UV-Vis measurement. Hence, the naringin content in each of the spray dried samples was measured using Folin-Ciocalteu method which is a specific method of analysis for polyphenols. A 2000 ppm stock solution was prepared by dissolving naringin in pure ethanol. Standard solutions of naringin (125-1000 μg/mL) were prepared to construct the standard curve, by suitably diluting the stock solution with ultrapure water. A 10 mL solution for final absorbance measurement was prepared by adding the necessary chemicals in the following order: 0.5 mL naringin standard solution + 4.5 mL ultrapure water + 0.2 mL Folin's reagent + 0.5 mL saturated sodium carbonate solution + 4.3 mL ultrapure water. The samples were then kept at room temperature for 1 h for full color development, following which the absorbance was measured in a 3 mL quartz cuvette at 975 nm using a UV-Vis spectrophotometer (Varian Cary 50, Agilent Technologies, US). Although the standard protocol for Folin-Ciocalteau method for detection of bluish complex is around 730-760 nm, this work has followed the measurement of peak at 975 nm according to the work of Espinosa et al. (2008).

For measurement of naringin content in spray dried samples, 100 mg of each spray dried formulation was completely dissolved in 5 mL of 1:1 ultrapure water- ethanol solvent mixture and stirred for 1 h to ensure complete solubility of the powders. The solutions were then passed through a 0.2 µm Nylon filter. A 10 mL aliquot for absorbance reading was prepared, composed of 0.5 mL sample extract and rest, all chemicals as described for standard curve preparation. 3 mL of the sample was used to measure the absorbance at 975 nm. Everette et al. (2010) have shown minimal to no reactivity of the Folin's reagent with an extensive range of carbohydrates which does not include RMD. Hence, 0.5 mL of 100 mg RMD dissolved in 5 mL of solvent was used as a blank solution for absorbance measurements. All samples were analyzed in triplicate.

2.2.4. Powder X-ray diffraction (PXRD)

PXRD was employed to qualitatively detect the presence of crystalline NN phase within the structure of the encapsulated composite as well as the physical mixtures of the naringin and RMD. The samples were loaded onto a 1 mm thick Poly Methyl Methacrylate (PMMA) circular sample holder and 16 mm diameter. The analysis was carried out on a Bruker D8 Advance X-Ray Diffractometer (Bruker AXS GmbH, Germany) equipped with a Nickel-filter, 0.3° divergence slit and a linear position sensitive detector (Vantec-1). Measurements were performed using monochromatized Cu Kα radiation (λ = 1.5406 Å), with a scanning rate of 2° per minute between diffraction angles (2 θ) *of* 4° to 55° at room temperature. The diffractometer was operated at 35 kV and 40 mA.

2.2.5. Thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC)

The weight changes of the samples were measured using Simultaneous DSC-TGA (SDT Q600, TA Instruments, USA). Approximately 20 mg of sample was used per trial in an alumina crucible. The samples were heated at a rate of 5°C/min from 25 °C to 400 °C. Nitrogen was used as a purge gas with at 100mL/min flow rate. All samples were analyzed in duplicate.

Thermal analysis of all samples was performed using PYRIS Diamond DSC Calorimeter (PerkinElmer, USA). About 5mg of each sample was placed in a hermetically closed aluminum pan. The sample was heated from 25 °C to 200 °C at a rate of 10 °C/min after an equilibration of the samples at 25 °C for 10 min. The samples were purged with a stream of flowing nitrogen at 25 mL/min.

2.2.6. Dynamic vapor sorption (DVS)

Moisture sorption isotherms of pure RMD, naringin and all spray dried samples were obtained at 25 °C by employing the gravimetric vapor sorption technique (DVS Advantage 1, Surface Measurement Systems, UK). By varying the Relative Humidity (RH) from 0 to 95% in steps of 10%, any mass changes during sorption/desorption on the samples were recorded. A mass change rate of 0.005%/min^{-1} over a 5 min interval was used as a limit to determine attaining of equilibrium in order to proceed to the next humidity step in the cycle. Analysis was conducted with an initial sample mass of 15 -25 mg. Each sample was subjected to two cycles of adsorption-desorption. Only one measurement per sample was possible due to long experimental times (4-5 days).

2.2.7. Aqueous solubility of naringin

The solubility of naringin in ultrapure water was measured using the USP solubility method. An excess of pure NN, NN-155, NN-180 and each of the four spray dried samples was dissolved in 10 mL of ultrapure water. The samples were stirred at 1000 rpm for 4 h in a light protected environment. The samples were then centrifuged at 11600 g for 15 min. Since centrifugation was not sufficient to obtain a clear solution, the supernatant was filtered through a 0.2 µm Nylon filter. The naringin content in 0.5 mL of supernatant of each sample was measured using Folin-Ciocalteu method as described in Section 2.2.3. All samples were analyzed in triplicate.

3. Results and discussion

The spray drying of NN and RMD were performed at temperatures of 155 and 180 °C and the results are discussed.

3.1. Particle size distribution and morphology

The particle morphology of RMD, NN and spray dried particles are shown in Figure 1 A-F. RMD particles were found to be smooth and spherical in nature while naringin particles were needle shaped (Figures 1A and 1B respectively). All spray dried particles were found to be smooth, spherical in nature with smaller particles sintered on larger ones. No traces of needle shaped naringin particles were found for spray dried formulations B,C and D, indicating the possible conversion of naringin into an amorphous

form and forming a composite particle with RMD. For formulation A, few smooth needle shaped particles were found indicating encapsulation but possible incomplete conversion of naringin to an amorphous form. The particle size distribution measured from laser diffraction was found to be unimodal and varied between 0.15-32 μm for all the final spray dried formulations (Figure 2). The d_{10}, d_{50} and d_{90} of the formulations are shown in Table 2. The median particle size was found to vary between 5.6-6.9 μm. Although increase of RMD loading from 20 to 40% was found to increase the viscosity by ~ 7.5x (data not shown here), the influence on final particle size distribution was found to be insignificant. Our results are in agreement with the observations of Vicente et al. (2013) who have shown for a two-fluid atomizing nozzle such as the one used for this research, that feed viscosity has a minor impact on final particle size.

Table 2. The 10th percentile, median and 90th percentile of particle size distribution for all spray dried formulations.

Formulation	d_{10} (μm)	d_{50} (μm)	d_{90} (μm)
A	1.40 ± 0.08	6.24 ± 0.18	14.03 ± 0.38
B	1.56 ± 0.02	5.58 ± 0.08	12.01 ± 0.09
C	1.56 ± 0.07	6.38 ± 0.19	14.24 ± 0.20
D	2.20 ± 0.08	6.86 ± 0.14	14.90 ± 0.30

3.2. Encapsulation efficiency of naringin

The encapsulation efficiency of naringin in each of the formulations is shown in Figure 3. An increased fiber loading from 20 to 40% (w/v) was found to increase the encapsulation efficiency from 60 to 80% most probably due to an increase in the thickness of microparticle shell walls. Balasubramani et al.

(2015) and Kha et al. (2010) have reported increase in encapsulation efficiency when carrier (maltodextrin) concentrations were increased. They attributed the increase to the additional protection offered by the higher concentration of the carrier solids in the feed. Lauro et al. (2007) have reported that naringin, which is considered as a poorly soluble drug, has tendency to undergo phase separation and stick to the dryer surface, thus resulting in poor encapsulation efficiency. Thus, increasing RMD loading possibly increased the encapsulation efficiency due to reduced phase separation. From Figure 3, the effect of temperature of encapsulation is unclear with slight decrease at 20% RMD loading and a slight increase at 40% RMD loading. Hence statistical analysis using 2-factor ANOVA was used to analyze the results which confirmed the insignificant effect of temperature on encapsulation efficiency ($p<0.05$) but highly significant influence of fiber loading (p- value $2.34 * 10^{-7}$).

3.3. Powder X-ray diffraction

The X-ray diffractograms of RMD, naringin, physical mixes and spray dried forms are shown in Figure 4. Naringin was found to be a highly crystalline material as confirmed by various peaks in the diffractogram (a in Figure 4) in agreement with the work of Ficarra et al. (2002). On the other hand, RMD was found to be represented by a fully amorphous halo (b in Figure 4). Based on extensive literature research, we believe this to be the first report of RMD X-ray diffraction pattern. For both physical mixtures PM2 and PM1, four of the most prominent peaks from naringin diffractogram at angles of 4.4º, 9.8º, 14.5º and 16.59º were detected, confirming the presence of naringin in a crystalline form (Curves c-d in Figure 4). The respective peak intensities for the PM1 were also found to be lower than that of PM2, consistent with its lower naringin content.

The X-ray diffractograms of spray dried naringin controls NN-155 and NN-180 show that an increase in spray drying temperature from 155 to 180 ºC resulted in a decrease of peak intensity, which indicated a decrease of degree of crystallinity (Figure 4). These results are in agreement with the works of Ueno et al. (1998), and Sahoo et al. (2009) who also reported decreasing crystallinity of API with increasing spray drying temperatures. Among spray dried formulations, other than formulation A, rest (B, C &D) were found to be fully X-ray amorphous indicating conversion of crystalline naringin to amorphous form. For formulation A, the peaks were observed at the same diffraction angle as that of physical mixtures but at intensity lower than that of PM1. Although the degree of crystallinity was not measured in this work, from the peak intensities, it could be inferred that of the total naringin in this formulation (~7.8%), a considerable portion still existed in a crystalline form which was also observed in SEM images. The presence of crystalline naringin in Formulation A could be the result of drying kinetics as influenced by inlet air temperature, which is described in detail by Paudel (2013) as follows: A lower drying temperature results in "Tetris effect" that occurs during slow solvent evaporation and provides sufficient time for molecular stacking or reorganization, hence facilitating phase separation or at worst, to nucleation/recrystallization. Due to a combination of lower RMD content (which could facilitate aggregation of NN molecules) and lower drying rates, re-crystallization of a portion of naringin might have occurred. On the other hand, a higher temperature results in faster solvent evaporation rate, resulting in a "rush hour effect" during which the fast diffusion is followed by turbulent mixing of the components without getting time for reorganization or ordering, hence low possibility of recrystallization. This phenomenon is most probably the driving force for obtaining a fully amorphous powder for formulation B, which was dried at 180 °C.

The fully amorphous structures for formulations C and D were most probably a result of naringin being well dispersed in the presence of larger RMD matrix, thus preventing their re-organization in a crystal

form. Feed concentration is directly proportional to Peclet number and hence inversely related to the evaporation time (Paudel et al. 2013). Thus, the overall higher solids concentration at 40% RMD loading could have also lead to lower drying time resulting in the formation of a fully amorphous naringin dispersed in a RMD matrix.

3.4. Thermal analysis

The results of TGA and DSC analysis of naringin, RMD and all spray dried formulations are shown in Figure 5. In TGA profiles, a mass loss of approx. 5.2% was observed for all samples between 25 to 100 °C, which could be ascribed to the loss of surface water. While the onset of naringin decomposition was found to be around 250 ºC as shown by the significant mass loss, the decomposition of pure RMD and all spray dried formulations was around 275 ºC. Notably, the TGA profiles of all spray dried samples were found to overlap with that of pure RMD.

DSC profiles show that for naringin, a broad endothermic heat flow with an onset of 154ºC and peak of 162 °C was observed. This was the melting point of naringin which was confirmed by visual observation using Buchi melting point apparatus. Our observation is in agreement with the reports of Kanaze et al. (2006 b) and Cui et al. (2012). For RMD, a small peak was observed at 170 °C, which was confirmed to be the glass transition temperature (T_g = 170.7 °C). None of the spray dried formulations showed melting point of naringin, although XRPD showed the presence of naringin crystals in formulation A. Plausible cause could be the solubilization of naringin in the glassy RMD matrix at the slow rate of heating (10 °C/

min) used for DSC experiments. Kanaze et al. (2006b) have reported detection of crystalline naringin in solid dispersions of PVP using XRPD but absence of naringin melting in DSC. The authors attributed this phenomenon to the miscibility of the two materials. Furthermore, a decrease in T_g for all spray dried formulations was observed (Table 3), which is also consistent with the report of Kanaze et al. (2006b) that was ascribed to the plasticizing effect of naringin on PVP. In conclusion, DSC experiments indicated the miscibility of naringin in RMD matrix and its plasticizing effect when dispersed in the fiber.

Table 3. Glass transition temperature (for all samples except naringin) and naringin melting point were estimated by DSC.

Sample	T_g (℃)
Pure RMD	170.77 ± 0.18
Pure NN	161.83 ± 0.13 (T_m ℃)
Formulation A	155.78 ± 0.43
Formulation B	164.82 ± 0.32
Formulation C	152.49 ± 0.25
Formulation D	167 ± 0.21

T_g or T_m data presented in triplicate (n=3); T_m – melting point of pure naringin.

3.5. Moisture sorption behavior

The moisture sorption behavior of RMD, naringin and spray dried formulation B is shown in Figure 6. The other formulations (A, C and D) were found to show sorption behavior similar in nature with that of formulation B and hence are not displayed on the graph. Naringin exhibited a Type II sigmoidal shaped sorption isotherm as described by Andrade et al. (2011). It was found to absorb moisture, corresponding

to a moisture gain of 5% at all RH above dry conditions up to a RH of about 65%. The moisture loss in the TGA curve of naringin (Figure 4) up to a temperature of 100 ºC and the one measured in drying curve for 360 min prior to start of adsorption cycle were both equal to approx. 5%. No endothermic peaks were observed in the DSC, confirming this moisture to be loosely bound surface water. Beyond 65% RH, the polyphenol rapidly absorbs moisture and stabilizes at approx. ~ 18% moisture gain. On desorption, naringin completely loses the water of hydration reverting back to its anhydrous form.

On the other hand, RMD was found to exhibit extremely hygroscopic type III sorption behavior (Andrade et al. 2011) consistent with oligosaccharides such as maltodextrins, which have shorter polymer chain lengths and more hydrophilic groups (Tonon et al. 2009; Cai and Corke, 2000). The maximum moisture sorption was found to correspond to 41.36% w/w on a dry basis. On continuous exposure to high humidity, RMD irreversibly converts into a glassy gel like material which is represented by residual moisture content of 10%, after complete desorption. A second adsorption-desorption cycle was found to completely follow the first desorption curve and exhibited no hysteresis, confirming the irreversible change in moisture sorption behavior due to gel like structure formation. To the best of our knowledge, this is the first report on RMD moisture sorption. This irreversible change in physical form could pose a significant challenge for the stability of final product formulated using RMD.

The moisture sorption patterns of spray dried formulations were found to be almost superimposable with that of RMD. Since the naringin content in all spray dried formulations was very low (5.6-7.8%), its overall contribution towards moisture sorption was expectedly insignificant. The sorption part of the isotherm was fit to GAB model as shown in Equation 2 using MATLAB curve fitting tool ® (Mathworks, MA, USA). In Eq.2, M_w and a_w are the equilibrium moisture content (g/g dry solids) and water activity

(RH/ 100) respectively. M_0 is the monolayer moisture content while C and K are the adsorption constants related to the energies of interaction between the first and the further sorbed molecules at the individual sorption sites (Andrade et al. 2011). The estimated model parameters are shown in Table 4. Moisture sorption data for all powders was found to be a good fit with the GAB model (R^2> 0.99) and the parameters for spray dried formulations were found to be similar to that of pure RMD confirming its dominance for moisture sorption.

$$M_{\mathrm{w}} = \frac{M_0 C K a_{\mathrm{w}}}{(1 - K a_{\mathrm{w}})(1 - K a_{\mathrm{w}} + C K a_{\mathrm{w}})} \quad \text{(Eq. 2)}$$

Table 4. GAB model parameters and correlation co-efficient estimates for pure RMD and all spray dried samples.

Formulation	M_0 (g g^{-1})	C	K	Model fit (R^2)
Pure RMD (Control)	0.07778	3.778	0.8667	0.9995
A	0.07196	4.495	0.8482	0.9980
B	0.0731	3.725	0.8698	0.9991
C	0.06705	5.437	0.8832	0.999
D	0.07101	4.481	0.8496	0.9986

3.6. Naringin water solubility increase

Sansone et al. (2009) have reported a rapid decrease in naringin water solubility with dissolution time following attaining of equilibrium within a span of 60 min. They experimentally demonstrated the cause for this phenomenon to be recrystallization of naringin upon contact with water. The saturation

solubility in current work was measured after 4 h of dissolution and hence can be assumed to be made at equilibrium of lowest saturation solubility.

The water solubility of naringin was found to be 0.98 ± 0.08 g/L, which is close to the reported 1.1 g/L by recent findings (Lauro et al. 2007; Sansone et al. 2009; Prota et al. 2011). The absolute measurable solubility of naringin in the spray dried formulations and controls, are shown in Figure 7. For the spray dried formulations other than A, an increase of naringin solubility in the range of 20-55% was observed. Increasing RMD content in the solution from 20% to 40% and spray drying inlet temperature from 155 °C to 180 °C were both found to increase the solubility, indicating their significant influence. To the best of our knowledge, this is the first report of achieving naringin water solubility enhancement resulting from encapsulation using a food grade polymer and water as the sole solvent for spray drying. Sansone et al. (2009) have reported a maximum of 50x increase in water solubility for naringin that was measured at 37 °C for only first 5 min. However, their strategy was based on use of ethanol as a co-solvent (naringin is freely soluble in ethanol) in equal proportions with water. Cui et al. (2012) have reported an increase in solubility of 15x, which was due to formation of inclusion complex of naringin in β-cyclodextrin. However, they used a dropping method which is not a technology that can be scaled up.

The naringin controls spray dried at 155 °C and 180 °C exhibited statistically insignificant increases in solubility compared to native naringin, which was expected due to their high degree of crystallinity. For formulation A, a major portion of naringin existed in a crystalline form which was responsible for its low solubility. On the other hand, naringin was converted to a fully amorphous form in formulations B,C and D resulting in greater saturation solubility. Another critical factor that could have contributed towards solubility increase is the reduction of naringin particle size. Although not measured, from SEM micrographs it can be inferred that native naringin particle size was much larger compared to that in the

spray dried dispersions. Thus, achieving a stable dispersion of smaller particles of naringin in RMD facilitated by spray drying might be another factor for achieving solubility enhancement.

Sahoo et al. (2009) have reported increase in solubility of poorly soluble anti-malarial drug artemisinin with increase of spray dryer inlet air temperature and polymer: drug ratio. However, they attributed this observation to the decrease in crystallinity of the solid dispersions. In current work, a difference in solubility was observed for formulations B, C andD, despite all powders being in an amorphous form. More recently, Li et al. (2013) have reported increase in solubility of naringenin (aglycone of naringin) when amorphous solid dispersions were formed with increasing polymer (PVP, HPMCAS etc.) component in the drug-polymer blend. They attributed the differences in observed solution concentration to the differences in release rate caused in part by polymer solubility, and the degree of the interaction between polymer and naringenin in solution, which is likely impacted by factors like polymer hydrophobicity, specific interactions, polymer flexibility, and degree of polymer charge. They experimentally demonstrated that the more hydrophilic the encapsulating polymer, the higher the final solution concentration of the poorly soluble drug. In current work, the encapsulating polymer (RMD) is highly water soluble and increasing its proportion in the formulation led to the observed increase in solubility. We hypothesize the existence of weak interactions between RMD and naringin, which are enhanced at higher RMD: naringin ratio, leading to this solubility enhancement. Using quantum calculations, Liu et al. (2012) have shown that the hydroxyl group on the aromatic ring of naringin molecule not linked to the rhamnose to be most likely to be involved in hydrogen bonding.

One possible explanation for increase of NN solubility with temperature is the miscibility of the system as demonstrated in DSC experiments. Higher spray drying air contact temperatures might have caused

greater amount of naringin to solubilize in the glassy RMD matrix resulting in a molecular dispersion with significant solubility enhancement.

4. Conclusions

To the best of our knowledge, this is the first report of solid state properties of RMD such as amorphous nature, moisture sorption and thermal properties. In the current study, naringin was encapsulated in a RMD matrix using spray drying. This work demonstrated the production of amorphous dispersions of naringin in RMD matrix, whose solubility can be enhanced by increasing the RMD: naringin ratio and spray drying temperature. The solubility enhancement was the result of conversion of naringin to an amorphous form, its stabilized dispersion in form of smaller particles in the RMD matrix and possibly, partial molecular dispersion with increased temperature. Finally this work describes the development of a soluble fiber-polyphenol bicomponent nutraceutical using industrial technology such as spray drying and a low cost solvent (water).

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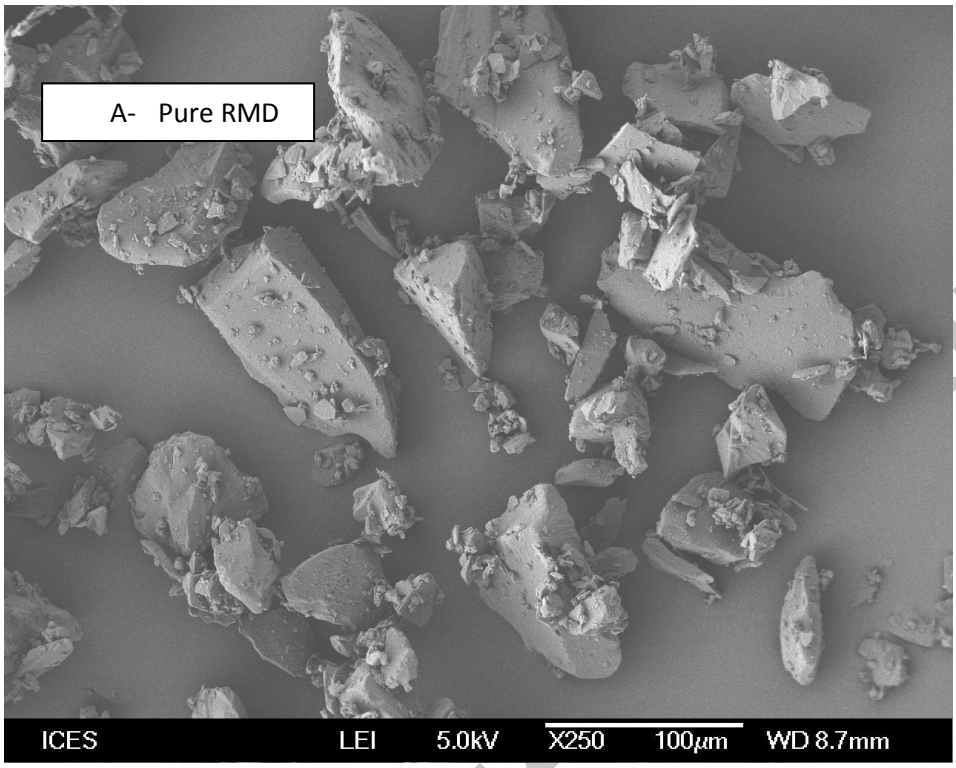

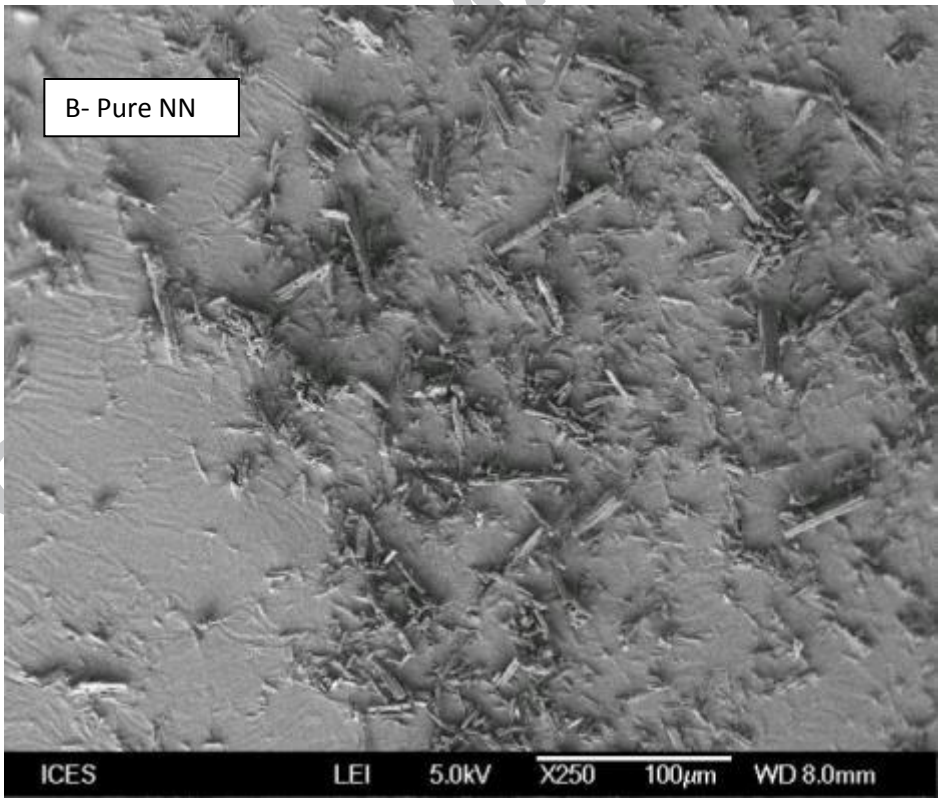

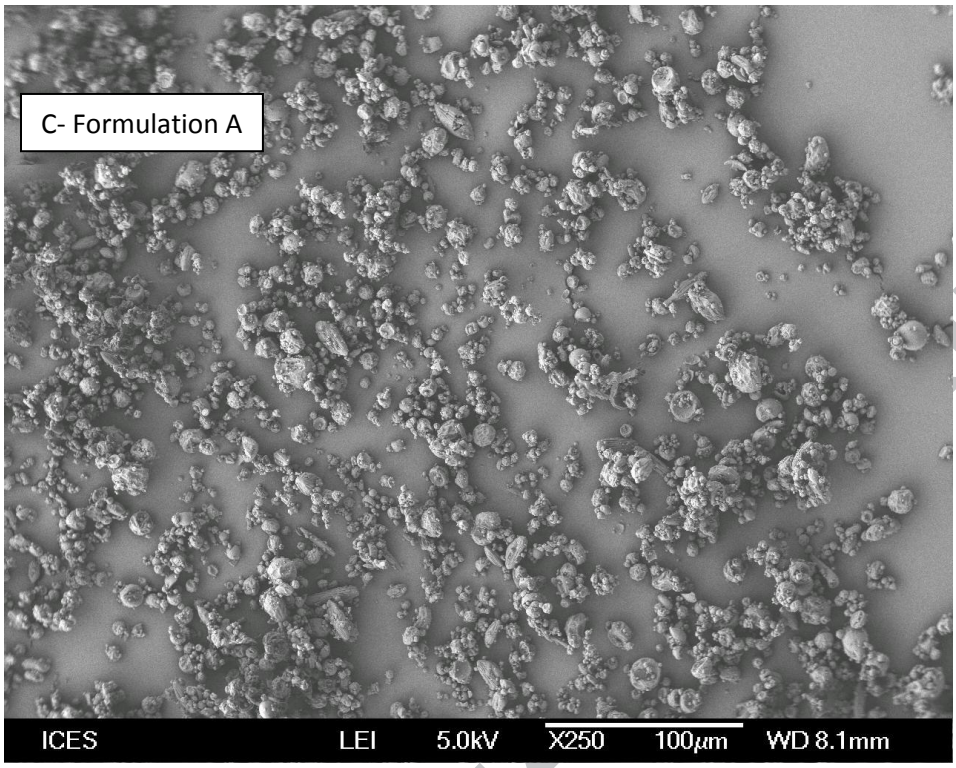

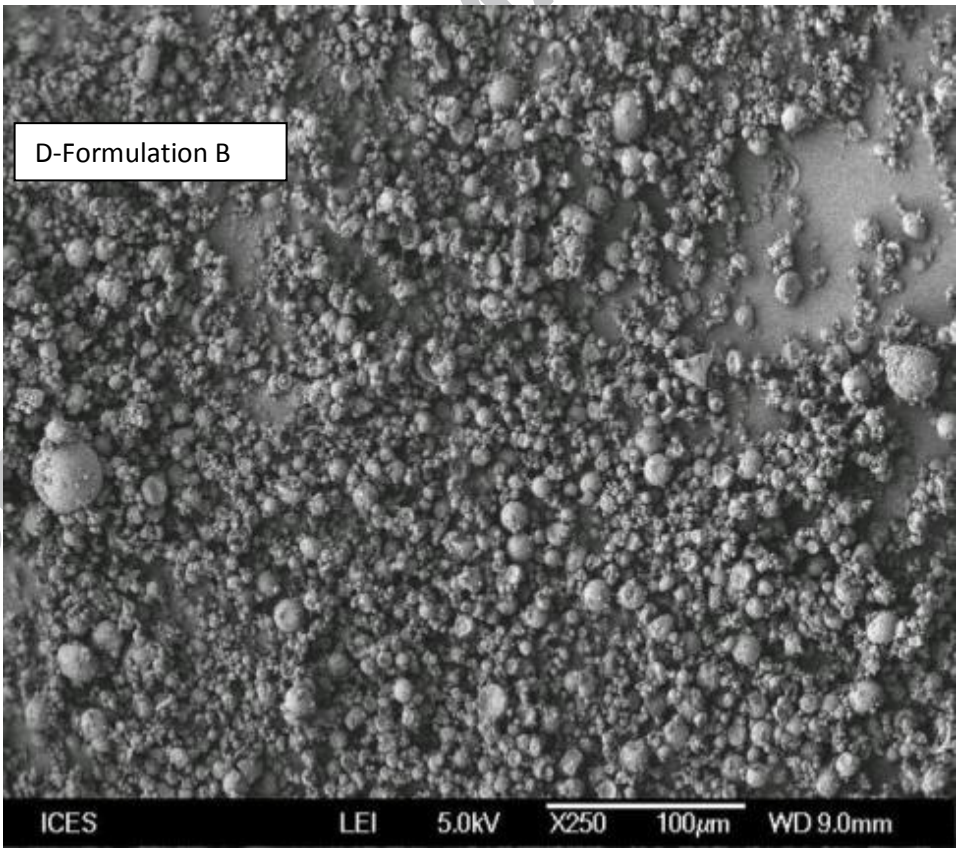

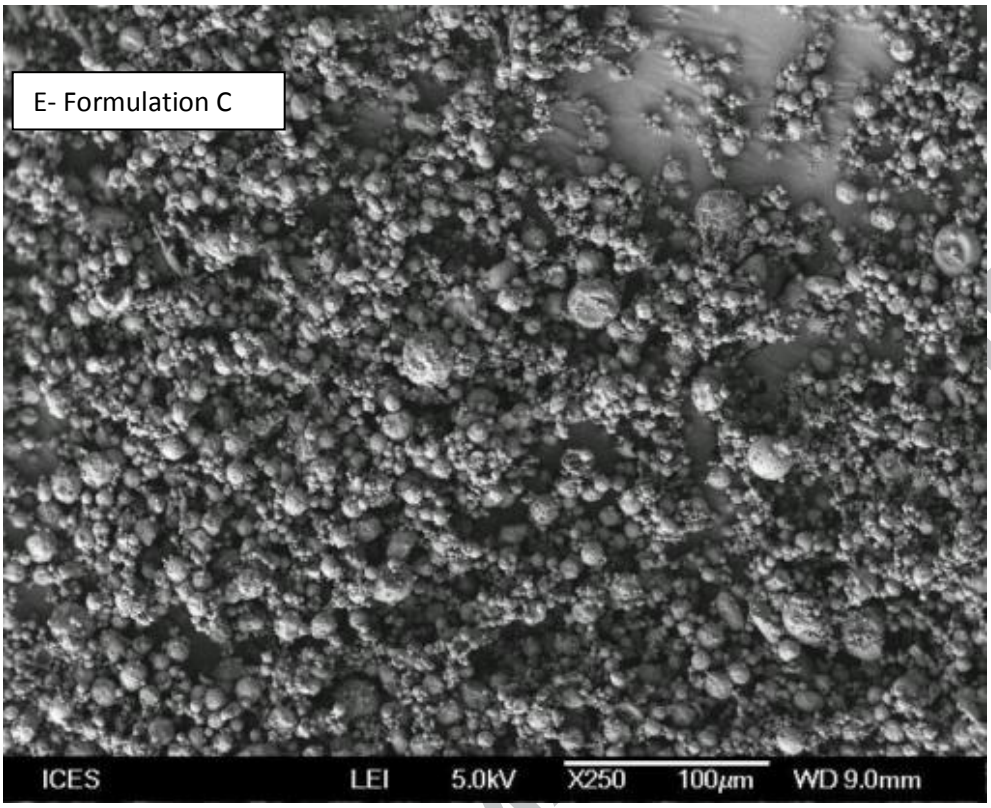
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ICES
LEI
5.0kV
X250
100μm
WD 9.0mm

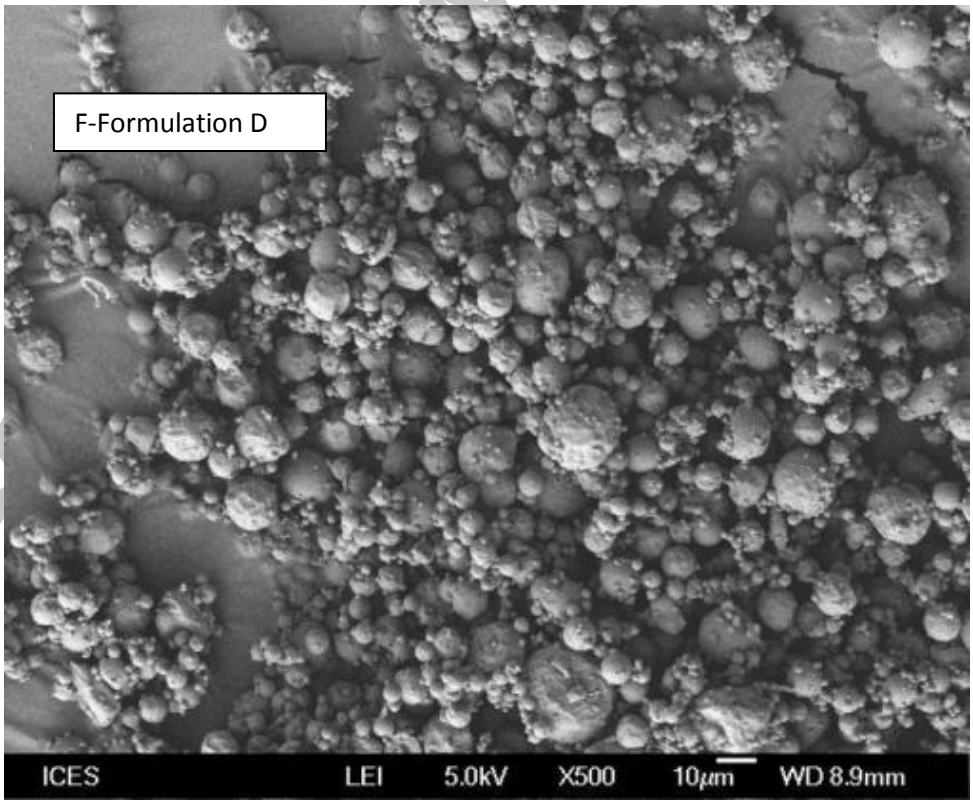
F-Formulation D
ICES
LEI
5.0kV
X500
10μm
WD 8.9mm

Figure 1. Particle morphology of pure starting materials and spray dried formulations: (A) Pure RMD (B) Pure Nn (C) Formulation A (D) Formulation B (E) Formulation C (F) Formulation D.

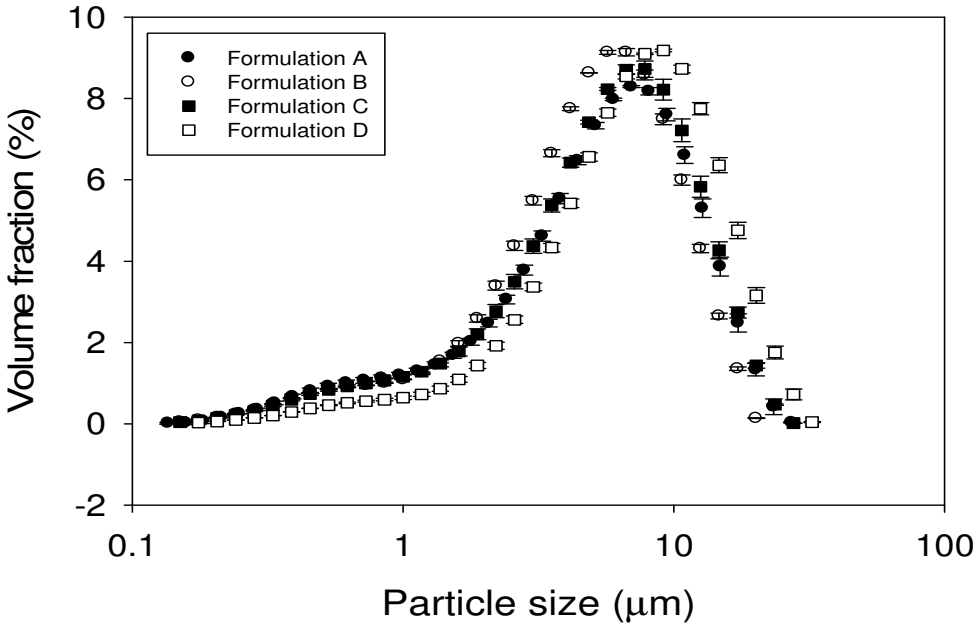

Figure 2. Particle size of formulations measured using laser diffraction. Error bars indicate standard deviation (n=3).

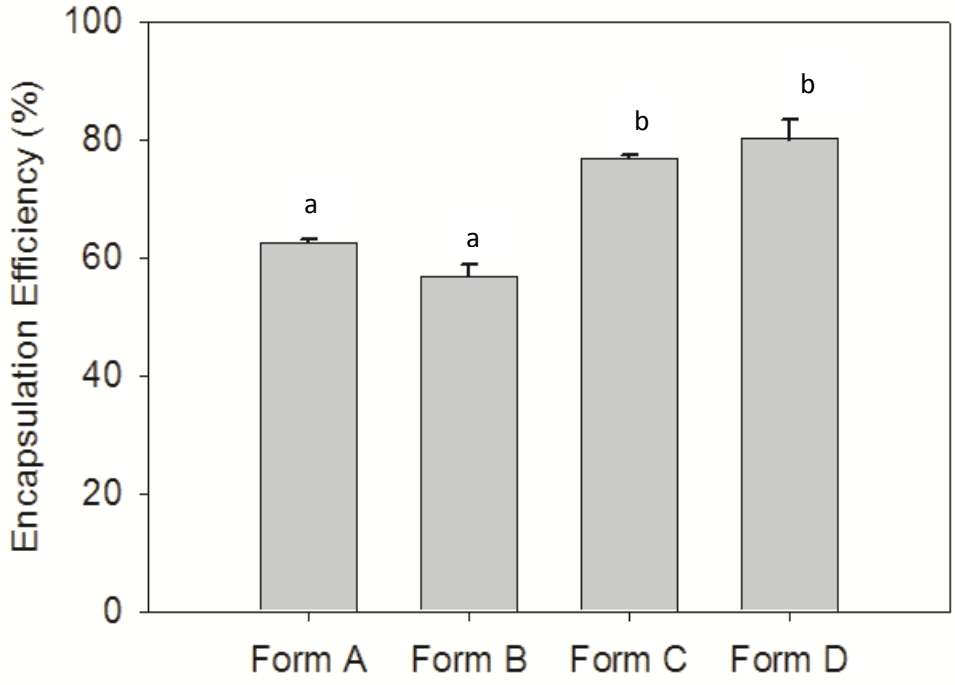

Figure 3. Encapsulation efficiency of naringin in spray dried formulations. Error bars indicate standard deviation (n=3). Bars marked 'a' and 'b' indicate statistically significant difference in encapsulation efficiency ($p<0.001$)

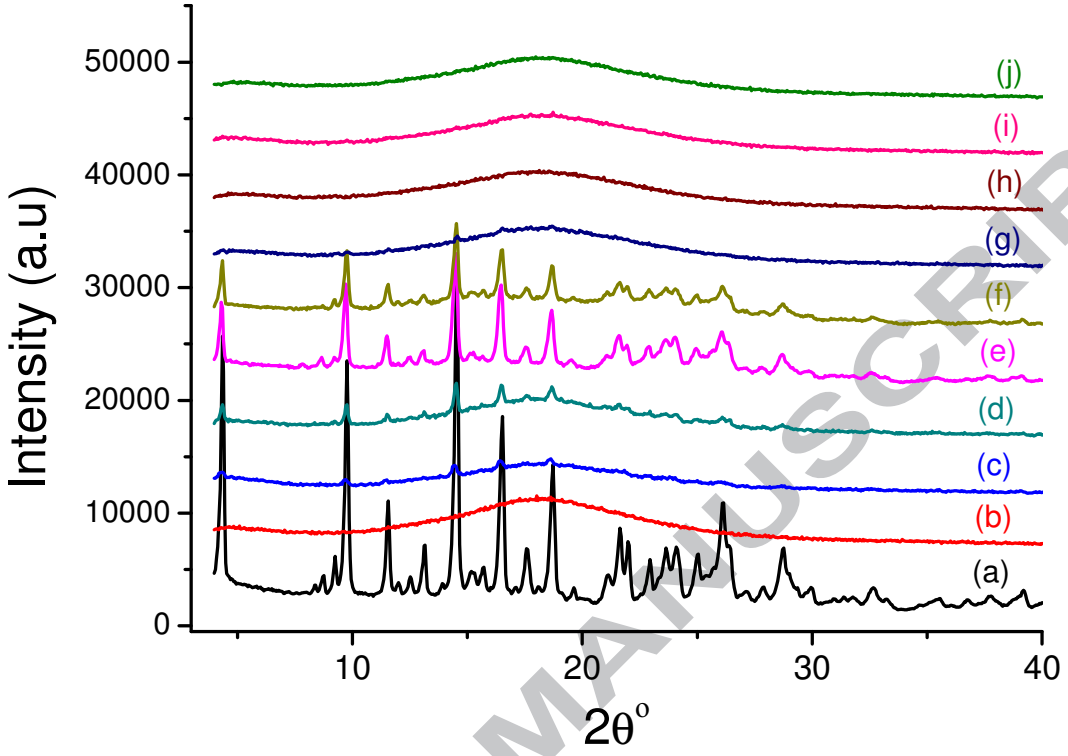

Figure 4. X-ray diffractograms of (a) Pure NN, (b) Pure RMD, (c) PM1, (d) PM2, (e) NN155, (f) NN180, (g) formulation A, (h) formulation B, (i) formulation C, and (j) formulation D.

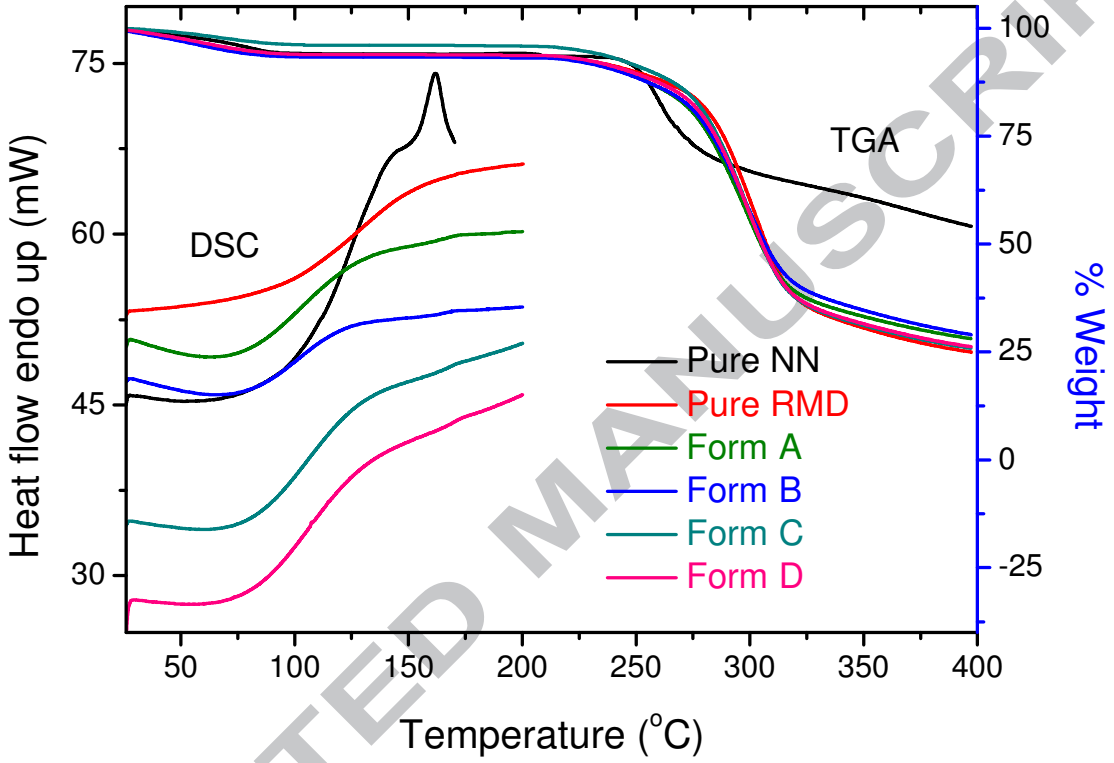

Figure 5. TGA and DSC profiles of pure materials and spray dried formulations.

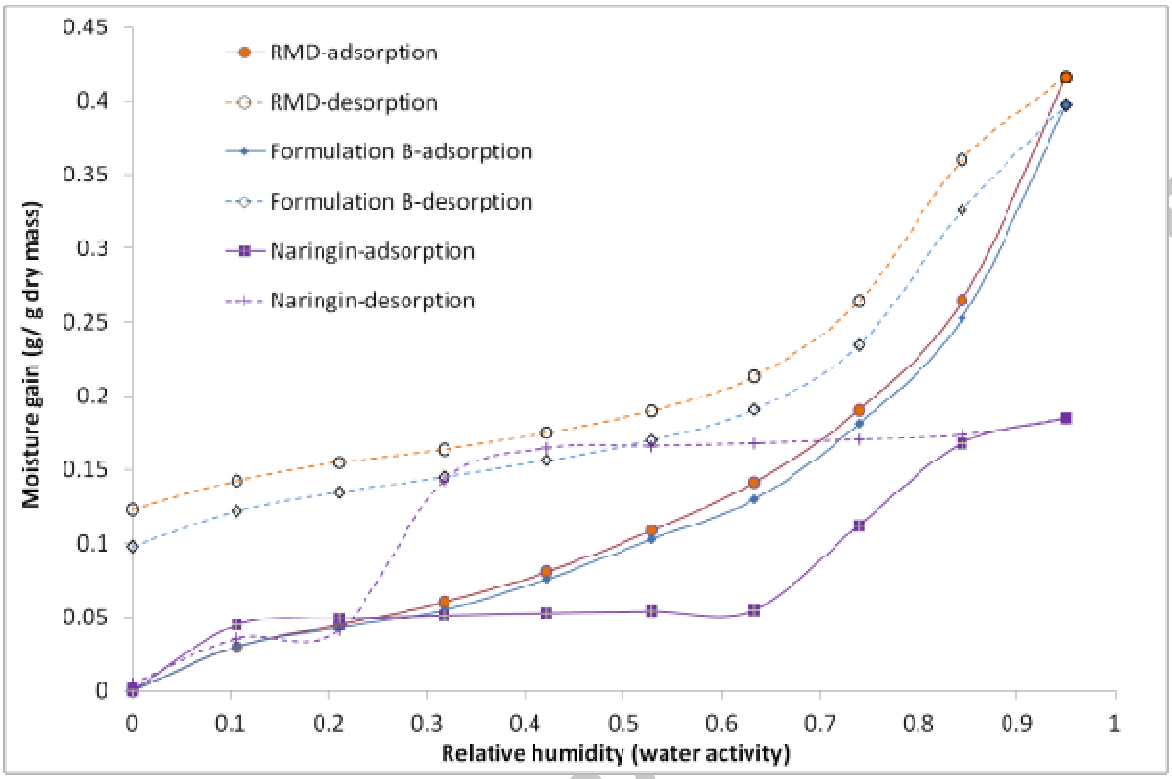

Figure 6. Moisture sorption isotherm (first cycle) of Pure naringin, RMD and spray dried formulation B.

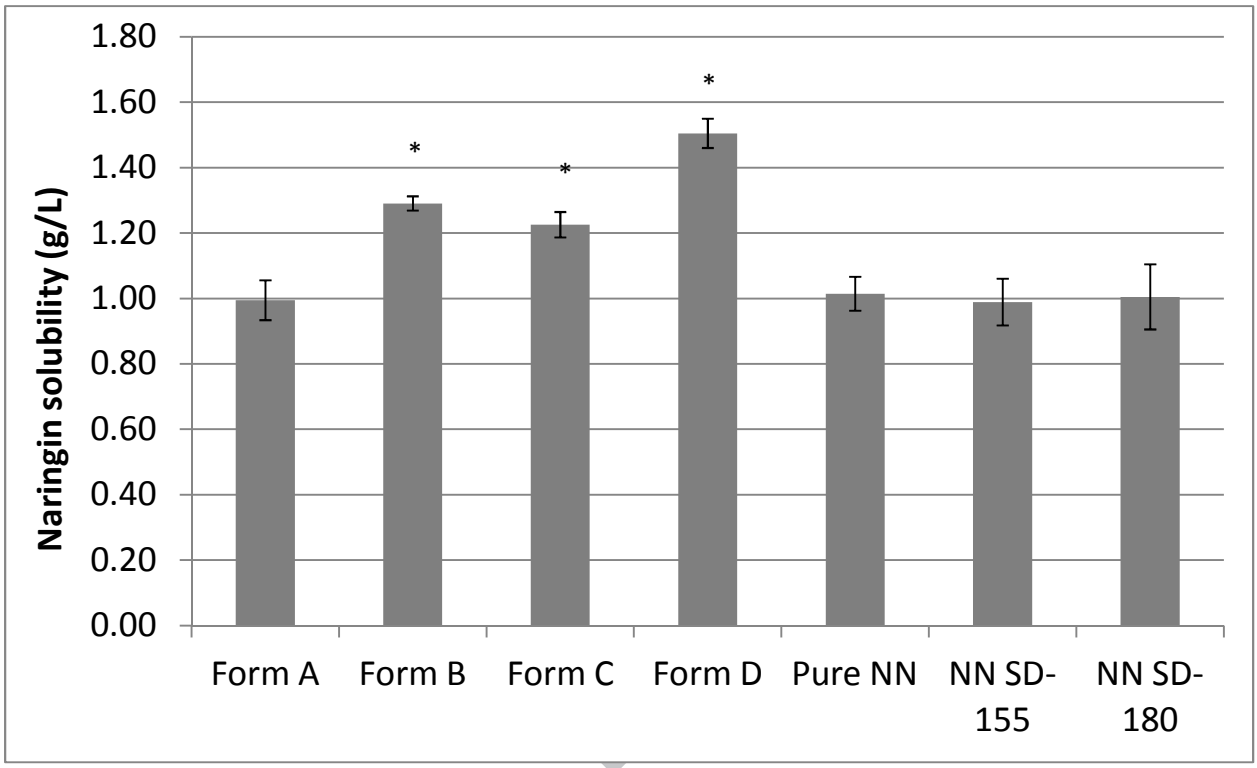

Figure 7. Increase in aqueous solubility of naringin in spray dried formulations A to D and controls, compared to pure naringin. Error bars indicate standard deviation (n=3).

***-Solubility differences are statistically significant ($p<0.05$)**

Highlights

- First report of solid state properties of a relatively new water soluble fiber, resistant maltodextrin (RMD).
- Demonstrated the potential of the RMD as an encapsulating shell material for polyphenol, naringin.
- The results suggest the production of amorphous dispersions of naringin in RMD matrix, which led to a 20-55% increase in aqueous solubility.
- Developed a soluble fiber-polyphenol bicomponent nutraceutical using industrial technology like spray drying and a low cost solvent (water).