Non-Uniformity of Pellets Coating, Effect on the Dose Release Profile and How to Improve the Coating Process by Reducing the Electrostatic Charging of the Pellets

M. Marucci,[a,*] A. Holmgren,[a] H. Carlsson,[a] A. Jarke, M. Johansson, and C. von Corswant
AstraZeneca R&D Mölndal, SE-431 83 Mölndal, Sweden
[a]the authors have equally contributed to the work

Original scientific paper
Received: June 17, 2012
Accepted: September 11, 2012

The aim of this work was to study the effect of several process parameters used during pellets coating in two wurster fluid beds of different scales on: a) the uniformity of pellets coating, and b) the presence of an initial burst in the release profile caused by the existence of a significant fraction of pellets having a very thin film coating. The pellets used in this work presented high insulating properties. The pellets were coated with extended release films made mainly of ethyl cellulose and it was shown that larger pellets had a thicker coating. The choice of the process parameters had a large effect on the amount of pellets that were subtracted from the coating process due to the buildup of electrostatic charges on the pellets. Using not too high fluidizing air flows, pellets of larger size, a smaller pellets load and humidified air to fluidize the pellets resulted in more uniform coatings and, consequently, in more favorable release profiles that did not present or presented a reduced initial burst release.

Key words:
Pellets, coating non-uniformity, electrostatic charging, process parameters, wurster, bottom spray fluid bed

Introduction

Polymer film coating is often used in oral modified release systems. A modified release formulation may consist of a single unit, or of many modified-release units, e.g. pellets. Multiple-unit systems offer several advantages over single units: the risk of dose dumping is considerably reduced[1], a more consistent residence time in the GI tract is obtained[2], and the higher area-to-volume ratio provides a higher release rate[1].

The vast majority of film-coated formulations are produced by a process that involves atomization of the coating liquid and spraying onto the tablets or pellets[3]. In a fluid bed the particles to be coated continually rise and fall in a stream of gas while the coating liquid is sprayed onto them[4]. Fluidized bed technology has been used in the pharmaceutical industry for a long time and several alternatives are available. Bottom spray fluidized beds have a higher efficiency in terms of deposited material and material quality compared, for example, to top spray fluidized beds. The coating of multi-particulate systems is mainly performed in a bottom spray fluid bed equipped with a wurster insert (see Figure 1) due to its ability to well coat small particles. The wurster insert is mounted above the centre of the air distribution base plate and surrounds an upwards-directed spraying nozzle. The type of perforation of the air distribution plate (larger holes beneath the wurster), facilitates a strong fluidizing air stream inside the wurster insert and an upwards-di-

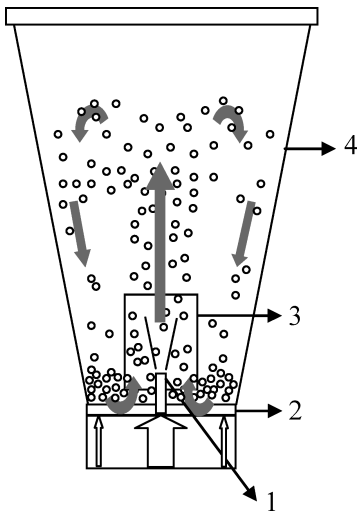


Fig. 1 – *Schematic drawing of a bottom spray fluid bed equipped with a wurster insert, (1) spraying nozzle, (2) air distribution plate, (3) wurster insert, (4) expansion chamber. The gray colored arrows indicate the particle flow, the white colored arrows indicate the fluidizing inlet air flow.*

*Corresponding author: tel.: +46 31 7064532; fax: +46 31 7763729; E-mail: mariagrazia.marucci@astrazeneca.com, mariagrazia.marucci@gmail.com

rected movement of the particles. The air velocity decreases outside the wurster due to the broadening of the cross-section of the expansion chamber, and the particles drop outside the wurster, in the down bed. The particles are then horizontally transferred again through the gap between the wurster and the air distributor plate, in a matter of seconds, for the next coating cycle[5]. The circulation of the particles increases the drying rate and reduces the potential for agglomeration[6], and particles of various size, even down to 100 μm, can be coated.

The quality of the coating process can be measured at a macroscopic level (coater performance) or at a microscopic level (coating quality)[7]. At the microscopic level, quality can be characterized as a function of different parameters, one of which is the coating mass uniformity[8]. The coating mass uniformity refers to the variation in the amount of coating material each particle receives during a batch coating operation[8]. The non-uniformity in coating level among different particles in a coated batch is due to two different aspects: 1) each particle receives a different amount of coating each time it passes through the spray zone, and 2) the number of times a particle passes though the spray zone varies from particle to particle[9]. Significant variation in particles levels among particles may occur even when pellets of uniform size are used. It has been shown that the presence of dead/slow zone in the fluid bed where particles are retained has a negative effect on the coating uniformity[10,11]. The situation becomes more complicated when particles having a wide size distribution are used[12]. It has been reported that the larger particles receives a larger portion of coating material compared to the smaller ones in the case of bottom spray fluid beds equipped with a wurster insert[11,12]. All this is further complicated by the buildup of electrostatic charges on the particles. Electrostatic charges are created by particle to particle and particle to walls collisions, and by induction. The electrostatic charges can make the particles to adhere onto the walls of the fluid bed and onto the wurster insert. In this way a fraction of the particles are definitely or temporally subtracted from the coating process and will have a thinner coating. It has been shown that the problem of particles sticking to the fluid bed walls due to electrostatic forces can be alleviated using a stainless chamber instead of a polyacrylate chamber, and incorporating an air ionization cartridge before the nozzle[13]. However, the solution of incorporating an air cartridge is not always easy. Moreover, the amount of particles sticking to the wurster and the fluid bed walls can be significant for particles having high insulating properties even when the wurster insert and the fluid bed chamber are made of stainless steel. The choice of the conditions may have a strong effect on the electrostatic charging of the particles and on the amount of particles that is temporally or permanently subtracted from the coating process. However, to the best of our knowledge, this has not been investigated in detail.

For multi-particulate systems, the release of the drug from a whole dose is the result of the combination of the release from each single unit[14]. When the units are coated with a sustained-release film, the drug release rate is mainly controlled by the film thickness and the film quality[15]. The thinner the coating the faster the release. The thickness and the uniformity of coating may play a crucial role in the manufacturing of sustained release coated formulations. The measurement of the coating thickness of individual pellets has been the object of several studies and different techniques have been used, e.g. scanning electron microscopy[16], confocal laser scanning microscopy[17,18] and terahertz pulsed imaging[19]. Single-unit release experiments from units whose coating thickness was characterized[17], or dose release experiments from fraction of units whose coating thickness was characterized[16], have also been performed in some isolated cases. However, the quantitative effect of a non-uniform coating on the dose release profile is still poorly understood.

In this paper we have reported some of our results obtained over the last five years from coating experiments performed in bottom-spray fluid beds of two different scales equipped with a wurster insert. Among the different substances formulated in pellets and covered with sustained-release films, the two that gave rise to the most pronounced electrostatic charging of the pellets during the coating process are presented. The aim the work was to study, for pellets coated with a sustained-release polymer film, the effect of different process parameters, e.g. pellets load, use of dry contra humidified air to fluidize the pellets, fluidizing air flow and pellets size, on the extent of the electrostatic charging of the pellets, on the uniformity of the pellets coating and on the dose release profile.

Materials and methods

Pellets coating

Two types of pellets, one containing drug A and the other containing drug B, were coated. Both drugs were antiarrhythmic drugs. The film coating was mainly made of ethyl cellulose (Dow, USA), and the coating polymers were sprayed from ethanolic solutions. Two different wurster fluid beds of two different scales were used in the coating experiments. One fluid bed was in-house built, and the diameter of the air distribution plate was

Table 1 – *Relevant process conditions used in the coating experiments.*

Experiment number	1	2	3	4	5	6	7	8
Drug substance	A	A	A	A	A	A	B	B
Fluid bed	In-house built	In-house built	GPCG3	GPCG3	GPCG3	GPCG3	In-house built	In-house built
D[4,3] of the uncoated pellets, μm	626	626	660	762	591	591	571	565
Pellets load, g	200	500	2000	2000	2000	2000	250	250
Fluidizing air flow, Nm^3/h	34	34	80	80	180	105	35	35
Dew point of the fluidizing air, °C	< –10	< –10	6	6	6	6	< –10	25
Coating load, g coating/ 100 g coated pellets	16	16	15	15	15	12	74	74

10.0 cm. The other one was a Glatt GPCG3 fluid bed (Glatt Gmbh, Germany), and the diameter of the air distribution plate was 17.5 cm. The process conditions used for each coating experiment and relevant to this work are reported in Table 1.

Film coating thickness and size determination of individual pellets

In order to understand the relationship between pellets size and coating thickness, some pellets were characterized in terms of pellets size and coating thickness.

The coating thickness was obtained imaging the pellets coating with a Nikon C1 laser scanning confocal unit (Nikon D-Eclipse C1) attached to an inverted fluorescence microscope (Nikon Eclipse TE 2000-e) equipped with a krypton/argon laser (wavelength 405 nm). The confocal fluorescence images were obtained using a 20 × objective. The film coating fluoresced at the wavelength used, so no dye was added to the coating. Four z-scans were performed for each pellet. Images of the coating were obtained in the x–z and y–z planes from the series of z-images. The coating thickness was then determined from the images of the coating in the x–z and y–z planes. The coating thicknesses determined from the images were multiplied by the refractive index of ethyl cellulose (1.47[20]) to correct for the difference in the refractive index between air (1.00[21]) and the coating.

The pellets size was determined using a system for automatic analysis of dry particles (BeadCheckTM 830, Mastersizer, Lund, Sweden).

Pellets size distribution

The size distribution of some of the uncoated and of the coated pellets was measured using a system for automatic analysis of dry particles (BeadCheckTM 830, Mastersizer, Lund, Sweden). About 2000 pellets were used for each measurement.

Pellets release experiments

The release experiments of drug doses were performed in a USP apparatus II dissolution tester (Hanson SR). The release medium was 900 ml phosphate buffer pH 6.8, the stirring rate was 50 rpm and the temperature was 37 °C. The concentration of drug A was analyzed using an UV–visible spectrophotometer (Agilent 8453 UV sample detection system), while the concentration of drug B was analyzed using a liquid chromatography method together with a mass spectrometry method.

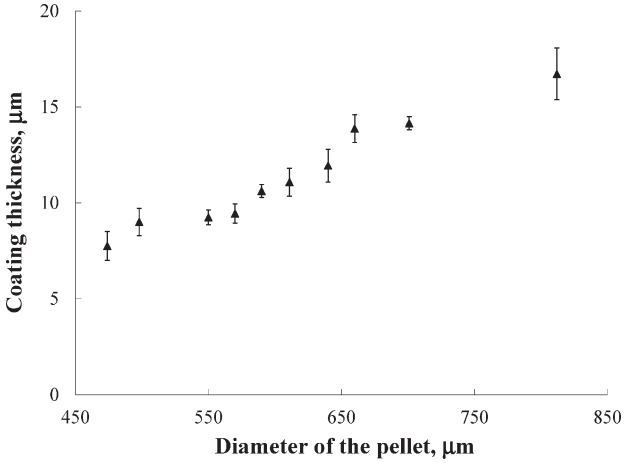
Results and discussions

Some of our results from the coating experiments collected over the last five years are presented and discussed in this section. Among the different substances formulated using the pellets technology and covered with a sustained-release film, the two that gave rise to the most pronounced electrostatic charging of the pellets during the coating process are presented. The effect of several parameters on the resulting uniformity of pellets coating and drug release profiles are presented and discussed below.

Non-uniformity of pellets coating and effect of the pellets load on the presence of an initial burst in the drug release profile

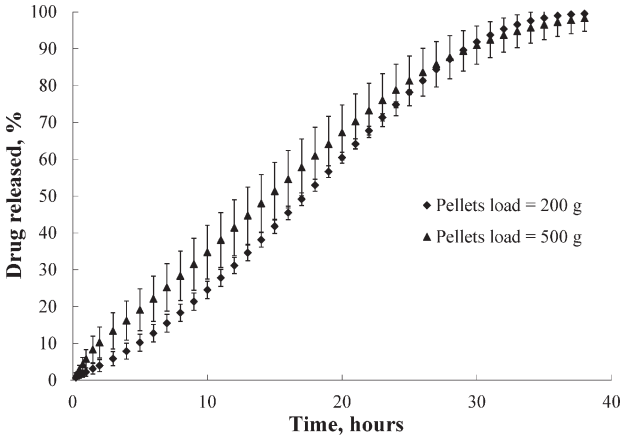
Pellets containing drug A were coated in an in-house built fluid bed and a pellets load of 200 g was used (experiment number 1). During the coating experiment it was observed that many pellets adhered to the observation window present in the expansion chamber and then went back into the fluidized system. This indicates that electrostatic charges were built up on the pellets. It was estimated that about 65% of the observation window was covered with pellets (only a few percentage of the window is covered with pellets when electrostatic effects

are not observed). The coating thickness and the diameter of some individual pellets were measured (see Figure 2). Clearly, the film thickness was dependent on the pellets size: the larger the pellet the thicker the coating. This is in accordance with the consideration that the smaller pellets receive less film during the coating process[12]. The coating thickness varied from about 8 μm for the smallest pellet (diameter of 475 μm) to 17 μm for the largest pellet (diameter of 810 μm).



F i g . 2 – *Coating thickness as function of the pellet diameter for pellets coated in experiment number 1*

Coating experiment number 2 was performed using the same process parameters and the same fluid bed used for the coating experiment number 1, but having a pellets load of 500 g instead of 200 g. This time it was observed that about 90% of the observation window was covered with pellets during the coating experiment. The release profiles of the two coated batches are shown in Figure 3. It should be pointed out that the two pellets batches had the same amount of coating and the same coating composition. No significant burst release was observed for the batch produced in the coating experiment number 1. Instead, an initial burst release was observable in the release of the pellets produced in the coating experiment number 2. This indicates that, among the pellets coated during experiment number 2, a larger fraction of pellets received a thinner coating compared to the pellets coated during experiment number 1. This can be attributed to the fact that a larger fraction of pellets was subtracted temporally or permanently from a normal fluidization during experiment number 2. It can be deduced that the electrostatic charges built up on the pellets during the coating must have been larger when a larger pellets load was used. It has been reported that in a Wurster fluid bed

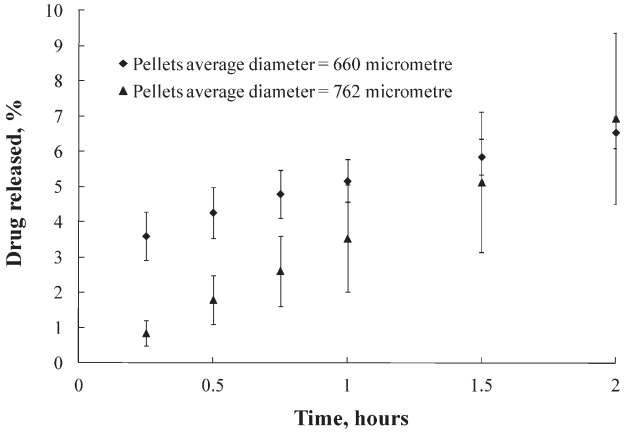


F i g . 3 – *Effect of the pellets load on the presence of an initial burst in the release profile*

higher pellets mass flow rates were achieved by increasing the pellets load[22]. The larger build up of electrostatic charges for a larger pellets load can be explained considering that higher particles mass flows results in more particle to particle and particle to walls collisions. Moreover, when the pellets load is increased, the particle to particle collisions increases much more than the particle to walls collisions and, consequently, the unchanging possibility of the metal walls become less relevant.

Effect of the pellets size on the presence of an initial burst in the drug release profile

Two batches of pellets containing drug A and having an average diameter of 660 and of 762 μm, were coated in the GPCG3 fluid bed in the coating experiments number 3 and 4, respectively. The same process parameters were used in the two coating experiments. The proportion of the polymers present in the coating was slightly different between the two coated batches. Small differences in

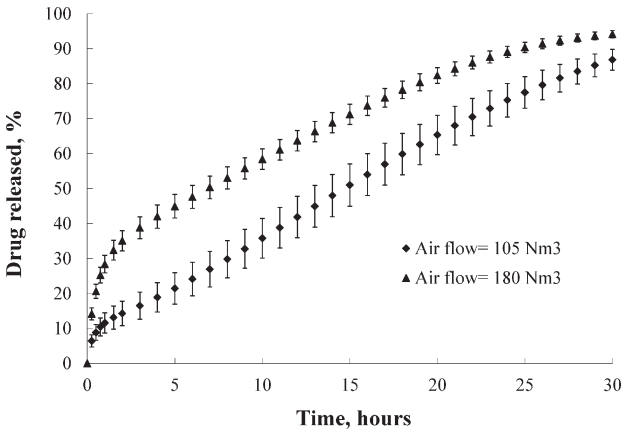


F i g . 4 – *Effect of the pellets size on the presence of an initial burst in the release profile*

the coating composition are not expected to effect the coating performance. The coating of the pellets coated in experiment number 3 was the less permeable one to water and to the drug substance. The release profiles of the coated batches are shown in Figure 4. Interestingly, an initial burst release was observed for the smaller coated pellets but not for the bigger ones. This can be attributed to the fact that a larger fraction of pellets was subtracted temporally or permanently from a normal fluidization when smaller pellets were coated resulting in a larger fraction of pellets with a thinner coating. The results obtained can be explained considering the fact that smaller particles have a higher specific surface and thus more electrostatic charges per weight. Consequently, it is easier for small pellets to adhere to the chamber walls and to the wurster insert, while gravity will help larger pellets to fluidize more uniformly in the fluid bed.

Effect of the fluidizing air flow on the initial burst in the drug release profile

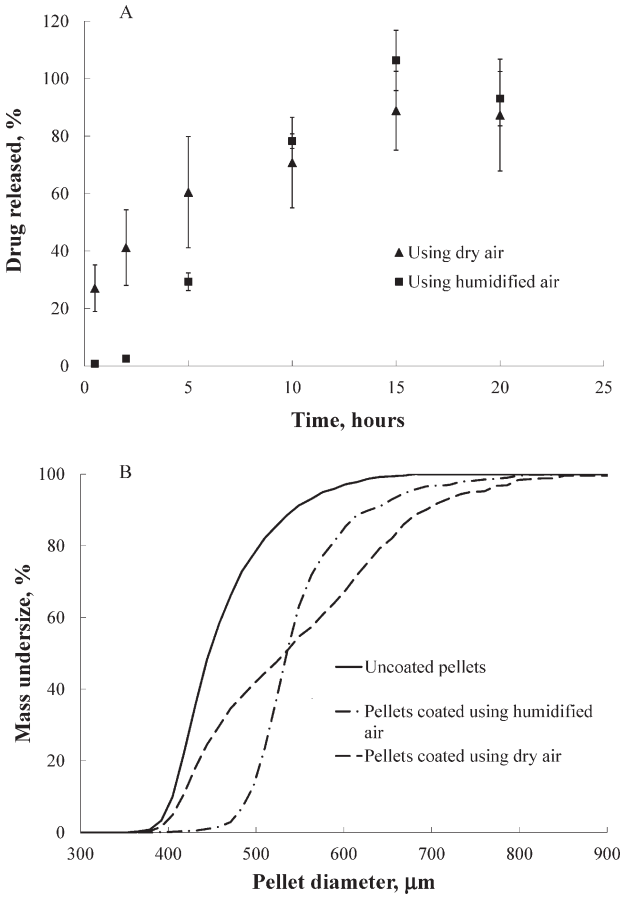
Two batches of coated pellets containing drug A where prepared in the GPCG3 fluid bed and fluidizing air flows of 180 Nm^3/h (experiment number 5) and of 105 Nm^3/h (experiment number 6) were used. The presence of pellets adhering to the wurster insert was observed during the coating experiments. The drug release profiles are shown in Figure 5. A high initial burst release was present in both release curves. Approximately 20 and 10% of the whole drug was released during the burst for the pellets coated during experiment 5 and 6, respectively. The fact that a larger fraction of drug was released during the burst from the pellets coated during experiment number 5 indicates that this batch contained a larger fraction of pellets with a thin coating, and that higher electrostatic charges on the pellets were built up when a higher fluidizing air flow was used. It has been shown that higher pellets mass flow rates are achieved for higher fluidizing air flows during the coating process[22]. Consequently, the results obtained are in accordance with the fact that more particle to particle and particle to wall collisions are expected for higher air flows.



F i g . 5 – *Effect of the fluidizing air flow on the presence of an initial burst in the release profile*

Effect of the use of humidified air on the presence of an initial burst in the drug release profile and on the pellets coating uniformity

Two batches of coated pellets containing drug B where prepared in the in-house built fluid bed using dry air (experiment number 7; dew point of the fluidizing inlet air lower than –10 °C) and humidified air (experiment number 8; dew point of the fluidizing inlet air equal to 25 °C) to fluidize the pellets. All the remaining process parameters were kept constant between the two experiments. The drug release profiles are shown in Figure 6A. The two release profiles were very different. An initial large burst release, during which approximately 30% of the drug was released, was obtained for the coated pellets produced using dry air for the



F i g . 6 – *Effect of the use of humidified air contra dry air to fluidize the pellets on the presence of an initial burst in the release profile (A) and on the cumulative pellets size distribution (B)*

fluidization. Instead, no burst release but a lag phase of about 2 hours was observed in the release profile of the coated pellets produced using humidified air. The results from the release profiles indicate that a larger fraction of pellets was subtracted from the normal fluidization due to the build up of electrostatic charges on the pellets when dry air was used. This was confirmed by the pellets size measurements of the uncoated and coated batches. A large fraction of pellets had a very thin coating and the coating thickness varied from about 6 μm to about 90 μm for the pellets prepared using dry air, as it can be deduced comparing the cumulative size distribution curves of the coated and of the uncoated pellets (Figure 6B). Instead, a much more uniform coating was achieved by using humidified air. In this case the coating thickness varied from about 40 μm to about 60 μm (Figure 6B). The obtained results can be explained considering that the water present in the humidified air may conduct the electrostatic charges that would otherwise accumulate on the pellets, and, in this way, discharge the pellets and favor a more uniform pellets fluidization.

Conclusions

When pellets are coated in a fluid bed it is fundamental to reduce the electrostatic charges created on the pellets when materials with high insulating properties are used, in order to achieve better coating uniformity and, consequently, more favorable release profiles. The use of not too high fluidizing air flows, larger pellets, a smaller pellets load and humidified air to fluidize the pellets had a positive effect on the release profile and on the uniformity of the pellets coating.

ACKNOWLEDGMENTS

Fredrik Winge is thankfully acknowledged for technical support with the release experiments.

References

1. *Lövgren, K.*, Pellet preparation, in: *E. Sandell* (Ed.), Industrial Aspects of Pharmaceutics, Swedish Pharmaceutical Press, Stockholm, pp. 200–211, 1993
2. *Abrahamsson, B., Alpsten, M., Jonsson, U.E., Lundberg, P.J., Sandberg, A., Sundgren, M., Svenheden, A., Toelli, J.*, International Journal of Pharmaceutics, **140** (1996) 229–235
3. *Aulton, M.E.*, Pharmaceutics, The Science of Dosage Form Design, Churchill Livingstone, New York, 2002
4. *Van Savage, G., Rhodes, C.T.*, Drug Development and Industrial Pharmacy, **21** (1995) 93–118
5. *Jones, D. M*. Air suspension coating. *Swarbrick, J and Bovlan, J. C*. Encyclopedia of Pharmaceutical Technology. 1, Marcel Dekker, New York, 189–216, 1988
6. *Teunou, E., Poncelet, D.*, Journal of Food Engineering, **53** (2002) 325–340
7. *Werner, S.R.L., Jones, J.R., Paterson, A.H.J., Archer, R.H., Pearce, D.L.*, Powder Technology, **171** (2007) 25–33
8. *R. Turton, G.I. Tardos, B.J. Ennis*. Fluidized bed coating and granulation, in: *W.-C. Yang* (Ed.), Fluidization, Solids Handling and Processing, Noyes Publications, Westwood, pp. 331–434, 1999
9. *Cheng, X.X., Turton, R.*, Pharmaceutical Development and Technology, **5** (2000) 311–322
10. *Shelukar, S., Ho, J., Zega, J., Roland, E., Yeh, N., Quiram, D., Nole, A., Katdare, A., Reynolds, S.*, Powder Technology, **110** (2000) 29–36
11. *Dreu, R., Luštrik, M., Perpar, M., Zun, I., Srcic, S.*, Drug Development and Industrial Pharmacy, **38** (2012) 501–511
12. *Sudsakorn, K., Turton, R.*, Powder Technology, **110** (2000) 37–43
13. *Maa, Y.-F., Nguyen, P.-A., Hsu, C.C.*, International Journal of Pharmaceutics, **144** (1996) 47–59
14. *Gross, S.T., Hoffman, A., Donbrow, M., Benita, S.*, Int J Pharm, **29** (1986) 213–222
15. *Haddish-Berhane, N., Jeong, S.H., Haghigi, K., Rark, K.*, International Journal of Pharmaceutics, **332** (2006) 64–71
16. *Wesdyk, R., Joshi, Y.M., Jain, N.B., Morris, K., Newman, A.*, International Journal of Pharmaceutics, **65** (1990) 69–76
17. *Marucci, M., Ragnarsson, G., Corsvant von C, Welinder, A., Jarke, A., Iselau, F., Axelsson, A.*, International Journal of Pharmaceutics, **411** (2011) 43–48
18. *Depypere, F., Van Oostveldt, P., Pieters, J.G., Dewettinck, K.*, European journal of pharmaceutics and biopharmaceutics, **73** (2009) 179–186
19. *Ho, L., Cuppok, Y., Muschert, S., Gordon, K.C., Pepper, M., Shen, Y., Siepmann, F., Siepmann, J., Taday, P.F., Rades, T.*, International Journal of Pharmaceutics, **382** (2009) 151–159
20. Food chemicals codex, First ed, National Academy of Science, Washington, D.C., 1966
21. *Denny, M.W.*, Air and water: the biology and physics of life's media, Princeton University Press, Princeton, 1993
22. *Chan, L.W., Tang, E.S.K., Heng, P.W.S.*, AAPS PharmSciTech, **7** (2006) E1-E9