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Original Research Article

COMPARATIVE EVALUATION OF HYDROPHILIC AND HYDROPHOBIC POLYMERS ON THE IN VITRO RELEASE OF A MODEL WATER SOLUBLE DRUG FROM CONTROLLED RELEASE TABLETS

Y.DEEPA*, VINAY UMESH RAO, M.SUDHAKAR

Malla Reddy College of Pharmacy, Maisammaguda, Post Dhulapally, Secunderabad-500014, India.

Author for Correspondence: yelugamdeepa@gmail.com

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ABSTRACT

The effect of two different viscosity grades of hydrophilic, hydroxy propyl methyl cellulose (HPMC K4M and K100M) and hydrophobic, Stearic Acid and Glyceryl Behenate on the in vitro dissolution of a model water soluble drug was evaluated. Fluoxetine HCl (FLX-HCL) was selected as the model drug due to its high aqueous solubility. Direct compression process was followed for the hydrophilic polymers and the melt granulation technique was followed for the wax matrix tablets. The dose of the drug (20 mg) and weight of the tablets (500mg) was maintained as constant.The wax matrix polymers are required to be used in significantly lower concentrations as compared to the hydrophilic HPMC polymers in order to control the drug release rate of a model water soluble drug like FLX-HCL.

Key words: Hydrophilic polymers, hydrophobic waxes, melt granulation, Fluoxetine HCl (FLX-HCL)

INTRODUCTION

A hydrophilic matrix is a homogeneous dispersion of the drug molecules within a skeleton in which one or several of the excipients are incorporated. Hydrophilic polymers like HPMC K4M and K100M are widely used in formulation of controlled release products[1].Wax matrix systems are one of the oldest and most widely used drug delivery systems for sustained release of oral solid products[2].Waxes like Stearic acid (SA) and Glycerly Behenate (GB) have been extensively used, Drug release from a water soluble HPMC system primarily occurs by a process of diffusion from the swollen matrix while from the wax matrix the route of drug release is mainly by erosion[3]. The current work focuses on evaluating how the concentration of the release retarding polymer affects the drug release from a hydrophilic system as well as from a hydrophobic system for a model water soluble drug. Fluoxetine Hcl (FLX-HCL) was selected as the model water soluble drug, HPMC K4M and K100M in concentrations ranging from 15% to 60% w/w and SA and GB from 5% to 30% were used to prepare tablets of FLX-HCL 20 mg. The drug release was evaluated in vitro by measuring dissolution profile for a time period of 24 hours.

FLX-HCL is an antidepressant of the selective serotonin reuptake inhibitor (SSRI) class.It is approved for the treatment of major depression (including pediatric depression), obsessive-compulsive (in both adult and pediatric populations), bulimia nervosa, panic disorder, and premenstrual dysphoric disorder[6].

MATERIALS AND METHODS

Fluoxetine hydrochloride USP(EMCO Industries,Hyderabad),HPMC K4M and HPMC K100M (DOW Chemicals,USA),Stearic acid (Abitec Corporation ,US),Glyceryl Behenate (Compritol-888 ATO ,Gattefosse GMBH),Microcrystalline cellulose USP (Avicel PH 102,FMC,USA),Poly vinyl pyrrolidone USP (AshlandSpecialty Chemicals, US),Magnesium stearate USP (Ferro,US) were used. All other chemicals used were Analytical Reagent grade. Purified Water USP(Millipore MilliQ system) was used where ever required.

EXPERIMENTAL

Hydrophilic Matrix Tablets:

Formulations using HPMC matrix tablets were fabricated using the direct compression technique (Fig 1). The unit composition formula is given in Table1. All tablets were compressed at 500 mg weight using 10.5 mm circular biconvex die punch set usingRimek Minipress-II MT 12 station rotary compression machine at a hardness of approximately 60 to 80 N and thickness of 4.5 to 4.75 mm. All tablets had friability levels of below 0.5% w/w and assay and content uniformity values within acceptable limits of 96.5 to 98.75%.

Wax Matrix Tablets:

Formulations using wax matrix systems were fabricated by the melt granulation process (Fig 2) [7]. The unit composition formula is given in Table 2. Compression parameters were similar to the HPMC matrix tablets but the hardness achieved was significantly lower (40 to 60N). This is line with the wax matrix formulations which may cap at higher compression forces due to their inherently low melting nature. However this did not compromise the friability of the tablets (< 0.5% w/w).

Dissolution Profile Testing:

In vitro dissolution profile testing for all batches was performed at n=6 sample size. The dissolution test was performed using USP type II apparatus (paddle type), 50 rpm, and 900 ml 0.1N HCl was used as the dissolution medium. 5 ml samples were withdrawn at 1, 2, 4, 8, 12, 16 and 24 hours interval and analyzed spectrophotometrically at 226 nm. The % drug dissolved was calculated by measuring the absorbance of a standard 10 mcg/ml solution of FLX-HCL prepared in 0.1N HCl.

RESULTS

Table.1.Unit Composition Formula for Hydrophilic Matrix Tablets

Ingredients	HF1	HF2	HF3	HF4	HF5	HF6	HF7	HF8
FLX-HCl(mg)	20	20	20	20	20	20	20	20
HPMC K4M(mg)	75	150	225	300	-	-	-	-
HPMC K100M(mg)	-	-	-	-	75	150	225	300
AVICEL PH102(mg)	360	285	210	135	360	285	210	135
PVP K30(mg)	40	40	40	40	40	40	40	40
MAGNESIUM STEARATE (mg)	5	5	5	5	5	5	5	5
TABLET WEIGHT(mg)	500	500	500	500	500	500	500	500

Table.2.Unit Composition Formula for Wax Matrix Tablets

Ingredients	WF1	WF2	WF3	WF4	WF5	WF6	WF7	WF8
FLX-HCl (mg)	20	20	20	20	20	20	20	20
Stearic Acid(mg)	25	50	100	150	-	-	-	-
Glyceryl Behenate(mg)	-	-	-	-	25	50	100	150
AVICEL pH102 (mg)	450	425	375	325	450	425	375	325
Magnesium Stearate (mg)	5	5	5	5	5	5	5	5
Tablet Weight (mg)	500	500	500	500	500	500	500	500

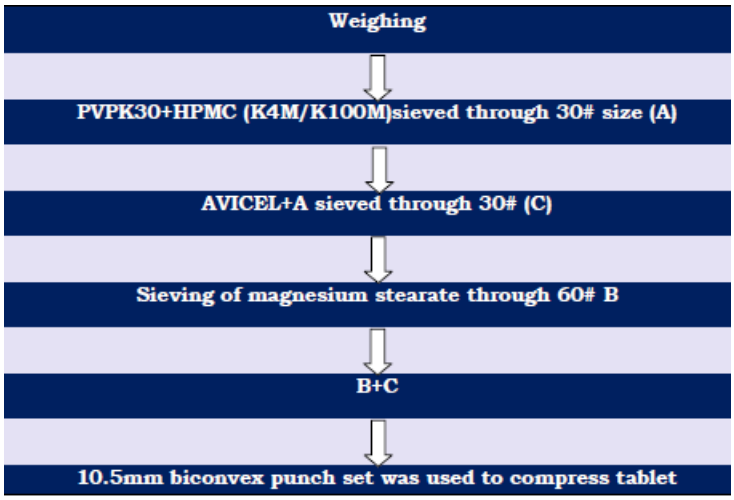

Fig.1.Blending and Compression Technique for HPMC Matrix Tablets

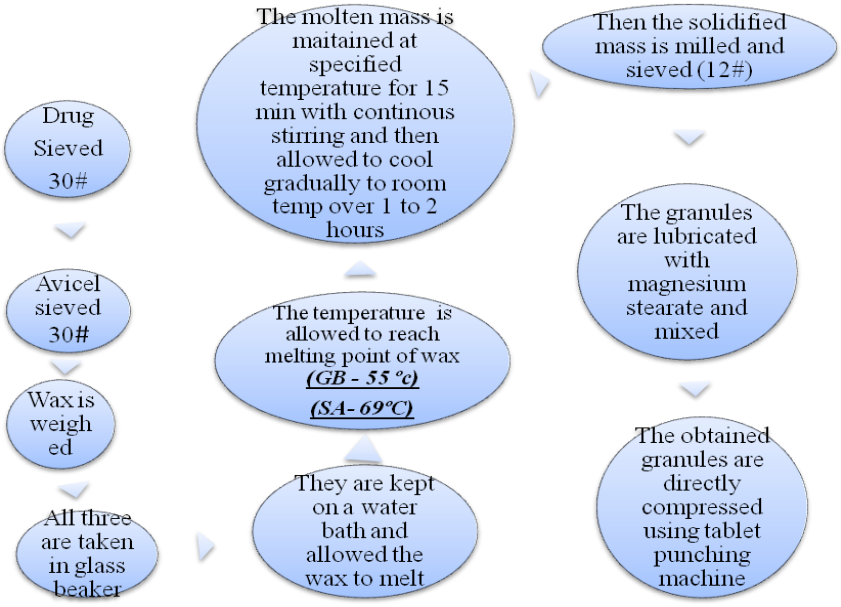

Fig.2.Hot Melt Granulation for Wax Matrix Tablets

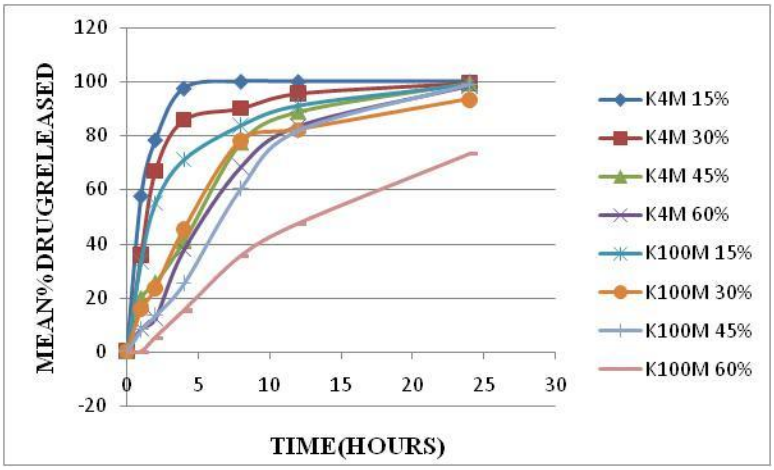

Fig.3.Dissolution Profile of HPMC Matrix Tablets

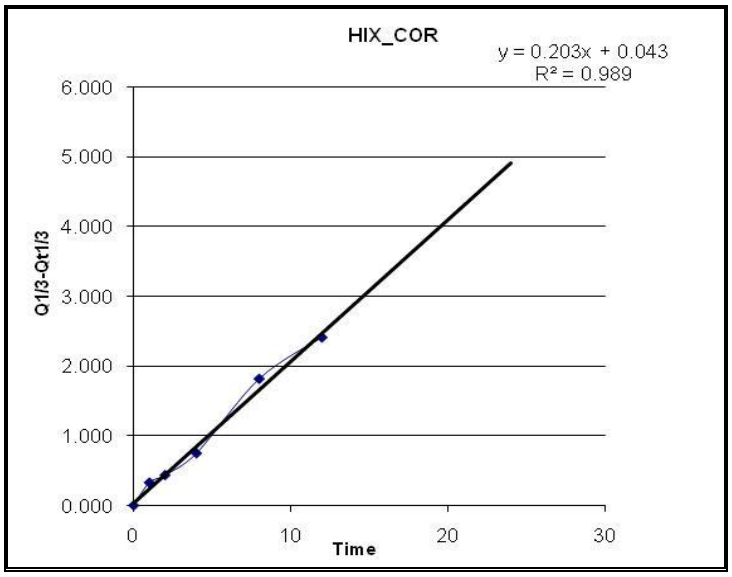

Fig.4.The Hixson-Crowell release rate kinetics for release of FLX from Formulations HPMCK4M (45%)

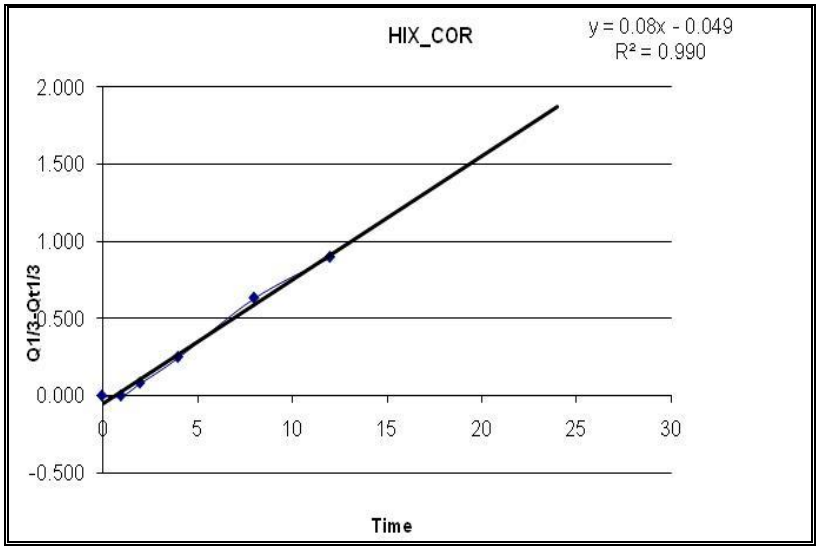

Fig.5.The Hixson-Crowell release rate kinetics for release of FLX from formulations HPMC K100M (60%)

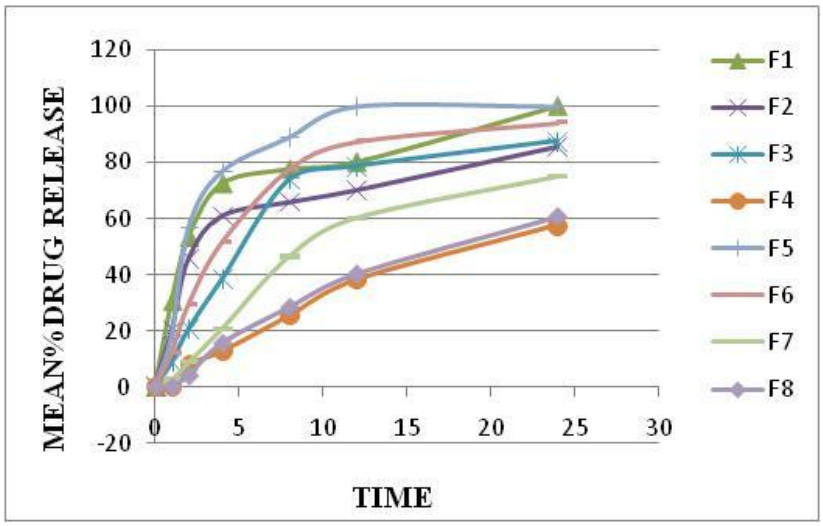

Fig .6.Dissolution Profile Of Wax Matrix Tablets

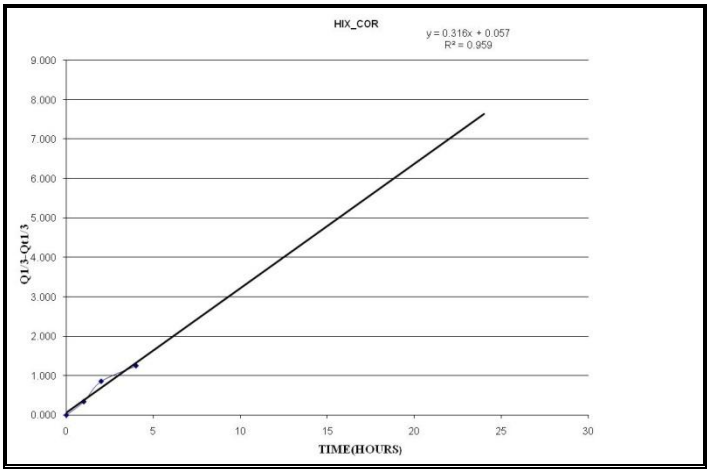

Fig .7.The Hixson-Crowell Release Rate Kinetics For Release Of FLX-HCL From Formulation SA (10%)

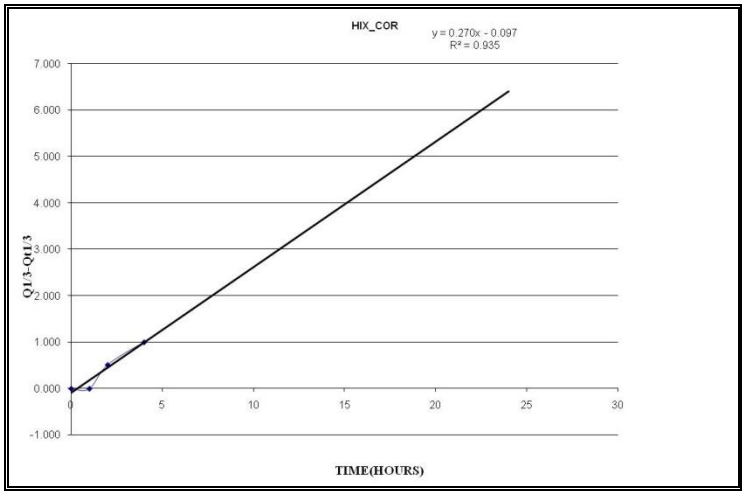

Fig .8.The Hixson-Crowell Release Rate Kinetics For Release Of FLX-HCL From Formulation GB (10%)

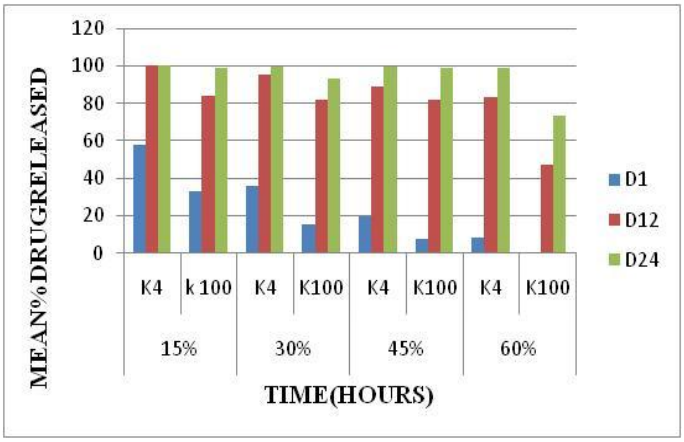

Fig.9.Comparison Of The Drug Release Values At The 1 Hour (D1), 12 Hours (D12) And 24 Hours (D24) For K4M And K100M At All Use Levels

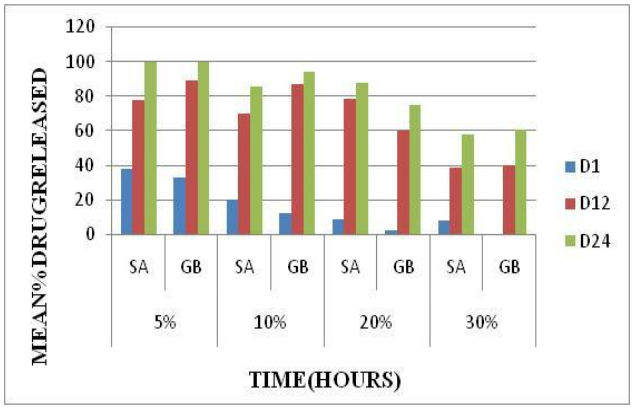

Fig.10.Comparison Of The Drug Release Values At The 1 Hour (D1), 12 Hours (D12) And 24 Hours (D24) For SA And GB At All Use Levels

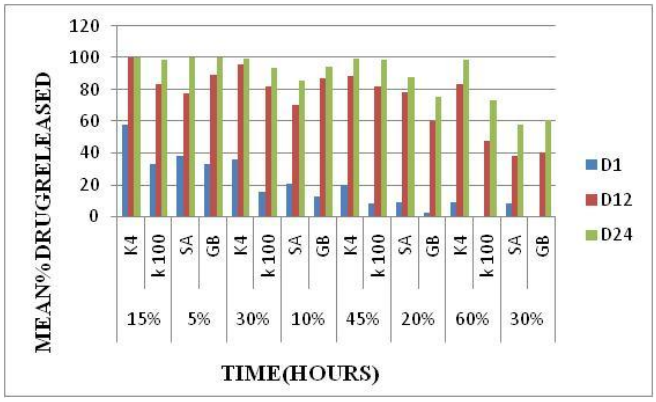

Fig.11.Comparison Of The Drug Release Values At The 1 Hour (D1), 12 Hours (D12) And 24 Hours (D24) For Each Level Of HPMC Matrix With The Corresponding Level Of The Wax Matrix

DISCUSSION

The physical properties for all batches were evaluated and considered as within the acceptable ranges of average weight variation, hardness and friability. The content uniformity and assay values were also within the range of 96.5% to 98.3%. The dissolution profiles for the HPMC matrix formulations are shown in Fig 3 and the wax matrix tablets are given in Fig 4. The release rate kinetics for each formulation was calculated. It was observed that for the hydrophilic matrix the release rate for K4M at all levels was defined by the Hixson-Crowell model (fig 4) while for K100M at higher concentrations (45% and 60%) was Hixson –Crowell model (fig 5) Wax matrix tablets, irrespective of the wax used followed the Hixson- Crowell model for drug release at all concentrations used (Fig 7, Fig 8). This indicates that for the hydrophilic matrix, system follows the dissolution pathway while for the wax

matrix; the system follows the dissolution pathway for control of drug release.

The drug release values at the 1 hour (D1), 12 hours (D12) and 24 hours (D24) for K4M and K100M at all use levels are compared in Fig 9. In case of K4M, the increasing concentration of the polymer is significantly affecting the rate of drug release but not the extent of release over 24 hours. All formulations with K4M achieve complete release over 24 hour period. However, in case of K100M, both the rate as well as extent of drug release is affected by increasing concentration of the polymer. Formulation with 60% K100M fails to achieve complete drug release over 24 hour's period.

The D1, D12 and D24 values for both the wax matrices are compared in Fig 10. A strong concentration dependency of the waxes on the rate and extent of drug release was observed for both the waxes. However, no significant differences between the two waxes were observed.

The D1, D12 and D24 values achieved for each level of HPMC matrix was compared with the corresponding level of the wax matrix (Fig 11). It was observed that the wax matrix polymers are required to be used in significantly lower concentration as compared to the HPMC formulations in order to control the release of the water soluble drug. This may be due to the differences in the mechanism of drug release followed by both the polymer types.

Whereas the hydrophilic polymers control release by dissolution, the wax matrix mainly control drug release through reducing the aqueous dissolution of the drug.The melt granulation process employed for the processing the wax matrix polymers may be coating the drug particles and rendering them hydrophobic and hence reducing its aqueous solubility.

CONCLUSIONS

The hydrophilic polymers like HPMC K4M and K100M are required in significantly higher concentrations (> 45%) in order to control drug release of water soluble of the drug. Again, at higher levels, K100M affects both the release rate as well as its extent. The drug release is defined by Hixson-Crowell model.

The hydrophobic wax matrices are required in only 10 to 15% concentrations in order to control drug release. Both the different types of waxes do not show a significant difference in the pattern of drug release. However, the rate and extent of drug release both are significantly affected by change in concentration of the waxes. This may be due to the fact that the waxes may be altering the solubility of the drug in order to modify the drug release.

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