

EFFECT OF SOLUBILITY OF DIFFERENT EXCIPIENTS ON DRUG RELEASE OF CHITOSAN MATRIX TABLET OF ACECLOFENAC: A STUDY

Ramesh G. Katedeshmukh^{1*}, Adhikrao V. Yadav²

¹Govt. College of Pharmacy, Karad, Dist-Satara, MS, India-415 110.

²Gourishankar Institute of Pharmaceutical Education and Research, Limb, Satara, MS, India-415 206.

ABSTRACT

Until now numerous oral controlled drug delivery systems have been developed to prolong drug release. The crucial point in this respect is that the drug has to be absorbed well throughout the whole gastrointestinal tract. Chitosan, a linear binary heteropolysaccharide, composed of β -1, 4-linked glucosamine (GlcN) with various degrees of N-acetylation of GlcN residues. It is a non-toxic, biocompatible and biodegradable natural polymer of high molecular weight (~500,000 kDa). Chitosan is prepared by alkaline N-deacetylation of chitin using concentrated sodium hydroxide (NaOH) solutions at high temperature for a long period of time. The degree of deacetylation (DD) and molecular weight (MW) are two fundamental parameters that can affect the properties and functionality of chitosan. Hydrophilic polymers are widely used in controlled release systems due to their favorable functionality. Enhancing the mobility of the polymer chains and diffusing of the drug out from such polymer matrices could be done by inclusion of different types of excipients at different concentrations. The present manuscript describes the attempt made to investigate the influence of the excipient type on matrix hydration, erosion and drug release from matrix systems with a highly soluble excipients and water-insoluble excipients and varying concentration of chitosan A (20% & 30%).

Key words: Matrix systems, chitosan A, Aceclofenac, MCC, drug release.

INTRODUCTION

Chitosan, a linear binary heteropolysaccharide, is composed of β -1,4-linked glucosamine (GlcN) with various degrees of N-acetylation of GlcN residues¹⁻⁵. Chitosan occurs naturally in some microorganisms, yeast and fungi⁶⁻⁸. It is a non-toxic, biocompatible and biodegradable natural polymer of high molecular weight (~500,000 kDa)^{9,10}. It is the second most common polysaccharide occurring in nature after cellulose. Chitosan is prepared by alkaline N-deacetylation of chitin using concentrated sodium hydroxide (NaOH) solutions at high temperature for a long period of time^{1, 11}. Another approach to produce chitosan is by enzymatic N-deacetylation under relatively mild conditions.¹²⁻¹⁵ The commercially available chitosan is mostly derived by alkaline N-deacetylation from chitin of crustaceans because it is easily obtainable from the shells of crabs, shrimps, lobsters and krill^{16,17}. The degree of deacetylation (DD) and molecular weight (MW) are two fundamental parameters that can affect the properties and functionality of chitosan^{11, 13, 18}. These properties include solubility^{12, 19, 20}, viscosity¹⁰, reactivity such as heavy metal ion chelation²¹ and proteinaceous material coagulation², loading (enzyme-loaded) properties and film properties such as tensile strength, elasticity, elongation and moisture absorption²²⁻²⁷. With the apparent pKa value of the amino group of about 6.5^{22,23}, chitosan is only soluble in aqueous acidic solutions and insoluble in water and alkaline solutions²⁴.

Matrix systems generally consist of dissolved or dispersed drug within a swelling or slowly eroding polymer matrix. The drug release from such systems is controlled by water penetration into the matrix followed by either diffusion of the drug into the surrounding medium, erosion of the matrix, or combination of both. A potential disadvantage of the simple monolithic matrix system is the lack of zero-order release kinetics resulting from time-dependent changes in the diffusion path length and surface area. Such delivery systems are widely used to

*Corresponding author:

Email: krganpati55@gmail.com

control the drug release due to their low cost, broad FDA acceptance, ease of manufacturing, favorable in-vivo performance and wide range of physicochemical properties which help modulate the drug release kinetics. Hydrophilic polymers are widely used in controlled release systems due to their favorable functionality. At the molecular level, the drug release rate from polymer matrix is determined by the polymer swelling front, drug dissolution diffusion, and matrix erosion. These occur by the interaction of water molecules with polymer matrix and drug molecules. Enhancing the mobility of the polymer chains and diffusing of the drug out from such polymer matrices could be done by inclusion of different types of excipients at different concentrations²⁷⁻³¹. Aceclofenac (2-[(2, 6-dichlorophenyl) amine] phenylacetoxyacetic acid) is an orally effective non-steroidal anti-inflammatory drug (NSAID) of phenyl acetic acid group³²⁻³⁴. Aceclofenac appears to be particularly well-tolerated among the NSAIDs, with a lower incidence of gastrointestinal adverse effects^{35, 36}. Unfortunately, aceclofenac suffers from low aqueous solubility (0.058 µg/ml), leading to poor dissolution and

matrix hydration, erosion and drug release from matrix systems with a highly soluble excipients and water-insoluble excipients.

EXPERIMENTAL-

MATERIALS

Aceclofenac was obtained as gift sample from Aarti Drugs, Mumbai. Chitosan was procured as gift samples from India Sea Foods, Kerala. MCC was obtained from Anshul Life Sciences, Mumbai as gift sample. HPMC was provided by Scope Ingredients Pvt. Ltd., Chennai. All the solvent used for the study were of analytical grade. Magnesium stearate and aerosil were of laboratory grade.

METHODS

Preparation of matrix tablet of aceclofenac:

Several lots of matrix tablets with a theoretical weight of 250 mg were prepared, each containing aceclofenac (100 mg) as drug and MCC and HPMC, as polymeric matrix materials in combination with chitosan A (20% and 30%) Matrix tablet containing 100mg aceclofenac were prepared by non aqueous

Table 1: Formulation containing lactose and MCC with chitosan A 20 and 30% for 1 tablet (mg)

Ingredients	Formulation A-1	Formulation A-2	Formulation A-3	Formulation A-4
Aceclofenac	100	100	100	100
Lactose	97.5	72.5	0	0
MCC	0	0	97.5	72.5
Chitosan A 20%	50	0	50	0
Chitosan A 30%	0	75	0	75
Aerosil 200 0.5%	1.25	1.25	1.25	1.25
Magnesium Stearate	1.25	1.25	1.25	1.25

insufficient oral bioavailability. Aceclofenac is an example of BSC class II compound, its oral bioavailability is determined by dissolution rate in the gastrointestinal tract³⁷⁻⁴⁰. Therefore, the improvement of aceclofenac dissolution is an important issue for enhancing its bioavailability and therapeutic efficacy.

In the context of a wider research project to develop matrix tablets of aceclofenac with varying concentration of chitosan along with different grades available, the purpose of this study was to investigate the influence of the excipient type on

wet granulation technique. The composition of each tablet with varying concentration of chitosan grade A 20 and 30% along with lactose and MCC is shown in Table no. 1. All the ingredients along with aceclofenac were separately weighed and sifted using mesh no. 40. The above dry mixture was granulated with ethanol and dried in the tray drier at the temperature of 40-50°C until the solvent gets evaporated. The dried granules were passed through mesh no. 24. The dried granules were blended for ten minutes and the above blend was lubricated with Magnesium stearate, Aerosil for two minutes. The powder blends were evaluated for the flow

properties and were found to be in good agreement with the standards. The evaluated blend was compressed into tablets to get tablets of 250 mg each matrix tablet. A minimum of fifty tablets were prepared for each batch.

EVALUATION

Evaluation of Tablets:

The prepared tablets were evaluated for weight variation, hardness, thickness, Disintegration test, *In-vitro* drug release studies and Swelling behavior.

Weight variation test:-

In weight variation test twenty tablets were selected at a random and average weight was calculated using an electronic balance, and the test was performed according to the procedure given in USP. Then individual tablets were weighed and the weight was compared with an average weight.

Hardness and Friability: -

Pfizer hardness tester was used for the determination of the hardness. For each formulation, the hardness of 6 tablets was determined using the Pfizer hardness tester. The friability of the tablets was determined using Roche friabilator. This device subjects the tablets to the combined effect of abrasions and shock in a plastic chamber revolving at 25 rpm and dropping the tablets at a height of 6 inches in each revolution. Prewighed sample of tablets was placed in the friabilator and were subjected to 100 revolutions. Tablets were dedusted using a soft muslin cloth and reweighed. The friability (F) is given by the formula:

$$F = (1 - W_0 / W) \times 100$$

Where W_0 is the weight of the tablets before the test and W is the weight of the tablet after the test.

Thickness: -

The crown-to-crown thicknesses of five tablets from each batch were determined using a Digital Vernier caliper and average values were calculated.

Disintegration test:

The Disintegration of the designed and developed tablet was studied using Disintegration apparatus. Tablets were placed in distilled water as disintegrating medium at $37 \pm 0.5^\circ\text{C}$.

In-vitro drug release studies:-

The *In-vitro* dissolution studies were carried out using 8 station USP TDT-08L (Electro lab, Mumbai.) apparatus at $37 \pm 0.5^\circ\text{C}$ and at 50 rpm. The dissolution medium consisted of phosphate buffer p^{H} 6.8 for 300 minutes (900 mL). At every interval 10 mL of sample was withdrawn from the dissolution medium and replaced with fresh medium to maintain the volume constant. After filtration and appropriate dilution, the sample solutions were analyzed by UV- visible spectrophotometer.

Swelling behaviour of matrix tablets: ⁴¹

The extent of swelling was measured in terms of % weight gain, axial and radial swelling by the tablet. The swelling behavior of formulation was studied using reported method. One tablet from each formulation was kept in a petridish containing pH 6.8 phosphate buffer. At the end of particular time interval, the tablet was withdrawn, soaked with tissue paper, and weighed. Percent weight gain by the tablet was calculated by formula;

$$S.I = \{(Mt - Mo) / Mo\} \times 100,$$

where, S.I = swelling index, Mt = weight of tablet at time 't' and Mo = weight of tablet at time t = 0.

The matrices obtained were circular in shape with 8-mm diameters. Hence, using computer-aided design software, concentric circles were drawn with diameters of 7, 8, 10, 12, 14, 16, 18, 20, 22, 25, and 30 mm. The paper was laminated to make it hydrophobic. On either side of this piece, special arrangements were made to facilitate the raising and lowering of the assembly. The concentric circles are drawn to measure the increase in the radial direction, which makes it unnecessary to disturb the gel layer that formed, and the diameter of the outermost circle arbitrarily was fixed at 30 mm as the matrices underwent dissolution above this parameter. The area A of the circular face was determined using the equation

$$A = \pi r^2$$

in which π is the constant and r is the radius of the circle.

The tablet matrix under investigation was placed in the center so that it occupied the innermost circle with a 7-mm diameter. The assembly was weighed and then lowered in a 100-mL glass beaker containing 35 mL of deionized water that was maintained at $37 \pm 0.5^\circ\text{C}$.

After predetermined time periods, this assembly was raised out of the beaker and was reweighed after wiping off the water droplets that adhered to the surface of the assembly. The difference in the two weight values gives the amount of water absorbed by the matrix. The amount of water absorbed by the matrix is plotted against the time to determine the water absorption pattern.

The average velocity of water penetration front was determined using the equation

$$U = (dW_g/dt) * (1/p_w 2A)$$

in which dW_g/dt is the weight of water absorbed by the matrix per unit time, p_w is the density of water at 37°C, A is the area of the matrix, and the factor 2 accounts for diffusion taking place through both the faces.

Results and Discussion

Pre compressional parameters:

Some of the Pre compressional parameters of granules are shown in **Table 2**. Bulk density, tapped

to 1.379 %), weight variation (0.324 to 0.488) and thickness (5.15 to 5.50 mm). Drug content was found to be (68.120 to 99.189 %) within the acceptable official limits.

Dissolution study of all the formulations was carried out using 8 station USP TDT-08L (Electro lab, Mumbai.) apparatus at 37±0.5°C and 50 rpm. The dissolution medium consisted of phosphate buffer pH 6.8 for 300 minutes (900 mL). Formulations A1 to A4 were prepared by using Lactose, MCC and varying concentration of Chitosan i.e. 20 and 30%. **Figure 1** shows the drug release profile of formulations A1 to A4. Among these formulations, formulation A1 and A3, prepared with chitosan 20% with lactose and with MCC shown faster and sustained drug release over a period of 300 minutes as compared to the formulations prepared with high concentration of chitosan 30%. With all developed formulations containing lactose, an initial burst drug release followed by a steady-state release was observed which could be accounted for the concentration of highly soluble lactose at the surface that dissolves

Table 2: Pre-compressional evaluation parameters for granules

Sr No.	Formulation	Bulk Density (g/mL)	Tapped Density (g/mL)	Compressibility Index (%)	Hausner's ratio
1	A1	0.561±0.003	0.897±0.004	06.267±3.216	1.106±0.006
2	A2	0.641±0.003	0.900±0.004	21.816±3.163	1.375±0.005
3	A3	0.532±0.003	0.992±0.005	10.656±1.068	1.365±0.001
4	A4	0.501±0.002	0.974±0.003	10.003±1.654	1.541±0.002

density, % compressibility (06.267to 21.816%), and Hausner's ratio (1.106 to 1.541) of the prepared granules are found in good agreement as given in official standards.

Post compressional parameters:

Table 3 shows post compressional parameters i.e. hardness (5.04 to 5.21 kg/cm²), friability (0.323

immediately.

CONCLUSION

The formulations **A1** to **A4** were prepared with water soluble lactose & MCC along with chitosan A 20% and chitosan A 30%. All the prepared formulations shown 68.120 to 99.189 % drug release in 300 minutes and formulations could sustain the

Table 3: Post-compressional evaluation parameters for developed formulations

Sr. No.	Formulation	Dissolution time (Minute)	Weight Variation (%) (±SD)	Thickness (mm.) (±SD)	Friability (%) (±SD)	Hardness (Kg./cm ²) (±SD)	Axial Swelling	Radial Swelling	Maximum cumulative drug release (%) (±SD)
1	A1	6	0.488 ± 0.306	5.21 ± 0.182	1.241 ± 0.733	5.14 ± 0.01	0.5	2	99.167 ± 0.252
2	A2	120	0.324 ± 0.421	5.50 ± 0.276	0.323 ± 0.014	5.16 ± 0.02	4.7	2	68.120 ± 0.167
3	A3	180	0.451 ± 0.156	5.15 ± 0.420	0.667 ± 0.224	5.04 ± 0.01	4	1	99.189 ± 0.212
4	A4	48	0.403 ± 0.317	5.19 ± 0.217	1.379 ± 0.095	5.21 ± 0.02	4.1	2	85.426 ± 0.301

drug release up to the desired time period. The matrix tablets of aceclofenac containing chitosan A in lesser concentration disintegrate rapidly and shows faster drug release from the tablet (**A1 & A3**) and in formulation **A2** drug release was found to be retarded because of insoluble MCC. The matrix tablets of aceclofenac containing chitosan A in higher concentration retards the disintegration process and thereby drug release. In formulation **A4** drug release was observed to follow zero order kinetic but release was further retarded because of higher concentration of chitosan A (30%).

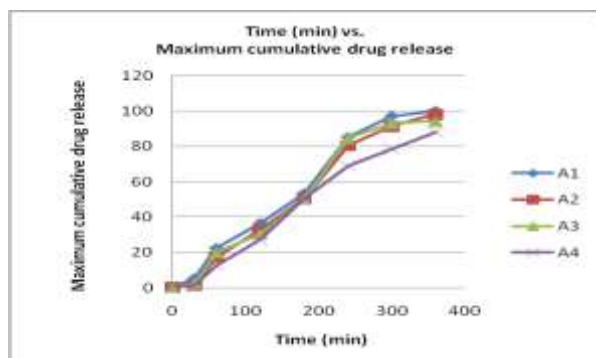
From the release study it is observed that, the release of drug is decreased from the tablet may be because of retardation in disintegration process by higher concentration of chitosan A. In conclusion, soluble lactose with chitosan A 20% could be used as drug release controlling polymers by appropriate selection of the level of polymers in the matrix.

Table 4: Maximum cumulative drug release for formulation A1-A4.

Sr. No.	Time in Minute	Maximum cumulative drug release (%) (\pm SD)			
		A1	A2	A3	A4
1	0	0	0	0	0
2	30	3.25 \pm 0.14	0.1 \pm 0.41	4.09 \pm 0.28	1.24 \pm 0.17
3	60	18.28 \pm 0.29	14.21 \pm 0.43	16.27 \pm 0.54	8.25 \pm 0.42
4	120	25.13 \pm 0.36	23.43 \pm 0.31	36.61 \pm 0.31	30.48 \pm 0.37
5	180	47.22 \pm 0.45	45.13 \pm 0.17	48.73 \pm 0.10	38.62 \pm 0.31
6	240	77.57 \pm 0.35	60.83 \pm 0.32	79.97 \pm 0.21	78.77 \pm 0.33
7	300	86.96 \pm 0.47	70.14 \pm 0.51	88.02 \pm 0.37	89.13 \pm 0.51
8	360	105.28 \pm 0.41	70.14 \pm 0.28	98.59 \pm 0.35	99.1 \pm 0.41

REFERENCES AND NOTES

Figure 1- Plot of time in minute v/s maximum cumulative drug release



1. R. N. Tharanathan and F. S. Kittur. Chitin: The Undisputed Biomolecule of Great Potential, *Crit. Rev. Food Sci. Nut.* 43 (1) 61-87 (2003).
2. S. Sabnis and L. H. Block. Chitosan as an enabling excipient for drug delivery systems. I. Molecular modifications, *Int. J. Biol. Macromol.* 27(3): 181-6 (2000).
3. A. El-Ghaouth, R. Ponnampalam, F. Castaigne, and J. Arul. Chitosan Coating to Extend the Storage Life of Tomatoes, *Horticult. Sci.* 27: 1016-1018 (1992).
4. T. S. George, K. S. Senthil Guru, N. S. Vasanthi, and K. P. Kannan. Extraction, purification and characterization of chitosan from endophytic fungi isolated from medicinal plants, *World J Sci and Tech.* 1(4): 43-48 (2011).
5. J. D. Dee, O. Rhode, and R. Wachter. Chitosan-Multi-functional marine polymer, *Cosmetics and Toiletries.* 116: 39-42 (2001).
6. A. K. Singla, M. J. Chawla. Chitosan: Some pharmaceutical and biological aspects- an update, *Pharm. Pharmacol.* 53: 1047-1067 (2001).
7. G. Crini. Non-conventional low-cost adsorbents for dye removal: a review, *Bioresour. Technol.* 97: 1061-1085 (2006).
8. N. R. Sudarshan, D. G. Hoover, and D. Knorr. Antibacterial Action of Chitosan, *Food Biotechnol.* 6: 257-272 (1992).
9. A. V. Yadav, S. B. Bhise. Chitosan : A Potential Biometrial Effective Against Typhoid, *Curr. Sci.* 87(9): 1176 (2004).
10. J. Berger, M. Reist, J. M. Mayer, R. Felt O, Gurny. Structure and interactions in chitosan hydrogels formed by complexation or aggregation for biomedical applications, *Eur. J. Pharm. Biopharm.* 57: 35-52 (2004).
11. M. L. Duarte, M. C. Ferreira, M. R. Marvão, and J. Rocha. An optimized method to determine the degree of acetylation of chitin and chitosan by FTIR spectroscopy, *Int. J. Bio. Macromolecules.* 31: 1-8 (2002).
12. A. Baxter, M. Dillon, K. D. A. Taylor, and G. A. F. Roberts. Improved method for I. R. determination of the degree of N-acetylation of chitosan. *Int. J. Biol. Macromol.* 14: 166-169 (1992).

13. M. R. Kasaai. A review of several reported procedures to determine the degree of acetylation for chitin and chitosan using infrared spectroscopy. *Carbohydrate Polymers*, 71: 497–508 (2008).
14. M. R. Kasaai. Various methods for determination of the degree of N-acetylation of chitin and chitosan: A review. *J. Agric. Food Chem.* 57: 1667–1676 (2009).
15. R. V. S. Amorim, W. M. Ledingham, K. Fukushima, and G. M. Campos-Takaki. Screening of chitin deacetylase from mucoralean strains (zygomycetes) and its relationship to cell growth rate, *J. Ind. Micro. Biotech*, 32(1): 19-23 (2005).
16. M. F. J. Cervera, H. Krogars, K. A. C. Jorgensen, M. Karjalainen, A. I. Colarte, and J. Yliruusi, Solid-state and mechanical properties of aqueous chitosan-amylose starch films plasticized with polyols, *AAPS Pharm. Sci. Technol.* 5: E15-E15 (2004).
17. Y. W. Cho, Y. N. Cho, S. H. Chung, and W. Ko. Water-soluble chitin as a wound healing accelerator, *Biomaterials*. 20: 2139-2145 (1999).
18. P. R. Rege, L. H. Block. Chitosan processing: influence of process parameters during acidic and alkaline hydrolysis and effect of the processing sequence on the resultant chitosan's properties, *Carbohydrate Res.* 321(3): 235-245(11) (1999).
19. J. K. Hwang, and H. H. Shin. Rheological properties of chitosan solutions, *Korea-Australia Rheology J.* 12: 175-179 (2000).
20. R. A. A. Muzzarelli. *Natural chelating polymers*, Pergamon Press Ltd, Oxford, 1973.
21. R. Chen, and M. Tsaih. Effect of temperature on the intrinsic viscosity and conformation of chitosans in dilute HCl solution, *Int. J. Biol. Macromol.* 23: 135–141 (1998).
22. K. K. Myong, S. J. Hwa, K. Sung-Koo, L. W. Curtis, and H. Milford, Properties of Chitosan Films as a Function of pH and Solvent Type. Biological Systems Engineering: Papers and Publications. (2006) Paper 111.
23. M. R. Kasaai. Calculation of Mark–Houwink–Sakurada (MHS) equation viscometric constants for chitosan in any solvent–temperature system using experimental reported viscometric constants data, *Carbohydrate Polymers.* 68: 477–488 (2007).
24. O. Pillai, and R. Panchagnula. Polymers in drug delivery, *Curr. Opin. Chem. Biol.* 5: 447-451 (2001).
25. E. Khor, and L. Y. Lim. Implantable applications of chitin and chitosan, *Biomater.* 24, 2339-2349 (2003).
26. S. Yuan, and T. J. Wei. New contact lens based on chitosan/gelatin composites, *Bioact. Compat. Polym.* 19: 467-479 (2004).
27. H. I. Bolker. Natural and synthetic polymer: an introduction. Marcel Dekker Inc, New York, 1974.
28. R. Kale, A. Bajaj, and D. Mathew, Development of matrix diffusion controlled drug delivery system of pentoxifylline, *Int. J. Pharm. Pharma. Sci.* 2(1): 22-30 (2010).
29. N. Lordi, Sustained release dosage forms. In: Lachman, L., Lieberman, H.A., Kanig, J.L. (Eds.), *The theory and practice of Industrial Pharmacy*, 3rd. Lea and Febiger, Philadelphia, 1986, pp 430–478.
30. H. Rey, K. G. Wagner, P. Wehrle, and P. C. Schmidt, Development of matrix-based theophylline sustained-release microtablets, *Drug Dev. Ind. Pharm.* 26: 21–26 (2000).
31. L. Rodriguez, O. Caputo, M. Cini, C. Cavallari, and R. Grecchi, *In vitro* release of theophylline from directly compressed matrices containing methacrylic acid copolymers and/or dicalcium phosphate dehydrate, *Il Farmaco*, 48: 1597–1604 (1993).
32. A. Pareek, A. S. Chandanwale, J. Oak, U. K. Jain, and S. Kapoor. Efficacy and safety of aceclofenac in the treatment of osteoarthritis: a randomized double blind comparative clinical trial versus diclofenac – an Indian experience, *Cur. Med. Res. Opinion*, 22 (5): 977-988 (2006).
33. Indian Pharmacopoeia. Vol. 2. New Delhi: Controller of Publication; 1996. p. 267-8.
34. British Pharmacopoeia, The Stationary Office, MHRA, Vol. 1, British Pharmacopoeial Commission office, London, 2005.
35. K. Parfitt, Analgesics anti-inflammatory and antipyretics, in: J.E.F. Reynolds (Ed.),

Martindale: The Complete Drug Reference. 32nd ed., 1999, 2–12, Massachusetts.

36. K. V. Gowda, D. S. Rajan, U. Mandal, P. S. Selvan, W. D. Sam Solomon, A. Bose, A. K. Sarkar, T. K. Pal, and T. K. Chattaraj, Evaluation of bioequivalence of two formulations containing 100 mg of aceclofenac, *Drug Dev. Ind. Pharm.* 32: 19–25 (2006).
37. A. L. Gorden, and R. Loebenberg, Modern bioavailability, bioequivalence and biopharmaceutics classification system. New scientific approaches to international regulatory standards, *Eur. J. Pharm. Biopharm.* 50: 3–12 (2000).
38. B. Lee, and H. Jung, Enhanced bioavailability of poorly water-soluble aceclofenac using PEG-based solid dispersion in rats, beagle dogs and human subjects, *AAPS Annual Meeting, New Orleans, LA, USA, Pharm. Sci. Suppl.*, 4: 14–18 (1999).
39. T. Kim, J. Shin, and B. Lee, Enhanced dissolution and bioavailability of poorly watersoluble aceclofenac using solid dispersion system, Denver, Colorado, USA: *AAPS, Annual Meeting*,: 21–25 (2001).
40. S. Bhardwaj, V. Jain, R. C. Jat, A. Mangal, and S. Jain, Formulation and evaluation of fast dissolving tablet of aceclofenac, *Inter J Drug Delivery*, 2: 93-97 (2010).
41. S. R. Parakh, A. V. Gothoskar, and M. T. Karad, A novel method for the study of water absorption rates by swellable matrices, *Pharm. Tech.* 5: 40-48,(2003).