Research Articles

Indian Journal of Agricultural Sciences **85** (12): 1523–8, December 2015/Article

Development of spray freezer for production of freeze granulations

DARSHAN M B[1], ABHIJIT KAR[2] and DEBABANDYA MOHAPATRA[3]

ICAR-Indian Agricultural Research Institute, New Delhi 110 012

Received: 4 April 2015; Accepted: 26 June 2015

ABSTRACT

Spray freezer is an essential component of spray freeze drying (SFD) technique to produce microspheres during encapsulation. In this study, a lab scale spray freezer unit was developed to produce freeze granulations, which could be used for encapsulation of bio-pigments and other useful bio-active compounds. The components of spray freezer were spray nozzle, freezing chamber, magnetic stirrer, feed reservoir, homogenizer, peristaltic pump, air compressor, liquid nitrogen tank and hose fittings. The maltodextrin 'MD' solution (10%) was atomized into liquid nitrogen using spray freezer to produce freeze granulations and these granulations were freeze dried to obtain spray freeze dried maltodextrin (SFDMD) particles. The produced SFDMD particles were characterized and compared with classical freeze dried maltodextrin (FDMD) particles to evaluate the performance of spray freezing unit. The drying period for producing maltodextrin granules in SFD and freeze drying (FD) technique was between 12 to 24 and 36 to 48 hr, and their % moisture absorption was found to be 2.37 and 2.17%, respectively. The SFD technique produced microspheres of maltodextrin with particle size ranging from 2 to 60 µm, whereas FD technique produced irregular macro-size flakes. The morphological studies revealed that SFD microstructure particles had smooth surface and freeze dried particles had rough surface; however, porous appearance was observed in both samples. There were no significant differences in colour values; however, the flow properties of SFDMD particles were relatively better than FDMD particles. The developed spray freezer can be used for production of freeze granulations during SFD technique.

Key words: Atomization, Encapsulation, Freeze granulation, Microspheres, Spray freezer

Spray freeze drying (SFD) is a modification of the lyophilisation procedure with an additional unit operation, spray-freezing, to create discrete spherical particles of a defined size. This process consists of the atomization of a liquid solution into a cryogenic gas or liquid with instant freezing of the generated droplets followed by sublimation of the ice at low temperature and pressure during freeze-drying. The benefit of SFD over classical freeze-drying (FD) or spray drying (SD) is that the particle size of the final powder can be well controlled, as it mostly depends on the atomization conditions during spray-freezing (Schiffter 2007). In contrast, the final particle size during SD will be influenced by a number of factors including atomization conditions, solution concentration and evaporation rate. Furthermore, particles with a diameter of 50 mm and narrow size distribution cannot be achieved easily in a laboratory SD system, as the residence time of large droplets in the drying chamber is not sufficiently long enough (Masters 1991, Maury *et al*. 2005). Microsphere size is about 2-fold larger in case of spray drying compared to SFD under the tested conditions (Burke *et al*. 2004). FD does not lead to distinct particles, but rather to the well-known cake structure that has to be disaggregated in a subsequent step; leading to a very wide particle size distribution with a substantial fine powder fraction.

In SFD, spraying yields spherical particles of controllable size, fast cooling of the small droplets minimizes the risk of phase separation during freezing. The ideal preparation of a powder suspension by applying colloidal processing combined with sufficient mechanical treatment, which provides optimal homogeneity, can be preserved by freezing and subsequent freeze-drying. The ice leaves voids producing a rigid porous product that helps in the drying process by providing pathways through the material for vapour deposition, while enabling the product to rehydrate quickly through capillary action (Stapley and Rielly 2007). The pharmaceutical industry utilized the SFD for pharmaceutical powders preparation (Costantino *et al*. 2000, 2002, Maa *et al*. 1999, Maa and Prestrelski 2000, Webb *et al*. 2002). SFD powders have a controlled size, larger specific surface area and a better porous character than spray-dried

[1]Assistant Research Engineer (e mail: darshandachan@gmail.com), All India Coordinated Research Project on Post Harvest Technology, University of Agricultural Sciences, GKVK, Bengaluru, Karnataka 560 065; [2]Senior Scientist (e mail: abhijit8366@yahoo.com), Division of Food Science and Post Harvest Technology, Indian Agricultural Research Institute, Pusa Campus, New Delhi; [3]Senior Scientist (e mail: debabandya@gmail.com), Agro-Produce Processing Division, Central Institute of Agricultural Engineering, Bhopal, Madhya Pradesh 462 038

powders. The particles retain their spherical and porous morphology and can be further coated with an enteric food grade biological polymer which is designed to disintegrate at specific loci in the gastrointestinal track. The advantages of this procedure also include high yields, control over granule density, the absence of cavities in the granules and high degree of granule homogeneity, as there isn't any migration of small particles or binder taking place. Additionally, the SFD process doesn't involve any capillary action and shrinkage of the droplet due to elimination of the evaporation step, so the achieved homogeneity and density of the granule are retained after sublimation (Nyberg *et al*.1993).

SFD technique can be best solution to produce encapsulation of heat sensitive bio-pigments, probiotics, vitamins, and other bio-active compounds. Therefore, it is very important to develop a spray freezer to control the product size and shape, as drying rate in freeze dryer largely controlled by product size and shape. The SFD unit is sophisticated equipment; its availability is limited to few developed countries. In the present scenario, conducting the experimental trials using SFD technique on encapsulation is very essential. To the best of our knowledge, the SFD technique has not been used yet to encapsulate the beta carotene and other pigments. Our survey revealed that neither commercial SFD unit nor spray freezers are available in India for production of encapsulated products. Therefore, in the present investigation, we developed a laboratory scale spray freezer unit considering several process parameters in order to produce spray freeze microspheres using SFD technique. The performance of the developed unit was tested using maltodextrin 'MD' solution (10%) to produce atomised freeze granulations and compared with the existing FD technique.

MATERIALS AND METHODS

The design parameters such as nozzle size, operating pressure, feed flow, capacity, cost and safety measures were considered during development of spray freezer. The different components used in development of spray freezer were spray nozzle, freezing chamber, feed reservoir, peristaltic pump, air compressor, liquid nitrogen tank, magnetic stirrer, hose and pipe fittings. Liquid Nitrogen was used as freezing medium to produce freeze granulations of maltodextrin solution. The materials and specifications of different components used in development of spray freezer are discussed as follows.

Two fluid glass nozzles (CIPHET model, Central Institute of Post Harvest Engineering and Technology, Ludhiana, India) having 0.8 mm nozzle size (internal diameter of opening) were locally manufactured using glass as nozzle material. Length, width and thickness of glass layer of nozzle were 165, 25 and 1 mm, respectively. There were two concentric channels - internal taper type channel for feed flow and external cylindrical bulb type for air flow. Both channels were connected to respective inlets through an integral bent having 5 and 6 mm inner diameter for air and feed inlet, respectively. The internal tapered end of feed channel formed a tip of inner ring with fixed diameter 2 mm with varied thickness 1.6, 1.4 and 1.2 mm to form nozzle size opening 0.8 mm at center, respectively. The outer concentric bulb was tapered at nozzle head to form an annular space with 1 mm thickness for air outlet.

The desiccator type freezing chamber was procured from local glassware supplier, which consisted of two halve-bottom bowl and upper closure. The bottom bowl was made up of polypropylene having 300 mm diameter with 20 mm collar at top and 170 mm height including 30 mm base. The top closure was made up of polycarbonate having 295 mm diameter with 15 mm collar and 180 mm height. The top closure was drilled to 30 mm wide opening at centre to hold the nozzle with the help of ring cork. The bottom side of closure had outlet for atomized air and cryogenic gas. Both bowl and closure were resistance to corrosion and can withstand very low temperature of liquid nitrogen. The whole freezing chamber was placed over a magnetic stirrer (MT2A 576Amicon, USA) to avoid agglomeration by generating the flow currents in liquid nitrogen during the experiments.

Feed reservoir or feed tank was a simple plastic beaker (one litre) procured from reliable chemical glassware laboratory. The homogenizer (IKAT25, Ultra turrax, Germany) was used to avoid settlement of emulsion in the feed tank.

Peristaltic pump (3200, Welch, USA) having maximum pumping capacity of 140 ml/min (water) was procured from Bengaluru, India. The flow rate of feed was controlled by the speed of the pump using speed knob. The speed range of peristaltic pump was 0 to 200 rpm and calibration curve of pump for 10% maltodextrin was similar to water (data not shown).

Air compressor (Model: ZA-0.12/8) having 1 hp motor and 8 l capacity was procured form TengzhouUni Tech Co Ltd, China. The maximum air flow rate and maximum pressure of compressor was 120 l/min and 8 kg/cm, respectively. The pressure gauge and control valve were provided with air compressor. For the experimentation, the air pressure was kept below 1 bar.

Dewar flask was used as liquid nitrogen tank to store liquid nitrogen and the pure liquid nitrogen for studies was supplied freely by the liquid nitrogen unit, Defense Research and Development Organization, New Delhi, India. Suitable hose, pipes, joints (connectors) and fittings were provided with peristaltic pump.

Different components of spray freezer unit were properly assembled with the help of suitable hose, pipes, joints (connectors) and fittings as shown in AUTOCAD outline diagram. The whole freezing chamber was placed over a magnetic stirrer to avoid agglomeration by generating the flow currents in liquid nitrogen during the experiments. Liquid nitrogen was used as freezing medium for producing freeze granulations of MD solution. The MD solution (10% w/v) was prepared with hot distilled water,

cooled at room temperature and sprayed into liquid nitrogen using spray freezer to produce atomised freeze granulations. The process parameters of spray freezer such as nozzle size (0.8 mm), feed flow rate (30 ml/min) and air compressor (0.25 bar) were kept constant to obtain freeze granulation of MD solution. The spray freeze granules obtained from spray freezer were kept at -80°C for 30 min to achieve equilibration and dried in two cycles using freeze dryer (7753020 LABCONCO, FreeZone12 PRAMA, USA). During first cycle of freeze drying, the freeze granulations were placed in a freeze dryer at -55°C and 0.125 millibar for different drying time (12, 24, 36 and 48 h). Prior to withdrawal of samples from drying chamber, MD granules were heated for second cycle at 20°C for 30 min using heater. The final spray freeze dried maltodextrin (SFDMD) particles were subjected to characterization such as hygroscopsity, particle size, surface morphology, bulk and tapped densities, flow properties.

For comparison studies, the classical freeze dried maltodextrin (FDMD) samples were obtained by layer freezing of 10% (w/v) maltodextrin solution in borosillicate flask using shell freezer (LABCONCO, PRAMA, USA) at -55°C for 4 h followed by drying in a freeze dryer (7753020 LABCONCO, FreeZone12 PRAMA, USA) at -55°C and 0.125 millibar vacuum for drying time of 12, 24, 36 and 48 h. Prior to withdrawal of samples from drying chamber, the granules were heated at 20°C for 30 min similar to SFD technique. As FDMD samples were obtained in flakes form, they were also crushed and passed through 152 µm sieve (BSS 100) to obtain micro particles and subjected to characterization. All trials in SFD and FD methods were conducted in five replications.

The SFDMD and FDMD samples obtained for different drying time (12, 24, 36 and 48 hr) were subjected to water activity 'a_w' analysis to estimate drying time at which samples achieved a_w of 0.4. Water activity of dried samples was measured using a Water Activity Meter (Rotronic probe AW d-210) with three standard reference liquids having fixed a_w at a constant temperature of 25°C. About 3g of the sample was placed in the sample holder and the direct reading of a_w was noted down for five replications. Hygroscopsity of the samples were measured using the method described by Musa *et al*. (2011) with little modifications. Two g of the samples poured in an evaporating dish were exposed to atmospheric condition by placing them in open space and left for 24 h. The final weight of sample was recorded and percentage loss was calculated. The number of replications taken for hygroscopicity measurement analysis was five and results were expressed in % moisture absorption.

Particle size distribution of samples obtained by SFD and FD method was performed by using laser scattering particle size distribution analyser, PSDA (Partica: LA-950V2, Horiba, Japan). The analysis range of the instrument was 0.010 µm to 3000 µm. To avoid agglomeration of particles, prior to particle size analysis 1 ml of 0.25% ethanolic polysaccharide solution was sonicated within the instrument. The morphological studies of samples were characterized using scanning electron microscope, SEM (Zeiss EVO MA 10, Germany) operating at acceleration voltage of 20 kilovolt under 53 Pascal with different magnifications (100 X to 25000 X). The sample was prepared by coating with gold and palladium before exposure to SEM.

The L^*, a^*, b^* color values of SFDMD and FDMD granules were measured using Hunter-Lab Colorimeter (Miniscan® XE Plus 4500 L, USA) as described by Dutta *et al*. (2011). Both metric chroma (C^*) and metric hue angle (H^o) are calculated by the transformation of the a^* and b^* using the following equations (1 and 2) as described by Ersus and Yurdagel (2007):

$$C^{*2} = (a^{*2} + b^{*2})^{1/2} \quad (1)$$

$$H° = \tan^{-1}(b^*/a^*) \quad (2)$$

Flow properties of SFDMD and FDMD granules such as bulk density, tapped density, Hausner ratio, Carr's compressibility index and angle of repose were measured using following methods. The bulk density was determined by filling the granules into a tarred graduated cylinder to the 100 ml mark. The graduated cylinder was weighed and the bulk density was calculated as the ratio of the sample weight to the sample volume. The graduated cylinders were then tapped for 3 min (which was found practically to be enough time) from a height of about 2 inches till constant volume was obtained. The tapped density was calculated as the ratio of the sample weight to the final sample volume (Phadke and Anderson 1990). Hausner ratio was calculated as the ratio of the tapped density to the bulk density (Alanazi *et al*. 2008). Carr's index was the percentage ratio of the difference of both densities to the tapped density (Malamatris *et al*. 1994). Angle of repose was measured by the fixed funnel and free standing cone method to observe the flow properties of granules (Banker and Anderson 1986). The method employed a funnel secured with its tip at a given height (H), above the graph paper placed on horizontal surface. Samples were poured through the funnel until the apex of the conical pile touches the tip of the funnel. The radius (r) of the base of the pile was determined and the angle of repose (u) was calculated by the following equation (3):

$$\tan = \left(\frac{H}{r}\right) \quad (3)$$

The capacity of developed spray freezer unit was evaluated using 10% maltodextrin solution at 30 ml/min flow rate of peristaltic pump. The weight of maltodextrin granules produced after freeze granulation was measured using electronic balance.

The results are presented with their means and standard deviation using Microsoft Office Excel 2010.The hygroscopicity and colour comparison of samples were statistically analysed using student t-test and analysis of variance (single factor), respectively, at asignificance level of 0.05 using Excel 2010.

RESULTS AND DISCUSSION

Water activity of dried MD at four different times (12, 24, 36 and 48 hr) using SFD and FD techniques are presented in Table 1. The result of drying characteristics showed the decreasing trend of a_w with increased drying time (Fig 1). The SFDMD samples took 12 to 24 hr to achieve a_w of 0.4, whereas it was 36 to 48 h for FDMD particles. Therefore, SFD technique took lesser drying time to achieve 0.4 a_w of maltodextrin compared to FD. There was a significant difference ($p<0.05$) in % moisture absorption values of SFDMD (2.37% ±0.155) and FDMD (2.17% ±0.026). However, it was observed that both samples were hygroscopic in nature.

The histogram of particle distribution of SFDMD granules and particles obtained from FD after crushing and sieving, are presented in Fig 2a and Fig 2b, respectively. PSDA showed SFDMD granulations had narrow particle distribution with median size 16.12 µm, mean size 17.09 µm and mode size 21.32 µm. But FDMD particles had broad size distribution, where more than 90% were below 152 µm due to the effect of crushing and sieving after drying. The median, mean and mode size of FDMD granulations were 60.43, 67.72 and 82.52 µm, respectively. SFD techniques produced micro particles whereas, grinding is essential for classical freeze dried products to obtain micro size.

The SEM image of raw maltodextrin, MD (Fig3a) revealed that particles had spherical shape with rough surface and shrinkage. This may be due to the effect of spray drying on particles during its production.The morphological study showed SFD technique produced microspheres of maltodextrin (Fig 3b), whereas classical FD method produced large macro size flakes (Fig 3c and Fig 3d). Micro particles from classical FD method (Fig 3e and Fig 3f) was obtained only after crushing and passing through sieve (BSS 100) having size of 152 mm. SFDMD microspheres were homogenous in nature with spherical in shape and smooth surface, whereas FDMD flakes and FDMD micro-particles had irregular shape with rough surface morphology. In both SFD and FD method, the sublimation of ice leaved voids producing a rigid porous product that helped in the drying process by providing pathways through the material for vapour deposition. This porous surface of products made them more hygroscopic. However, it could facilitate the product to rehydrate quickly through capillary action. The color values of SFDMD and FDMD micro particles were compared with MD. The *L*, a*, b*, C** and H^o values indicated that all three samples were lighter in color. For all three samples, there were no significant differences ($P>0.05$) in color values; therefore, both the techniques not affected the final products.

The flow properties such as bulk density, tapped density, Hausner ratio, Carr's compressibility index and angle of repose are often referred to as the derived properties of powder, which depend mainly on particle size distribution, particle shape and tendency of the particles to adhere together. The bulk density and tapped density of SFDMD were found to be 0.51(±0.002) and 0.57 (±0.002) g/ml, whereas it was 0.64 (±0.004) and 0.78 (±0.004) g/ml for FDMD particles, respectively. The powder with Hausner's ratio less than 1.18, 1.19 to 1.25, 1.3 to 1.5 and greater than 1.5 indicates excellent, good, passable and very poor flow

Table 1 Water activity 'a_w' of SFDMD and FDMD granules at different drying time

Drying time in first cycle of freeze drying (hours)*	Water activity 'a_w' (Mean values± standard deviation, n=5)	
	Spray freeze dried maltodextrin particles (SFDMD)	Freeze dried particles (FDMD)
12	0.46 ± 0.006	0.62 (±0.000)
24	0.40 (±0.021)	0.51(±0.006)
36	0.37(±0.015)	0.42(±0.015)
48	0.30 (±0.017)	0.39(±0.012)

*Drying time in second cycle of freeze drying (30 minutes) was kept constant for all samples.

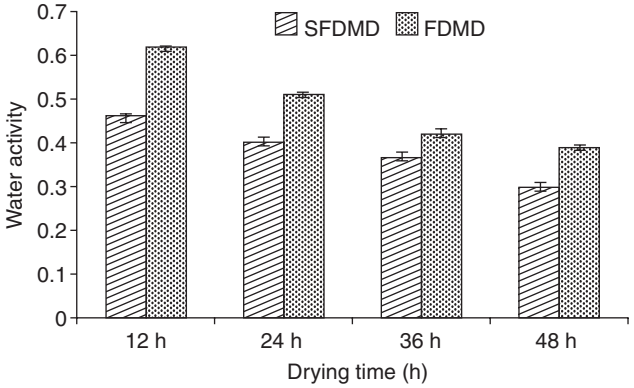

Fig 1 Drying characteristics of maltodextrin during SFD and FD techniques.

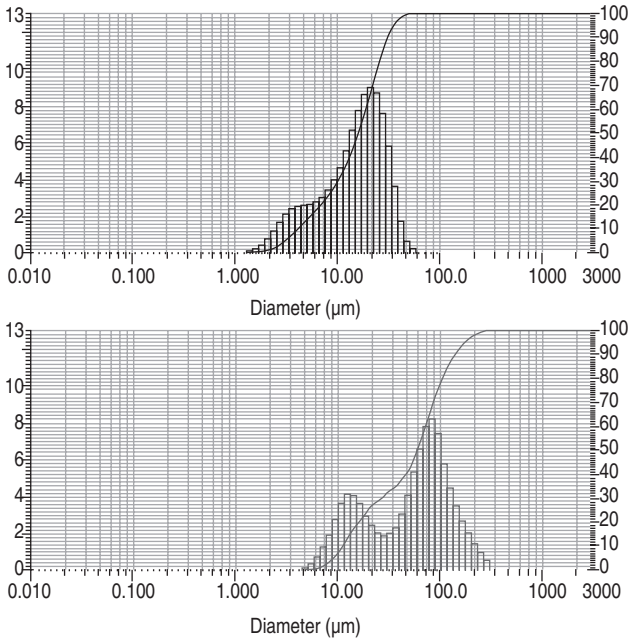

Fig 2 Histogram of particle size distribution for (a) SFDMD and (b) FDMD granules.

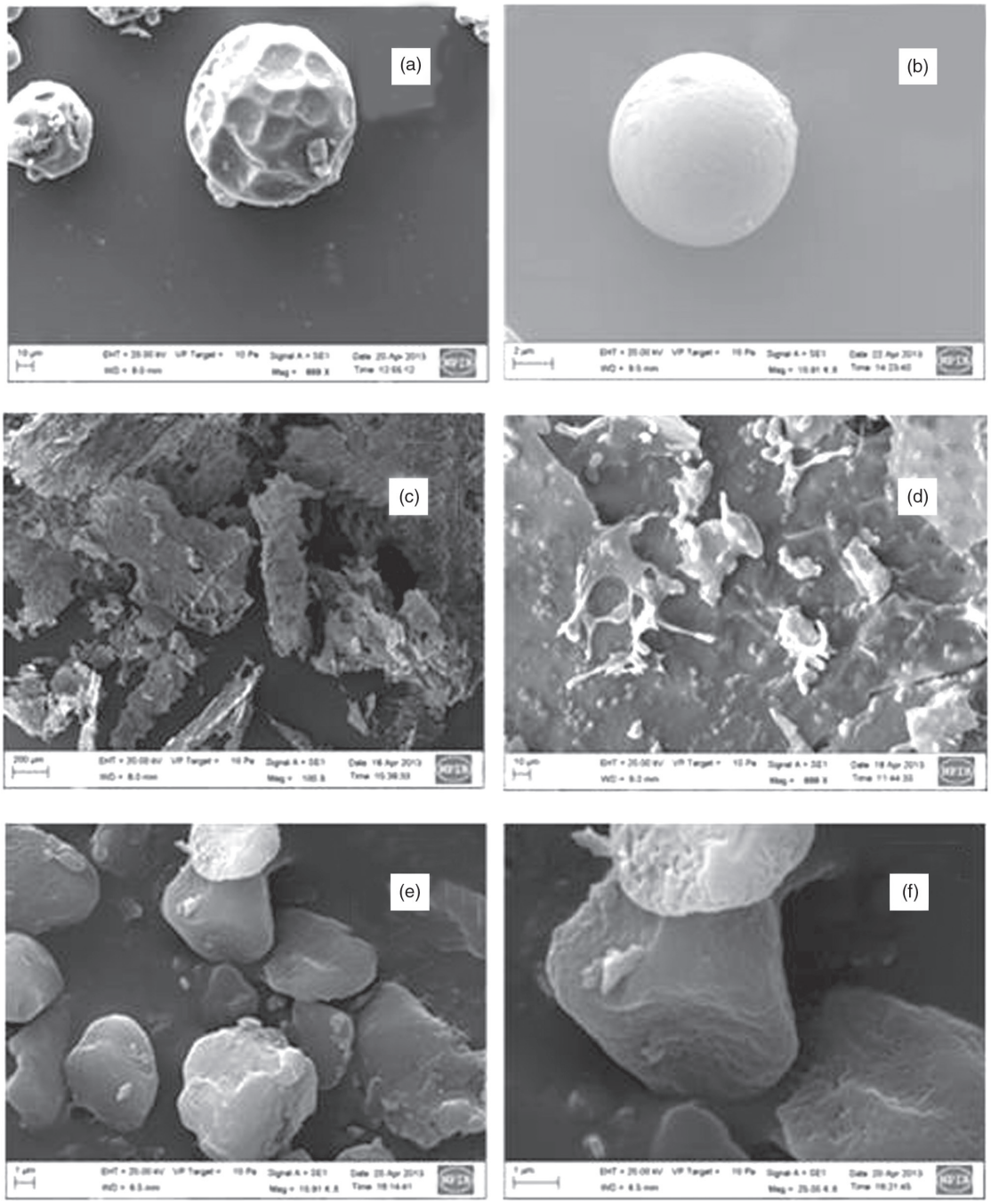

Fig 3 SEM images of maltodextrin granules (a) Raw MD, (b) SFDMD microsphere, (c & d) FDMD flakes, and (e & f) FDMD micro particles with porous surface (after crushing and sieving)

properties, respectively (Staniforth 1996). Hausner ratio of SFDMD (1.13±0.007) was lesser compare FDMD particles (1.21±0.008); indicated that SFDMD had excellent flow properties compare to FDMD particles. Carr's indexes 5 to 15 and 15 to 20 indicate excellent and good flowability, respectively; a value greater than 21 indicates poor flow (Fieseand Hagen 1986; Patel *et al*. 2008). Therefore, Carr's compressibility index also confirmed SFDMD (11.67%) and FDMD (17.33%) had excellent and good flowability, respectively. Hausner ratio (< 1.34) and Carr's index (< 25%) are considered to be acceptable (Djuris *et al*. 2012), therefore, both SFDMS and FDMD particles could be considered to be accepted. A static angle of repose greater than 40° indicates a cohesive powder and greater than 50° indicates a very cohesive powder (Cain 2002). In our study, the angle of repose indicated that SFDMD (33.15^{o} ±0.62) were less cohesive due to its spherical shape and less hygroscopic nature compare to FDMD granules (39.23^{o} ±0.20). Although Hausner ratio, Carr's compressibility index and angle of repose of FDMD granules found to be accepted but their flow properties were not excellent. Results revealed that flow properties of MD could be improved by SFD technique. SFD technique could also be used for drying hydrolyzed starches during production of

maltodextrin with excellent flow properties. The capacity of the spray freezer unit was matched with the capacity of the feed pump. For 30 ml/min flow rate of 10% maltodextrin solution, the spray freeze unit produced 26.8 g freeze granulations per min.

It may be concluded that the developed laboratory scale spray freezer unit successfully produced spray freeze granules and also facilitated fast drying of granulations and production of homogenous micro-particles in SFD technique. Low a_w of samples can be achieved at a faster rate in SFD technique, as compared to FD. Production of micro particles in freeze drying needs additional unit operations like crushing and sieving. SFDMD granules had spherical and smooth surface, whereas FDMD had rough surface. MD granules from both SFD and FD techniques were porous and hygroscopic in nature. Porous appearance of both samples could facilitate the product to rehydrate quickly through capillary action. Flow properties were improved by SFD techniques, however, colour of samples were not affected by both the techniques. Developed unit could be used for encapsulation of bio-pigments and other bio-active compounds, tablet preparation in pharmaceutical industries. It can also be used in food industries to produce maltodextrin and other microspheres of food components.

ACKNOWLEDGEMENTS

We are grateful to Dr H S Gupta (Former Director), Dr H S Gaur (Former Dean), Dr V V Ramamurthy, and Mr Islam Khan, Indian Agricultural Research Institute (IARI), New Delhi, India for their support and for provision of different facilities in their respective divisions. We are also grateful to Dr Alok Roy (Indian Institute of Technology, Delhi, India), members of Advisory committee (Dr D V K Samuel, Dr R K Pal, Dr Pritam Kalia, Dr Rajender Prasad and Dr Lata), all teachers, friends and SRFs especially Mr. Chirag, Division of Food Science and Post Harvest Technology, IARI, New Delhi, India for their support and useful advice. We appreciate and thank the Department of Science and Technology, Government of India, for provision of INSPIRE fellowship.

REFERENCES

Alanazi F K, El-Bagory I M, Alsarra I A, Bayomi M A and Abdel-kawy M A. 2008. Saudi-corn starch as a tablet excipient compared with imported starch. *Saudi Pharmaceutical Journal* **16**(2): 112–21.

Banker G S and Anderson N R. 1986. Tablets. (*In*) *The Theory and Practice of Industrial Pharmacy,* pp 293–345, 3rd Edn.Lachman L, Liberman H A and Kanig J L (Eds). Lea and Febiger, Philadelphia.

Burke P A, Klumb L A, Herberger J D, Nguyen X C, Harrell R A and Zordich M. 2004. Poly (Lactide-Co-Glycolide) microsphere formulations of *Darbepoetinalfa*, spray drying is an alternative to encapsulation by spray-freeze drying. *Pharmaceutical Research* **21**(3): 500–6.

Cain J. 2002. An alternative technique for determining ANSI/ CEMA Standard 550 flowability ratings for granular materials. *Powder Handling and Processing* **14**: 218–20.

Costantino H R, Firouzabadian L, Hogeland K, Wu C, Beganski C, Carrasquillo K G, Co'rdova M, Griebenow K, Zale S E and Tracy M A. 2000. Protein spray-freeze drying: Effect of atomization conditions on particle size and stability. *Pharmceutical Research* **17**: 1 374–83.

Costantino H R, Firouzabadian L, Hogeland K, Wu, Carrasquillo K G, Griebenow K, Zale S E and Tracy M A. 2002. Protein spray freeze drying: Effect of formulation variables on particle size and stability. *Journal of Pharmaceutical Sciences* **91**: 388–95.

Djuris J, Medarevic D, Krstic M, Vasiljevic I, MasicI and Ibric S. 2012. Design space approach in optimization of fluid bed granulation and tablets compression process. *Scientific World Journal* **2012**: 1–10.

Ersus S and Yurdagel U. 2007. Microencapsulation of anthocyanin pigments of black carrot (*Daucus carota* L.) by spray drier. *Journal of Food Engineering* **80**: 805–12.

Fiese E F and Hagen T A. 1986.Preformulation.*The Theory and Practice of Industrial Pharmacy,* pp 171–94, 3rd Edn. Lachman L, Liberman H A and Kanig J L (Eds). Lea and Febiger, Philadelphia.

Maa Y F and Prestrelski S J. 2000. Biopharmaceutical powders, particle formation and formulation considerations. *Current Pharmaceutical Biotechnology* **1**(3): 283–302.

Maa Y F, Nguyen P A, Sweeney T, Shire S J and Hsu C C. 1999. Protein inhalation powders spray drying vs spray freeze drying. *Pharmaceutical Research* **16**(2): 249–54.

Malamatris S, Karidas K and Goidas P. 1994. Effect of particle size and adsorbed moisture on the compression behavior of some hydroxypropyl methylcellulose (HPMC) polymers. *International journal of pharmaceutics* **103**: 205–15.

Masters K. 1991.*Spray Drying Handbook*, 4thEdn. Longman Scientific & Technical, Harlow, UK.

Maury M, Murphy K, Kumar S, Shi L and Lee G. 2005. Effects of process variables on the powder yield of spray dried trehalose on a laboratory spray-dryer. *European Journal of Pharmaceutics and Biopharmaceutic* **59**: 565–73.

Musa H, Gambo A and Bhatia B G. 2011.Studies on some physicochemical properties of native and modified starches from *Digitaria iburua* and *Zea mays. International Journal of Pharmacy and Pharmaceutical Sciences* **3**(1): 28–31.

Nyberg B, Carlstrom E and Carlsson R. 1993.Granulation of ceramic powders for pressing by spray-freezing and freeze-drying. *EuroCeramicsII,Deutsche Keramische Gesellschaft* **1**: 447–51.

Patel S S, Patel M S and Patel N M. 2008. Flowability and packability testing of directly compressible expedients. *Indian Pharmacist* **7**(71): 9–65.

Phadke D S and Anderson N R. 1990. Effect of cross povidone on the wet granulation aspects of acetaminophen.*Drug Development and Industrial Pharmacy* **16**: 983–94.

Schiffter H. 2007. Spray freeze drying in the manufacture of pharmaceuticals. *European Pharmaceutical Review* **12**: 67–71.

Staniforth J N. 2007. Powder flow.*Pharmaceutics- the Science of Dosage form Design*, pp 168–79, 3rd Edn. Aulton M E (Ed). Churchill Livingstone, London.

Stapley A and Rielly C. 2007. Advances in unconventional freeze drying technology.*Chemical Engineer* **790**: 33–5.

Webb S D, Golledge S T, Cleland J L, Carpenter J F and Randolph T W. 2002.Surface adsorption of recombinant human interferon-g in lyophilized and spray-lyophilized formulations. *Journal of Pharmaceutical Sciences* **91**: 1 474–87.