Research Article

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Evaluation of Comparative Efficiency of Plastic Polymer in Development of Controlled Release Drug Delivery System.

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The present study was made to evaluate the comparative efficiency of plastic polymer in sustaining the release of active ingredients having different physical and chemical properties. Kollidon SR was selected as a representative of plastic polymer in the study. Three model drugs theophylline as a soluble neutral drug, diclofenac sodium as an acidic drug with pH dependent solubility and diltiazem HCl as a basic drug of acidic salt were used. The active ingredient, release retardant and filler were blended together by dry mixing and compressed directly at a fixed compression force. The tablets were subjected to thickness, weight variation test, drug content, hardness, friability and *in vitro* release studies. All the tablets showed acceptable pharmacotechnical properties and complied with in-house specifications for tested parameters. The release rate profiles were subjected to data treatment. The results indicated that the release of water-soluble drugs was higher than the drugs with lower solubility and the mechanism of release changed with the nature and content of polymer in the matrix.

Keywords: Controlled release, Diclofenac sodium, Diltiazem HCl., Kollidon SR, Theophylline.

INTRODUCTION

In the last two decades, sustained release dosage forms have made a significant progress in terms of clinical efficacy and patient compliance.[1] Preparation of drug embedded matrix involves the direct compression of a blend of drug, retardant material and additives is one of the least complicated approaches for delivering drug in a temporal pattern in to the systemic circulation.[2] A wide array of polymers has been employed as drug retarding agents and each polymer presents a different approach to the matrix concept.[3] Polymers forming insoluble or the skeleton matrices constitute the first category of retarding materials, also called as plastic matrix systems. Sustained release tablets based upon an inert compressed plastic matrix tablet were first introduced in 1960. Release is usually delayed as the dissolved drug has to diffuse through the capillary network between the compacted polymer particles. Commonly used plastic materials are polyvinyl chloride, polyethylene, polyvinyl acetate/vinyl chloride copolymer, acrylate/methyl methacrylate copolymer, ethyl cellulose, cellulose acetate etc. Plastic matrix tablets, in which the active ingredient is embedded in a tablet with coherent and porous skeletal structure, can be easily prepared by direct compression of the drug with plastic material. Drug release from the inert plastic matrices was affected by varying formulation factors such as matrix material, amount of drug incorporated in the matrix, drug solubility in the dissolution medium and in the matrix.[4] Kollidon SR as a plastic material for direct compression to formulate sustained release dosage forms has been reported.[5, 6] .It is particularly suitable for the manufacture of pH independent sustained release matrix tablets. It contains no ionic group, which renders the polymer inert to the drug molecule.[7] All the three drugs chosen in this study are proven candidates to be formulated in the sustained release dosage forms and have been subjected to thorough investigation for their candidature.[8, 9, 10] So the comparative efficiency of plastic polymer in sustaining the release of active ingredients having different physical and chemical properties was studied. The release mechanisms of the drug from

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the matrix systems has been explored and explained with the help of exponential model.

MATERIALS AND METHODS

Theophylline was obtained as gift sample from Cipla Ltd., Mumbai, India. Diltiazem HCl was obtained as gift sample from Sun Pharmaceuticals Ltd., Ahmedabad, India. Diclofenac Sodium was obtained as gift sample from Lupin Laboratories Ltd., Pune, India. Kollidon SR was procured from BASF Ltd., Bangladesh, Ludipress, Tribasic sodium ortho phosphate were purchased from modern Scientifics, Nashik, India. All other materials used for the study were of analytical grade.

Preparation of Tablets

The formulations of the tablets with their codes are listed in Table [I]. The characteristic of these formulations is that, the amount of matrix forming polymers decreases gradually for each set of formulation and the reduced amount of matrix forming polymer was replaced by Ludipress. In all cases, the amount of the active ingredient was 100 mg and the total weight of the tablet was 400 mg. Properly weighed matrix-forming polymers, with or without Ludipress and the active ingredient was blended in a laboratory mixture for 10 minutes. Particular attention had been given to ensure the thorough mixing and phase homogenization. All the powders were passed through sieve no. 80. Required quantities of drug and polymer were mixed thoroughly. Before compression, the surfaces of the die and punch were lubricated with magnesium stearate. All the preparations were stored in airtight containers at room temperature for further study. This method of tablet production has previously been described by several authors who showed reproducible experimental results in terms of *in vitro* release.[11, 12]

Table II: Properties of compressed tablets

Code	Thickness	Deviation in weight variation test (%)	Hardness (Kg/cm2± SD)	Friability (%) ± SD	Drug content (%) ± SD
TPK-3	2.23 ±0.03	2.76 ±0.28	8.6 ±0.03	0.08 ±0.01	99.25 ±0.25
TPK-2	2.27 ±0.04	2.25 ±0.25	8.4 ±0.4	0.06±0.008	98.40 ±1.36
TPK-1	2.24 ±0.02	2.10 ±0.41	8.4 ±0.1	0.04 ±0.007	98.80 ±1.12
DSK-3	2.26 ±0.03	2.54 ±0.24	8.2 ±0.2	0.06±0.002	98.25 ±1.02
DSK-2	2.24 ±0.05	2.10 ±0.50	8.6 ±0.3	0.04 ±0.034	97.15 ±1.25
DSK-1	2.28 ±0.02	2.12 ±0.12	8.2 ±0.2	0.02 ±0.005	98.32 ±0.89
DLK-3	2.28 ±0.01	2.62 ±0.25	8.4 ±0.2	0.04±0.006	98.52 ±1.15
DLK-2	2.22 ±0.02	2.04 ±0.10	8.2 ±.0.3	0.02±0.002	99.15 ±0.52
DLK-1	2.27 ±0.03	1.65 ±0.24	8.9 ±0.2	0.06 ±0.001	98.64±1.00

Table I: Composition in (mg) of 100 mg drug loaded matrix tablets.

Code	Active ingredient		Polymer		Ludipress (mg)
	Name	(mg)	Name	(mg)	
TPK-3	Theophylline	100	Kollidon-SR	300	-
TPK-2	Theophylline	100	Kollidon-SR	200	100
TPK-1	Theophylline	100	Kollidon-SR	100	200
DSK-3	Diclofenac-Na	100	Kollidon-SR	300	-
DSK-2	Diclofenac-Na	100	Kollidon-SR	200	100
DSK-1	Diclofenac-Na	100	Kollidon-SR	100	200
DLK-3	Diltiazem HCl	100	Kollidon-SR	300	-
DLK-2	Diltiazem HCl	100	Kollidon-SR	200	100
DLK-1	Diltiazem HCl	100	Kollidon-SR	100	200

Evaluation of tablets

The compressed matrix tablets were evaluated for thickness, weight variation test, hardness and friability and for drug content.[13] The thickness of the tablets was determined using a thickness gauge. Five tablets from each batch were used, and average values were calculated. To study weight variation, 20 tablets of each formulation were weighed using an electric balance, and the test was performed according to official method. For each formulation, the hardness and friability of six tablets were performed using the Monsanto hardness tester, (Cadmach, Ahmedabad, India) and Roche friabilator (Remi Electronics, Mumbai, India) respectively. Five tablets were weighed individually, and the drug was extracted.

Table III: Cumulative % drug release ± S.D. of all the formulations

Time(Hr)	TPK-3	TPK-2	TPK-1	DSK-3	DSK-2	DSK-1	DLK-3	DLK-2	DLK-1
1	8.7±1.9	12±0.5	22±3	0.4±0.02	0.5± 07	1±0.1	19.9±1.8	37.6±2.5	61±1
2	11.4±1.9	18±2	39±2	0.6±0.06	0.8±0.07	1.4±0.05	22.8±1.9	48±3	70±1.5
3	13.1±1	22±2	48±2	6.4±1.0	8.88±0.9	10.5±1.3	30.1±1.6	57±3	75±2
4	15.2±2.0	25±1	57.6±2.5	7±0.9	11±1	19±2	35.7±2.0	59.3±2.5	79.3±2.0
5	17.1±2.0	28±2	64.8±2.2	7.8±1.0	13.2±1.2	29.6±3.0	39±2	60.3±2.5	84±2
6	19.3±1.7	33.6±1.5	70±2	9.6±1.0	16.5±1.1	35.6±1.1	41.1±1.6	62.6±2.0	89±1
7	20.7±2.2	37.3±1.5	74±3	11.1±1.1	19±0.1	40.3±±1.5	42.8±1.9	65.4±2.2	89.6±0.5
8	2.6±2.4	40±1	76.6±2.5	12.8±1.0	22.5±1.2	44.6±0.5	43.1±2.0	66.3±2.4	94±1
9	21.7±2.5	42±1	79.3±2.5	13.5±1.1	25.5±1.1	48.3±0.5	44.6±1.5	67.2±2.1	96.3±0.5
10	22.0±2.4	43.6±1.9	81.6±2.0	14.3±0.8	27.6±1.3	52±1	45.1±1.5	68.2±1.9	96.9±0.5
11	22.1±2.5	45.6±1.2	83.3±1.5	14.8±0.8	29.5±1.0	56.3±0.5	45.8±1.1	68.7±1.0	97.3±0.7
12	22.4±2.4	47.6±1.6	85±1	15.5±0.7	30±1.1	60.2±2	47±1.0	70±2.1	98±0.8

The drug content was determined by following procedure.[14] An accurately weighed amount of power equivalent to 100 mg of theophylline was extracted with 100 ml of 0.1N NaOH. It was shaken for five minutes and diluted to 200 ml with 0.1 N NaOH. Set aside for two hours and filtered through Whatmann filter paper. Then 3 ml of above solution was diluted to 200 ml with 0.1N NaOH. The extinction of both standard and sample was measured at 271 nm against 0.1N NaOH as blank. An accurately weighed amount of power equivalent to 100 mg of theophylline was extracted with three 25 ml portions of 0.1N NaOH. The solution was filtered through Whatmann filter paper. The filtrate was diluted to 100 ml with 0.1N NaOH. Further dilutions were carried out appropriately with 0.1N NaOH to get the final concentration of 10 µg/ml. The extinction of standard and sample solution was measured at 277 nm using 0.1N NaOH solution as blank. An accurately weighed amount of power equivalent to 100 mg of Diltiazem HCl was extracted with 200 ml methanol. The solution was filtered through Whatmann filter paper. The filtrate was diluted to 500 ml with methanol. Further dilutions were carried out appropriately with methanol to get the final concentration of 10 µg/ml. The extinction of standard and sample solution was measured at 236 nm using methanol solution as blank. *In vitro* drug release study of the prepared matrix tablets was conducted for a period of 12 hours using eight station USP XXII type II Apparatus (Labindia, Mumbai, India) at 37 ± 0.5° C with 50 rpm speed. The dissolution studies were carried out in triplicate for 12 hours (initial 2 hours with 0.1N hydrochloric acid of pH 1.2 and rest 10 hours in phosphate buffer of pH 6.8) under sink condition. At every 1-hour time interval samples of 5 ml were withdrawn from the dissolution medium and replaced with fresh medium to maintain the volume constant. After filtration and appropriate dilution, the sample solution was analyzed at 271 nm for theophylline, 277 nm for diclofenac sodium and 236 nm for diltiazem HCl by a UV spectrophotometer (Shimadzu UV-250 1PC double beam spectrometer). The amounts of drug present in the samples were calculated with the help of appropriate calibration curves constructed from reference standards. Dissolution Data of matrix tablets of theophylline, diclofenac sodium and diltiazem HCl containing Kollidon SR is shown in (Table III). Release data was given zero order, first order, and Higuchi's square root treatment.

Table IV: Kinetic values obtained from different plots of all formulations

Code	Correlation coefficient Zero order plots	Correlation coefficient First order plots	Correlation coefficient Higuchi's square root plot
TPK-3	0.8207	0.8243	0.9814
DSK-3	0.9466	0.9575	0.9940
DLK-3	0.7631	0.8396	0.9509
TPK-2	0.9396	0.9699	0.994
DSK-2	0.9092	0.9887	0.9094
DLK-2	0.6167	0.8396	0.9567
TPK-1	0.8488	0.9751	0.9756
DSK-1	0.9016	0.9866	0.9493
DLK-1	0.6211	0.9718	0.9419

RESULTS AND DISCUSSION

The deviation in weight variation test ranged from 1.65 ± 0.24 to 2.76 ± 0.28. The drug content varied from 97.15 ± 1.25 to 99.25 ± 0.25. The thickness ranged from 2.22 ± 0.02 to 2.28 ± 0.02. The hardness and percentage friability values of the tablets of all the batches ranged from 8.2 ± 0.2 to 8.9 ± 0.2 and 0.02 ± 0.005 to 0.08 ± 0.01 respectively which is shown in (Table II). The percent cumulative release data is shown in the (Table III). From this data the following conclusions can be made.

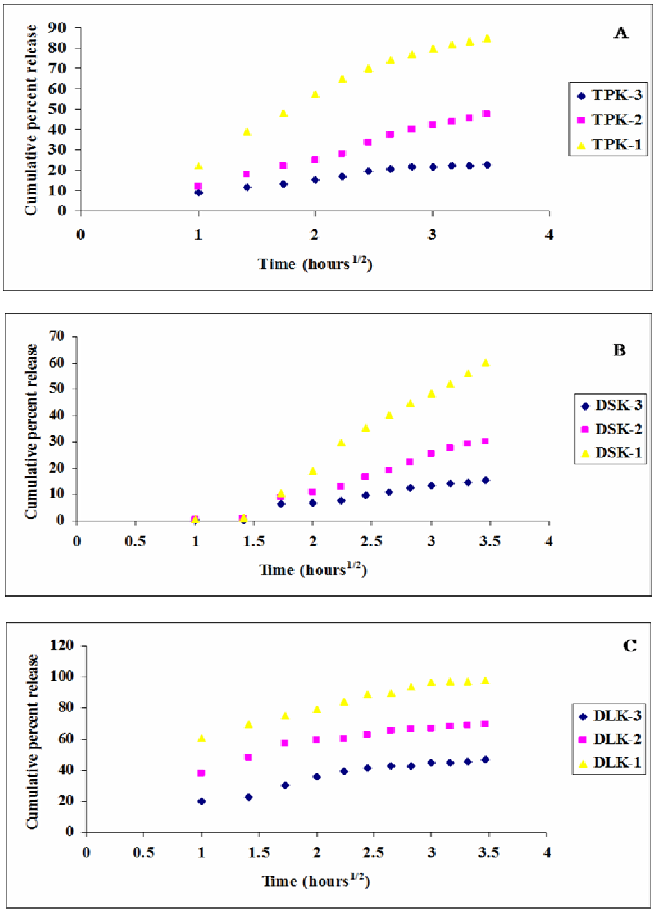
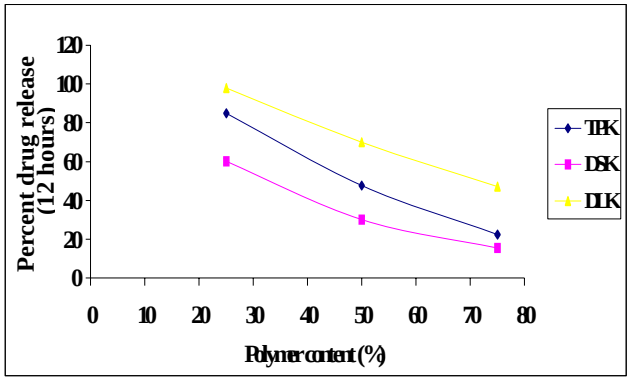


Fig. I: Mean (± S.D.) Higuchi's square root treatment for various tablets (A) Theophylline (B) Diclofenac sodium (C) Diltiazem HCl.

Effect of physicochemical property of drug on release rate

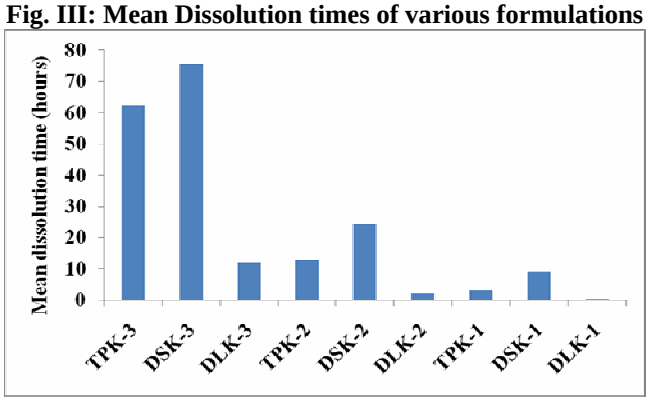
The effect of physicochemical property of drug molecule on release retarding ability of Kollidon SR at 75%, 50% and 25% polymeric content was studied. The release rates (% drug released / $hr^{1/2}$) of theophylline, diclofenac sodium and diltiazem HCl were found to be significantly different. ($p<0.0001$, single factor ANOVA). This indicates that the release-retarding efficiency of the polymer critically depends on the physicochemical nature of the drug molecule. Fig. II showed that, at any particular polymeric level, Kollidon SR can exert the highest drug retarding effect on diclofenac sodium. Only 16%, 29% and 60% of diclofenac sodium was released after 12 hours from formulations containing 75%, 50% and 25% Kollidon SR respectively. Furthermore, an insignificant amount of diclofenac sodium was released in the first two hours of dissolution period. Release of diltiazem HCl was highest from Kollidon SR matrix tablets. Formulation DLK-3, DLK-2 and DLK-1 containing 75%, 50% and 25% of Kollidon SR released 46%, 71% and 98% of diltiazem HCl respectively after 12 hours. However, a burst release of diltiazem HCl was observed with formulation DLK-1 and DLK-2. About 61% and 38% of drug was released from DLK-1 and DLK-2 within the first hour of dissolution period. Kollidon SR exerted a more controlled effect on the release of theophylline, e.g., 25%, 48% and 85% of theophylline was released after 12 hours from formulation TPK-3, TPK-2 and TPK-1 containing 75%, 50% and 25% of Kollidon SR respectively. Neither a lag phase nor a burst release was observed with theophylline. Diltiazem HCl is an acidic salt of basic drug having a pKa value of 7.7 and the molecule is freely soluble in water. Alderman [15] reported that, the release kinetics of hydrosoluble drugs is mainly governed by diffusion from hydrophilic matrices. Diltiazem HCl present on the surface of Kollidon SR matrix tablet rapidly leaves the matrix system because of its basic nature. The burst effect observed with diltiazem HCl from formulations DLK-2 and DLK-1 can be attributed

Fig. II: Effect of % polymer content on % drug release



to rapid ionization and higher solubility of diltiazem in acidic medium as well as the non-swellable property of Kollidon SR. Release of theophylline from Kollidon SR matrix, on the other hand, was found to be higher than that of diclofenac sodium. The fact is attributable to the higher pKa value (pKa 8.6) and solubility profile of theophylline in both type of dissolution medium with pH value of 1.2 and 6.8. It has been reported that, theophylline shows the solubility of

Fig. III: Mean Dissolution times of various formulations



12.76 mg ml^{-1} in acidic medium while 9.03 mg ml^{-1} in basic medium[4, 5]. In dissolution medium with acidic pH, theophylline release is less than that of diltiazem HCl in spite of higher pK_a value of theophylline. The observation can be explained in the way that, diltiazem HCl, being a salt of weak base was rapidly ionized and subsequently get solvated than anhydrous form of theophylline.

Effect of Polymeric content on the release profile of drugs

The effect of polymer content on drug-release as a function of time was found to be significantly different ($p<0.0001$, single factor ANOVA) for a specific set of drug and polymer irrespective of their chemical nature. Comparing the corresponding release profile for a particular drug and polymer system it has been observed that, for all the drugs under investigation, drug release is inversely proportional to the level of rate retarding polymer present in the matrix system, i.e. the rate and extent of drug release increases with decrease in total polymeric content of the matrix. It has been observed that, for Kollidon SR matrix system, 25%, 48% and 85% of theophylline was released from formulation TPK-3, TPK-2 and TPK-1 containing 75%, 50% and 25 % of polymer. On the other hand 16%, 29% and 60% of diclofenac sodium and 47 %, 72 % and 98 % of diltiazem HCl was released from formulations containing 75%, 50%and 25 % of Kollidon SR respectively. A linear relationship exist between the polymer content and rate of drug release irrespective of physicochemical nature of drug and polymer as characterized by higher values of correlation-coefficient (r^2 > 0.98). The rate of drug release was calculated from the slope of the Higuchi curve expressed as % drug released / $hr^{1/2}$. Such increase in the polymer content results in a decrease in the drug release rate due to a decrease in the total porosity of the matrices (initial porosity plus porosity due to the dissolution of the drug).[16] The reduced amount of drug-retarding polymer was replaced by ludipress, which contains lactose and Kollidon CL.[6] Lactose caused a decrease in the tortuosity of the diffusion path of the drug and Kollidon CL, by its swelling effect, weakened the matrix integrity. These two factors can be ascribed for the higher release rate of drug with formulations containing lower percentage of polymers. Analogous result was reported with previous investigations.[17, 18]

Release kinetics

The values of release exponent (n), kinetic rate constant (k) was calculated and presented in (Table IV). As observed from the table, the values of correlation co-efficient for all the formulations were high enough to evaluate the drug dissolution behavior. The value of the release exponent (n) was found to be a function of polymer used and the physicochemical property of the drug molecule itself. At 75% polymeric content theophylline and diclofenac sodium loaded Kollidon SR tablets, by their very nature of releasing drug by pore-diffusion, demonstrated drug release mechanism by Fickian (Case I) transport as observed from their n values. Reducing the Kollidon SR level in formulations containing theophylline and diclofenac sodium showed a significant deviation from Fickian or diffusional transport. This can be attributed to the presence of higher proportion of ludipress that contains a swellable component i.e. Kollidon CL. Diltiazem HCl-Kollidon SR system released drug by Fickian (Case I) mechanism at 75% and 50% polymeric level. However, at 25% Kollidon SR content, such matrix system showed a significant deviation from diffusional transport mechanism. Though, higher molecular weight of diltiazem HCl can be held responsible for its lower diffusivity and consequent deviation from Fickian mechanism, this may not be the single operative factor in this case. Reduced polymer content with respect to active ingredient, failure of the matrix material to form a non-erodible frame work,

presence of swellable component (i.e. Kollidon CL in Ludipress) at relatively higher proportion may be considered for such deviation. In general, solubility of drug molecule itself crucially governs the rate and extent of diffusional release. For diffusion to occur, the first step is wetting of drug by water, followed by its dissolution so that the drug molecule is available in molecular form to diffuse out of the matrix. Hence, the net release rate observed is a cumulative effect of drug's solubility (influenced by its structure, molecular weight and pKa), polymer property (hydrophilicity/lipophilicity, molecular weight, and tortuosity) and the relative ratio of drug and polymer in the tablet. The values of n had no definite relationship with polymer content for any of the drugs. Mean dissolution time (MDT) value is used to characterize the drug release rate from the dosage form and the retarding efficacy of the polymer.

$MDT = (n/n+1)* k^{-1/n}$

A higher value of MDT indicates a higher drug retarding ability of the polymer and vice-versa. The MDT value was also found to be a function of polymer loading, polymer nature and physicochemical property of the drug molecule. Fig. 3 showed that a direct relationship can be found with MDT value and polymer loading irrespective of drug and polymer nature which is linear in nature (r^2>0.98). From all the polymers, the MDT of soluble drugs (diltiazem HCl and theophylline) were significantly lower than those of less soluble drugs (e.g. diclofenac sodium) as illustrated in Fig. 3. The difference was significant at $p< 0.0001$ (unpaired t-test). This indicates that the release of soluble drugs is faster than the release of insoluble drug from all the matrix systems under investigation. This discrepancy in release rate between soluble and less soluble drugs can be attributed to the difference in their release mechanisms.

CONCLUSION

At present, all the polymers being studied are used extensively in pharmaceuticals to control the release of drug. The approach of the present study was to study the effect of physicochemical nature of the active ingredient on drug release profile. The study reveals that, the release of water-soluble drugs was higher than the drugs with lower solubility and the mechanism of release was changed with the content of polymer in the matrix. However, a number of critical parameters such as granulation process, tabletting conditions, hardness and porosity of the tablet and compression pressure will markedly affect drug release pattern from different matrices.

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REFERENCES

1. Merkus F.W.H.M.; Controlled and rate-controlled drug delivery; CRC Press, Boca Raton: (FL) USA, 1986, 15-47.
2. Langer R.S., Wise D.L; Medical Applications of Controlled Release, Volume 1; Classes of Systems, CRC Press, Boca Raton: (FL) USA, 1984, 41-67.
3. Lachman L., Lieberman H.A., Kanig J.L; The Theory and Practice of Industrial Pharmacy, 3 (edition); Varghese Publishing House, Bombay, 1990, 430-456.
4. Talukder. M.M., Michoel. A., Rombaut. P., Kinget. R; Int. Journal. Pharm., 1996; 129, 231-241.
5. Lee. B.J., Ryu. S.G., Cui. J.H; Drug Dev. Ind. Pharm., 1999; 25, 493-501.
6. The Dow Chemical Company, Technical Research presentation: Formulation for con-trolled release with METHOCEL cellulose ethers, USA, 1987.
7. BASF, Technical Information**,** ME 397e, June 1999.
8. Verma. P.R.P., Banu. V; Drug Dev. Ind. Pharm., 1996; 22, 1243-1247.
9. Chattaraj. S.C., Das. S.K; Drug Dev. Ind. Pharm., 1996; 22, 555-559.
10. Shah. D., Shah. Y., Pradhan. R; Drug Dev. Ind. Pharm., 1997; 23, 567-574.
11. Ritger. P.L; J. Control Release, 1987; 5, 37-42.
12. Shato. H., Miyagawa. Y., Okabe. T., Miyajima. M., Sunada. H; Journal. Pharm. Sci., 1997; 86, 929-934.
13. Reddy. K.R., Shrinivas. M., Reddy. S; AAPS Pharm. Sci., 2003; 4, 1-9.
14. Sethi P.D; Quantitative analysis of drugs in pharmaceutical formulations; 3(edition) CBS Publishers and Distributors, New Delhi., 1997, 182 – 317.
15. Alderman. D.A; Int. Journal. Pharm., 1984; 5, 1-9.
16. Sungthongjeen. S., Pitaksuteepong. T., Somsiri. A., Sriamornsak. P; Drug Dev. Ind. Pharm., 1999; 25, 1271-1276.
17. Dakkuri A.., Schroeder. H.G., Deluca. P.P; Journal. Pharm. Sci., 1978; 67, 354-357.
18. Wong. L.P., Gilligan C.A., Li Won Po A; Int. Journal. Pharm., 1992; 83, 96-114.