Characterization and *In-Vitro* Release Study of Celecoxib Microspheres Synthesized from Polymethacrylate and Polyvinyl Pyrolidone

[1]MUHAMMAD KHURRAM SHAHZAD, [1]MAHBOOB-E-RABBANI, [2]ASADULLAH MADNI*
[2]MAHMOOD AHMAD, [2]MUHAMMAD USMAN, [2]MAHTAB AHMAD KHAN,
[2]HASSAN AHMAD AND [2]MD EKWAL
[1]*Department of Pharmacy*, *Faculty of Pharmacy*, *Bahauddin Zakariya University*, *Multan*, *Pakistan.*
[2]*Department of Pharmacy*, *Faculty of Pharmacy and Alternative Medicine*,
The Islamia University of Bahawalpur, *Bahawalpur*, *Pakistan.*
asadpharmacist@hotmail.com*

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Summary: The aim of the present study was to formulate and characterize microspheres of celecoxib for controlled delivery. Celecoxib controlled release microspheres were prepared by solvent evaporation technique and were evaluated for physical characteristics and *In-Vitro* release profile. Drug was entrapped into microspheres of biodegradable polymers Polymethacrylate (PMA) and Poly-Vinyl Pyrrolidone-K30 (PVP) at different ratios. Microsphere recovery decreased with increasing the concentration of PVP in the formulations. Entrapment efficiency of the drug in microspheres increased with decreasing PMA and increasing PVP concentrations. Micrometric properties showed free flowing nature of microspheres. *In-Vitro* dissolution studies showed pH-dependent nature of the microspheres. Under acidic environment (pH 1.2) almost 11–19% of drug was released in first 2 hrs. Almost all of the formulations of microspheres showed a sustained release behavior up to 12 hrs (pH of 6.8). Drug release kinetics followed zero order at pH 1.2 while at pH 6.8 Higuchi model was best fitted.

Keywords: Celecoxib; Controlled release; Biodegradable; Higuchi model, Microsphere

Introduction

Many patients with chronic diseases require administration of drugs for a long period of time with multiple doses, which may lead to non-compliance due to side effects and frequent dosing. The problem is mainly associated with drugs having shorter biological half-lives and immediate release dosage forms. The only way to overcome such situations is to design a dosage form capable of releasing the drug at a controlled rate. Microencapsulation has been used as one of the dosage forms to deliver drugs in a well-controlled manner [1]. Microencapsulation is the application of a thin coating to individual core materials that have an arbitrary particle-size ranging from 5 to 5,000μm [2]. The formulations based on microspheres provide an optimum control of drug release kinetics [3]. Moreover, controlled release preparations are preferred for their ability to produce maximum therapeutic effects with lesser side effects [4]. Microspheres designed with biodegradable controlled release polymers are getting more importance in pharmaceutical technology because microspheres degrade within the body as a result of natural biological processes, so there is no need to eliminate the delivery system after its function is over [5].

Several methods are used to prepare microspheres (form natural and synthetic polymers) by various methods. Currently available methods are solvent extraction/evaporation, phase separation and spray-drying technique [6]. Spray-drying is quite simple technique but cannot be used for temperature-sensitive compounds. Furthermore, the control of particle size is not easy job, and small batches can be produced [7]. Phase separation is frequently impaired by residual solvents and coacervating agents found in the microspheres [8]. Moreover, it is not suited for production of microspheres with low micrometer size range. The role of supercritical gases as phase separating agents have been studied to minimize the amount of harmful residue produced during the process such as precipitation with compressed antisolvent (PCA) [9]. Solvent extraction/evaporation methods do not require high temperatures and phase separation-inducing agents. Controlled particle sizes (ranging from nano to micrometer) can be achieved, however careful selection of encapsulating materials and experimental conditions are required for high efficient encapsulation. Microsphere preparation by solvent extraction/evaporation usually consists of four basic steps: (i) dissolution or dispersion of the active substance often in an organic solvent containing matrix forming material; (ii)

emulsification of this organic phase in a continuous (frequently aqueous) phase which is immiscible with the organic one; (iii) extraction of the solvent from the dispersed phase by the continuous phase, which is usually accomplished by solvent evaporation and this ultimately results in transforming the droplets into solid microspheres; (iv) collection and drying of the microspheres. Due to uniformity of particle size and its reproducibility, Emulsification by solvent evaporation is the common technique for preparing microspheres [10]. Different combinations of polymers are being frequently used for sustained release dosage forms, which show better performance and desired release kinetics than the individual polymers [11]. Celecoxib is used for acute pain, osteoarthritis, rheumatoid arthritis, painful menstruation and to reduce the number of colon and rectal polyps. It is primarily given to the patients who need a regular and long lasting pain relief [12].

In the current study different proportions of Celecoxib, Polymethacrylate and Polyvinylpyrrolidone are used for the preparation of microspheres. These microspheres were characterized for drug loading, entrapment efficiency, recovery of microspheres, hydration rate, rheological properties and release studies at pH 1.2 and 6.8.

Results and Discussion

Recovery of Microspheres

Celecoxib microspheres were prepared by solvent evaporation technique. The prepared microspheres were white, free flowing and spherical in shape. The method used for the preparation in this study was advantageous for the entrapment of water-insoluble drugs. Low concentration of surfactant was tried to prepare Celecoxib loaded microspheres, but failed and it resulted in an aggregated cake. So the current amount of surfactant (tween80) 0.5%w/v was sufficient enough to prepare stable microspheres. The recovered total weight periodically decreased with an increase in the concentration of the PVP in the formulation medium as given in Table-1, 2. This low recovery is the result of the loss of hydrophilic PVP to the external phase. Stirring rate also influenced the yield and size of microspheres [13-16]. In this study, a stirring speed of 700 rpm produced microspheres of appropriate particle size and yield also remained almost constant. By increasing the stirring speed above 700rpm, there was a decrease in recovery. This low recovery was due to the formation of smaller microspheres which were lost during washings process. While decreasing the stirring speed lower than 700 rpm, aggregates were found and material also adhered to the walls of the container which also resulted in low recovery. Similar findings were reported by Giannola et al. and Varshosaz and Keihanfar [13-14].

Table-1: Composition of formulations.

Formulation	Drug/Polymers	Drug/Polymers ratio
F-1	Celecox/PMA/PVP	2:9:1
F-2	Celecox/PMA/PVP	2:8:2
F-3	Celecox/PMA/PVP	2:7:3
F-4	Celecox/PMA/PVP	2:6:4
F-5	Celecox/PMA/PVP	2:5:5
F-6	Celecox/PMA/PVP	2:4:6
F-7	Celecox/PMA/PVP	2:3:7
F-8	Celecox/PMA/PVP	2:2:8
F-9	Celecox/PMA/PVP	2:1:9

Table-2: Recovery of microspheres.

Formulation	Mean Input (gm)	Mean output (gm)	% Recovery
F1	2.4	1.9	79.3
F2	2.4	1.88	78.7
F3	2.4	1.75	73.2
F4	2.4	1.63	67.9
F5	2.4	1.54	64.1
F6	2.4	1.43	59.7
F7	2.4	1.36	56.9
F8	2.4	1.23	51.2
F9	2.4	1.17	48.7

Entrapment Efficiency

The entrapment efficiency of microspheres varied from 73.8 to 96.1% as shown in Table 3. The entrapment efficiency was found to be dependent on the nature of polymer used. Increase in the concentration of PVP resulted in increased entrapment efficacy. The probable reason behind this might be the loss of polymer from dispersed phase into continuous phase. Hence the formulation containing higher concentration of PVP has more entrapment efficiency.

Table-3**:** Entrapment efficiency of microspheres.

Formulation	Entrapment Efficiency
F1	73.3
F2	79.2
F3	82.6
F4	83.4
F5	85.8
F6	89.3
F7	92.7
F8	94.3
F9	96.1

Micromeritic Properties

The results of the micromeritic properties for all the formulations are shown in Table-4, 5. The values of compressibility index for all formulations are ranged between 7.1 and 18.6 indicating good flow properties [15]. The Hausner's ratio for all batches is less than 1.25 which also indicates free powder flow. This behavior of the microspheres was further confirmed by the results of angle of repose having values not less than 20 indicating the good flow properties of microspheres.

Table-4: Micromeritic properties of microspheres.

Formulation	Bulk Density	Taped Density	Carr's Index	Hausner's Ratio	Angle of Repose
F1	0.34	0.41	18.6	1.23	35.26
F2	0.31	0.38	17.9	1.23	34.90
F3	0.29	0.35	17.2	1.21	34.33
F4	0.29	0.34	15.1	1.17	34.10
F5	0.28	0.31	14.6	1.11	33.66
F6	0.26	0.29	12.7	1.10	33.17
F7	0.23	0.25	10.3	1.09	32.90
F8	0.21	0.22	9.6	1.07	32.30
F9	0.17	0.18	7.1	1.06	29.10

Table-5: Percent celecoxib release from all formulations at pH 1.2.

Time(h)	F1	F2	F 3	F 4	F 5	F 6	F 7	F 8	F 9
0	0	0	0	0	0	0	0	0	0
0.5	2.6	3	4	3.3	4.8	5.3	5.6	6.3	7
1	5.8	6.7	7.9	9.2	9.38	11.1	10.7	11.6	12
2	11.85	12.8	13.6	14.16	15.2	15.56	16.54	17.7	18.3

In-vitro Drug Release Study

In-Vitro drug dissolution studies of microspheres showed that the sustaining effect was depended on the polymer type and the concentration used. When the amount of drug released from the were plotted against time, the resulting release profiles were found to follow almost the regular trend indicating that different combinations of polymers produced predictable change in drug release pattern as shown in Fig. 1 and 2.

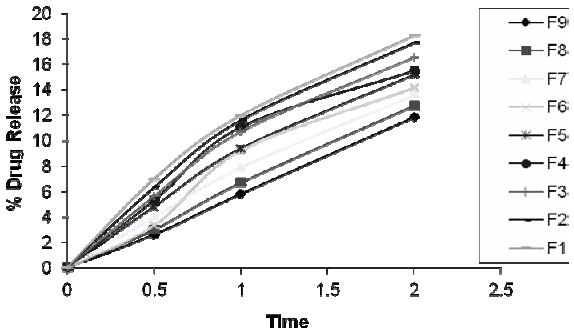

Fig. 1: Percent celecoxib release of all formulations at pH 1.2.

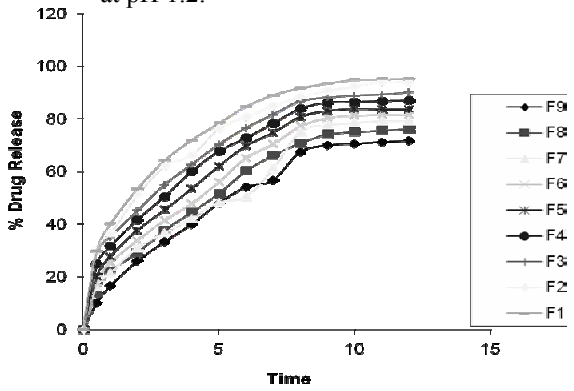

Fig. 2: Percent celecoxib release of all formulations at pH 7.4.

Under acidic environment (pH 1.2) almost 11–19% of drug was released in first 2 hrs. While with the decrease in PMA and increase in PVP concentrations the release of Celecoxib increased predictably. Slow release profile in acidic media might be due to partial hydrolysis of polymer under acidic conditions. At basic environment (pH 6.8), almost all of the formulations of microspheres showed a sustained release behavior up to 12 hrs with 26–54% drug release in first 2 hrs and 71.5 to 95.3% in 12 hrs. Formulation F-9 showed maximum release within 12 hrs having higher concentration of PVP (Fig. 2). Similar types of results were observed by Babu et al. [16] and investigated the preparation of microspheres with cellulose acetate butyrate-PVP. The microspheres with highest concentration of PMA i.e.; F1 showed 71.6% release of drug during the 12 hrs due to its strong binding property, hence the drug release persisted beyond the limit required. The release constants were determined from the slope of the respective plots, and the regression coefficient (R2) by the linear regression analysis.

In all the formulations the in vitro drug release at pH 1.2 was best explained by zero order equation (Table-6 and Table-7), with the highest linearity indicating that the drug release is independent of its concentration. All formulation followed Higuchi kinetics at pH 6.8 as plots showed the highest linearity, which suggested that the drug release from insoluble matrix is time dependent diffusion process based on Fick's law.

Experimental

Materials

PMA was received as gift from Jawa Chemicals Pvt. Ltd, Lahore while PVP was received as donation from Mediceena Pvt. Ltd, Lahore. Celecoxib was received as a gift from Wilshire

Pharmaceuticals, Lahore. Tween 80 and n-hexane were purchased from Buchs, Sigma Aldrich Switzerland. All other materials/chemicals used were of analytical grade.

Method

Microspheres were prepared by solvent evaporation technique. Different ratios of Celecoxib, PMA and PVP were dissolved in 40 ml of acetone using a magnetic stirrer. Then the core material, Celecoxib, was added to the polymers solution and stirred for further 15 minutes. The resulting dispersion was added slowly to a mixture of 360 ml light liquid paraffin, 0.5% tween 80 and 40 ml n-hexane contained in a 500 ml beaker. A mechanical stirrer, with a blade of 4 cm diameter, was used to stir the solution at 700 rpm for 3 hrs until acetone was evaporated completely. The microspheres formed were collected by filtration on Whatman filter paper #1 and were washed for 5 times with n-hexane [17].

The products were then dried at 40 ºC in hot air oven for 12 hours. Formulations were coded as F-1, F-2, F-3, F-4, F-5, F-6, F-7, F-8 and F-9 respectively. All batches were prepared in triplicate.

Table-6: % Celecoxib release of all formulations at pH 7.4.

Time	F1	F2	F 3	F 4	F 5	F 6	F 7	F 8	F 9
0	0	0	0	0	0	0	0	0	0
0.5	10.1	13.9	16.2	17.8	20.1	24.8	29.9	30.1	29.6
1	16.6	22.2	21.6	25.4	27.8	31.6	35.2	36.4	40.1
2	26	29.3	31	34	37.8	41.7	45.2	51.3	53.5
3	33.4	37.8	36.7	41.7	45.5	50.5	55	62.1	64.3
4	40	44.6	42.3	48	53.5	60	62.7	66.4	72.1
5	48	51.7	48.2	56.2	62.1	67.7	70.3	76.3	78.4
6	54.1	60.3	50.5	65.3	69.8	72.7	76.6	80.8	84.8
7	56.7	66.2	61.2	70.6	74.8	78.3	81.6	84.9	89.1
8	67.4	70.9	75.1	77.3	80.8	83.8	86.7	88.3	91.8
9	69.9	74.1	77.5	80.5	83.1	86.2	88	90.7	93.5
10	70.5	75.1	78.4	81.3	83.8	86.4	88.8	92.3	94.9
11	71.2	75.6	79.1	81.7	83.6	86.7	89.2	94.1	95.1
12	71.6	76.3	79.1	81.5	83.6	86.9	90	93.8	95.3

Table-7**:** Release kinetics of microspheres.

Formulation	Dissolution Media	Zero Order		First Order		Higuchi		Hixson		Korsmeyer–Peppas	
	pH	r^2	K_o	r^2	K_1	r^2	KH	r^2	KHC	r^2	n
F-1	1.2	0.999	5.98	0.941	1.208	0.886	8.075	0.818	1.039	0.339	1.094
	7.4	0.930	0.156	0.587	0.222	0.985	24.20	0.648	0.228	0.648	0.923
F-2	1.2	0.998	6.451	0.915	1.231	0.904	8.799	0.803	1.063	0.290	1.046
	7.4	0.914	6.101	0.536	0.211	0.991	25.34	0.609	0.222	0.580	0.867
F-3	1.2	0.991	6.76	0.857	1.222	0.943	9.455	0.761	1.069	0.196	0.882
	7.4	0.939	6.365	0.546	0.211	0.973	24.75	0.627	0.225	0.563	0.849
F-4	1.2	0.969	7.242	0.863	1.285	0.918	10.10	0.779	1.108	0.253	1.050
	7.4	0.908	6.427	0.506	0.206	0.992	26.88	0.587	0.221	0.537	0.839
F-5	1.2	0.982	7.530	0.820	1.258	0.957	10.65	0.744	1.105	0.157	0.831
	7.4	0.881	6.430	0.475	0.200	0.995	27.70	0.557	0.217	0.508	0.820
F-6	1.2	0.946	7.728	0.778	1.263	0.965	11.19	0.716	1.112	0.129	0.776
	7.4	0.857	6.384	0.437	0.193	0.993	27.98	0.520	0.210	0.463	0.784
F-7	1.2	0.971	8.157	0.789	1.283	0.968	11.67	0.727	1.131	0.128	0.781
	7.4	0.839	6.337	0.408	0.186	0.987	28.03	0.491	0.205	0.426	0.752
F-8	1.2	0.966	8.685	0.770	1.302	0.974	12.50	0.718	1.153	0.110	0.745
	7.4	0.818	6.474	0.396	0.185	0.981	28.90	0.477	0.205	0.421	0.757
F-9	1.2	0.961	8.897	0.750	1.303	0.982	12.89	0.705	1.158	0.093	0.693
	7.4	0.793	6.536	0.386	0.185	0.977	29.93	0.465	0.205	0.416	0.758

Recovery of Formed Microspheres

After preparation, the microspheres were recovered and dried overnight at 40 ºC in hot air oven. Recovery is the ratio of the weight of microspheres recovered to the total weight of solid contents charged at the beginning of the process.

$$\%\ Yield = W / Wc \times 100$$

Where "W" is the weight of microspheres while "Wc" is the weight of all species charged.

Characterization of Microspheres

Drug Loading

The dried microspheres (50 mg) were dispersed in 10 ml of phosphate buffer (pH 6.8), placed in ultrasonic bath for 15 min and filtered through 0.22 mm filters. To determine the amount of drug in microspheres the absorbance of the filtrate was noted at 251 nm UV Spectrophotometer UV-1601 (Shimadzu, Japan) [18].

Drug loading is determined by the following formula [19]:

$$DrugLoadin\ g = W_d / M_m \times 100$$

Where "W_d" is the mass of drug in microspheres and "M_m" is the mass of microspheres.

Entrapment Efficiency

Entrapment efficiency can be determined by following formula [20].

$$\varepsilon\varepsilon^\circ = D_l / T_l \times 100$$

Where "$\varepsilon\varepsilon^\circ$" is the % entrapment efficiency, D_l is the % drug loading and T_l is the % theoretical loading.

Measurement of Micromeritic Properties of Microspheres

The flow properties of microspheres were studied by measuring the bulk density, tapped density, Carr's indexes and packing factors.

Bulk Density

Bulk density was determined by pouring the microspheres into a graduated cylinder via a large funnel and measured the weight and volume.

Bulk density can be represented by following formula [21]:

$$BulkDensit\ y = W_s / V_s$$

Where "W_s" is the sample weight and "V_s" is the sample volume.

Tapped Density

The sample contained in the measuring cylinder was tapped manually at constant rate while rotating the cylinder (100 tapings were sufficient). The initial bulk volumes and final volumes after tapping were noted, from which their respective densities were calculated by the following formula [22]:

$$TappedDens\ ity = \frac{W_m}{V_m}$$

Where "W_m" is the weight of microspheres and "V_m" is the Volume of microspheres after 100 tappings.

Carr's Indexes

The Carr index is an indirect indication of the powder compressibility. It was calculated by the formula given below.

$$C = 100\ \frac{V_B - V_T}{V_B}$$

Where "V_B" is the freely settled volume of powder and "V_T" is the tapped volume of the same mass of the powder. It has been investigated that the Carr's index greater than 25 shows poor flowability, while below 15 it shows good powder flowability [23].

Hausner's Ratio

The Hausner ratio is the indirect measurement of the powder flowability. It is calculated by the formula given as.

$$H = \rho_T / \rho_B$$

Where "ρ_B" is the bulk density of the powder, and "ρ_T" is the tapped density of the powder. However, Hausner's ratio is not an absolute measurement of the powder flow property; its value varies with the methodology used. The ratio greater than 1.25 indicates poor flowability [21-25]. The Hausner's ratio (H) is related to the Carr's index and can be calculated by the formula given as.

$$H = 100 / (100 - C)$$

Both the Hausne's ratio and the Carr's index are usually criticized for not having strong theoretical basis. However, use of these methods persists because the technique is easy and equipments required are relatively cheap.

Angle of Repose

Angle of repose was measured by Funnel and cone method. A petri dish was taken and its diameter was measured, a funnel was fixed above the petri dish. Weighed amount of beads were poured from funnel until the apex of the heap reached the lower end of the funnel. The mean radius of the base "r" for the powder cone was measured and the angle of repose was calculated by the following equation.

$$Tan\ \theta = h / r$$

In-vitro Drug Release Study

The in vitro release studies of drug-loaded microspheres were carried out both at gastric pH 1.2 and intestinal 7.4 respectively [30]. It was performed according to the United States Pharmacopeia using (USP) paddle method using Pharma test dissolution apparatus PTWS-11/P, TPT (Hunburg, Germany). The 700 mg of microspheres were placed in the dissolution medium (900 ml), using HCl Buffer (pH 1.2) and Phosphate Buffer (pH 7.4) solutions without enzymes at 37°C with a speed of 100 rpm. The samples (3 ml) were withdrawn and replaced with an equal volume of fresh dissolution medium at predetermined time intervals, filtered through 0.45 µ nylon disc filters and were analyzed by UV spectrophotometer at 254 nm wavelength [26].

The drug concentration was estimated by using Calibration curves and the studies were carried out in triplicate. The mean values were plotted against the respective time.

Data Analysis

Drug release kinetics reflects the different release mechanisms of controlled release drug delivery systems. Hence, five kinetics models were applied to analyze the in vitro drug release data to find the best fitting equation.

Zero-order release equation [27]:

$$Ft = K_{\bullet} t$$

Where Ft is the fraction of drug released at time t and $K_{\bullet}$ is the rate constant of zero-order release.

First-order equation [28]:

$$\ln(1 - F) = -K1t$$

Where "F" is the fraction of drug released in time t and $K1$ is the first-order release constant.

Higuchi equation [29];

$$F = K_2 t^{1/2}$$

Where "F" is the fraction of drug released in time t and K_2 is the Higuchi constant.

Hixson–Crowell equation [30];

$$Q_o - Qt^{1/3} = kHCt^{1/3}$$

Peppas equation [31];

$$Mt / M\infty = K_3 t^n$$

Where Mt and $M\infty$ show the amount of drug released at times t and ∞ respectively and "n" is the diffusional coefficient. In spherical matrices, if n<0.43, it is called as Fickian release (case-I), 0.43<n<0.85, a non-Fickian, and if n>0.85, it is case-II (zero order) drug release mechanism [32].

Conclusion

Various formulations of biodegradable microspheres were successfully with different polymeric composition. Product recovery was decreased with increasing amount of PVP and drug loading efficiency was gradually increased with decreasing concentration of PMA. Micromeritic

characteristics showed an angle of repose was decreased along increased concentration of PVP. All formulations showed a pH dependent release. At pH 1.2, only a fraction of drug was released but at pH 7.4 comparatively a rapid release of drug was observed. Biodegradable microparticles followed zero-order release at pH 1.2. At pH 7.4, Higuchi model was followed by all formulations. The mechanism of solute release of microspheres was non-fickian. The findings of this work concludes that combined polymeric microspheres are suitable for controlled delivery of celecoxib over extended period of time and can be optimized for once daily dosing.

References

1. T. Yamuda, H. Onishiand and Y**.** Machida, *Journal of Control Release*, **75**, 271 (2001).
2. A. Nokhodchi, and D. Farid, *Pharmaceutical Technology*, **26**, 54 (2002).
3. L. Giannola, V. De Caro and M. Rizzo, *Drug Development and Industrial Pharmacy*, **21**, 797 (1995).
4. B. Wall, J. Perkin, V. Sunderland and A. Zorbas, *Journal of Pharmacy and Pharmacology*. **34**, 601 (1982).
5. R. Mundargi, N. Shelke, A. Rokhade, S. Pati and T. *Carb. Polymer*, **71**, 42 (2008).
6. C. Aftabrouchad and E. Doelker, *Pharmaceutical Sciences*, **2**, 365 (1992).
7. P. Johansen, H. Merkle and B. Gander, *European Journal of Pharmaceutics and Biopharmaceutics*, **50**, 413 (2000).
8. C. Thomasin, P. Johansen, R. Alder, R. Bemsel, G. Hottinger, H. Altorfer, E. Wright, A. Wehrli, H. Merkle and B. Gander, *European Journal of Pharmaceutics and Biopharmaceutics*, **46**, 16 (1996).
9. R. Falk and T. Randolph, *Pharmaceutical Research*, **15**, 1233 (1998).
10. M. Tuncay, S. C¸alis¸, H. Kas, M. Ercan, I. Peksoy and A. Hincal, *International Journal of Pharmaceutics*, **195**, 179 (2000).
11. M. R. Nazar, I. U. Khan and N. Shahzad, *Jouranl of Sol-Gel Science and Technology*, **50**, 281 (2009).
12. M. Yelland, C. Nikles, N. McNairn, C. B. Del Mar, P. Schluter and R. Brown, *Rheumatology*, **46**, 135 (2007).
13. L. Giannola, V. D. Caro and M. Rizzo. *Drug Development and Industrial Pharmacy*, **21**, 797 (1995).
14. J. Varshosaz and M. Keihanfar, *Journal of Microencapsulation* **18**, 277 (2001).
15. G. Mark (2001). In *The Theory and Practice of Industrial Pharmacy* (3ed). Philadelphia: Lea & Febiger, p316 (1986).
16. V. R. Babu, K. Reddy, M. Sairam, M. Subha, N. Mallikarjuna, P. Kulkarni and T. A. Des, *Monomers Polymers*, **10**, 155 (2007).
17. B. C. Behera, S. K. Sahoo, S. Dhal, B. B. Barik and B. K. Gupta. *Tropical Journal of Pharmaceutical Research*, **7**, 879 (2008).
18. M. Tuncay, S. Calis¸ H. S. Kas, M. T. Ercan, I. Peksoy and A. A. Hincal, *International Journal of Pharmaceutics*, **195**, 179 (2000).
19. S. Wang, S. Guo and L. Cheng, *International Journal of Pharmaceutics*, **137**, 130 (2008).
20. C. Raghavendra, A. Mundargi, B. Namdev, B . Shelke, P. Ajit, B. Rokhade, A. Sangamesh, A. Patil, M. Tejraj and Aminabhavi, *Carbohydrate Polymers*, **71**, 42 (2008).
21. A. Shariff, P. K. Manna, K. L. K. Paranjothy and M. Manjula, *Pakistan Journal of Pharmaceutical Sciences*, **20**, 9 (2007).
22. R. O. Grey and J. K. Beddow, *Powder Technology*, **2**, 323 (1969).
23. S. L. Rough, D. I. Wilson and D.W. York, *Advanced Powder Technology*, **16**, 145 (2005).
24. R. A. Garcia, R. A. Flores and C. E. Mazenko, *Bioresearch and Technology*, **98**, 2852 (2007)
25. A. B. M. kumar and K. R. Panduranga, *International Journal of Pharmaceutics*, **149**, 107 (1997).
26. M. R. Narender, R. Tasneem, S. Ramakrishna, K. P. R. Chowdary and V. D. Prakash, *AAPS PharmScience*, **6**, Article 7 (2004) (http://www.aapspharmsci.org).
27. N. Najib and M. Suleiman, *Drug Development and Industrial Pharmacy*, **11**, 2169 (1985).
28. S. J. Desai, P. Singh, A. P. Simonelli and W. I. Higuchi, *Journal of Pharmaceutical Sciences*, **55**, 1230 (1966).
29. T. Higuchi, *Journal of Pharmaceutical Sciences*, **50**, 1145 (1963).
30. A. W. Hixon and J. H. Crowel. *Industrial and Engineering Chemistry*, **23**, 923 (1931).
31. N. A. Peppas, *Pharmaceutica Acta Helvica*, **60**, 110 (1985).
32. L. E. Shi, X. J. Fang, L. X. Xing, M. Chen, D. S. Zhu, X. F. Guo, L. M. Zhao and Z. X. Tang, *Journal of the Chemical Society of Pakistan*, **33**, 929 (2011).