The preparation of the sustained release metformin hydrochloride microcapsules by the Wurster fluidized bed

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Abstract: The main objective of this study was to prepare sustained release metformin hydrochloride microcapsules by the Wurster fluidized bed and to obtain the optimized coating process and formulation. Fine microcapsules without agglomeration were obtained in a continuous coating process with the atomization air pressure of 0.2Mpa and an appropriate coating speed temperature. With other design variables of coating process fixed, the effects of different fluidizing air volume, coating temperature, coating speed, coating material, coating materials amount, plasticizer type and plasticizer amount on drug release were investigated respectively. Coating solution was achieved by dissolving EC45cps of 21 g, EC100cps of 7 g, DBS of 2.8 g and talcum powder of 8 g in ethanol to get a final volume of 500 ml. Particles of 150g along with 500mL coating solution would be fine. The results showed that with the air volume of 35 $m^3 \cdot h^{-1}$, coating temperature of 35º, coating speed of 6 $mL \cdot min^{-1}$ and proper amount of coating solution, fine microcapsules were obtained. The mean diameter of the microcapsules obtained eventually were 213 μm and the drug content were 23%, which was suitable for producing a suspension. Particle diameter distribution corresponded to the normal distribution and obviously prolonged drug-release was achieved.

Keywords: Wurster fluidized bed; metformin hydrochloride; ion-exchange resin; sustained-release microcapsule; suspension.

INTRODUCTION

Metformin hydrochloride is chemically formulated of N,N-dimethylimidodicarbonimidic diamide hydrochloride. It is a highly water-soluble biguanide anti-hyperglycaemic agent which is widely used in the treatment of type II diabetes (Thomas *et al.,* 2011; Corti *et al.,* 2008).

Ion-exchange resin can be used as a drug carrier in preparing the sustained release suspension (Junyaprasert *et al.,* 2008). Reversible complex are formed by bounding the ion-exchange resin with ionizable water-soluble drug molecule. When drug molecule replaces by another ion with same charge, the drug releases from the drug-resin complex (Jeong and Park, 2008).

Using ion-exchange resins has the advantages of no uncontrolled burst effect in the drug-resin complex even at high drug loading (Jeong and Park, 2008; Kulkarni *et al.,* 2011).

Emulsion solvent diffusion method and fluidised bed method are widely used for microparticle-coating technology. In the previous study, the authors in the current study have microencapsulated venlafaxine

hydrochloride ion-exchange resins with emulsion solvent diffusion method (Liu *et al.,* 2007). However, emulsion solvent diffusion method is not suited for large scale production, which is a huge limitation of this method.

The fluidised bed is also widely used for coating particles and pellets. Compared with the other methods, it can be applied to coat particles with a wide range of diameters, which is suitable for pharmaceutical industry production (Ichikawa *et al.,* 2001; Rambali *et al.,* 2001). In industrial applications, different fluidised bed technologies are used (top-spray, Wurster type bed, spouted bed etc.) to attain desired granular properties for different products. As for top-spray fluidised bed, fluidized particles are difficult to enter coating district, resulting in a low utilization rate of coating solution on account of the contra-direction of boiling air and spraying air. But in Wurster type bed, the spraying direction of boiling air and spraying air are the same, thus obtaining a high utilization rate.

However, investigations of using Wurster type bed for production of microcapsules have been seldom published. In this article, we coated Metformin hydrochloride resin with Wurster type bed. Design variables of coating process such as fluidizing air volume, coating temperature, coating speed, coating material, coating materials amount, plasticizer type, and plasticizer amount

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were investigated to obtain an optimized process and formulation of coating.

MATERIALS AND METHODS

Materials
Metformin Hydrochloride was purchased from the Fourth Pharmacy Factory (Chang Zhou, China). EC (45cps) and EC (100cps) were purchased from Colorcon Company (Shang Hai, China). The cation-exchange resins Amberlite® IRP69 (sodium polystyrene sulfonate) were purchased from Rohm and Haas Company (Philadelphia, USA).

Preparation of the drug-resin complexes
The drug-resin complexes were prepared by the batch method. In short, suspended 10g gel-type cation exchange resins in the hydrogen form in 500ml deionized water. Then, 10g Metformin Hydrochlorides were added to the water with agitation until solubility equilibrium. The drug-resin complexes were formed by the ion exchange reaction. After washing the drug-resin complexes with deionized water and drying them at 40°, the drug-resin complexes were successfully prepared.

Preparation of the microcapsules with Wurster fluidized bed
Drug resin of 180~200 μm was put in the Wurster tube. Particles were blown ebulliently in the wurster tube by a spray gun with a diameter of 1 mm and an appropriate fluidizing air volume. Fine microcapsules without agglomeration were obtained in a continuous coating process with the atomization air pressure of 0.2 Mpa and an appropriate coating speed and temperature.

Selection of the coating process parameters and coating formula
The parameters of coating process which were investigated were as follows: fluidizing air volume (25 $m^3 \cdot h^{-1}$, $35m^3 \cdot h^{-1}$, $45m^3 \cdot h^{-1}$), coating temperature (25°, 35°, 45°) and coating speed ($3mL \cdot min^{-1}$, $6mL \cdot min^{-1}$, $9mL \cdot min^{-1}$).

The parameters which were used to investigate coating formula were as follows: coating material (EC45 cps, EC100 cps), coating materials amount (400ml, 500ml, 600mL), plasticizer type (dibutyl sebacate, glycerol triacetate) and plasticizer amount (5%, 10%, 15%).

Characterization of the optimized microcapsules
Morphology of the Microcapsules
The morphology of the microcapsules was tested by scanning electron microscopy (SEM) (Jeol JSM-6400, Tokyo, Japan). Microcapsules were coated by gold sputter (BAL-TEC SCD004, Liechtenstein) at 15 mA for 165 seconds in an atmosphere of argon.

Particle size analysis
A laser light scattering particle size analyzer (LS230, Beckman Coulter, USA) was used to measure the mean particle size of the microcapsules prepared before. The microcapsules sample was suspended in distilled water and stirred under ultrasonic during measurement (n=3).

MH content in the drug-loaded microcapsules
The MH content in the drug-loaded microcapsules was measured as follows: Firstly, accurately weighed 100 mg dry drug-loaded microcapsules and then added them in the conical flask. Then surged the conical flask for 10 hours in water bath at 65° after adding 100ml NaCl solution of 1 $mol \cdot L^{-1}$. After filtration, the concentration of MH in the supernatant was determined by UV spectroscopy at 233nm.

In vitro drug release
The studies of drug release *in vitro* were performed refer to the USP paddle (apparatus II) method. The ZRS-8G Intelligent Dissolution Tester (Tian Jin University Radio Factory, China) was used and the rotation speed is 50 rpm. The MH release from the microcapsules was studied in 0.15 $mol \cdot L^{-1}$ NaCl solution at the temperature of 37 ± 0.1^o. The drug-loaded microcapsules were accurately weighed to obtain an equivalent of 100mg MH. At predetermined time intervals, 5ml dissolution medium was sampled. The amount of drug release was measured by UV spectrophotometry at 233 nm after passing the samples through a 0.45 μm membrane filter.

On account that the absorption window of Metformin was in small intestine, the release limitation was determined as 30% within 1 h, 50% within 3h and 75% within 10h in accordance with the standard of Glucophage® XR, which was on the market abroad.

Statistical Analysis was as follows: The date was expressed as mean ±SD. The orthogonal experiment results were statistical evaluated by ANOVA. P-value of <0.05 was considered to represent a statistically significant difference. F_2 factor was used to evaluate the similarity of release curves.

RESULTS

Fluidizing air volume
The release behavior show that with an air volume of $25m^3 \cdot h^{-1}$ and 45 $m^3 \cdot h^{-1}$, the MH release from the coated resins was of a faster speed and a larger batch difference (fig. 1 and table 1).

Coating temperature
The release behavior show that with the coating temperature of 25° and 45°, the MH release from the coated resins was of a faster speed and a larger batch difference (fig. 2 and table 2).
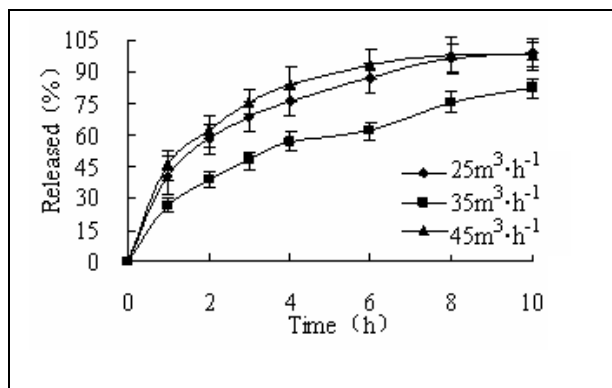
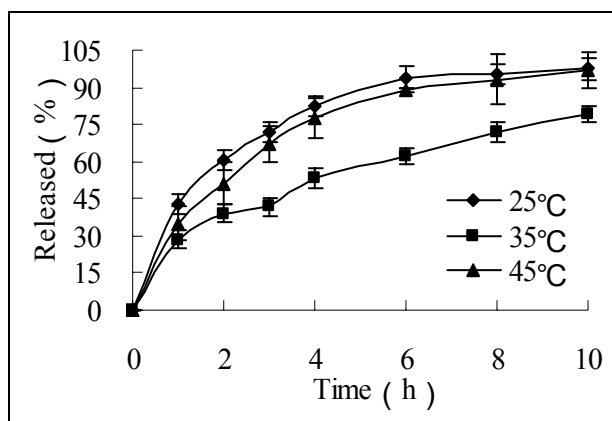**Fig. 1**: Effect of the fluidizing air volume on the MH release

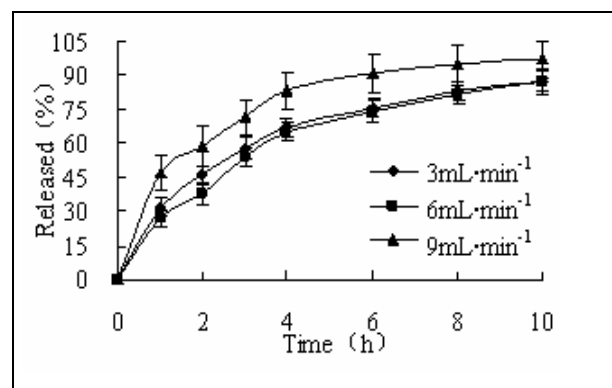**Fig. 2**: Effect of the coating temperature on the MH release

Fig. 3: Effect of the coating speed on the MH release

Coating speed
The release behavior show that with the coating speed of 9 mL·min^{-1}, the MH release from the coated resins was of a faster speed and a larger batch difference. The release behavior showed no significant difference between the coating speed of 3mL·min^{-1} and 6mL·min^{-1} (fig. 3 and table 3).

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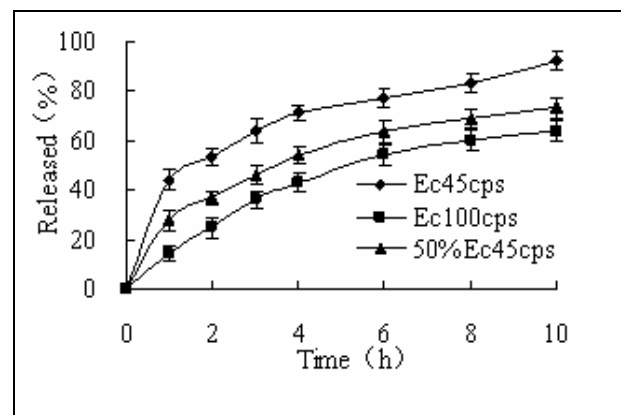

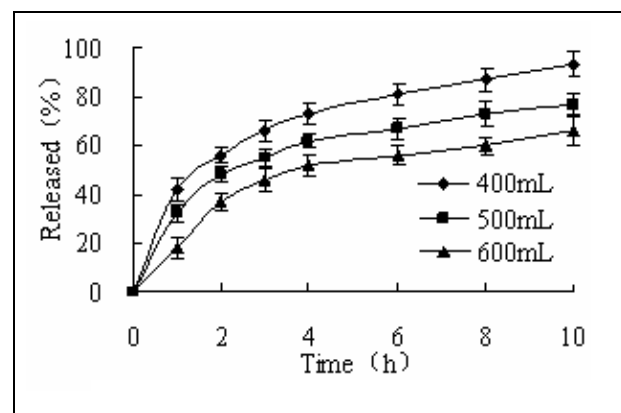**Fig. 4**: Effect of the coating materials on the MH release

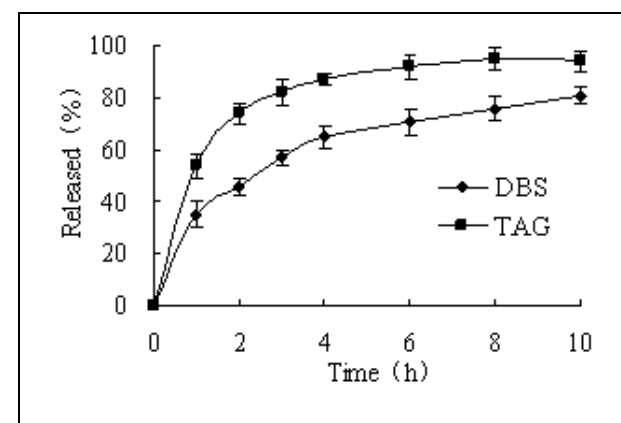**Fig. 5**: Effect of the coating materials amount on the MH release

Fig. 6: Effect of the plasticizer on the MH release

Coating materials amount
The release behavior show that with the increasing of coating materials amount, the MH release from the coated resins decreased significantly (fig. 5 and table 5).

Selection of plasticizer

The release behavior show that with the plasticizer of glycerol triacetate (TAG), drug released from the coated resins too fast (fig. 6 and table 6).

Plasticizer amount

The release behavior show that with the plasticizer amount of 10%, a complete and well-distributed coating was produced (fig. 7 and table 7).
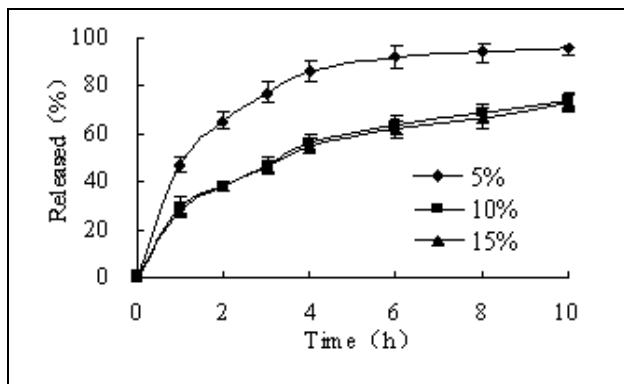

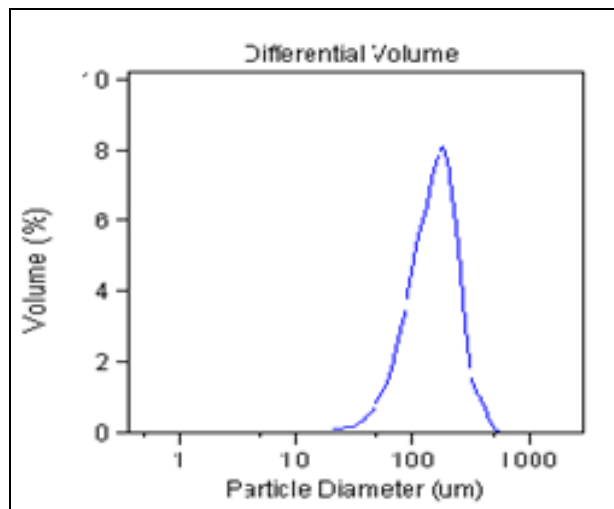**Fig. 7**: Effect of the plasticizer amount on the MH release

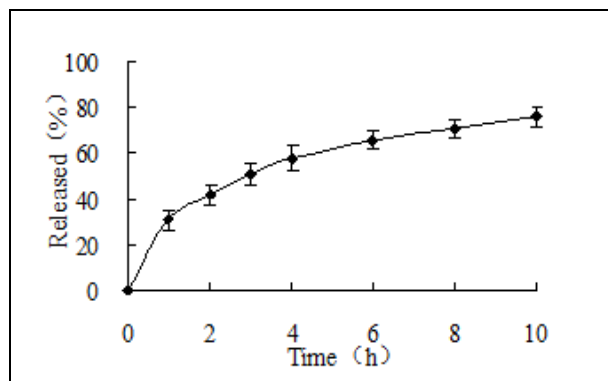**Fig. 8**: The particle size distribution of coated ion exchange resins

Fig. 9: The MH release from the microencapsuled made by the optimum formula.

Table 1: Analog analysis of the effect of fluidizing air volume on MH release

Related factors		f_2
25 $m^3 \cdot h^{-1}$	35 $m^3 \cdot h^{-1}$	36.7
25 $m^3 \cdot h^{-1}$	45 $m^3 \cdot h^{-1}$	65
35 $m^3 \cdot h^{-1}$	45 $m^3 \cdot h^{-1}$	32.1

Table 2: Analog analysis of the effect of coating temperature on MH release

Related factors		f_2
25°	35°	31.7
25°	45°	63.4
35°	45°	35.9

Table 3: Analog analysis of the effect of coating speed on MH release

Related factors		f_2
3mL·min^{-1}	6mL·min^{-1}	70.3
3mL·min^{-1}	9mL·min^{-1}	44.6
6mL·min^{-1}	9mL·min^{-1}	39.7

Table 4: Analog analysis of the effect of coating materials on MH release

Related factors		f_2
EC45cps100% 100%	EC45cps 0%	29.9
EC45cps 100%	EC45cps 50%	40.8
EC45cps 0%	EC45cps 50%	49.6

Table 5: Analog analysis of the effect of coating materials amount on MH release

Related factors		f_2
400mL	500mL	46.9
400mL	600mL	32.9
600mL	500mL	48.5

Table 6: Analog analysis of the effect of plasticizer on MH release

Related factors		f_2
DBS	TAG	34.8

Optimized Process and formulation of microcapsules

Process: Wurster type fluidized bed was used in our study. Drug resin of 180-200 μm was put in the Wurster tube. Particles was blown ebulliently in the Wurster tube with a spray gun with a diameter of 1 mm and a fluidizing air volume of 35m$^3 \cdot$h^{-1}. Fine microcapsules without agglomeration were obtained in a continuous coating process with the atomization air pressure of 0.2 Mpa, coating speed of 6mL·min^{-1} and coating temperature of 35□.

Formulation: Coating solution was achieved by dissolving EC45cps of 21g, EC100cps of 7g, DBS of 2.8g and talcum powder of 8g in ethanol to get a final volume of

782

500 ml. Particles of 150g along with 500ml coating solution would be fine.

Table 7: Analog analysis of the effect of plasticizer amount on MH release

Related factors		f_2
5%	10%	30.5
5%	15%	29.7
15%	10%	91.8

Quality evaluation of the microcapsules with prolonged drug-release

The SEM of the microcapsulated ion-exchange resin beads containing DH were shown in the figs. 2, 3. The micrographs showed that the microencapsules were predominately mononucleated. The mean diameter of the microcapsules obtained eventually were 213 μm and the MH content were 23%. The particle diameter distribution corresponded to the normal distribution (fig. 8), which was ready to produce a suspension. Results show that significant prolonged drug-release was achieved (fig. 9).

The dissolution media should be similar to the digest fluid in gastrointestinal tract. The drug release process is an ion exchange process from the drug-resinate. The ion concentration of electrolytes in the digest fluid was approximately $0.15mol \cdot L^{-1}$. As a result, $0.15mol \cdot L^{-1}$ NaCl was used as the dissolution media.

DISCUSSION

Fluidizing air volume

Selection of fluidizing air volume was crucial to coating process when we used fluidized bed of bottom-spray because proper fluidizing air could guarantee the sufficient fluidization of particles and improve the efficiency of drying and coating. However, the product yield might decrease because of the big fluidizing air volume at the preliminary stage of coating which might lead the small particles to fly off across the filter screen. With an air volume of $25m^3 \cdot h^{-1}$, the drug release from the coated resins was of a high speed and a large batch difference because at that air volume, not all ion-exchange resins and especially the heavier ones could fluidize in fluidized bed which might lead to incomplete and uneven coating. When improved to $45m^3 \cdot h^{-1}$, air volume was too large for ion-exchange resins to cross coating region, for most of them still staying on top of fluidized bed. Consequently, we selected $35m^3 \cdot h^{-1}$ as fluidizing air volume.

Coating temperature

Coating temperature has double effects of evaporating water and softening polymer particles. So coating temperature determines not only drying efficiency but also the quality of the film (Rajniak *et al.*, 2009; Karlsson *et al.*, 2006).

The surface temperature of core material should be 10°-20° higher than the minimum film forming temperature. There may be cracks on film when coating temperature is too low, thus influencing the drug release characteristics. The polymer may be softened with a too high coating temperature, leading the adhesion of the film. The results of costing temperature tests showed that coating temperature of 25° was below the minimum film forming temperature which caused the cracks on film and failed to work as a permeation barrier against drug release. On the contrary, coating temperature of 45° is too high to form a complete and flat film as well. Consequently, we selected 35° as coating temperature.

Coating speed

Coating speed is controlled by constant flow pump. With a certain spray flow rate, the higher coating speed is, the worse atomization effect is, and the more easily particles adhere together. But low coating speed may lead to long coating time and low efficiency. In this experiment, we observed the motion status of particles in fluidized bed and evaluated the spray effect. The results showed that fluidized state of particles was well at the coating speed of $3mL \cdot min^{-1}$ and $6mL \cdot min^{-1}$. At the coating speed of 9 $mL \cdot min^{-1}$, particles adhered together and incomplete and uneven film was obtained, and the drug release from the coated resin was of a faster speed and a larger batch difference. In consideration of coating time, $6mL \cdot min^{-1}$ would be an appropriate coating speed (Shelukar *et al.*, 2000; Arimotoa *et al.*, 2004).

Selection of plasticizer

Ethyl cellulose (EC) has difficulty in forming a film because its glass transition temperature is 89° and common coating process is difficult to achieve this temperature. As a result, plasticizer is added to decrease the glass transition temperature. Whether to have a good affinity with EC is the standard to choose a plasticizer. PEG400, dibutyl sebacate (DBS), TEC and glycerol triacetate (TAG) are usually used as plasticizer of EC because they all have good affinity with it. The release character of film was not so good when we used TAG as the plasticizer, so TAG was usually used as moisture proofing and taste masking coating. PEG400 is a kind of water-soluble polyalcohol plasticizer, while TEC and DBS are carboxylic ester plasticizer without water solubility and TEC has a better hydrophilicity than DBS. To improve the stability of suspension, we selected DBS as plasticizer for its low water-solubility (KuShaari *et al.*, 2006).

CONCLUSION

Metformin hydrochloride microcapsules were prepared successfully with Wurster fluidized bed. The results showed that with the optimized process and formulation mentioned above, fine microcapsules were obtained. The

results clearly demonstrated that the microspheres obtained had a proper diameter and sufficient drug content, which was ready to produce a suspension. Particle diameter distribution corresponded to the normal distribution and significant prolonged drug-release was achieved.

ACKNOWLEDGEMENTS

REFERENCES

Arimotoa M, Ichikawa H and Fukumori Y (2004). Microencapsulation of water-soluble macromolecules with acrylic terpolymers by the Wurster coating process for colon-specific drug delivery. *Powder Technol.*, **141**: 177-186.

Corti G, Cirri M, Maestrelli F, Mennini N and Mura P (2008). Sustained-release matrix tablets of metformin hydrochloride in combination with triacetyl-β-cyclodextrin. *Eur. J. Pharm. Biopharm.,* **68**: 303-309.

Ichikawa H, Fujioka K, Adeyeye MC and Fukumori Y (2001). Use of ion-exchange resins to prepare 100 μm-sized microcapsules with prolonged drug-release by the Wurster process. *Int. J. Pharm.*, **216**: 67-76.

Jeong SH and Park K (2008). Drug loading and release properties of ion-exchange resin complexes as a drug delivery matrix. *Int. J. Pharm.,* **361**: 26-32.

Jeong SH and Park K (2008). Development of sustained release fast-disintegrating tablets using various polymer-coated ion-exchange resin complexes. *Int. J. Pharm.,* **353**: 195-204.

Junyaprasert VB and Manwiwattanakul G (2008). Release profile comparison and stability of diltiazem-resin microcapsules in sustained release suspensions. *Int. J. Pharm.,* **352**: 81-91.

Karlsson S, Björn IN, Folestad S and Rasmuson A (2006). Measurement of the particle movement in the fountain region of a Wurster type bed. *Powder Technol.*, **165**: 22-29.

Kulkarni RV, Mangond BS, Mutalik S and Sa B (2011). Interpenetrating polymer network microcapsules of gellan gum and egg albumin entrapped with diltiazem-resin complex for controlled release application. *Carbohyd. Polym.*, **83**: 1001-1007.

KuShaari K, Pandey P, Song Y and Turton R (2006). Richard T. Monte Carlo simulations to determine coating uniformity in a Wurster fluidized bed coating process. *Powder Technol.*, **166**: 81-90.

Liu HF, Zhang CY, Chao XL, Sun TH, Ju CY, Li N and Pan WS (2007). Study of the formulation parameters affecting the preparation of microencapsulated ion-exchange resins containing venlafacine hydrochloride. *Indian J. Pharm. Sci.*, **7**(8): 550-555.

Rajniak P, Stepanek F, Dhanasekharan K, Fan R, Mancinelli C and Chern RT (2009). A combined experimental and computational study of wet granulation in a Wurster fluid bed granulator. *Powder Technol.*, **189**: 190-201.

Rambali B, Baert L, Thone D and Massart DL (2001). Using experimental design to optimize the process parameters in fluidized bed granulation. *Drug Dev. Ind. Pharm.*, **27**: 47-55.

Shelukar S, Ho J, Zega J, Roland E, Yeh N, Quiram D, Nole A, Katdare A and Reynolds S (2000). Identification and characterization of factors controlling tablet coating uniformity in a Wurster coating process, *Powder Technol.*, **110**: 29-36.

Thomas AB, Patil SD, Nanda RK, Kothapalli LP, Bhosle SS and Deshpande AD (2011). Stability-indicating HPTLC method for simultaneous determination of nateglinide and metformin hydrochloride in pharmaceutical dosage form. *Saudi Pharm. J.,* **19**: 221-231.