Academic Sciences International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 5, Issue 3, 2013

Research Article

EFFECT OF PARTICLE SIZE ON THE DISSOLUTION OF GLIBENCLAMIDE

KURTAGIĆ HARUN[1], MEMIĆ MUSTAFA[2*], SELOVIĆ ALISA[2]

[1]Federal Institute for Agriculture Sarajevo, Butmirska cesta 40, 71000 Sarajevo, Bosnia and Herzegovina, [2]Department of Chemistry, Faculty of Science, University of Sarajevo, Zmaja od Bosne 33-35, 71000 Sarajevo, Bosnia and Herzegovina. Email: m_memic@yahoo.com

Received: 29 Apr 2013, Revised and Accepted: 13 Jun 2013

ABSTRACT

According to the regulation of the good manufacturing practice, pharmaceutical producers of solid oral forms have obligation to carry out drug dissolution test (*in vitro*) which can predict the absorption of the active components in the gastrointestinal tract (*in vivo*) which represents an indicator for bioequivalent.

Objective: The objective of present study was to investigate the effect of particle size on the dissolution of glibenclamide from tablets. Final granulates from ten different batches were used for determination of particle size distribution.

Methods: Particle size analysis was performed by laser diffraction method. The dissolution of glibenclamide from tablets was performed using USP dissolution apparatus type II (paddle).

Results: Mean values of percentage of glibenclamide dissolution from tablets ranged from 80% to 99%. Obtained results showed that dissolution of glibenclamide decreased with increasing particle size fraction d(0.1) and increased with increasing particle size fractions d(0.9) and D(4,3).

Conclusion: The optimal ratio of the particle size and percentage of dissolution of glibenclamide was observed for the sample with particle size distribution of d(0.1) = 36 μm, d(0.5) = 172 μm, d(0.9) = 499 μm and D(4,3) = 229 μm. Mean value of percentage dissolution for glibenclamide from this sample is 97%.

Keywords: Glibenclamide, Particle size, Dissolution, Granulate, Tablet

INTRODUCTION

The effect of particle size on bioavailability of drugs or their absorption in gastrointestinal tract is very important for pharmaceutical companies and their decision on which form and technology to use while producing medicinal products [1]. In the pharmaceutical industry, particle characterization of powder materials has become one of the crucial aspects in drug product development and quality control of solid oral dosage forms. The particle size distribution (PSD) of the drug substance may have significant effects on final drug product performance (e.g., dissolution, bioavailability, content uniformity, stability, etc.). In addition, many publications have shown that the PSD of pharmaceutical powders has an impact on almost every step of manufacturing processes of solid oral dosage forms, including pre-mixing/mixing, granulation, drying, milling, blending, coating, encapsulation, and compression [2,3,4]. The pharmaceutical powders and granulates, in a physical sense, have the particles with different shapes: spherical, cubes, plates, fiber and other [5,6]. Only the size of the spherical particles can be expressed numerically [7]. The goal for pharmaceutical technology is to make powders with spherical shape but this is often not possible [8].

Methods for determination of particle size can be divided into direct and indirect [9]. Among the direct methods, optical and image analysis are of major interest. The indirect methods are: sieving, sedimentation, fluid classification, and scanning. Laser Diffraction, also known as Static Light Scattering, has become one of the most widely used particle sizing distribution techniques [10]. The sample material is passed through a laser beam which results in the laser light scattered at a wide range of angles. Laser diffraction uses Mie theory [11] of light scattering to calculate the particle size distribution, assuming a volume equivalent sphere model. Mie theory requires knowledge of the optical properties (refractive index and imaginary component) of the sample being measured along with the refractive index of the dispersant.

Dissolution testing is a required test, currently used to demonstrate the performance of all solid oral dosage forms in which absorption of the drug is necessary for the product to exert a therapeutical effect. Dissolution is defined as the process by which a known amount of drug substance goes into solution at a given time under standardized conditions. In pharmaceutical terms, dissolution is a process by which the drug released from the oral form, dissolved in the gastrointestinal tract and absorbed into the systemic circulation [12]. Drug dissolution test is a fundamental part of drug production and is also used as a quality control tool to monitor batch-to-batch consistency of the drug release from a product.

In order to drug component act after oral use it must pass into solution and diffuse through the intestine walls into the body. The first step in that process is the disintegration of the drug dosage form [13] followed by dissolution of the active ingredient. Effect of particle size on the degree of dissolution depends on the physical-chemical characteristics of the drug pharmaceutical form and the degree of absorption of active ingredient depends on the physiological conditions of the gastrointestinal tract [14]. Dissolution of a pure substance follows the Noyes Whitney equation dc/dt = kS (Cs- Ct) where dc/dt is the rate of dissolution, k is the dissolution rate constant, S is the active surface of the dissolved solid, Cs is the concentration of drug in the diffusion layer and Ct is the concentration of drug in dissolution media (or the bulk). Different approaches are being explored to enhance the solubility of poorly water soluble drugs. Some of these approaches are using different solid dispersion techniques [15,16,17] or increasing the available surfaces for dissolution [18,19,20]. Recently, the dependence of the dissolution degree of the crystal drug forms geometric shape is the subject of many studies [21,22,23,24]. There are several techniques for the quantitative determination of the degree of drug release from tablets [25].

The aim of this study was to determine the percentage of dissolution of glibenclamide from tablets depending on the particle size distribution of final granulates used for tablet manufacture.

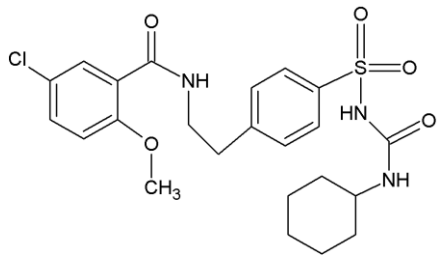

Fig. 1: Structural formula of glibenclamide

Glibenclamide is the second generation sulphonylureas oral hypoglycemic agent used in the treatment of diabetes mellitus type 2. Molecular formula of glibenclamide is $C_{23}H_{28}ClN_3O_5S$, and IUPAC chemical name is 5-chloro-N-[2-[4-(cyclohexylcarbamoylsulfamoyl) phenyl]ethyl]-2-methoxy-benzamide. Structural formula of glibenclamide is given in Fig. 1.

MATERIALS AND METHODS

Instruments and equipment: Particle size analyzer - Malvern Master Sizer 2000, Sciroco 2000 A (Worcestershire, UK), HPLC (High Performance Liquid Chromatography) system – Shimadzu, Class VP 5-03, Dissolution tester - Erweka DT 6R, Analytical balance - Mettler AJ 150, Centrifuge - Hermle Z200A Labuct, Ultrasonic bath 40 Watts, Magnet mixer, pH meter - Mettler Toledo MP 220.

Chemicals: Glibenclamide 99% (Sigma Aldrich), HPLC grade acetonitrile, potassium dihydrogen phosphate (Merck), lactose (Molkerei Meggle Wasserburg GmbH&C), microcrystalline cellulose (FMC Biopolymer), corn starch (Roquette Freres), povidone (BASF Chem Trade GmbH), talc (Merck KgaA), magnesium stearate (Magnesia GmbH).

Particle size analysis

Particle size analysis was performed using particle size analyzer with dry dispersion unit. Refractive index values for dispersant (air) and samples were 1.000 and 1.5. The absorption coefficient was 0.01 with air pressure 0.3 bars. Ten samples of final granulate, from ten batches, were used in particle size analysis. Six different representative samples from the same batch were measured. The samples were collected in 75 mL glass bottles, using a metal spoon. To obtain homogenous dispersion, bottles with samples were stirred lengthwise, 20 seconds in one direction and 20 seconds in the other direction. Amount of 1 g granulate was placed in measuring cell of the laser sizer. After the particle dispersion was completed, the measurement was performed and the particle size distribution of each granulate was obtained.

Dissolution testing

In order to obtain the final product (tablets), prepared granules (wet granulation) were compressed. The compression was done by rotary press where the sampling of tablets was performed. Dissolution testing on ten tablets of glibenclamide was conducted using USP XXIII apparatus 2 - paddle method [26]. The dissolution medium consisted of 500 mL of USP phosphate buffer (pH 7.8) which is kept at 37 ± 0.5 °C and stirred at a speed of 75 rpm. The duration of dissolution was 45 minutes. Samples were then filtered through a 0.45 μm filter. Volume of 10 μL of sample was injected into the HPLC column. This volume represents 100% content of glibenclamide per tablet. Analysis of glibenclamide was performed by HPLC method with UV/VIS detection. To construct a calibration curve three different volumes of glibenclamide standard were injected in the HPLC column: 8 μL, 10 μL and 12 μL which represents the amount of 80%, 100% and 120% of glibenclamide per tablet. The mobile phase consisted of 0.05 M KH_2PO_4 (pH 3) / acetonitrile (1:1) was pumped at a flow rate of 1.2 mL min−1. The column used was 5 μm, 100 mm× 4.6 mm Spheri RP 18. Glibenclamide was detected at 230 nm. For the blank analysis placebo tablets were used. All ten samples were analyzed in six replicates in the same way.

RESULTS AND DISCUSSION

Results of particle size distribution are shown in Table 1 where the samples of final granulate are labeled as x_1 to x_{10}.

Table 1: Particle size distribution of final granulates

Sample	d(0.1) (μm)	d(0.5) (μm)	d(0.9) (μm)	D(4,3) (μm)	SSA (m^2/kg)
x_1	45.1	174.8	650.2	271.1	0.0644
x_2	35.7	172.1	499.0	228.6	0.0735
x_3	58.5	203.4	471.9	242.2	0.0587
x_4	48.3	178.5	424.1	224.6	0.0645
x_5	55.4	196.6	430.4	225.6	0.0592
x_6	51.2	165.1	360.4	191.2	0.0633
x_7	43.7	151.5	340.4	178.3	0.0698
x_8	23.0	170.1	651.2	266.4	0.1158
x_9	46.6	178.6	663.8	280.1	0.0628
x_{10}	45.4	176.3	664.4	276.5	0.0636

d(0.1) μm, d(0.5) μm and d(0.9) μm represent particle diameter corresponding to 10%, 50% and 90% of the cumulative distribution, respectively. D(4,3) represents the average mass-volume diameter and SSA is the specific surface area (m^2/kg).

Dissolution testing was performed for all ten glibenclamide tablets, six determination for each sample (tablets). Glibenclamide content was determined by HPLC with UV / VIS detector. Fig. 2 represents the chromatogram of sample x_6 where the peak area corresponding to the percentage of glibenclamide dissolved from tablets.

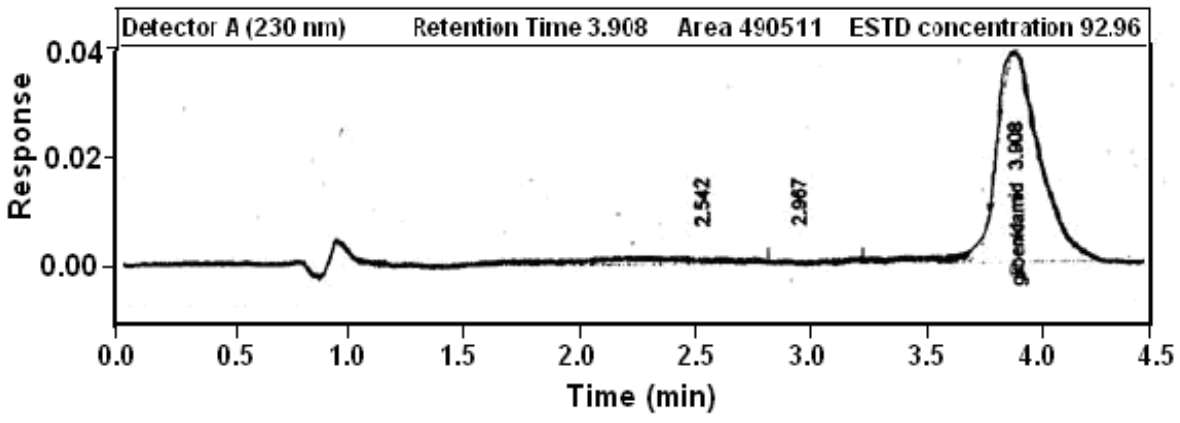

Fig. 2: HPLC chromatogram for sample x_6

Interval of dissolution percentage and mean value are calculated for each sample and results are shown in Table 2. The percentage of dissolution of glibenclamide ranged from 80% (sample x_{10}) to 99% (sample x_3).

Table 2: Dissolution of glibenclamide from tablets (%)

Samples	Dissolution interval (%)	Mean value (%)
x_1	92 - 96	94
x_2	93 - 99	97
x_3	92 - 102	99
x_4	87 - 92	89
x_5	69 - 94	85
x_6	78 - 98	86
x_7	66 - 96	89
x_8	95 - 100	98
x_9	87 - 94	89
x_{10}	85 – 103	80

From the results obtained for distribution of particle size (Table 1) and the percentage of dissolved glibenclamide (Table 2) values of mean, standard deviation, coefficient of variation and confidence intervals at 90% and 99% confidence levels for n = 10 were calculated [27]. The effect of particle size on the percentage of glibenclamide dissolution is presented graphically (Fig. 3, 4, 5 and 6). Confidence limits at 90% and 99% confidence levels for particle size distribution are represented on the x-axis and the confidence limit at 99% confidence level for percentage of drug dissolution on the y-axis.

Crossing the lines for 90% and 99% confidence intervals for particle size with 99% confidence interval for percentage of glibenclamide dissolution so-called rectangles reliability were obtained.

Smaller rectangle represents the relationship between 90% confidence level for particle size and 99% confidence level for the percentage of dissolution. Larger rectangle represents the relationship between 99% confidence level for particle size and 99% confidence level for the percentage of dissolution.

Mean values of percentage of glibenclamide dissolution from ten different tablets ranged from 80% (sample x_{10}) to 99% (sample x_3). 99% confidence interval for the mean value of all samples ranged from 84.4% to 96.8%.

The effect of particle size d(0.1) on the percentage of glibenclamide dissolution is presented in Fig 3.

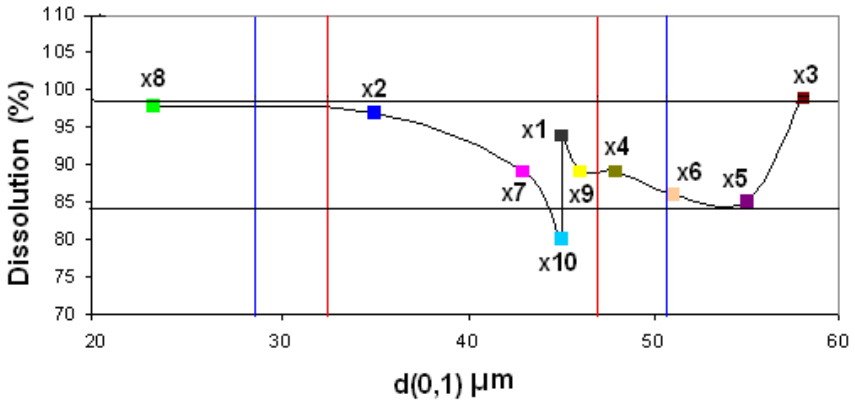

Fig. 3: The effect of particle size d(0.1) on percentage of glibenclamide dissolution from tablets

Mean values for particle size d(0.1) ranged from 23 µm (sample x_8) to 58.5 µm (sample x_3). 90% confidence interval for mean value of all samples within d(0.1) ranged from 33.4 µm to 46.6 µm and for 99% confidence level from 28.5 µm to 51.1 µm. Points x_1, x_2, x_7 and x_9 are within 90% confidence region and within 99% confidence region also point x_4. The other five points are outside the rectangular reliability.

The effect of particle size d(0.5) on percentage of glibenclamide dissolution is presented in Fig. 4.

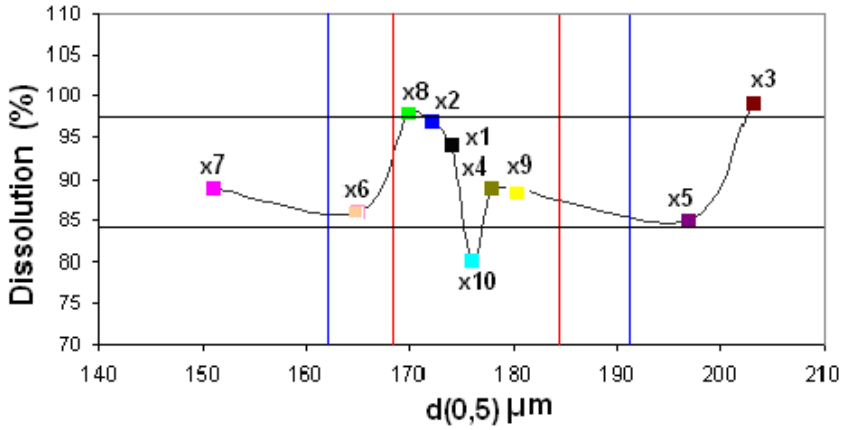

Fig. 4: The effect of particle size d(0.5) on percentage of glibenclamide dissolution from tablets

Mean values for particle size d(0.5) ranged from 151.5 µm (sample x_7) to 203.4 µm (sample x_3). 90% confidence interval for mean value of all samples within d(0.5) ranged from 168.3 µm to 185.1 µm and for 99% confidence level from 162.0 µm to 191.4 µm. Points x_1, x_2, x_8 and x_3 are within 90% confidence region and within 99% confidence region also point x_6. The other five points are outside the rectangular reliability.

The effect of particle size d(0.9) on the percentage of glibenclamide dissolution is presented in Fig. 5.

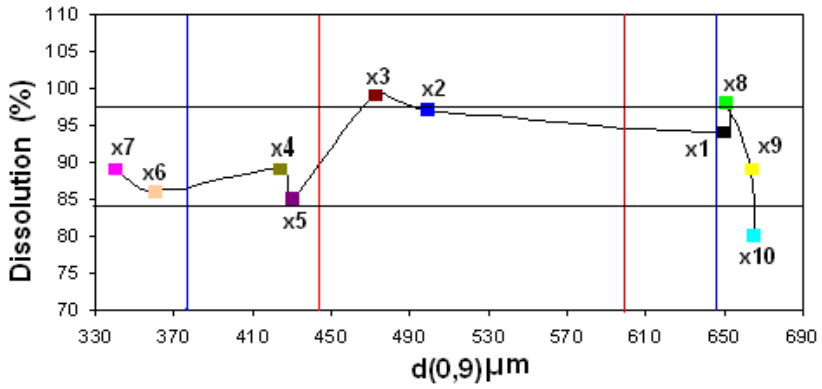

Fig. 5: The effect of particle size d(0.9) on percentage of glibenclamide dissolution from tablets

Mean values for particle size d(0.9) ranged from 340.4 µm (sample x_7) to 664.4 µm (sample x_{10}). 90% confidence interval for mean value of all samples within d(0.9) ranged from 440.8 µm to 590.4 µm and for 99% confidence level from 384.6 µm to 646.4 µm. Point x_2 is within 90% confidence region and within 99% confidence region also points x_4 and x_5. The other seven points are outside the rectangular reliability.

The effect of particle size D(4,3) on the percentage of glibenclamide dissolution is presented in Fig. 6.

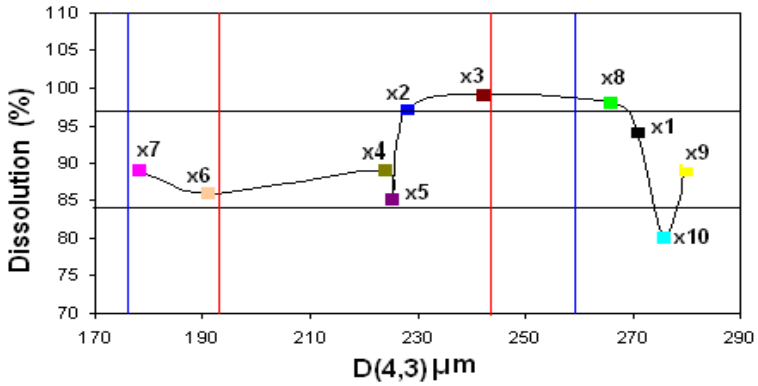

Fig. 6: The effect of particle size D(4,3) on percentage of glibenclamide dissolution from tablets

Mean values for particle size D(4,3) ranged from 178.3 µm (sample x_7) to 280.1 µm (sample x_9). 90% confidence interval for mean value of all samples within D(4,3) ranged from 194.1 µm to 241.7 µm and for 99% confidence level from 176.2 µm to 259.6 µm. Points x_2, x_4 and x_5 are within 90% confidence region and within 99% confidence region also points x_6 and x_7. The other five points are outside the rectangular reliability.

CONCLUSIONS

From the results obtained in this study it can be concluded that particle size of the final granulates used in tablet formulations affect the percentage of glibencalmide dissolution from these tablets. All particle size affect the percentage of glibencalmide dissolution, however, for optimal glibenclamide release from tablets relationship between dimensions of all particles is important. Influence of particle size on the dissolution percentage is more significant for smaller particles d(0.1) and d(0.5) then for particles with larger diameter d(0.9) and D(4,3). Dissolution of glibenclamide from tablets decreased with increasing particle size d(0.1). Dissolution of glibenclamide from tablets increased with increasing particle size d(0.9) and D(4,3). Optimal ratio of the particle size and percentage of glibenclamide dissolution was observed for sample x_2 with particle size distribution of d(0.1) = 36 µm, d(0.5) = 172 µm, d(0.9) = 499 µm and D(4,3) = 229 µm. Mean value of percentage dissolution for glibenclamide from sample x_2 is 97%.

REFERENCES

1. Shekunov BY, Chattopadhyay P, Tong HHY, Chow AHHL. Particle Size Analysis in Pharmaceutics: Principles, Methods and Applications. Pharm Res 2007; 24(2): 203-227.
2. Fayed ME, Otten L. Handbook of Powder Science & Technology. 2nd ed. New York: Chapman and Hall; 1997.
3. Hlinak AJ, Kuriyan K, Morris KR, Reklaitis GW, Basu PK. Understanding critical material properties for solid dosage form design. Journal of Pharmaceutical Innovation 2006; 1: 12–17.
4. Eichie FE, Kudehinbu AO. Effect of particle size of granules on some mechanical properties of paracetamol tablets. African Journal of Biotechnology 2009; 8(21): 5913-5916.
5. Brittain HG. Particle-Size Distribution, Part I Representations of Particle Shape, Size, and Distribution. Pharmaceutical Tehnology, North America 2001; 25(12): 38 – 44.
6. Gotoh K, Finney JL. Representation of the size and shape of a single particle. Powder Technology 1975; 12(2): 125-130.
7. Heywood H. Calculation of particle terminal velocities. J Imp Coll Chem Eng Soc 1948; 140–257.
8. Lieberman HA, Lachman L, Schwartz JB. Pharmaceutical dosage forms: Tablets Volume 1. 2nd ed. New York: Marcel Dekker; 1989.
9. Stanley-Wood NG, Lines RW. Particle size analysis. 1st ed. Royal Society of Chemistry; 1992.
10. Syroeshkin AV, Popov PI, Grebennikova TV, Frolov VA, Pleteneva TV. Laser diffraction for standardization of heterogeneous pharmaceutical preparations. J Pharm Biomed Anal 2005; 37(5): 927-930.
11. Mishchenko MI, Hovenier JW, Travis LD. Light Scattering by Nonspherical Particles: Theory, Measurements, and Applications. San Diego: Academic Press; 2000.
12. Sirisuth N, Eddington ND. In vitro in vivo correlations, systemic methods for the development and validation of an IVIVC metoprolol and naproxen drug examples. Int J Generic Drugs 2002; 3: 250-258.
13. United States Pharmacopeia/ National Formulary, USP28/NF 23, Rockville, MD: Official January 1, 2005; 2411–2412.

14. Dressman JB, Reppas C. In vitro–in vivo correlations for lipophilic, poorly water-soluble drugs. Eur J Pharm Sci 2000; 11(2): S73-S80.
15. Kaur J, Aggarwal G, Singh G, Rana AC. Improvement of drug solubility using solid dispersion. Int J Pharm Pharm Sci 2012; 4(2): 47-53.
16. Chaudhari MD, Sonawane RO, Zawar L, Nayak S, Bari SB. Solubility and dissolution enhancement of poorly water soluble glimepiride by using solid dispersion technique. Int J Pharm Pharm Sci 2012; 4(5): 534-539.
17. Gupta MM, Mitul PG, Nimesh PS, Kedawat M. Enhancement of dissolution rate of ibuprofen by preparing solid dispersion using different methods. Int J Pharm Pharm Sci 2011; 3(3): 204-206.
18. Galal S, El- Massik M, Abdallah O, Daabis N. Formulation of fast release glibenclamide liquid and semi-solid matrix filled capsules. Acta Pharm 2003; 53(1): 57-64.
19. Patel TB, Patel LD, Patel TB, Makwana SH, Patel TR. Formulation and characterization of solid dispersions containing glibenclamide. Int J Pharm Pharm Sci 2010; 2(3): 138-141.
20. Jyothi JB, Suneela G. Development of Fast Dissolving Tablets of Glibenclamide Using Crospovidone and its Kneading Mixture. Indian J Pharm Educ Res 2010; 44(4): 334-340.
21. Azarmi S, Roa W, Lobenberg R. Current perspectives in dissolution testing of conventional and novel dosage forms. Int J Pharm. 2007; 328: 12–21.
22. Papageorgion GZ, Bikiaris D, Karavas E, Politis S, Docoslis A, Park Y, Stergiou A, Georgarakis E. Effect of Physical State and Particle Size Distribution on Dissolution Enhancement of Nimodipine/PEG Solid Dispersions Prepared by Melt Mixing and Solvent Evaporation. The AAPS Journal 2006; 8(4): E623-E631.
23. Ansari MA, Stepanek F. The Evolution of Microstructure in Three-Component Granulation and Its Effect on Dissolution. Particul Sci Technol 2007; 26(1): 55–66.
24. Horkovics-Kovats S. Characterization of an Active Pharmaceutical Ingredient by Its Dissolution Properties: Amoxicillin Trihydrate as a Model Drug. Chemotherapy 2004; 50 (5): 234-244.
25. Dos Santos Gianotto EA, Arantes RP, Lara-Filho MJ, Casimiro Filho ACS, Fregonezi-Nery MM. Dissolution Test for Glibenclamide Tablets. Quimica Nova 2007; 30(5): 1218-1221.
26. United States Pharmacopeia. In vitro and in vivo evaluation of dosage forms, 1088, 23rd ed. Rockville: USP Convention, Inc; 1995; 1924–1929.
27. Valcarcel M. Principles of Analytical chemistry: a textbook. Springer-Verlag Berlin Heidelberg GmbH; 2000.