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MICROENCAPSULATION OF AGAR MICROSPHERULES INCORPORATED WITH SOLID DISPERSION OF NIMESULIDE-A NOVEL APPROACH FOR CONTROLLING DRUG RELEASE

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ABSTRACT : In pursuit of achieving a slow, controlled and complete release of the drug, solid dispersions of nimesulide in HPMC was prepared first. X ray diffraction studies, IR spectral analysis were included in the analytical studies. The formulation was incorporated with agar spherules and microencapsulated by ethyl cellulose as coating material. Different core: coat ratios were used. The drug release from these micro spherules was found to depend on the core: coat ratio and the release were suggested to govern by diffusion.

KEYWORDS : Nimesulide, microencapsulation, microspheres, HPMC, solid dispersion, remi motor stirrer, UV spectrophotometer, IR spectral analysis, X-ray diffractograms.

INTRODUCTION[1,2,3]:

Nimesulide,a sulphonamide, chemically 4-nitro-2 phenoxy methane sulfanilamide is a relatively new non-steroidal anti inflammatory analgesic drug. It is a relatively weak inhibitor of PG synthesis and appears to extend its action through a variety of mechanisms. The compound is a weakly acidic (Pka=6.5) and its light tan crystals from ethanol. Commercially, nimesulide is available as suspension, tablets and topical formulations. Nimesulide is clinically indicated for osteoarthritis, dental surgery, stomatitis, inflammation of the eye, rhinitis, acute and chronic bronchitis, mastodynia, prostatitis etc. In the present work, solid dispersions of nimesulide in HPMC was first prepared to enhance its dissolution rate and then the suspensions were incorporated with agar spherules using meltable disposition method. Agar, a hydrophilic colloidal substance which undergoes swelling and releases the dispersed drug in an aqueous environment act as the reservoir type. The reservoir type agar micro spherules are then encapsulated using ethyl cellulose as coating material to obtain slow release of nimesulide.

MATERIALS AND METHODS

Nimesulide (gift sample from Torrent Pharma,Ahmedabad), HPMC (Ace Laboratories, Mumbai), chloroform(SD Fine Chemi Ltd), agar-agar (NR Chem), liquid paraffin I.P(Medisan, Trichy), petroleum ether(Chemspure Chennai), cyclohexane(Loba Chem.),ethyl cellulose(Loba Chem. Pvt. Ltd, Mumbai), three blade motor stirrer (Remi motors, Mumbai)

PREPARATION OF SOLID DISPERSIONS: [4, 5]

Solid dispersions of nimesulide in HPMC were prepared by solvent evaporation method. Drug: carrier ratio of 1:1 was employed. The carrier was first dissolved in chloroform (30 ml) with the help of a magnetic stirrer. Then nimesulide was transferred into this polymer-chloroform solution part by part while stirring. The solvent was removed by evaporation at 40° under vacuum. The mass obtained was dried in a dessicator for

72 hours, crushed, pulverized and shifted through mesh no 80.

Preparation of physical mixture of drug: carrier ratio 1:1 was used. Nimesulide and HPMC was mixed thoroughly in a glass mortar.This was done by geometric dilution technique to ensure homogenous distribution.

X-RAY DIFFRACTION STUDIES:

X-ray diffractograms of solid dispersions and physical mixtures of nimesuide in HPMC (1:1) were obtained using JEOL JDX-8P power X-ray diffractrometer (Japan) at 1000 cps, 40 KV, 25Ma, 4°/min, CuK_2. X-ray diffractrograms of nimesulide and its solid dispersion in HPMC are shown in Fig.1

IR SPECTRAL ANALYSIS

IR spectra of solid dispersions and pure drug of nimesulide obtained by using FT – IR: 8101 M, Shimadzu. Samples of 2 mg KBr discs were prepared with a pressure of 1000 Kg. (Fig 2).

DISSOLUTION RATE STUDIES ON SOLID DISPERSIONS: [6, 7]

The dissolution rate of nimesulide in pure form, solid dispersion and from physical mixture was studied using USP XXII dissolution rate apparatus employing a paddle stirrer. Solid dispersion equivalent to 100mg of nimesulide was filled in hard gelatin capsules and externally wound with stainless steel wire as sink. 900 ml of pH 7.4 buffer solution was used as dissolution media. The temperature was maintained at 37±1° . A 5 ml aliquot of dissolution media were withdrawn at different time intervals and volume withdrawn was replaced with fresh quantity of dissolution media. The samples were suitably diluted and analyzed for nimesulide at 230 nm using UV spectrophotometer Shimadzu. Dissolution efficiency (DE%)was also found out as proposed by Khan is defined as the area under the dissolution curve upto a certain time 't' expressed as a % of the area of the rectangle described by 100% dissolution.

$$D.E. = \frac{\int_0^1 Y.dt}{Y.100t} X\ 100$$

PREPARATION OF AGAR SPHERULES: [8, 9, 10]

Powdered agar-agar 1.5g was dissolved in 75ml of water bath. The colloidal solution was gradually cooled to 55 ° and the solid dispersion of nimesulide (equivalent to 200g of nimesulide) was incorporated and mixed thoroughly. Dispersions was then transferred into 200ml liquid paraffin which was maintained at 55±2° in a water bath. The contents were stirred for 5 mts with a three blade stirrer at 200 rpm to form fine micro spherule. The mixture was cooled in an ice bath to 10° for rigidization of the spherules. The spherules were filtered through a 60 mesh sieve and washed thrice (100ml each) with petroleum ether until the adhering liquid paraffin was totally removed. The micro spherules were dried at room temperature in vaccum dessicator.

ENCAPSULATION OF AGAR MICRO SPHERULES: [11, 12, 13]

Dried agar micro spherules were taken into 100ml hot solution of ethyl cellulose in cyclohexane. The system was stirred at 50 rpm. The contents was slowly cooled to room temperature .The spherules were then separated through filtration through 60 mesh sieve and dried in a dessicator.Two different core: coat ratios 2:1 and 1:2 were used , referred as ME1 and ME2.

EVALUATION OF ENCAPSULATED MICROSPHERULES:

DRUG CONTENT UNIFORMITY

All the batches of uncoated ME1 and ME2 were subjected to drug content analysis. Then encapsulated microspheres equivalent to 200mg of nimusulide were taken and grounded. This was dissolved and filtered and the nimusulide was estimated spectrophotometrically at 230nm.

SIZE ANALYSIS

Particle size distribution analysis using method of microscopic measurement for not less than 1000 microspheres was performed.

SHAPE AND TOPOLOGY

Uncoated microspherules and encapsulated microspherules were investigated under phase contrast microscope. Uncoated microspherules were found to be smooth and spherical in the liquid manufacturing vehicle. After drying the surface of the microspheres became rough and spherical. Photomicrograph was taken (Fig.3). Encapsulated microspheres were found to be nearly spherical, rough surface and uniform coated with the coating material.

Table No.1: Dissolution of nimusulide from uncoated and encapsulated micro spheres incorporated with solid dispersion in HPMC.

Time (Hrs)	Microspheres (Uncoated)	(Core: Coat)	
		ME1(2:1)	ME2 (1:2)
0	0	0	0
2	33.12	19.76	18.55
4	78.15	49.15	46.12
6	100	70.1	63.75
8	100	88	82.3
10	100	100	98.12
12	100	100	100
T50 T90	2.75 4.85	4.1 8.3	4.5 9.0

DRUG RELEASE STUDIES ON ENCAPSULATED MICROSPHERULES

Buffer solution of pH 7.4, 900 ml was used as dissolution media. Encapsulated micro spherule (ME1,ME2), equivalent to 200 mg of nimesulide were filled in hard gelatin capsules and were externally wound with stainless steel wire as sink. Paddle type stirrer was adjusted to 100 rpm.The temperature was maintained at 37±1°. A 5 ml aliquot of dissolution media were withdrawn at different time intervals and volume withdrawn was replaced with fresh quantity of dissolution media. The samples were suitably diluted and analysed for nimesulide at 230 nm using UV spectrophotometer, Shimadzu.The percentage of nimesulide at various times were calculated and plotted against time (Fig4).

RESULT AND DISCUSSION

Solid dispersions prepared by solvent evaporation method were found to be fine and free flowing. X ray diffraction studies indicated the crystalline nature of nimesulide in SD was reduced when compare to pure drug. Dissolution efficiency was increased from 16 % in pure form to 68 % in nimesulide–HPMC solid dispersion. IR peaks of solid dispersion and pure drug of nimesulide were found to be almost identical which indicated no interaction.

The microspheres and its encapsulated products at different core: coat ratios (ME1, ME2) were found to be discrete, free flowing and nearly spherical. The size range could be separated and more uniform size range of microspheres could readly be obtained. The average diameter was found to be 123 µ, 190. 5 µ and 201. 2 µ for uncoated ME1 and ME2 respectively.

Dissolution rate studies indicated encapsulated microspheres ME1 and ME2 gave sustained action up to 10 hrs and 12 hrs respectively. When amount released was plotted against square root of time, a straight line was obtained indicating that the release may be of diffusion type (Fig. 5). Encapsulated agar spheres were found to have slow; controlled and complete release of nimesulide may be due to the molecular micronization that the drug undergoes which deposits on HPMC.

CONCLUSION

Solid dispersions of nimesulide in HPMC were prepared by solvent evaporation method. This was incorporated in the preparation of agar microspheres. Encapsulated microspheres of agar system containing solid dispersion of nimesulide were prepared by temperature change. The microspheres gave a slow, sustained and complete release of the drug from the reservoir type system over a period of 12 hrs. Release rate can be altered by the core: coat ratio of microsperules.

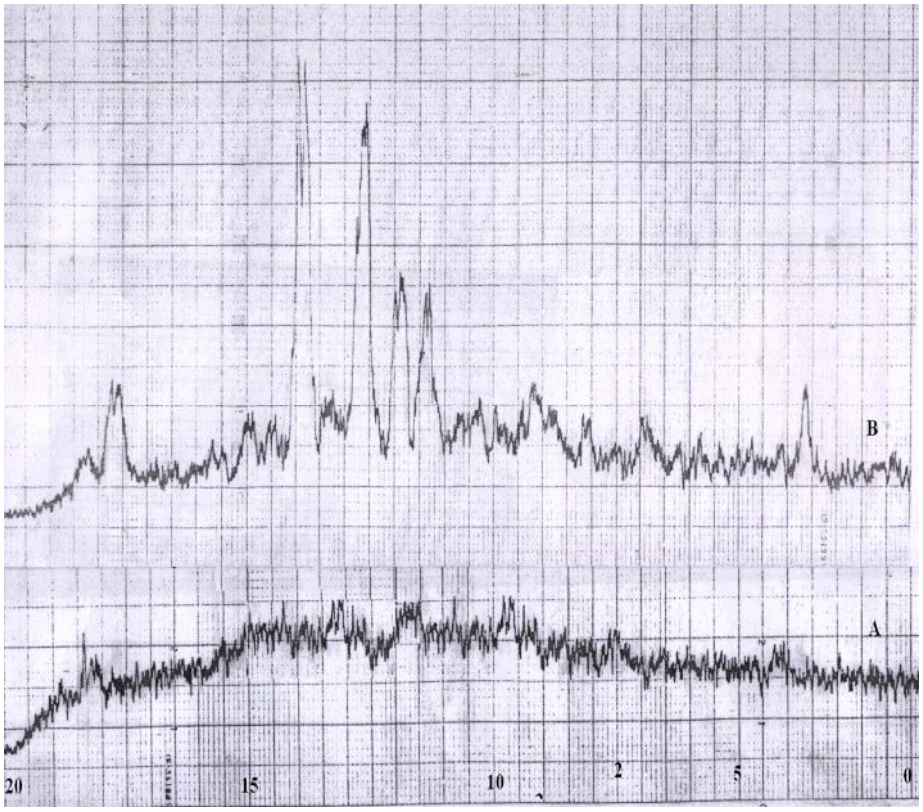

Fig: 1: X- ray diffractograms of solid dispersion of nimesulide in HPMC (A) and pure drug (B).

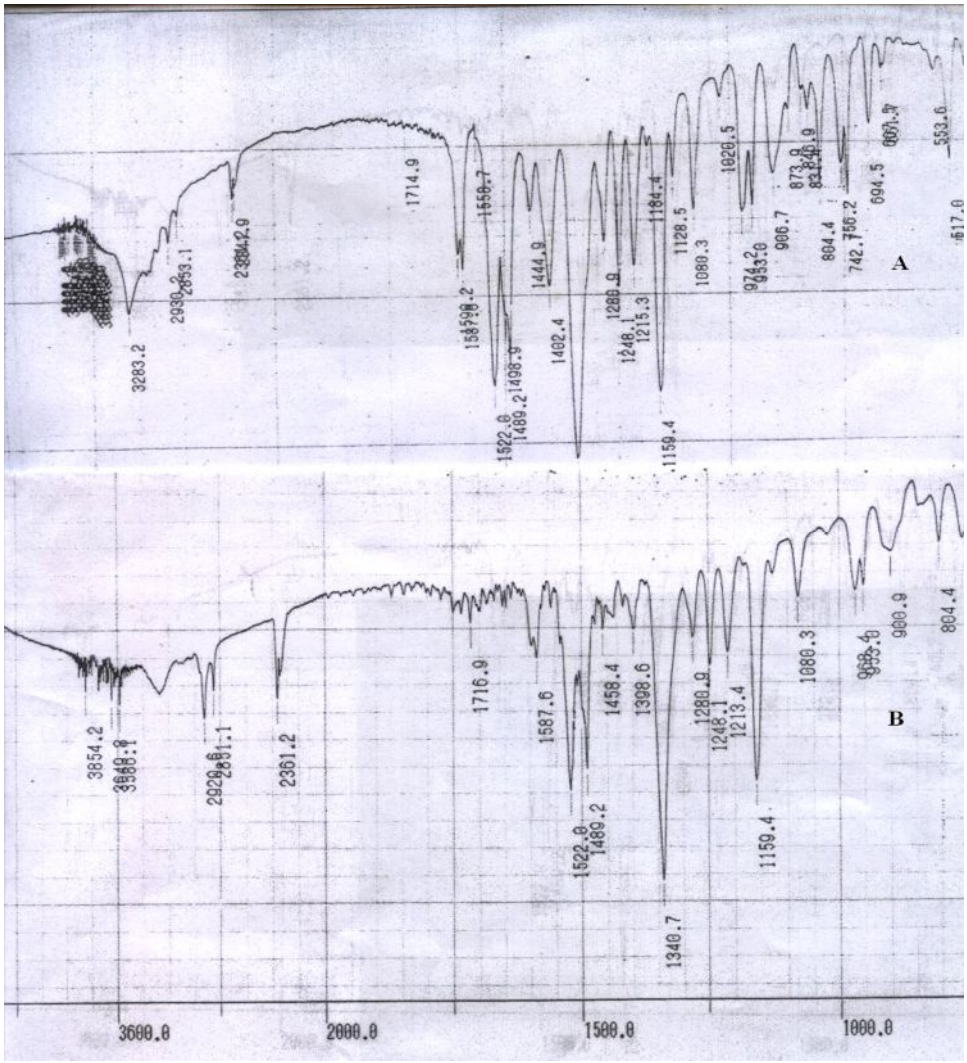

Fig 2: IR Spectra of solid dispersion of nimesulide in HPMC (A) and pure drug nimesulide (B

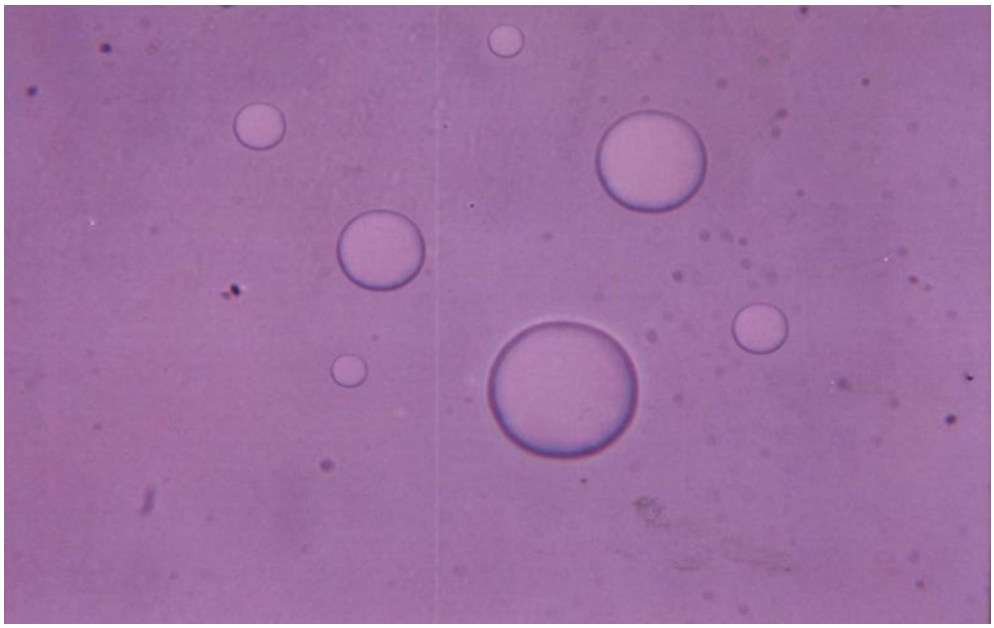

Fig.3: Phase Contrast micro photograph of microspheres in manufacturing vehicle.

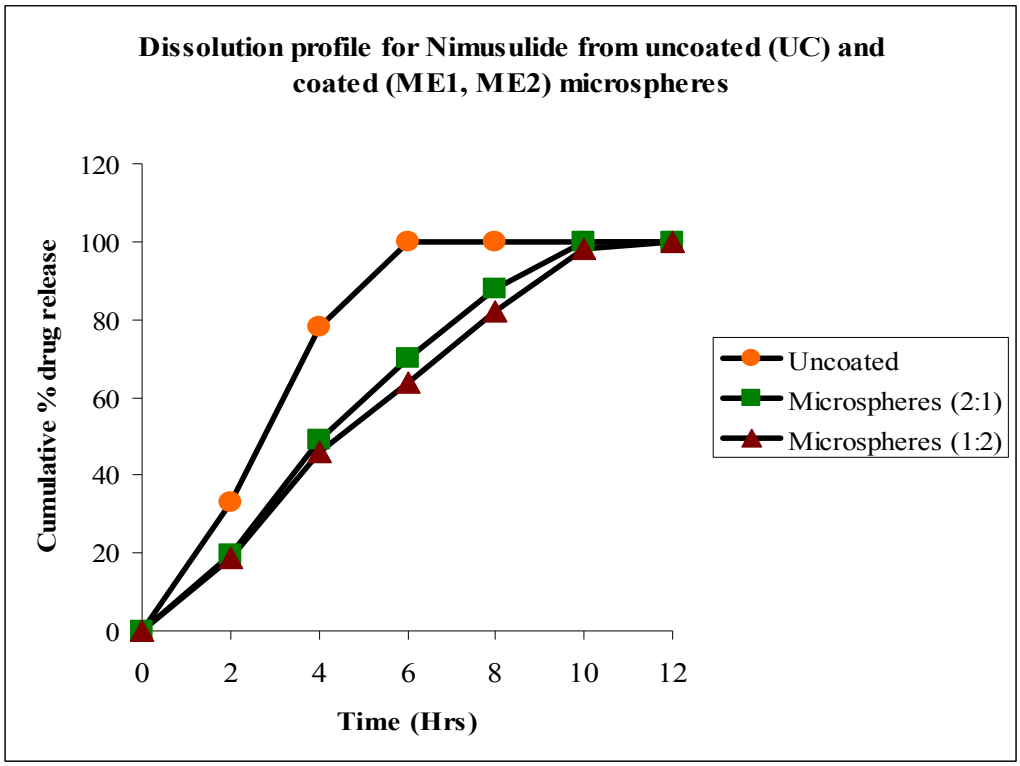

Fig 4: Dissolution kinetics of nimusulide from uncoated and coated (ME1, ME2) micro spheres.

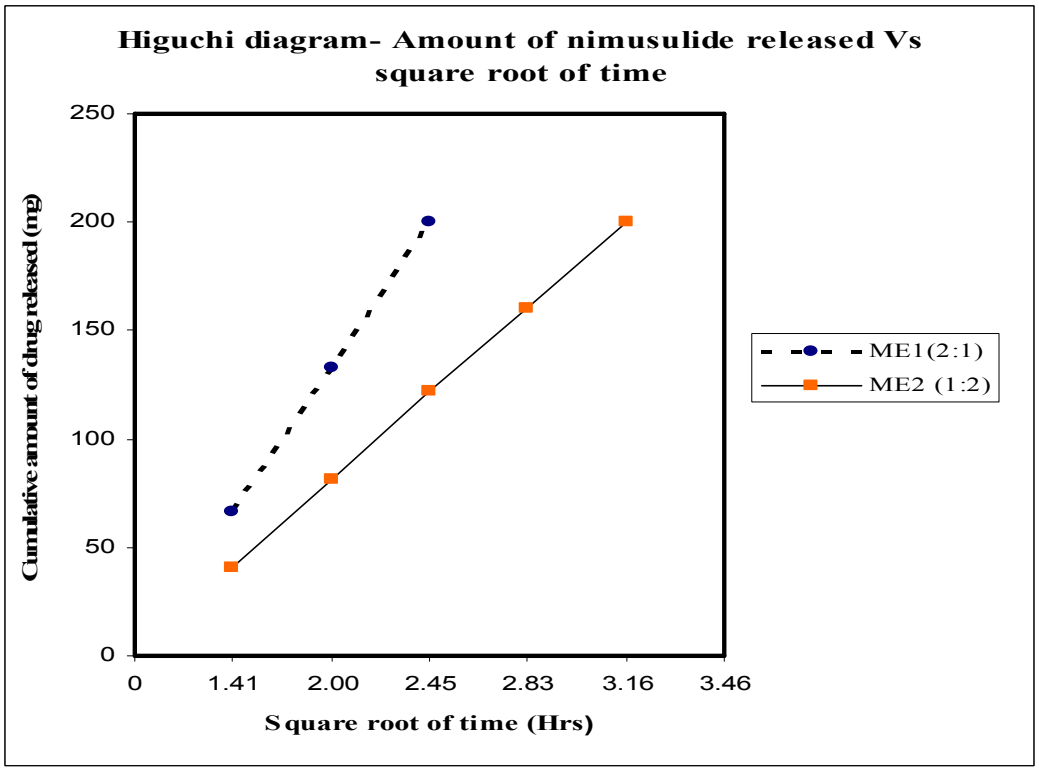

Fig 5: Higuchi diagram of amount of drug released vs. square root of time plots of encapsulated micro spheres.

REFERENCES

1. Mary Adele J.O. and Susan Budavari, The Merck Index, 13th Edn., Merck and Co.,Inc.,White house Station, NJ, USA, 2001, 6576.

2. Sean Sweetman C, Martindale: The complete Drug References, 34th Edn. Pharmaceutical Press, London, UK, 2005, 67-71.

3. Leon Shargel, Alan Mutnick H, Paul Souney Fand Larry Swanson N, Comprehensive Pharmacy Review, 5th edn., Lippincott Williams and Wilkins, London, 2004, 67.

4. Mahaparale P.R., Gudsorkar V.R., Gajeli G.B. and Kuohekar B.S. Studies on solid Dispersion of Meloxicam, Indian journal of Pharmaceutical Education and Research, 2006,(40), 241.

5. Ubaidulla U., Senthil Kumar B., Khar R. K. and Ahmad F. J. Studies on suspension of Nimesulide Solid dispersion development characterization and in vivo evaluation, Indian Journal of Pharmaceutical Education and Research, 2005(67), 422.

6. Patel V.P., Patel N. M. and Chaudhari B. G. Effect of Water soluble polymers on dissolution profile of Glipizide Cyclodextrins complex, Indian Drugs, 2008, 45(1), 31.

7. Chowdary K.P.R and Suresh Babu K. V. V. , Evaluation of Water soluble Cellulose Polymers as Carriers for Indomethacin solid dispersions, Eastern Pharmacist, 1992, 181.

8. Leon Lachman, Herbert Lieberman A, Joseph Kanig L, The Theory and practice of Industrial pharmacy, 3rd Edn., Varghese Publishing House, Mumbai,1990, 412-414.

9. Jain N. K., Jayakrishnan A and latha M. S., Controlled and Novel Drug Delivery, I st Edn. CBS Publishers and Distributers, New Delhi, 1997, 236-251.

10. Alfred Martin, Physical Pharmacy, 5 th Ed Lippincott Williams and Wilkins, USA, 2006, 602.

11.Laware R. B., Nirmal S.A., Joshi S. V., Gore S.T., Patel B.S., Bhagat A.K. and Kuchekar B.S. Preparation and Evaluation of Controlled one day release Microcapsules of Diclofenac Sodium, Indian Drugs, 2008, 45(4), 279.

12.Yie Chien W., Novel Drug Delivery System, Marcel Dekker Inc., New York, 1992, 154 – 156.

13. Shende P.K., Gaud R. S., Jaiswal S.B. and Kochar N. I , Formulation and evaluation of Alginate – Gelatin Beads for Controlled Release of Glipizide, Indian Drugs, 2007, 44 (12), 945 – 948.

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