ISSN 0975-6299 Vol 2/Issue 1/ Jan-Mar 2011

International Journal of Pharma and Bio Sciences

RESEARCH ARTICLE

Pharmaceutics

HOT MELT COATING TECHNIQUES IN SUSTAINED RELEASE FORMULATION AND EVALUATION OF WATER SOLUBLE DRUG

Corresponding Author

P.L.CHANDRIKAPURE

Department of Pharmaceutics, Smt. Kishoritai Bhoyar College of Pharmacy, New Kamptee, Nagpur-441002, Maharashtra, India

Co Authors

K.J.WADHER AND M.J.UMEKAR

Department of Pharmaceutics, Smt. Kishoritai Bhoyar College of Pharmacy, New Kamptee, Nagpur-441002, Maharashtra, India

ABSTRACT

Multiparticulate dosage forms are becoming an increasingly popular method for providing controlled release of drugs in the gastrointestinal (GI) tract as they minimize the risk of dose dumping. These multiparticulates usually consist of a drug entrapped in a sustaining matrix, or of a drug core over coated with a low permeability polymer film. Beads are one of the multiparticulate delivery systems and are prepared to obtain prolonged or controlled drug delivery, to improve bioavailability or stability and to target drug to specific sites.

Waxes are one of the material which can be use to coat the drug in order to control the release. Hot melt coating technique defined as the application of fine layer of coating material in molten state over the substrate. Ethyl cellulose is a hydrophobic polymer used as a rate-controlling membrane to modulate the drug release from dosage forms with organic or aqueous coating techniques.

The oral bioavailability of diclofenac potassium is around 60% with an excretion half-life between 1.1 and 1.8 h. It has an unpleasant taste and causes gastric irritation. As this drug is mainly absorbed from the gastrointestinal tract, an enteric coating provides sufficient taste masking without negatively affecting the availability of the drug.

In the present study, preparation of sustained release formulation of water soluble drugs as diclofenac potassium in vitro, prediction of the release, & drug release pattern to match target release profile was investigated. This was prepared by non-aqueous solvent free technique using ethyl cellulose as rate controlling polymer. The developed sustained release formulation using,hot melt coating may be used in clinic for prolonged drug release in stomach, thereby improving the bioavailability & patient compliance.

ISSN 0975-6299 Vol 2/Issue 1/ Jan-Mar 2011

KEY WORDS

hot melt coating, sustained release, cetyl alcohol, beeswax, multiparticulate system,

INTRODUCTION

Sustained release (SR) delivery systems represent one of the most rapidly advancing areas of science which offers numerous advantages compared to conventional dosage forms including improved efficiency, reduced toxicity, and improved patient compliance and convenience[1]. SR delivery systems for oral dosing are effective in achieving ideal therapy with drugs that have a narrow therapeutic range of blood concentration or eliminate rapidly[2]. These dosage forms can be classified as a single unit and multiple unit. Multiple-unit dosage forms have been accepted to provide advantages over single unit dosage forms. Multiparticulate dosage forms are becoming an increasingly popular method for providing controlled release of drugs in the gastrointestinal (GI) tract, partly because they have relatively reproducible upper GI transit profiles and partly because they minimize the risk of dose dumping. These multiparticulates usually consist of a drug entrapped in a sustaining matrix, or of a drug core over coated with a low permeability polymer film. Water insoluble film forming agents used to create a barrier to drug release include various cellulose derivatives and polymethacrylates. Film formation can be achieved by applying the polymer from an organic solution [3-5], from a coating emulsion or from an aqueous dispersion. There are several possible mechanisms by which release from multiparticulate dosage forms coated with water insoluble polymers may occur .The solution/diffusion mechanism has been demonstrated for many polymer films prepared from organic solvents [6-9].

Beads are one of the multiparticulate delivery systems and are prepared to obtain prolonged or controlled drug delivery, to improve bioavailability or stability and to target drug to specific sites. Beads can also offer advantages like limiting fluctuation within therapeutic range, reducing side effects, decreasing dosing frequency and improving patient compliance [10].

Diclofenac, a phenylacetic acid derivative, is a nonsteroidal anti-inflammatory analgesic with potent cyclooxygenase inhibition activity[11]. It is used for the relief of pain and inflammation in conditions such as rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, acute gout, and following some surgical procedures [12]. DS is mainly absorbed from the gastrointestinal tract with extensive hepatic metabolism [12, 13]. The oral bioavailability is around 60% with an excretion half-life between 1.1 and 1.8 h [14 15]. DS has an unpleasant taste and causes gastric irritation. As this drug is mainly absorbed from the gastrointestinal tract, an enteric coating provides sufficient taste masking without negatively affecting the availability of the drug. Furthermore, the formulation of a multiparticulate system is thought to be preferable to a single-unit dosage form because the small particles spread out more uniformly in the gastrointestinal tract. This results in more reproducible drug absorption and reduces the risk of local irritations. A process had hence to be selected which is applicable to the coating of these small particles.

Ethyl cellulose (EC) is a non-toxic, stable, compressible, inert, hydrophobic polymer that has been widely used to prepare pharmaceutical dosage forms. This polymer is often used as a rate-controlling membrane to modulate the drug release from dosage forms with organic or aqueous coating techniques[16-18]. The properties of ethyl cellulose sustained

release products for both soluble and poorly soluble drugs have been reported[19, 20]
The aim of this study was to better understand the underlying drug release mechanisms from pellets coated with aqueous ethylcellulose dispersion providing long term stable drug release profiles

MATERIALS AND METHODS

Diclofenac sodium was obtained as a gift sample from Zim Laboratories Ltd., Nagpur (India). Ethylcellulose was procured from Colorcon Asia Pvt. Ltd., Mumbai (India). Magnesium stearate, dicalcium phosphate and lactose monohydrate were purchased from M/s. Loba Chemie Laboratories Ltd., Goa (India). Avicel PH 102 was obtained from M/s. Signet Chemicals Ltd., Mumbai (India). Potassium dihydrogen phosphate, Propanol, methanol and sodium hydroxide were procured from M/s. Ranbaxy Fine Chemicals Ltd., New Delhi (India). All other ingredients were of alalytical grades and used as received.

METHODS

Preparation of Drug Loaded pellets

1.6 kg of non-pareil seeds were placed in the pre warmed chamber of a coating pan (16 inch diameter) which rotates at the speed of 30 rpm. Binder solution was prepared by dissolving polyvinyl pyrrolidine in a mixture of distilled water and isopropyl alcohol (20:80%). Spray application of drug-binder solution (4ml/min), along with simultaneous application of drug and talcum powder (10-20g/min) on non pareil seeds were carried out. After a sufficient quantity of powder was added to build the pellets to the desired size, spraying of the binder solution was terminated. The pellets were part & dried while still in the chamber, the blower air velocity was at 7m/s (measured by aneemeter). The dried pellets were screened and the 12-18-mesh fraction collected. Coated pellet were kept in a hot air oven and dried at 45-50^0 c for 12 hrs.

Hot Melt Wax Coating of Drug Loaded Pellets

These drug loaded pellets were coated with different concentrations of drug release controlling materials viz cetyl alcohol and bees wax (2, 5, &10%) using hot melt technique by ladling of melted wax over pre warmed drug loaded pellets (45-50^0 C) .After the desired weight of film was deposited cooling and congealing of wax coated pellets were carried out (congealing time 10 minutes). . The coating conditions are given in Table 1.

Film Coating on Wax-Coated Pellets

Film coating solution was prepared by dissolving required quantity of ethyl cellulose in isopropyl alcohol. Required amount of titanium dioxide and talc which were previously passed through sieve no 16 were added to the ethyl cellulose solution with constant stirring for 20 minutes, and plasticized with dibutyl phthalate . Finally wax coated pellets were sprayed with the help of this ethyl cellulose film coating solution at the rate of 100ml/hr. Film coated pellets were then dried at 40^{0}c in hot air oven. The film coating conditions are given in Table 2.

Film Coating on Plain Drug Loaded Pellets

Ethyl cellulose film coating was done on plain drug loaded pellet same as above procedure. . Film coated plain drug loaded pellets were then dried at 40^{0}c in hot air oven.

EVALUATION OF PHYSICAL PARAMETERS OF PELLETS

In Vitro Dissolution Studies:

Dissolution studies of the plain film coated pellets, wax coated pellets and film and wax coated pellets containing diclofenac potassium

equivalent to 100mg were performed using USP XXIII dissolution test apparatus, type - 2 (LABINDIA, India) at the paddle rotation speed of 100 rpm in 900 mL distilled water as dissolution medium at 37 ± 0.5 °C. The samples withdrawn were filtered through Whatman filter paper No. 1 and the drug content in each sample was analyzed after suitable dilution using a UV spectrophotometer at 267 nm (9) Dug release studies were conducted in triplicate.

Analysis of release data

The release data obtained were treated according to zero-order (cumulative amount of drug release versus time), first-order (log cumulative percentage of drug remaining versus time), higuchi (cumulative percentage of release versus square root of time) (17) and Korsmeyer-Peppas (log cumulative percentage of drug released versus log time) equation models (18).

Release Kinetics

In model-dependant approaches, release data were fitted to five kinetic models including the zero-order (Eq. 1), first order (Eq. 2), Higuchi matrix (Eq. 3), Peppas–Korsmeyer (Eq. 4), and Hixson–Crowell (Eq. 5) release equations to find the equation with the best fit .

$$R = k_1 t \quad \text{----------} \quad \text{Eq. 1}$$

$$\log UR = k_2 t / 2{:}303 \quad \text{----------} \quad \text{Eq. 2}$$

$$R = k_3 \sqrt{t} \quad \text{----------} \quad \text{Eq. 3}$$

$$\log R = \log k_4 + n \log t \quad \text{----------} \quad \text{Eq. 4}$$

$$(UR)^{1/3} = K_5 t \quad \text{----------} \quad \text{Eq. 5}$$

Where R and UR are the released and unreleased percentages, respectively, at time (t); k_1, k_2, k_3, k_4, and k_5 are the rate constants of zero-order, first-order, Higuchi matrix, Peppas–Korsmeyer, and Hixon–Crowell model, respectively.

Statistical Analysis

The data was subjected to two ways ANOVA followed by Bonferroni post test for analyzing the statistical difference using the software Graph pad prism (San Diego, CA).

RESULTS & DISCUSSION

As shown in Fig. 1 the release of diclofenac potassium lowered when the percent of wax coating was increased (2, 5, and 10%). Thus prolongation of release profile can be directly attributed to the amount of wax coating applied. Burst release was observed as more than 90% release of drug released within 1 hour, the reasons might be the erosion of wax layer due to vertex flow of fluid & paddle movement & hence immediate release was observed. Also non uniformity in coating which may result in some pellets remaining uncoated was responsible for higher release of drug. This wax coating alone was not sufficient in retarding the release of highly water soluble drugs. But our aim was to produce sustained release product, therefore hydrophobic film coating was applied over wax coated pellets.

In vitro dissolution studies on cetyl alcohol and bees wax coating (2, 5 and 10%) along with

ethyl cellulose film coated (5 and 10%) pellets of diclofenac potassium are shown in figure 2 and 3 respectively.. From figure it was shown that 5% ethyl cellulose film coating on cetyl alcohol bees wax coated pellets retards the drug release, but was insufficient to extended the release of drug. Therefore 10 % film coating was applied on wax coated pellets.

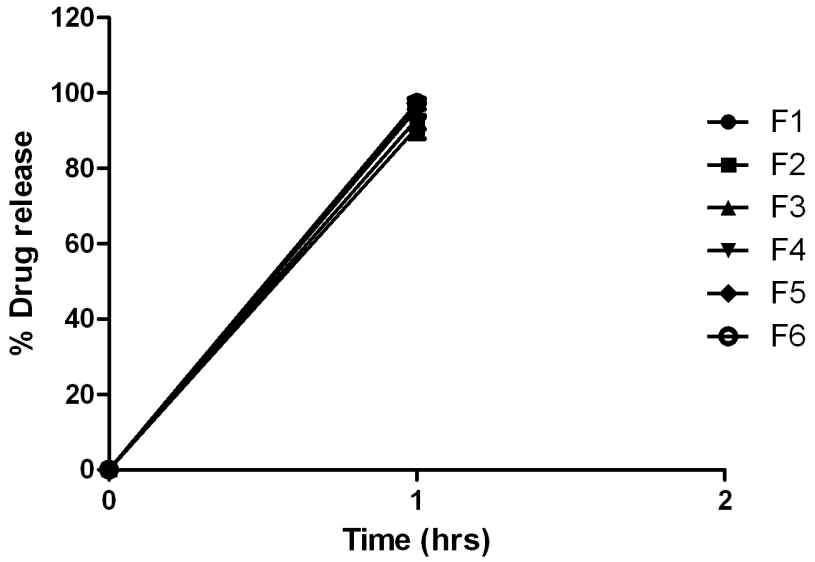

FIGURE 1

In vitro cumulative release of diclofenac potassium from formulation F1 (–♦–), F2 (–■–), F3. (–▲–)F4 (–▼–), F5 (–♦–), F 6(–ɵ–).Each point represents mean ± SD, n=3

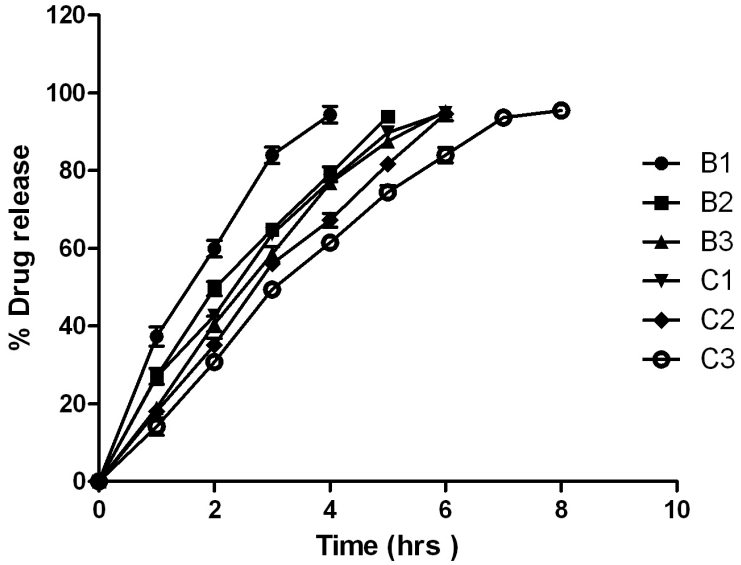

FIGURE 2

In vitro cumulative release ofdiclofenac potassium from formulation B1 (–♦–),B2(–■–), B3 (–▲–)C1 (–▼–), C2 (–♦–), C3 (–ɵ–).Each point represents mean ± SD, n=3

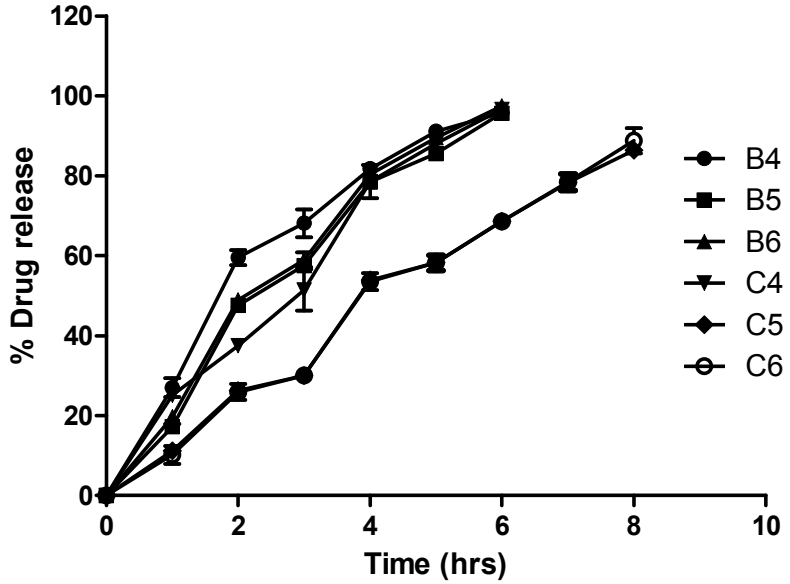

FIGURE 3

In vitro cumulative release of diclofenac potassium from formulation B4 (–♦–), B5 (–■–), B6 (–▲–), C4 (–▼–), C5(–♦–), C6 (–ɵ–).Each point represents mean ± SD, n=3

From the results, it was revealed that, beeswax was superior to cetyl alcohol in retarding the drug release. Sustained release product obtained with beeswax required less percentage of wax coating as compared to cetyl alcohol coated pellets. Probable reason for such results may be attributed to the solubility of waxes in solvents used for film coating solution. Isopropyl alcohol was used as solvent in film coating solution. Beeswax is insoluble in isopropyl alcohol whereas cetyl alcohol is soluble in isopropyl alcohol. Thus when film coating was applied over cetyl alcohol coated pellets, the wax layer was slightly disturbed by isopropyl alcohol. Thereby drug was migrated to the surface of pellets & gets solubilised in the medium (water) & gives higher release. In case of beeswax coating,beeswax being insoluble in iso-propyl alcohol, there was no solubilisation of wax layer. Thereore wax layer remained intact & thus there was no migration of drug to the surface. Ultimately beeswax coated pellets give more sustained release product as compared to cetyl alcohol, after the application of film coating.

Beeswax 10% along with 10 % film coated pellets of diclofnac potassium does not complied with the limits of drug release because the release of drug was highly suppressed, but they gave sustained release product which released the drug for longer period of time. To ascertain weather the wax coating prior to film coating is really a technique more advantageous over film coating alone the drug pellets were film coated.

Drug release kinetics:

To describe the kinetics of drug release from matrix tablets, release data was analyzed according to different kinetic equations. The data was analyzed by the regression coefficient method and regression coefficient value (r^2) of all batches as shown in Table 4. Based on various mathematical models, the magnitude of the release exponent "n" indicates the release mechanism (i.e. Fickian diffusion, case II transport, or anomalous transport). In the present study, the limits considered were n = 0.5 (indicates a classical Fickian diffusion-controlled drug release) and n > 1 (indicates a supercase II relaxational release transport). Values of n between 0.5 and 1 can be regarded as an indicator of case II transport commonly called (Non –fickian) anomalous transport (19). On analyzing regression coefficient values of all batches, it was found that Batch C5 and C6 tablet exhibited almost zero order kinetics. Batch B4,B5 and B6 tablet followed Hixon crowell kinetics, whereas Batches B1,B2,B3,C1,C2,C3 and C4 tablet followed Korsmeyer- Peppas kinetics. DS release from the investigated coated pellets is primarily controlled by drug diffusion through the intact polymeric films.

Table 4

Release kinetic parameters with correlation coefficient for designed formulations.

Formulation	zero order		First order		Higuchi		Hixon-crowe		Korsmeyer-peppas		
	r2	k	r2	k	r2	k	r2	K	N	r2	K
B1	0.9719	26.2229	0.9715	-0.6521	0.9889	45.6305	0.9959	-0.151	0.6909	0.9966	37.5032
B2	0.9826	20.1233	0.9478	-0.4575	0.9810	38.5168	0.9872	-0.110	0.5936	0.993	24.377
B3	0.9860	17.4934	0.9552	-0.4245	0.9646	36.2057	0.9899	-0.0993	0.9142	0.9936	20.3453
B4	0.9279	18.7623	0.9831	-0.4787	0.9870	39.5678	0.9965	-0.1098	0.6877	0.9708	30.8045
B5	0.9770	17.5806	0.9515	-0.4260	0.9665	36.4949	0.9887	-0.0996	0.9315	0.9770	20.1024
B6	0.9760	18.1111	0.9367	-0.4883	0.9704	37.6463	0.9866	-0.1079	0.8809	0.9824	22.2726
C1	0.9710	17.9154	0.9690	-0.4382	0.9814	37.3889	0.9954	-0.1023	0.7348	0.9957	26.9612
C2	0.9948	16.4898	0.9268	-0.3755	0.9571	33.9641	0.9760	-0.0901	0.9306	0.9975	18.5465
C3	0.9809	13.5544	0.9555	-0.3387	0.9622	32.1132	0.9892	-0.0781	0.9357	0.9909	15.7220
C4	0.9842	17.4533	0.9312	-0.4455	0.9588	36.0833	0.9756	-0.1014	0.7969	0.9851	23.5460
C5	0.9914	11.3313	0.9656	-0.2104	0.9422	26.6107	0.9860	-0.0556	0.9800	0.9901	11.8768
C6	0.9931	11.4123	0.9490	-0.2189	0.9373	26.7414	0.9789	-0.0570	1.0317	0.9896	11.0478

Statistical Analysis

The data was subjected to two ways ANOVA followed by Bonferroni post test and in all the cases $p < 0.001$ was considered as significant.

Table 1

Composition of Diclofenac potassium wax coated pellets formulations

Formulation code	Ingredients (%)	
	Cetyl alcohol	Beeswax
F1	5	
F2		5
F3	10	
F4		10
F5	15	
F6		15

Table 2

Composition of Diclofenac potassium Ethyl cellulose film coated pellets

Formulation code	Ethyl cellose Film coating (5%)		Formulation code	Ethyl cellulose Film coating (10%)	
	Cetyl alcohol	beeswax		Cetyl alcohol	beeswax
B1	5		**C1**	5	
B2	10		**C2**	10	
B3	15		**C3**	15	
B4		5	**C4**		5
B5		10	**C5**		10
B6		15	**C6**		15

CONCLUSION

The results revealed that hot melt coating with cetyl alcohol and beeswax alone, would not be able to retard the release of water soluble drug. This is due to reason that during dissolution process, wax layer was slightly eroded due to vertex flow of fluid &: paddle movement & hence immediate release was observed. Therefore ethyl cellulose film coating was applied to provide the rigidity & strength to wax layer on the surface of pellet & also to comply with the limits specified for drug release.

Application of wax coating prior to film coating was proved to be advantageous in comparison to film coating alone as lesser polymer concentration was required in former to meet limit of drug release. Thus hot melt coating technique was proved to be economic way of manufacturing sustained release formulation. Ethyl cellulose film coating (10%) over wax coated pellets, produced more sustained release product. . DS release from the investigated coated pellets is primarily controlled by drug diffusion through the intact polymeric films

REFERENCES

1. Uhrich KE, Cannizzaro S.M, Langer RS, Shakesheff KM, Polymeric systems for controlled drug release. Chem. Rev. 99: 3181–3198, (1999).
2. Nishihata T, Hirotani Y, Yamazi A, Takahashi K, Yoshitomo H, Preliminary study on sustained-release particles prepared with hydrogenated soya phospholipids and cholesterol. Int J Pharm 42: 257-260, (1988).
3 G.S. Banker, Film coating theory and practice, J. Pharm. Sci., 55 : 81-89, (1966).
4. Spitael J and Kinget R, Influence of solvent composition upon film-coating. Pharm. Acta Helv, 55: 157-160, (1980).
5. A.K. Doolittle, The Technology of Solvents and Plasticizers, Wiley, New York, NY, (1962).
6. Vidmar V, Jalsenjak I, Kondo T, Volume of waterfilled pores in the ethyl cellulose membrane and the permeability of microcapsules. Int. J. Pharm Pharmacol., 34:411-414, (1982).
7. Uno K, Arakawa M, Kondo T, and Donbrow M, Permeability of ethyl cellulose microcapsules towards phenobarbital, J Micro encapsulation, 1: 335- 341, (1984).
8. F.M. Sakr F, El-Dim Zin, E. Esmat and F.M. Hasheim, Release kinetics of some drugs from a suggested polymeric device, Acta Pharm. Technol., 33 :31-34, (1987).
9. Benita S, Donbrow M, Dissolution rate control of the release kinetics of water-soluble compounds from ethyl cellulose film-type microcapsules, Int. J. Pharm, 12: 251-264, (1982).
10. Haznedar S, Dortunc B, Preparation and in vitro evaluation of eudragit microspheres containing acetazolamide, Int. J. Pharm. 269:131–140, (2004).
11. Wasvary EC, J.M., Cash, WD., 1985. Diclofenac sodium a potent inhibitor of prostaglandin synthetase. Biochem. Pharmacol. 24: 641–643.
12. Brogen RN, Heel RC , Pakes E, Speight T M, Avery G.S, Diclofenac sodium a review of its pharmacological properties and therapeutic use in rheumatic diseases and pain of varying origin. 20: 24–48, (1980).
13 Fowler P D, Shadforth M F, Crook P R, John V A, Plasma and synovial fluid concentrations of diclofenac sodium and its major hydroxylated metabolites during long-term treatment of rheumatoid arthritis. Eur. J. Clin. Pharmacol. 25: 389–394, (1983).

14 Willis J V, Kendall M J, Flinn R.M, Thornik D P, Welling P G, The pharmacokinetics of diclofenac sodium following intravenous and oral administration. Eur. J. Clin. Pharmacol. 16: 405–410, (1979).

15 J.G. Hardman, L.E. Limbird (Eds.), Goodman and Gilman's, The Pharmacological Basis of Therapeutics, 9th Edn The McGraw Hill Company, (1996).

16. Shan-Yang Lin, Kung-Hsu Lin, Mei-Jane Li, Micronized ethylcellulose used for designing a directly compressed timecontrolled disintegration tablet. J.controlled release. 70: 321-328, (2001).

17. Siepmann F, Hoffmann A, Leclercq B, Carlin, Siepmann J, How to adjust desired drug release patterns from ethylcellulose-coated dosage forms J.Control.Release 119: 182–189, (2007).

18. Neau SH, Howard MA, Claudius JS, Howard DR ,The effect of the aqueous solubility of xanthine derivatives on the release mechanism from ethylcelluse matrix tablet. Int. J. Pharm. 179: 97- 105, (1999).

19. Katikaneni, PR, Upadrashta SM, Neau SH, Mitra AK, Ethylcellulose matrix controlled release tablets of water soluble drugs. Int. J. Pharm. 123: 119– 125, (1995).

20. S.M Upadrashta, P.R Katikaneni, G.A.Hileman, P.R. Keshary, Direct compression controlled release tablets using ethylcellulose matrices. Drug Dev. Ind. Pharm.1993, 19, pp.449–460.