Effects of Highly Hygroscopic Excipients on the Hydrolysis of Simvastatin in Tablet at High Relative Humidity

W. L. CHEN, D. W. GUO, Y. Y. SHEN*, S. R. GUO AND K. P. RUAN
School of Pharmacy, Shanghai Jiao Tong University, 800 Dongchuan Road, Shanghai-200 240, 1Pharmaceutical Technical Service Centre, International Specialty Products Inc., 2F, Block A, No. 39, Hongcao Road, Shanghai-200 233, China

Chen, et al.: Effects of Excipients on the Hydrolysis of Simvastatin

Effects of highly hygroscopic sorbitol, citric acid, sodium carboxymethyl cellulose or polyvinylpolypyrrolidone, on the hydrolysis of simvastatin in tablets at 25º/90% RH were studied. The simvastatin tablets were prepared by direct powder compression. Simvastatin and its hydrolyte, simvastatin acid, were quantitatively analysed by high performance liquid chromatography. The hygroscopicity, water swelling ratio, water solubility and pH of the four hygroscopic excipients were investigated. During the investigation period, the weight gain of sorbitol or citric acid increased faster than that of polyvinylpolypyrrolidone or sodium carboxymethyl cellulose at 25º/90% RH, accordingly, the moisture sorption of the tablets containing citric acid or sorbitol (T-3 or T-6) were more than that of the tablets containing sodium carboxymethyl cellulose or polyvinylpolypyrrolidone (T-4 or T-5). The increase of simvastatin acid content with time at 25º/90% RH for the tablets was in the following order: T-6 < T-4 < T-3 < T-5. The effects of the four excipients on the hydrolysis of simvastatin in tablet were related to not only their hygroscopicity but also their other properties, such as moisture retention capacity and pH. Sorbitol as hygroscopic excipient in tablet can most effectively prevent the hydrolysis of simvastatin in tablet.

Key words: Excipients, hydrolysis, hygroscopicity, simvastatin, tablets

Simvastatin (SIM) is an antilipemic agent similar to lovastatin, pravastatin and mevastatin[1], widely used for the treatment of hypercholesterolemia, dyslipidemia and coronary heart disease[2-4]. It is a pharmacologically inactive lactone[5] activated in organism after enzymatic degradation[6]. SIM is synthesised from lovastatin[7], by replacement of 2-methylbutyryl side chain with 2,2-dimethylbutyryl group[8]. Lovastatin is obtained biosynthetically from the fungus Aspergillus terreus[9,10]. SIM is quickly hydrolysed to the corresponding β-hydroxy acid in liver, an effective active ingredient, which is a regulator of cholesterol synthesis by 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibition[11,12]. Because SIM is a lactone, which is prone to hydrolysis, how to inhibit its hydrolysis and improve its chemical stability in tablet during storage is challenging.

The International Conference on Harmonization (ICH) for registration of pharmaceuticals for human use has issued workable guidelines regarding stability studies on pharmaceuticals and the identification and quantification of impurities in drug substances and drug products[13,14]. Regulatory guidelines of the ICH have led to an increasing need for identification and quantification of trace impurities in drugs[15,16]. All impurities, defined as any component of a pharmaceutical product which is not the chemical entity of active substance or excipient[17,18], present at levels higher than 0.1% or in some cases higher than 0.2% need to be identified[19,20]. According to Chinese Pharmacopoeia, 2010, the contents of single impurity and total impurities in SIM tablets should be no more than 1.0 and 3.0% after accelerated stability test and long-term stability test, respectively. Some SIM tablets in the market could not meet the requirement before the promulgation of Chinese Pharmacopoeia, 2010, they had to be withdrawn from the market. SIM acid is one of the most prominent impurity in SIM tablet. It is interesting to study what influences hydrolysis of SIM in tablet.
Moisture plays a key role in hydrolysis of SIM and protection of SIM in tablets from the moisture should be addressed for better stability of SIM. One approach is to use anhydrous excipients in the SIM formulation and keep the formulation under completely dry conditions to avoid moisture absorption. However, it seems to be difficult that all the excipients are anhydrous and no moisture is absorbed. Using hygroscopic excipients in SIM tablet may be feasible to prevent hydrolysis of SIM. The hygroscopic excipients in SIM tablets will preferentially absorb environmental moisture and then prevent SIM absorbing moisture further. In this study, we investigated the effects of four highly hygroscopic excipients on the hydrolysis of SIM in tablet at high relative humidity (RH). They are low molecular weight compounds (sorbitol and citric acid) and high molecular weight compounds (sodium carboxymethyl cellulose, NaCMC and polyvinylpolypyrrolidone (PVPP)).

MATERIALS AND METHODS

SIM was obtained as a gift sample from Zhejiang Hisun Pharmaceutical Co., Ltd., China. Internal standard SIM (National Institute for the Control of Pharmaceutical and Biological Products, Beijing, China), lactose monohydrate (Flowlac® 100, Meggle GmbH, Wasserburg, Germany), microcrystalline cellulose (MCC, Avicel® PH 102, ISP, Wayne, NJ, USA), magnesium stearate (Huzhou Hopetop Pharmaceutical Co. Ltd., China), butylated hydroxyanisole (BHA, Danisco Co. Ltd., China), PVPP (ISP, Wayne, NJ, USA), sorbitol (Fluka, Switzerland) and citric acid (Sigma-Aldrich, St. Louis, USA) were used in our study. High performance liquid chromatography (HPLC) grade acetonitrile was purchased from Shanghai Xingke Biochemistry Co. Ltd. (China). Polyvinylidene chloride-aluminium (PVDC-Al) blisters (ISP, Wayne, NJ, USA) were used as tablet package material. Buffer materials and all other chemicals were of analytical-reagent grade and ultrapure water was used throughout the study.

Swelling ratio, pH and water solubility measurement:

One gram of PVPP oe NaCMC was put in a 10 ml measuring cylinder and then 10 ml water was added to let the sample swell at room temperature. The swelling ratio ($q$) of NaCMC and PVPP was determined using the following equation: $q=V/V_0^{[21,22]}$, where $V_0$ is the volume calculated on the bulk density of the sample (0.213 g/cm$^3$ for PVPP and 0.529 g/cm$^3$ for NaCMC) and $V$ is the sample volume after swelling equilibrium was reached.

The pH of 1% w/v citric acid (sorbitol, PVPP or NaCMC) aqueous solution was measured by a pH meter (PHS-25, Shanghai Weiye Instrument Factory, Shanghai, China).

The water solubility of citric acid or sorbitol was measured by UV spectrometer (Spectrumlab 54, Lengguang Tech. Ltd. Co., Shanghai, China).

Simvastatin tablets manufacture:

A batch size of 200 g of 5 mg SIM tablets were manufactured by direct compression. The SIM was blended with hygroscopic materials as given in Table 1 in a mortar. Lactose (Lac) and MCC were added to the mixture and blended in a V-shape blender (Model Yoke, Patterson-Kelley Co., USA) for 15 min. The magnesium stearate was then added to the mixture and blended for an additional 5 min. SIM tablets (a diameter of 6 mm) were then compressed with a tablet machine (Rimek Mini Press-II, SF, India) to a final target tablet weight of 100 mg. The tablets were collected and stored in a tightly sealed glass bottle. The tablets were packaged into PVDC-Al blisters on a standard blister machine (Fantasy Buster Machine-Milano, O.M.A.R. fi cericola. G, Italy). The sealing temperature was 150°.

Moisture absorption study:

Approximately, 2 g of each powdery excipient or SIM sample was accurately weighed and spread flatly in the bottom of an open weighing bottle (40×25 mm), and then placed in a desiccator at 25°/90% RH. Saturated potassium nitrate solution was used to provide a 90% RH. Weight gain was measured at intervals. The moisture absorption of the unpackaged
SIM tablets was also investigated as described above.

**Hydrolysis of simvastatin in tablet:**
The unpackaged SIM tablets or the SIM tablets packaged in PVDC-Al blisters were placed in a desiccator at 25º/90% RH. Saturated potassium nitrate solution was used to provide a RH of 90%. The SIM acid content in tablet was measured at intervals to evaluate the hydrolysis of SIM in tablet.

**Measurement of simvastatin acid content in tablet:**
SIM acid in tablet was quantitatively analysed by HPLC, which is according to the regulation for the assay of related substances of SIM in tablet on the Chinese Pharmacopoeia 2010.

SIM acid content in tablet was measured by Agilent LC system (1100 Agilent, USA). A C18 column (3 µm C18, 50×4.6 mm, Venusil) was used. Due to multiple degradation products, the separation was achieved by gradient elution as Table 2. The injection volume was 20 µl and the total flow rate was 3 ml/min. The detection was carried out at 238 nm and the column oven temperature was set at 30°.

**Liquid chromatography-mass spectrometry for simvastatin acid identification:**
A liquid chromatography-mass spectrometry (LC-MS) (Agilent 6000, USA) system was used for SIM acid identification. The LC analysis method and sample preparation were the same as those mentioned above. The injection volume was also 20 µl. The mass spectrometer was operated in the positive ion electrospray mode in the mass range of 100-500 m/z. Ionization mode was set as both electron spray ionization (ESI) and atmospheric-pressure chemical ionizations (APCI) sources. The heated capillary temperature was set at 200° and its potential to 2.0 kV . Nitrogen was used as the sheath and auxiliary gas and set to 80 psi and 40 units, respectively.

**RESULTS AND DISCUSSION**
Four types of hygroscopic excipients were used to study their effects on the hydrolysis of SIM in tablet. They were sorbitol, citric acid, crosslinked NaCMC and PVPP. The chemical structures of the four hygroscopic excipients are shown in Scheme 1. Sorbitol and citric acid are small molecules, NaCMC and PVPP are high molecular weight compounds. Sorbitol is 1,2,3,4,5,6-hexanhexol, which can retain six water molecules via hydrogen bond in each molecule and thus should have great water retention capability[23,24]; citric acid is 2-hydroxypropane-1,2,3-tricarboxylic acid. As listed in Table 3, sorbitol and citric acid are all very water soluble. The pH of 1% citric acid aqueous solution is 2.3, indicating that it is relatively strong acidic. NaCMC can swell in water to form hydrogel and its swelling ratio is up to 4.9, indicating its high water retention capability. PVPP cannot form hydrogel and keep powdery in water implying that PVPP has a low water retention capability.

Moisture sorption characteristics of four types of highly hygroscopic excipients and others (MCC and Lac) were investigated. As shown in fig. 1, at the 25º/90% RH, the weight gain versus storage time curves were different for the six excipients. The weight gains of MCC and Lac increased slowly with time, and then reached constant, the constant values can be regarded as equilibrium moisture contents. The equilibrium moisture contents of MCC and Lac were about 12 and 2%, respectively, indicating that Lac is poorly hygroscopic and MCC a little hygroscopic. The weight gain curves of NaCMC and PVPP presented a first rapid phase with a later slow one. The moisture contents of NaCMC and PVPP on day 11 were 45.29 and 58.44%, respectively. The weight gains of sorbitol and citric acid increased rapidly with time. During the experiment, it was observed that the sorbitol and citric acid powder samples became liquid after 4 and 6 days, respectively. This is because that sorbitol or citric acid

| Table 2: Gradient Elution Condition |
| Time (min) | Pump A | Flow rate (ml/min) | Pump B |
|-----------|--------|-------------------|--------|
| 0         | 1.5    | 1.5               | 1.5    |
| 4.5       | 1.5    | 1.5               | 1.5    |
| 4.6       | 1.425  | 1.575             |        |
| 8.0       | 0.375  | 2.625             |        |
| 11.5      | 0.375  | 2.625             |        |
| 11.6      | 1.5    | 1.5               | 1.5    |
| 13.0      | 1.5    | 1.5               | 1.5    |

| Pump A=0.1% phosphoric acid in water, Pump B=Acetonitrile |

| Table 3: General Properties of Hygroscopic Excipients |
| Excipients | Water solubility (g/ml) | Swelling ratio (v/v) | pH (1% aqueous solution) |
|------------|-------------------------|----------------------|-------------------------|
| Sorbitol   | 2.67                    | -                    | 6.0                     |
| Citric acid| 1.28                    | -                    | 2.3                     |
| NaCMC      | -                       | 4.9                  | 5.5                     |
| PVPP       | -                       | 1.2                  | 5.8                     |

CMC-Na=Carboxymethylcellulose sodium, PVPP=polyvinylpyrrolidone
is highly water soluble. The adsorbed water in the samples led to dissolution of sorbitol or critic acid. Thus, NaCMC, PVPP, sorbitol and critic acid could be considered as highly hygroscopic excipients.

The formulations of the tablets (T-1 to T-6) are listed in Table 1. The SIM content for each tablet was 5% and the mean tablet weight was 100 mg. All the tablets had Lac, MCC and MS. In comparison with T-1, T-2 contained 0.02% BHA, an antioxidant with some antimicrobial properties, BHA is practically insoluble in water, T-3, T-4, T-5 and T-6 contained 5% of citric acid, NaCMC, PVPP and sorbitol, respectively.

As shown in fig. 2, during the investigated period, the weight gain of SIM was very small, that is, the moisture content of the SIM sample was very low. Thus, SIM is very poorly hygroscopic. The weight gains of the tablets (T-1 and T-2) after 10 days storage at 25\(^\circ\)/90% RH were about 3%, correspondingly, those of T-4 and T-5, T-3 and T-6 were about 6 and 8%, respectively. This result suggested that a small amount (5%) of the hygroscopic excipient (citric acid, NaCMC, PVPP or sorbitol) in tablet would lead to obvious increase of moisture content in tablet. The increase of moisture content could be mainly attributed to the moisture sorption of citric acid, PVPP, NaCMC or sorbitol in tablet. Sorbitol and citric acid were most hygroscopic (fig. 1), the weight gains of T-3 and T-6 containing citric acid and sorbitol were also the most. During the experiment, we also observed that after 10 days storage at 25\(^\circ\)/90% RH the tablets (T-6) containing 5% sorbitol became incompact. This indicated that the moisture sorption of T-6 would lead to the decrease of cohesion of the tablet.

SIM and its related substances in tablet were analysed by HPLC, which is according to the regulation on the Chinese Pharmacopoeia 2010. Ten tablets, stored at 25\(^\circ\)/90% RH for 10 days, were used for analysis, the chromatogram of SIM and its related substances in tablet was presented in fig. 3. There were five peaks

![Fig. 1: Moisture sorption characteristics of excipients.](image)

**Scheme 1: Chemical structures of carboxymethylcellulose sodium, citric acid, sorbitol, polyvinylpolypyrrolidone and butylated hydroxyanisole**

(C\(_6\)H\(_9\)NO\(_n\))

MW > 1000000
polyvinylpolypyrrolidone (PVPP)
Moisture sorption characteristics of the tablets (T-1 to T-6) and simvastatin when stored at 25º/90% RH.

High performance liquid chromatography of simvastatin and its related substances in tablet after 10 days storage at 25º/90 RH.

LC-MS was used to further identify SIM acid (S₁). The electrospray positive ion mass spectra were presented in fig. 5. The tablets stored at 25º/90% RH for 10 days were used for the assay. S₁ possessed an m/z 436.2 ion, and it was considered to be SIM acid with the molecular weight of 436.6.

SIM is a humidity-sensitive compound, containing a lactone ring labile to hydrolysis. The hydrolyte of SIM is SIM acid (Scheme 2). As listed in Table 4, for all the tablets at 0 day, the contents of the total related substances of SIM and SIM acid (denoted as ∑Sᵢ and S₁) were about 0.51-0.57 and 0.27-0.28, respectively. This indicated that there exited a certain amount of SIM acid and other related substances of SIM in tablet before the storage stability test at high humidity condition (25º/90% RH). It was also found that, the amount of SIM acid increased with the storage time, but the amount of other related substances (∑Sᵢ−S₁) had little change. The increase of ∑Sᵢ can be dominantly attributed to S₁ during the investigation period. Thus, the chemical instability of SIM in tablet should be mainly due to hydrolysis of SIM.

The lactones of SIM are susceptible to hydrolysis and its hydrolysis before administration may affect the pharmacological activity of SIM in vivo. Hence it is essential to prevent hydrolysis. The strategy to prevent hydrolysis is to protect SIM molecules from coming in contact with water. One way is to use anhydrous excipients in tablet during manufacturing and reduce water content in tablet to the greatest extent. However, there are only a few anhydrous excipients commonly used in pharmaceuticals. Strictly keeping the tablets apart from moisture sorption is also a very expensive approach. Another way is to introduce highly hygroscopic substances in the tablet, which preferentially absorbs moisture and thus decreases the absorption of water by SIM in the tablet.
TABLE 4: CONTENTS OF THE RELATED SUBSTANCES OF SIMVASTATIN IN TABLET

| Tablets | 0 d       | 5 d       | 10 d      |
|---------|-----------|-----------|-----------|
| T-1     | 0.28±0.03 | 0.26±0.02 | 0.26±0.02 |
| T-3     | 0.28±0.03 | 0.29±0.02 | 0.29±0.02 |
| T-4     | 0.27±0.02 | 0.29±0.02 | 0.29±0.02 |
| T-5     | 0.27±0.02 | 0.24±0.02 | 0.27±0.02 |
| T-6     | 0.27±0.03 | 0.27±0.02 | 0.27±0.02 |

RH=Relative humidity

It is interesting that the effects of various kinds of hygroscopic excipients on SIM hydrolysis in tablet were different (fig. 6). As discussed above, sorbitol, citric acid, NaCMC and PVPP were all highly hygroscopic excipients. In comparison with that in T-1 which contained no highly hygroscopic excipient, the SIM acid content in T-6 or T-4 increased slower at 25º/90% RH, implying decrease in the hydrolysis of SIM. This effect was not obvious in T-3 which has a similar hygroscopic capability. On the contrary, the SIM acid content in T-5 even increased faster than that in T-1 during the investigation period. Citric acid may play a key role in the hydrolysis of lactone ring of SIM. As we know, SIM undergoes hydrolysis under both acid and basic condition and acid can catalyse hydrolysis of esters. The effect of citric acid on hydrolysis of SIM in tablet should be attributed to the combination of its hygroscopic and acidity.

Sorbitol is a small molecule containing six hydroxyl groups. If one hydroxyl group forms one hydrogen bond with one water molecule, one sorbitol molecule can retain six water molecules via hydrogen bonds. Sorbitol is not only very hygroscopic, but also retains a large amount of water, it is well known that sorbitol can absorb moisture from the atmosphere when the amount of available water is low. NaCMC is a high molecular weight polysaccharide, having similar characteristics with sorbitol, its high water swelling ratio suggests that NaCMC can also retain a large amount of water. If sorbitol or NaCMC preferentially absorb and retain water in tablet, accordingly, the absorption of water by SIM or the other excipients should decrease. This might be why the hydrolysis of SIM decreased in T-6 and T-4. Although PVPP is also highly hygroscopic, its water swelling ratio is very low, implying that it has low capability of retaining water, that is, the water absorbed by PVPP in tablet will diffuse towards the other components (such as
SIM) in tablet. Hygroscopic PVPP in tablet could let more water contact with SIM and thus increase the hydrolysis of SIM in tablet.

The SIM acid contents had a little change for all the tablets packaged with PVDC-Al blisters (fig. 7). When the tablets were packaged in PVDC-Al blisters, they were protected against the ambient moisture, the hydrolysis of SIM in tablet was practically prohibited.

BHA is commonly used as an antioxidant in pharmaceuticals. The SIM acid content in T_2 (containing 0.02% BHA) increased faster than that in T_1 (fig. 8). It can be conferred that the low amount of BHA in SIM tablet also had an effect on drug hydrolysis.

The effects of hygroscopic sorbitol, citric acid, NaCMC and PVPP on hydrolysis of SIM in tablet were different, which could be related to their hygroscopicity, moisture retention capacity and pH. The moisture absorption of sorbitol or citric acid was greater than that of NaCMC or PVPP, correspondingly, the moisture content of the tablets containing sorbitol or citric acid increased faster than that of the tablets containing NaCMC or PVPP at 25°C/90% RH. Sorbitol (5%) could prevent hydrolysis of SIM in tablet at high RH. It was proposed that sorbitol could be used as the hygroscopic excipient for the tablets of SIM and improves the chemical stability of SIM in tablet.

REFERENCES

1. Vuletić M, Cindrić M, Koruznjak JD. Identification of unknown impurities in simvastatin substance and tablets by liquid chromatography/tandem mass spectrometry. J Pharm Biomed Anal 2005;37:715-21.
2. Garip S, Severcan F. Determination of simvastatin-induced changes in bone composition and structure by Fourier transform infrared spectroscopy in rat animal model. J Pharm Biomed Anal 2010;52:580-8.
3. Srinivasu MK, Raju AN, Reddy GO. Determination of lovastatin and simvastatin in pharmaceutical dosage forms by MEKC. J Pharm Biomed Anal 2002;29:715-21.
4. Zhang Z, Bu H, Gao Z, Huang Y, Gao F, Li Y. The characteristics and mechanism of simvastatin loaded lipid nanoparticles to increase oral bioavailability in rats. Int J Pharm 2010;394:147-53.
5. Di Giulio A, Saletti MA, Impagnatiello A, Lucarelli M, Strom R, Oratore A. Encapsulation and efflux of lactone and hydroxy acid forms of simvastatin in reverse-phase evaporation vesicles. Int J Pharm 2003;29:133-8.
6. Jeon JH, Thomas MV, Puleo DA. Bioerodible devices for intermittent release of simvastatin acid. Int J Pharm 2007;340:6-12.
7. Barrett B, Huclová J, Borek-Dohalský V, Nemec B, Jelínek I. Validated HPLC-MS/MS method for simultaneous determination of simvastatin and simvastatin hydroxy acid in human plasma. J Pharm Biomed Anal 2006;41:517-26.
8. Andelija M, Darko I, Mirjana M, Biljana J, Slavko M. Influence of structural and interfacial properties of microemulsion eluent on chromatographic separation of simvastatin and its impurities. J Chromatogr A. 2006;1131:67-73.
9. Casas López JL, Sánchez Pérez JA, Fernández Sevilla JM, Rodríguez Porcel EM, Chisti Y. Pellet morphology, culture rheology and lovastatin production in cultures of Aspergillus terreus. J Biotechnol 2005;116:61-77.
10. Nti-Gyabaah J, Chmielowski R, Chan V, Chiew YC. Solubility of lovastatin in a family of six alcohols: Ethanol, 1-propanol, 1-butanol, 1-pentanol, 1-hexanol, and 1-octanol. Int J Pharm 2008;359:111-7.
11. Bertacche V, Milanese A, Nava D, Pini E, Stradi R. Structural elucidation of an unknown Simvastatin by-product in industrial synthesis starting from Lovastatin. J Pharm Biomed Anal 2007;45:642-7.
12. Kang BK, Lee JS, Chon SK, Jeong SY, Yuk SH, Khang G, et al. Development of self-microemulsifying drug delivery systems (SMEDDS) for oral bioavailability enhancement of simvastatin in beagle dogs. Int J Pharm 2004;274:65-73.
13. Branch SK. Guidelines from the International Conference on Harmonisation (ICH). J Pharm Biomed Anal 2005;38:798-805.
14. Singh S, Bhutani H, Mariappan TT, Kaur H, Bajaj M, Pakhale S. Behavior of uptake of moisture by drugs and excipients under accelerated conditions of temperature and humidity in the absence and the presence of light. 1. Pure anti-tuberculosis drugs and their combinations. Int J Pharm 2002;245:37-44.
15. Allinson JG, Dansereau RJ, Sakr A. The effects of packaging on the stability of a moisture sensitive compound. Int J Pharm 2001;221:49-56.
16. Waterman KC, Adami RC. Accelerated aging: Prediction of chemical stability of pharmaceuticals. Int J Pharm 2005;293:101-25.
17. Basak AK, Raw AS, Al Hakim AH, Furness S, Samaan NI, Gill DS, et al. Pharmaceutical impurities: Regulatory perspective for abbreviated new drug applications. Adv Drug Deliv Rev 2007;59:64-72.
18. Bauer M, de Leede L, Van Der Waart M. Purity as an issue in pharmaceutical research and development. Eur J Pharm Sci 1998;6:331-5.
19. Boehlert JP. Regulatory aspects: ICH and pharmacopoeial perspectives. Prog Pharm Biomed Anal 2000;4:48-66.
20. Rahman N, Azmi S, Wu H. The importance of impurity analysis in pharmaceutical products: An integrated approach. Accred Qual Assur J Qual Comparability Reliab Chem Meas 2006;11:69-74.
21. Chen CH, Chen WJ, Chen MH, Li YM. Simultaneous full-interpenetrating polymer networks of blocked polyurethane and vinyl ester. Part I. Synthesis, swelling ratio, thermal properties and morphology. Polymer 2000;41:7961-7.
22. Milasinović N, Kalagasidis Krusić M, Knzrević-Jagović Z, Filipović J. Hydrogels of N-isopropylacrylamide copolymers with controlled release of a model protein. Int J Pharm 2010;383:53-61.
23. Jivraj II, Martini LG, Thomson CM. An overview of the different excipients useful for the direct compression of tablets. Pharm Sci Technol Today 2000;3:58-63.
24. Rowley G, Mackin LA. The effect of moisture sorption on electrostatic charging of selected pharmaceutical excipient powders. Powder Technol 2003;135:50-8.
25. Zhang N, Yang A, Rogers JD, Zhao JJ. Quantitative analysis of simvastatin and its beta-hydroxy acid in human plasma using automated liquid-liquid extraction based on 96-well plate format and liquid chromatography-tandem mass spectrometry. J Pharm Biomed Anal 2004;34:175-87.
26. Kaufman MJ. Rate and equilibrium constants for acid-catalyzed lactone hydrolysis of HMG-CoA reductase inhibitors. Int J Pharm 1990;66:97-106.
27. Idson B. Dry skin: Moisturizing and emolliency. Cosmet Toiletr 1992;107:69-78.

Accepted 7 December 2012
Revised 20 November 2012
Received 24 October 2011
Indian J. Pharm. Sci., 2012, 74 (6): 527-534