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Patient Compliant Ophthalmic Dosage form of Gatifloxacin

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Abstract: Gatifloxacin is a fourth generation fluoroquinolone derivative, gatifloxacin is an antibacterial used in the treatment of superficial bacterial eye infections like conjunctivitis, keratitis, bacterial corneal ulcer, dacryocistitis, scleritis caused by susceptible organisms. Gatifloxacin effective against Staphylococcus aureus, Staphylococcus epidermididis, Streptococcus mtis, Haemophilus influenzae, Corynebacterium propiquum. Gatifloxacin is available as a 0.3% w/v eye solution to be administered 8 times in a day in the eye. The present investigation was aimed at designing a twice a day ocular inserts of Gatifloxacin by melt extrusion technique to improve patient compliance, using hydroxypropylcellulose as a thermoplastic polymer. Also, the developed formulation would overcome the problem of frequent dosing. The developed inserts were stable, non – irritant and provided release of the drug over a period of 12 hours *in vitro*.
Key-Words: Ocular insert, Hot melt extrusion, Hydroxypropylcellulose, Klucel® .

INTRODUCTION

Topical ophthalmic application is considered the preferred way to achieve therapeutic levels of drugs used to treat ocular diseases[1]. The conventional formulations for this route are solutions, suspensions, semisolids like ointments, etc. Bioavailability, particularly for ocular solutions ranges from 1 – 10% of the total administered dose. This is due in part to the rapid precorneal clearance kinetics resulting from reflex tearing and blinking, where half-life times of instilled isotonic solutions or suspensions approximate only 15 s in humans. However can overcome these drawbacks to a certain extent but ophthalmic ointment have poor patient acceptance[2]. To overcome these drawbacks, various novel ophthalmic delivery systems such as inserts, *in – situ* gels, etc have been investigated in a in a recent time to extend the ocular residence time of medication for topical application to the eye.

Melt extrusion is a technique in which during extrusion, a polymer melt is pumped through a shaping die and formed into a profile. This profile can be a plate, a film, a tube, or have any shape of its cross section[3]. The process often is referred to as profile or line extrusion in which the shape of the extrudate like a tube is determined by the die. The extruded profile proceeds horizontally to the cutter equipment, which controls its length. Profiles may be further processed, for example, as in film extrusion, blow molding, or injection molding. In film extrusion, the polymer melt is extruded through a long slit die onto highly polished cooled rolls which form and wind the finished sheet. This is known as cast film[4].

Melt extrusion offers the advantages of being a single step, simple, continuous process with relatively high throughput rates. It provides the facility of mixing inside the extruder body thus bypassing problem of segregation during premixing. It obviates the need for organic solvents in processing and circumvents associated hazards. Also, it obviates the need for water and hence can work for water sensitive drugs. Also, there is no time consuming drying step involved. The bioavailability of the drug substance could be improved when it is dispersed at the molecular level in hot-melt extruded dosage forms.

Melt extrusion technology has been exploited in polymer industries since 1930's[5]. Since then it has been extensively used in polymer[6], food[7, 8], chemical[9], rubber[10] and metal industries[11]. In pharmaceutical industries this technology is also exploited in preparation of pellets[12, 13], solid dispersion[14, 15, 16], topical dosage forms[17], powder coating[18], gastroretentive dosage forms[19], tablets[20] and sustained release oral dosage forms[21, 22, 23]. However this technique has very recently exploited in preparation of sustained release ophthalmic formulations.

Gatifloxacin has an *in vitro* and *in vivo* inhibitory activity against Staphylococcus aureus, Staphylococcus epidermididis, Streptococcus mtis, Haemophilus. Gatifloxacin is available as a 0.3% w/v eye solution to be administered 8 times a day in the eye[25]. The objective of the present investigation was to prepare long acting ocular inserts of gatifloxacin to be placed in the eye twice a day, by melt extrusion technique.

MATERIALS AND METHODS

Formulation Considerations:

Extrusion of each plain polymer Methocel® A (Methylcellulose), Methocel® E and Methocel® K (Hydroxypropylmethylcellulose), Klucel® (Hydroxypropylcellulose) (HPC), Natrosol® (Hydroxyethylcellulose) and Starch 1500 were carried out on Melt Flow Rate Apparatus, Model 3/80, Davenport. Extrusion dies of dimensions 1 mm, 1.2 mm and 1.5 mm were tried to afford the product suitable for instillation in the eye. The polymer used for the study was medium viscosity grade Klucel® HF & MF. The dose of Gatifloxacin was calculated so that an ocular insert for twice a day use could be fabricated using the technique of melt extrusion. Plasticizers such as propylene glycol, glycerine and polyethylene glycol 400 were tried as they are non-irritant for ocular use and their concentrations were optimised.

Method of preparation of ocular insert:

Gatifloxacin and the polymer were sieved through 40# weighed and blended geometrically. The plasticizer was added and blended. The blend was then charged to the barrel of Melt Flow Rate Apparatus, Model 3/80, Davenport and extruded. The extrudate was cut into appropriate size of 4.5 mm X 1 mm and packed in polyethylene lined aluminium foil (thickness 100µ), heat sealed and sterilized by gamma radiation (2.5 Mrad for 4 h).

Evaluation of insert:

The developed inserts were evaluated for several parameters viz. appearance, uniformity of weight, dimensions, drug content, uniformity of content, Differential Scanning Calorimetric (DSC) analysis, eye irritation test and *in vitro* release studies. The inserts were observed for appearance / elegance, colour, surface irregularities, air bubbles, tackiness and suitability for ocular use. Twenty inserts were weighed and the average weight was determined. Deviation of individual insert's weight with respect to average weight was determined. Three inserts from a batch were powdered and dissolved in 50 ml of purified water by stirring on a magnetic stirrer for 2 h. The absorbance of this solution was then measured on a Jasco V530 UV/VIS Spectrophotometer at 285nm. The concentration was extrapolated from the standard curve. Six inserts from a batch were individually crushed and dissolved in 50 ml of purified water. The absorbance of this solution was then measured on a Jasco V530 UV/VIS Spectrophotometer at 287nm. The concentration was extrapolated from the standard curve.

Differential Scanning Calorimetric (DSC) analysis:

DSC of the selected samples was carried out to study the thermal behaviour under specified conditions. Each sample was heated over the temperature range from ambient to 300° at a heating rate of 10°/min under nitrogen environment (20 ml/min). The instrument used was Perkin Elmer Differential Scanning Calorimeter. Thermograms were integrated using Pyris 6 software.

Ocular irritation test:

Ocular irritation studies were performed according to the Draize technique. Assessment of ocular irritation potential of ophthalmic formulations is an extremely important step in the development of ophthalmic formulations. The test has been standardized at the international level, e.g. by the Organization for Economic Co-operation and

Development as OECD guideline No.405[26]. 'Acute eye irritation/corrosion' and it is the most widely used test for classification and labelling of chemicals according to their ocular safety. Six female albino rabbits each weighing 2 – 3 kg was used for the study of the formulations. The sterile formulations were placed twice a day for a period of 21 d and the rabbits were observed periodically for redness, swelling and watering of the eyes.

***In vitro* release studies:**
The *in vitro* release studies were performed in a modified dissolution apparatus as per USP specification[27]. The dissolution conditions were: Temperature: 37 ± 1°, Horizontal amplitude: 3.8 cm, Frequency: 32 cycles/min. Each insert was tied in muslin cloth and was placed in the test tube containing 10 ml dissolution medium with the help of the hanger, in triplicates. Aliquots were withdrawn at 1, 2, 4, 6, 8, 10 and 12 h. The aliquots were suitably diluted and analysed by Jasco V530 UV/VIS Spectrophotometer at 287nm. The % cumulative release of the drug was computed and graph of % cumulative release vs. time was plotted.

Sterilisation studies:
The inserts were packed in polyethylene lined aluminium foil (thickness 100 µ), heat sealed and sterilized by gamma radiation (2.5 Mrad for 4 h). Radio sterilised inserts were evaluated for appearance, uniformity of weight, dimensions, content and uniformity of content, *in vitro* release profile, DSC characterisation and sterility testing

Accelerated stability studies:
The optimized formulation in its final pack was stored at ambient conditions, 30 ± 2° / 65 ± 5% RH and 40 ± 2° / 75 ± 5% RH. Sampling was done at 0, 1, 2 and 3 months and the formulations were evaluated for physical parameters, *in vitro* release, sterility and drug content.

TABLE 1: SELECTION OF PLASTICIZER FOR EXTRUSION

Plasticizer	Concentration (% w/w)	Force applied	Extrusion Temperature	Appearance
Propylene glycol	**5**	**10 kgs**	**129.9 –130.1°C**	**Smooth Extrudate, Non-tacky,Translucent**
Glycerol	5	10 kgs	131.5 – 131.8°C	Rough Extrudate, Non – tacky, Translucent
PEG 400	5	10 kgs	143.6 – 143.7°C	Rough Extrudate, Non – tacky, Translucent

TABLE 2: OPTIMIZATION OF CONCENTRATION OF PROPYLENE GLYCOL AS A PLASTICIZER

Propylene Glycol (% /w)	Force applied	Extrusion Temperature	Appearance
0	20 kgs	178.4-178.6°C	Rough Extrudate, Non – tacky, Translucent
2.5	10 kgs	147.6-147.8°C	Rough Extrudate, Non – tacky, Translucent
5	**10 kgs**	**129.9-130.1°C**	**Smooth Extrudate,** Non – tacky, Translucent
7.5	10 kgs	129.3-129.7°C	Smooth Extrudate, slightly tacky, Translucent

TABLE 3: OPTIMIZATION OF GRADE OF KLUCEL

Composition No.	Klucel -HF: Klucel -MF	Plasticizer Conc%	Onset TempîC	Extrusion TempîC	Compression Kg	
I	50:50	5.0	105.2	125.0	10	Smooth, Transluscent, Non-Tacky
2	60:40	5.0	106.8	129.6	10	Smooth,Trans luscent,Non-Tacky
3	70:30	5.0	110.2	130.2	10	Smooth,Trans luscent,Non-Tacky

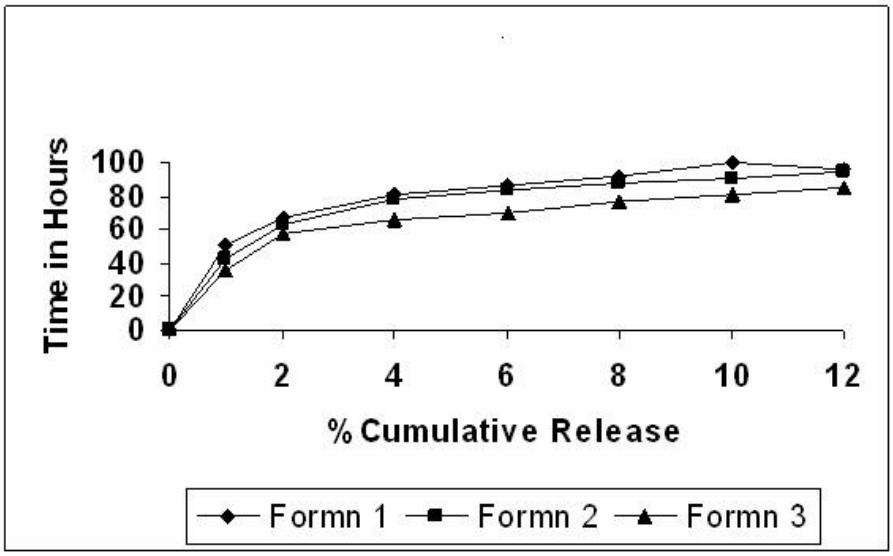

FIG. 1 *IN VITRO* RELEASE PROFILE OF GATIFLOXACIN TRIAL FORMULATION SELECTION OF DIFFERENT COMBINATION OF KLUCEL® AS A MATRIX FOR THE INSERT: KLUCEL® HF AND KLUCEL® MF .

RESULTS AND DISCUSSION

Various polymers evaluated for melt extrusion, only all grades of Klucel® could be melt extruded. Methocel® A, Methocel® E, Methocel® K, Natrosol® and Starch 1500 could not be melt extruded. Polymers were extruded using different die of diameters 1, 1.2 and 1.5 mm at 122 – 128°. The compression force required to extrude the polymer was found to be 15 kg for 1.5 mm die diameter and was 21.5 kg for 1 mm and 1.2 mm die diameter respectively. However, smallest diameter (1 mm) die was chosen for further studies after considering the size of the marketed formulation i.e. Lacrisert® (Dimension: 5 mm x 1.16 mm). The same die was used for further studies. Gatifloxacin is available as a 0.3%w/v eye drop to be placed in the eye eight times a day[25]. The concentration of drug in 8 times a day eye drop is approximates 600 mcg. Hence, it was decided to formulate ocular inserts containing.300 mcg of gatifloxacin for twice-daily use.

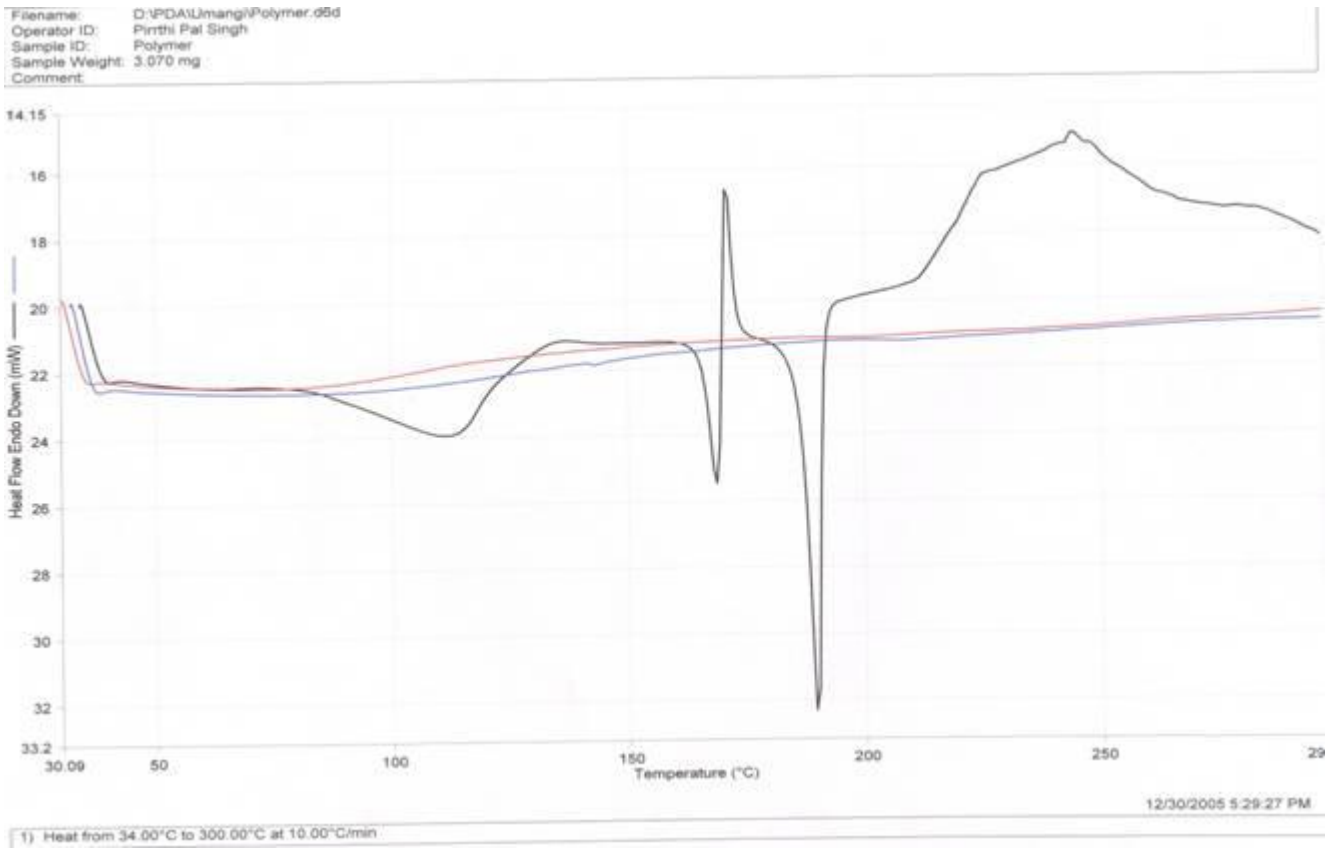

FIG 2: DSC THERMOGRAMS OF GATIFLOXACIN, BLANK EXTRUDATE AND GATIFLOXACIN FORMULATION.
KEY: BLUE- BLANK, BLACK- DRUG, RED- FORMULATION

TABLE 4: EVALUATION OF THE INSERTS

Parameter	**Results**
Appearance	Light yellow and smooth devoid of air bubbles
Uniformity of weight (mg) ± S.D	6.0 ± 0.10
Diameter (mm) ± S.D.	1.12 ± 0.0196
Length (mm) ± S.D.	4.51 ± 0.24
Content %	99.24
Content uniformity ± S.D.	99.24± 1.7
Ocular irritation test	-
Differential Scanning Calorimetric (DSC) Analysis	As shown in the figure 2
In-vitro release	More than 90% release at the end of 10 hours (Figure 3)
Sterility Testing	Sterile

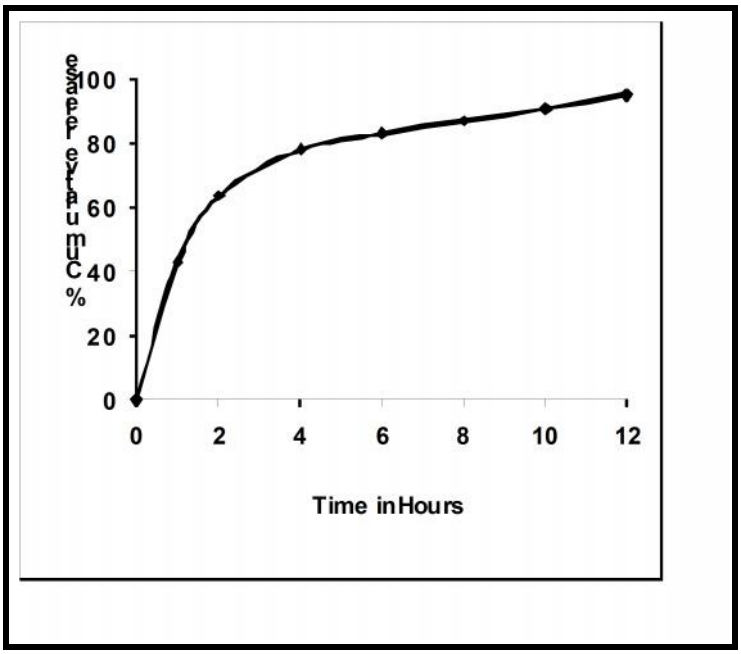

FIG 3: *IN VITRO* RELEASE PROFILE OF GATIFLOXACIN INSERT

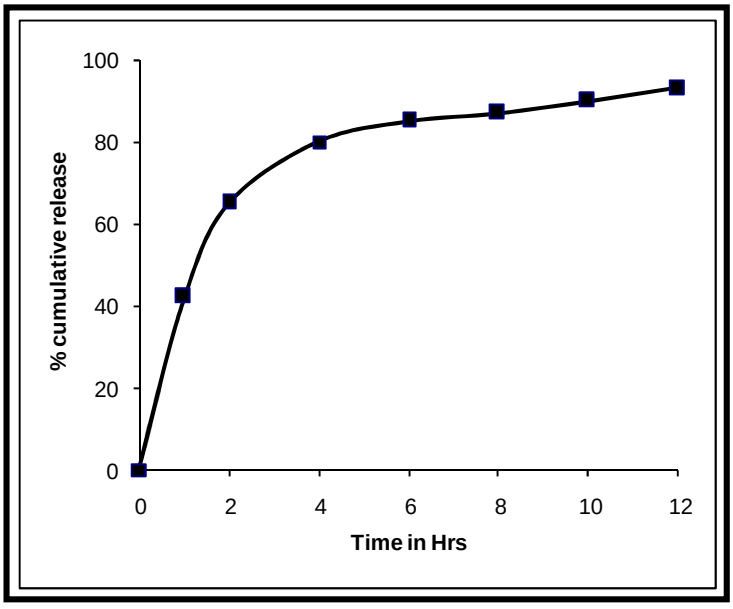

FIG 4: *IN VITRO* RELEASE PROFILE OF GATIFLOXACIN INSERT AFTER STERILIZATION

Plasticizers are normally used with polymers in melt extrusion to ensure smooth, uniform melt flow and flexible, homogeneous end products. The advantages of plasticizers in melt extrusion are lower processing temperatures and ease of manufacturing[3]. The effect of plasticizers at a concentration of 5 % w/w viz. propylene glycol, polyethylene glycol and glycerine on processing conditions using Klucel® HF was as shown in Table 1. The incorporation of the plasticizer was found to reduce the processing temperature as well as the compression force for melt extrusion. Propylene glycol was chosen as a plasticizer for further studies since it afforded a lowest processing temperature and therefore its concentration was optimised using Klucel® HF & MF as a melt extrudable polymer. Propylene glycol was optimised as a plasticizer at a concentration of 5% w/w. The results are as depicted in Table 2

From the *in – vitro* release studies result show that Klucel® HF alone not giving desirable release profile, so we tryout combination of Klucel® HF& Klucel® MF (Table 3) were tried as a matrix for the insert along with propylene glycol (5%w/w) as the plasticizer and the polymer that afforded a desired

release profile of more than 90% at the end of 12 h, in an *in – vitro* dissolution study was selected as the optimum formulation. Klucel® HF alone give not adequate result hence it was decided to replace some part of the polymer with a low viscosity grade i.e. Klucel® MF

The results of the evaluation of the ocular inserts of Gatifloxacin are depicted in Table 4. There were no changes in the quality control parameters of the insert before and after sterilization. Similarly, no change was observed in the release kinetics before and after sterilization

No irritation was observed in the rabbit eye during ocular irritation test on rabbit. The overall irritation was found to be 4 out of 110 on the scale of scores for reading the severity of ocular lesions given by OECD guidelines no. 405[26]. It was also observed that after 12 h, the inserts got completely dissolved in eye indicating biodegradable nature of the inserts.

Stability studies were carried out at Temperature30° ± 2°/65% RH ± 5%, 40° ± 2° / 75% RH ± 5% for a period of 3 mo. The formulation was found to be stable, sterile and the drug content was found to be within limits.

The technique of melt extrusion was applied to the fabrication of Gatifloxacin ocular inserts as solid polymeric rods to be placed in the cul de sac of the eyes. These inserts were retained in the eye for required period of time and sustained the release of the drug for 12h. The polymer slowly released the drug via swelling and dissolved slowly in the tear fluid, thus avoiding the need to remove insert after drug administration. Further, the polymer used is non-greasy, thus potentially increasing patient acceptability.

CONCLUSION

From the study it was found that the selected polymer gives the desired release profile i.e.90% at the end of 8 hours in artificial tear fluid. The inserts were translucent in appearance with smooth texture. No eye irritation was observed until 21 days of instillation in the rabbit eye. Gamma radiation was found to be the acceptable method for terminal sterilization

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REFERENCES

[1] Desai SD., Blanchard J.. Encyclopedia of Pharmaceutical Technology. In: J. Swarbrick, C .Boylan, editors. Ocular drug delivery systems. Vol. 11, New York: Marcel Dekker Inc.; 1995. p. 43–75.

[2] Olejnik O., Mitra AK., editors. Ophthalmic drug delivery systems. New York: Marcel Dekker Inc.; 1993.

[3] Mcginity JW., Koleng JJ., MA. Zhang Repka F. In: Swarbrick J, Boylan C, editors. Encylopedia of Pharmaceutical Technology. Vol. 19, New York: Marcel Dekker Inc.; 2000. p. 203–226.

[4] Breitenbach J., Euro. J. Pharm. Biopharm., 2002, 54, 107.

[5] Chokshi R.,. and Hossein Z. Iranian J. Pharm. Res., 2004, 3, 3.

[6] Dangtungee R., Desai S.S., Tantayanon S., and Supaphol P., Polymer Testing, 2006, 10, 888.

[7] Bengoechea C., Arrachid A., Guerrero A., Hill S.E. and Mitchell J.R., J. Cereal Sci., 2007, 5, 275.

[8] Babin P., Valle G.D., Dendievel R., Lourdin D., and Salvo L. Carbohydrate Polymers, 2007, 68, 329.

[9] Chen L., Pang X.J. and Yu Z.L. Material Sci. Eng.: A, 2007, 457, 287.

[10]Griffon J.M. Construction Building Materials, 1988, 2, 73.

[11]Tang Y., Tan D., Li W., Pan Z., Liu L. and Hu W. J. Alloys Compounds, 2007, 439, 103.

[12]Mehuys E.,Vervaet C. and Remon J.P. J. Control. Release, 2004, 94, 273.

[13]Siepmann F., Muschert S., Flament M.P., Leterme P., Gayot A. and Siepmann J. Int. J. Pharm., 2006, 317, 136.

[14]Ghebremeskel A.N., Vemavarapu C.,and Lodaya M. Int. J. Pharm., 2007, 328, 119.

[15]Patterson J.E., James M.B., Forster A.H., Lancaster R.W., Butler J.M., and Rades T., Int. J. Pharm., 2007, 336, 22.

[16]Verreck G., Decorte A., Heymans K., Adriaensen J., Liu D., and Tomasko D. Int. J. Pharm., 2006, 327, 45.

[17]Mididoddi P.K., and Repka M.A.Euro. J. Pharm. Biopharm., 2007, 66, 95.

[18]Sauer D., Zheng W., Coots L.B., and McGinity J.W. Euro. J. Pharm. Biopharm., 2007

[19]Fukuda M., Peppas N.A. and McGinity J.W. J. Control. Release, 2006, 115, 121.

[20]Fukuda M., Peppas N.A., and McGinity J.W. Int. J. Pharm., 2006, 310, 90.
[21]Lyons J.G., Devine D.M., nedy J.E., Geever L.M., O'Sullivan P., and Higginbotham C.L. Euro. J. Pharm. Biopharm., 2006, 64, 75.
[22]Verhoeven E., Vervaet C. and Remon J.P., Euro. J. Pharm. Biopharm., 2006, 63, 320.
[23]Lyons J.G., Hallinan M., Kennedy J.E., Devine D.M., Geever L.M., Blackie P., and Higginbotham C.L., Int. J. Pharm., 2007, 329, 62.
[24]Mandell G.L., Alfred G.G. editor. In: The Pharmacological basis of Therapeutics, 9th ed., 1996, 1193.
[25]The Merck index, An Encyclopaedia of Chemicals. Drug and Biologicals, 13th Edition, Merck and Co., NJ., 2001
[26]OECD (1981, 1987, 1994) Guidelines for testing the chemicals: Guideline No. 405, 'Acute eye irritation/corrosion' OECD Publication Office, Paris, 1981, 1987, 1994.
[27]Dissolution, In: The United States Pharmacopoeia XXIII, Asian Edition, The United States Pharmacopoeial Convention, Inc., Rockville, Maryland, U.S.A., 1995, 1227.

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