Development and Study of an Erodible Matrix Drug Delivery Platform for Sustained Release of Non-Steroidal Anti-Inflammatory Drugs Using Melt Granulation Process

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ABSTRACT

The aim of developing the platform was to have a general understanding on how an erodible matrix system modulates drug delivery rate and extent and how it can be optimized to give a delivery system which shall release the drug as per a common target product profile (TPP). Mefenamic Acid (one of the NSAID's) is prepared by using Melt Granulation Process. Commonly used waxes like Cetostearyl alcohol and stearic acid were used singly an in combination to achieve a TPP of not 15 to 35% in 1 hour and not less than 80% Q in 24hours. Full factorial design of experiments was followed for optimization of the formulation. Dissolution profile of the NSAID is taken and recorded. Market available brands of the same NSAID is taken for dissolution profile. The results are recorded. The two recorded results are then compared and verified with the USP standards.

Keywords: NSAIDs, Controlled delivery, Target product profile, Melt granulation.

INTRODUCTION

A simplest and most widely used method of controlling drug delivery[1] is by incorporating drug in the polymer matrix. Thus, drug dissolution and drug diffusion[2] through the polymer are important phenomena in controlling the release characteristics of the formulation. The present work deals with developing a wax matrix drug delivery platform[3] for controlled delivery of Mefenamic Acid which is a Non-Steroidal Anti-inflammatory Drug (NSAID). Even though a number of Non-Steroidal Anti-inflammatory drugs (NSAID's) are available with different chemistries, they share common solubility characteristics that they are relatively more soluble in alkaline environment and practically insoluble in acidic environment.

The present work deals with developing a wax matrix drug delivery platform for controlled delivery of Mefenamic Acid. It is used to treat pain. Since hepatic metabolism plays a significant role in Mefenamic acid elimination, patients with known liver deficiency may be prescribed lower doses. Mefenamic acid[4] is a competitive inhibitor[5] of COX-1 and COX-2, which are responsible for the first committed step in prostaglandin biosynthesis[6]. Decreasing the activity of these enzymes thus reduces the production of prostaglandins, which are implicated in inflammation and pain processes.

The full factorial 3^2 design of experiments[7] was conducted in order to study the effect of combination of polymers on the in vitro drug release. Factorial design[8,9] is an effective tool to obtain an opposite mathematical model with minimum experiments for optimization of formulation design. Factorial design allows all the factors to be varied simultaneously, thus enabling the evaluation of the effects of each variable at each level and showing inter-relationship among them. Most important variables which affect the system function are selected and systemic experiments are then performed. The number of independent variables selected decides the number of experiments that are to be performed.

MATERIALS AND METHODS

The materials needed namely Hydroxypropyl methylcellulose[10], Lactose[11], Magnesium stearate[12], Cetostearyl alcohol[13] were taken from the Malla Reddy General Hospital, Secunderabad. Stearic acid[14], Dextrose[15], Aerosil[16] were taken from the Pharmacy Lab, Malla Reddy College of Pharmacy, Secunderabad.

Preparation of mefenamic acid

Mefenamic Acid tablet was prepared in two ways using the direct compression method[17]. In the first way three grades of HPMC[18] were taken (k4, k15 and k100 m), magnesium stearate was used as lubricant and Lactose as diluent. In the second way, Cetostearyl alcohol, Stearic acid, sugar (diluent) and Magnesium stearate (lubricant) were used.

Mefenamic acid, HPMC and lactose were mixed and then Magnesium Stearate was added as lubricant and the whole mixture was punched into tablets with an average weight of 750 mg using Cadmach tableting machine. This was repeated for all the three grades of HPMC.

Cetostearyl alcohol was heated at a high temperature and after 24 hours mixed with Mefenamic acid, Stearic acid sugar. Magnesium stearate was added to that mixture and the whole mixture was punched into tablets with an average weight of 750 mg using Cadmach tableting machine.

RESULTS AND DISCUSSION

3X2 factorial experimental design

A full factorial statistical[8] design with 3 factors and 2 levels and 9 runs was selected for optimization. The polynomial equation generated by this experimental design was as follows.

$$Y_i = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + b_{12}X_1X_2 + b_{13}X_1X_3 + b_{23}X_2X_3 + b_{123}X_1X_2X_3 + b_{11}X_1^2 + b_{22}X_2^2 + b_{33}X_3^2.$$

Where,
- Y_i was the dependent variable.
- b_0 was the intercept, b_1 to b_{33} were the regression coefficients.
- X_1, X_2, X_3 were the independent variables. The main effects, X_1, X_2, X_3 represented the average value of changing factor one at a time.

- X_1X_2, X_1X_3, and X_2X_3 represented the interaction terms and the polynomial terms.
- The polynomial terms X_1^2, X_2^3 and X_3^2 were used to assess nonlinearity.

Independent and dependent variables were listed in table I.

In vitro drug release

The *in vitr*[19] dissolution study of the compressed matrix tablet of Mefenamic acid was carried out in 900ml of pH 7.4 phosphate buffer maintained at $37 \pm 0.5°C$. The drug release at various time intervals were analyzed spectrophotometrically[20,21] at 285 nm (Lab India UV 3000+ UV/Visible spectrophotometer, Japan).Aliquots of 5 ml was withdrawn at specified time interval and the content of Mefenamic acid was determined at 285nm spectrophotometrically. An equal volume of fresh dissolution medium, maintained at the same temperature, was added after withdrawing each sample to maintain the volume. The absorbance values were transformed to concentration by reference to a standard calibration curve obtained experimentally (r2 values in all the buffer was 0.98). The dissolution studies were performed in triplicate and mean values was plotted versus time.

The target dissolution profile parameters of a sustained-release product were set as follows: After 1 h: 15-35 %; After 5 h: 45-65%; After10 h: 65-85%; after 16h: 75-95%; and after 24h: not less than 80%.

Optimum formula

After developing the polynomial equation for responses Y1 at 1h, Y2 at 5h and Y3 at 24 h with the independent variables, the formulation was optimized for these responses. Figures 1 to 9 below represent the responses gotten at 1 hr, 5th hr, and 24th hr for different grades of HPMC. Optimization was done to find out the levels of independent

variables (X_1, X_2 and X_3) that would yield the value of responses within the target release profile.

CONCLUSION

In the present study the effects of variables on the release of Mefenamic acid from erodible matrix drug platform had been studied using Factorial design. The design of experiment has become a rapid, systematic and reliable screening tool to identify and quantitatively define the significant factors influencing the drug release. The derived polynomial equations and contour plots aids in predicting the values of independent variables for preparation of optimum controlled release matrix tablet of Mefenamic acid with the desired release profile matching the targeted dissolution profile.

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21. http://www.ijppsjournal.com/Vol3Issue2 /2085.pdf.

Table 1. Variables in 3X2 factorial design

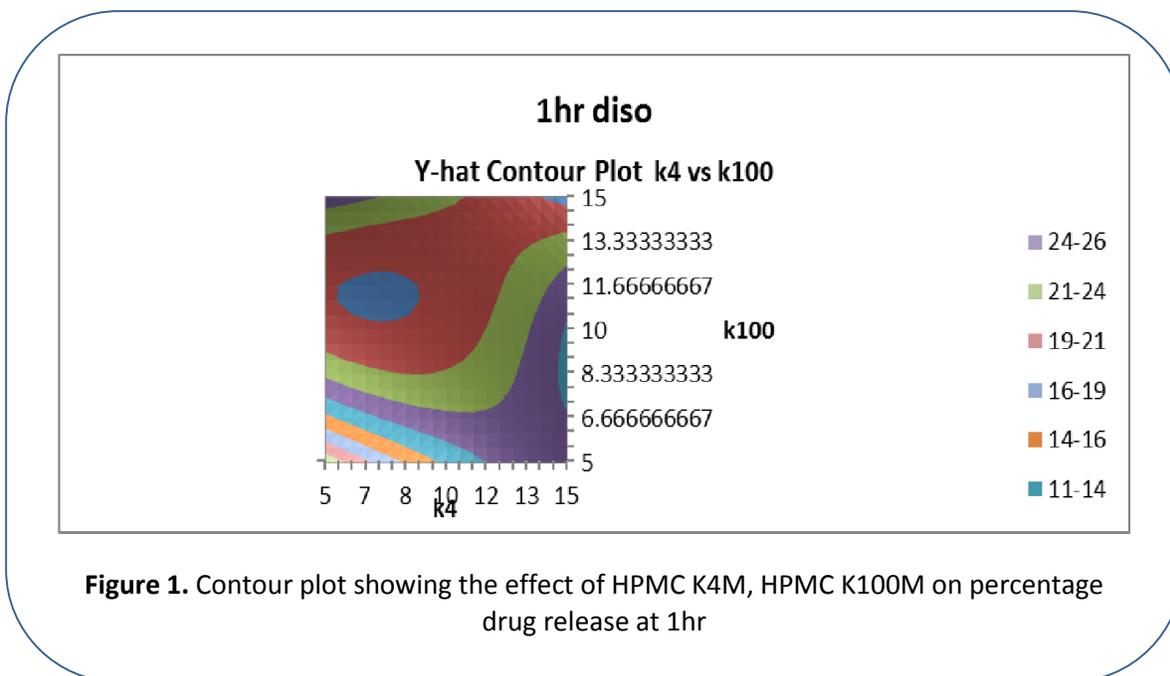| Independent variable	Level		
	Low	Medium	High
X1 Percentage of HPMC K4M	5	7.5	15
X2 Percentage of K15M	5	7.5	15
X3 Percentage of K100M	5	7.5	15
Transformed Value	-1	0	+1
Dependent variables			
Y1 amount of drug release at 1h			
Y2 Amount of drug release at 5 h			
Y3 Amount of drug release at 24 h			

Figure 1. Contour plot showing the effect of HPMC K4M, HPMC K100M on percentage drug release at 1hr
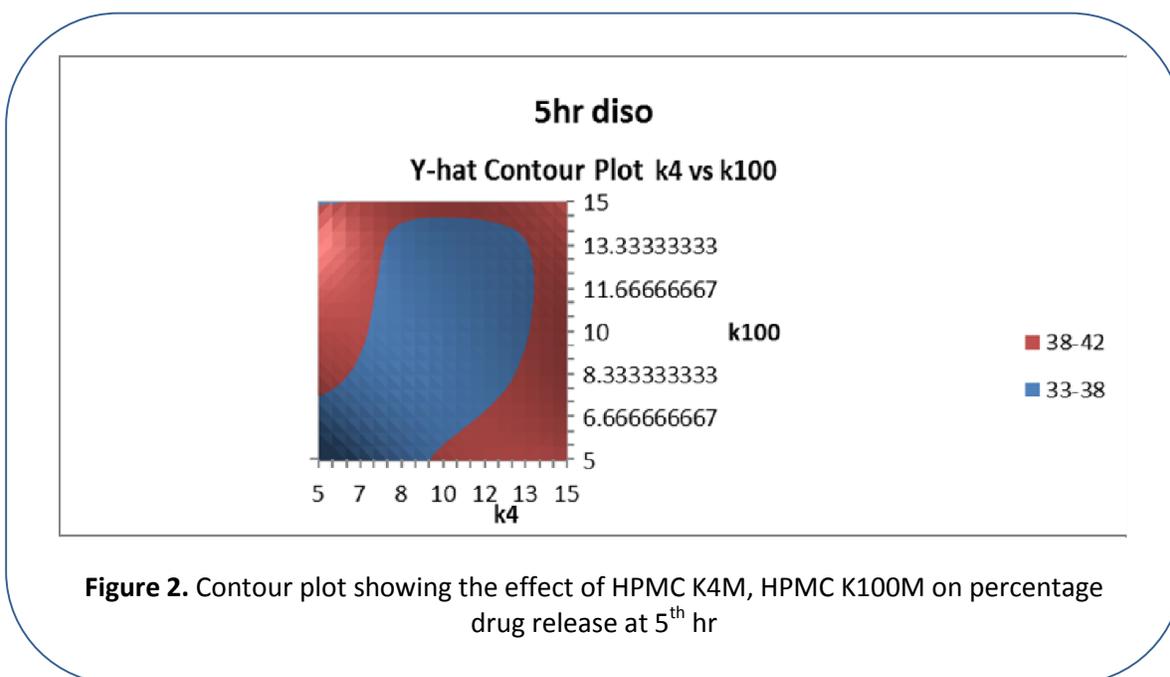
Y Contour k4 vs k100

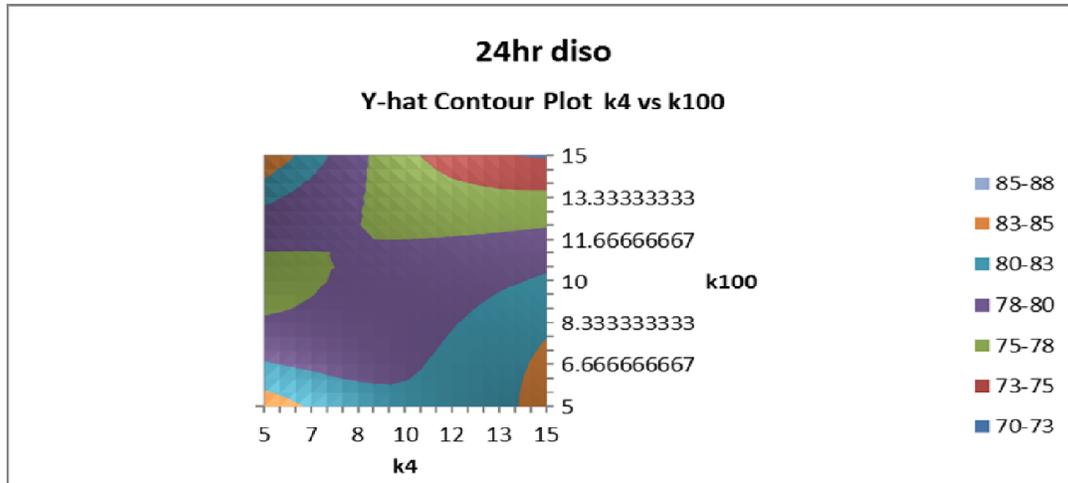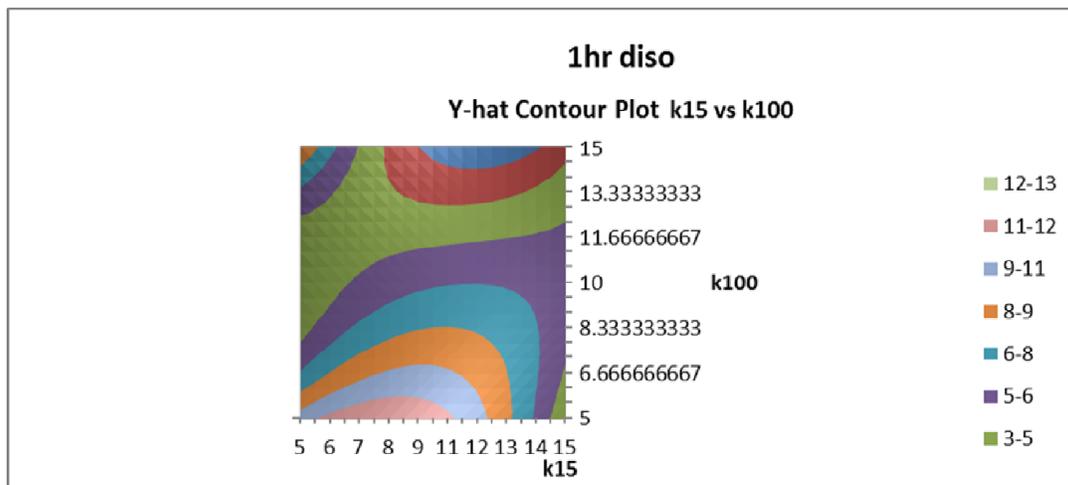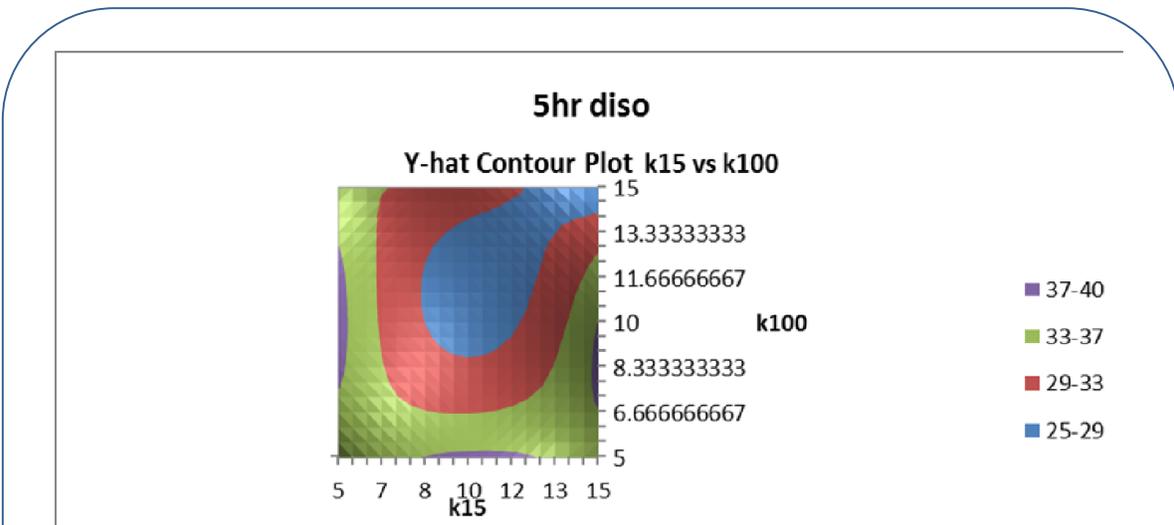**Figure 2.** Contour plot showing the effect of HPMC K4M, HPMC K100M on percentage drug release at 5th hr
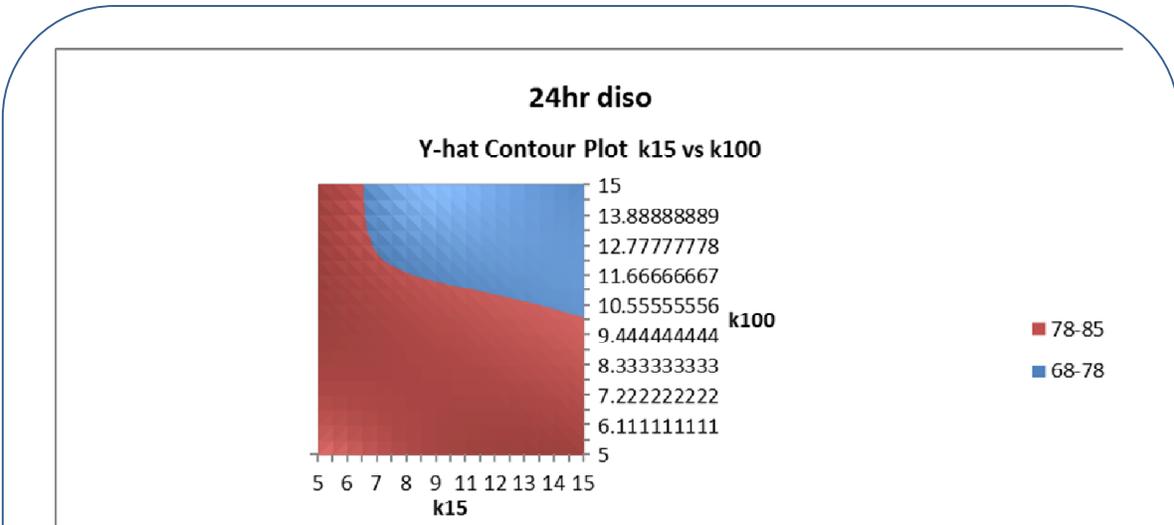
24hr diso
Y-hat Contour Plot k4 vs k100

Figure 3. Contour plot showing the effect of HPMC K4M, HPMC K100M on percentage drug release at 24th hr

1hr diso
Y-hat Contour Plot k15 vs k100

Figure 4. Contour plot showing the effect of HPMC K15M, HPMC K100M on percentage drug release at 1hr

Y Contour k15 vs k100

Figure 5. Contour plot showing the effect of HPMC K15M, HPMC K100M on percentage drug release at 5th hr

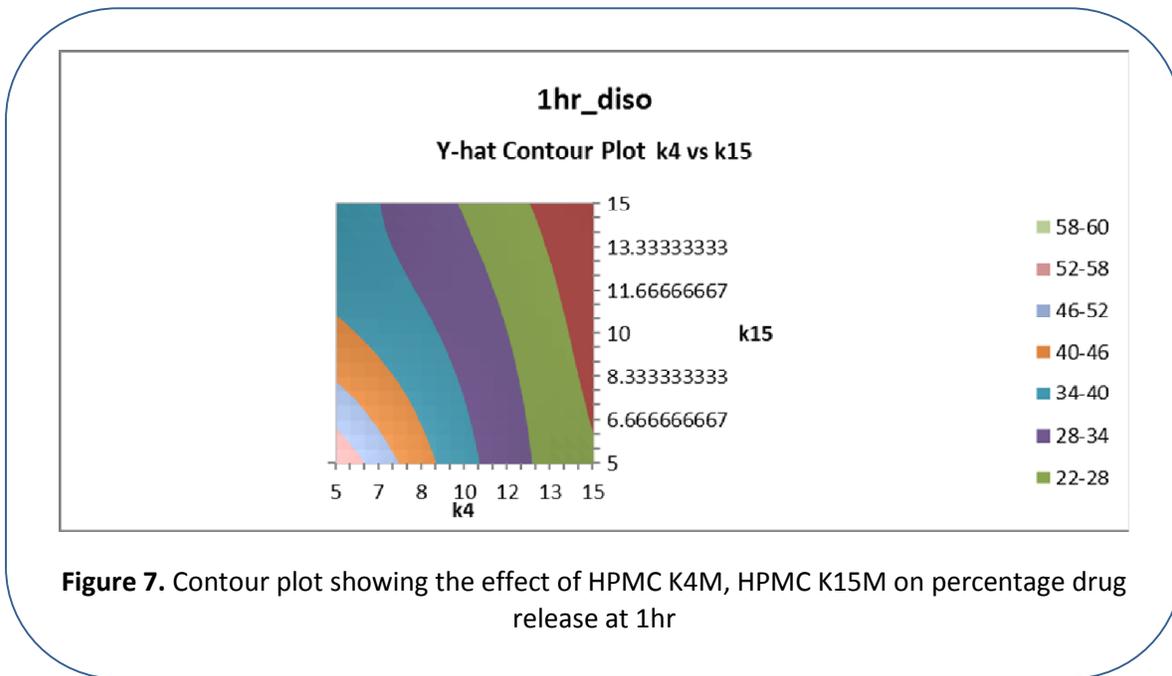**Figure 6.** Contour plot showing the effect of HPMC K15M, HPMC K100M on percentage drug release at 24th hr

Figure 7. Contour plot showing the effect of HPMC K4M, HPMC K15M on percentage drug release at 1hr
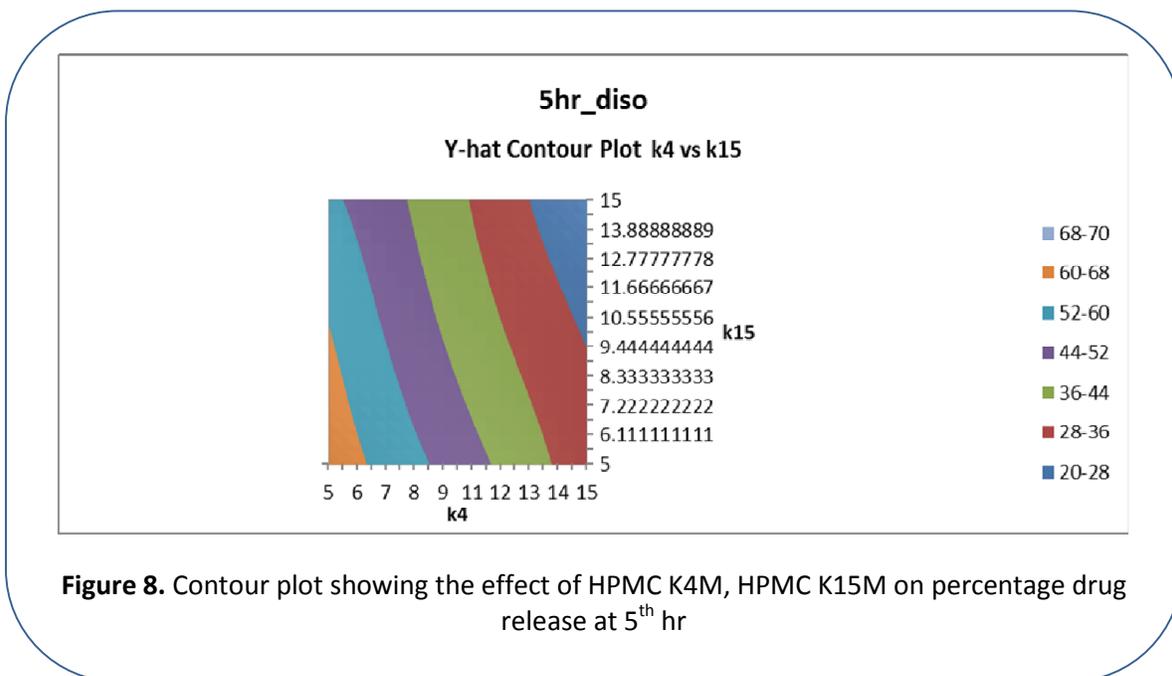
Y Contour k4 vs k15

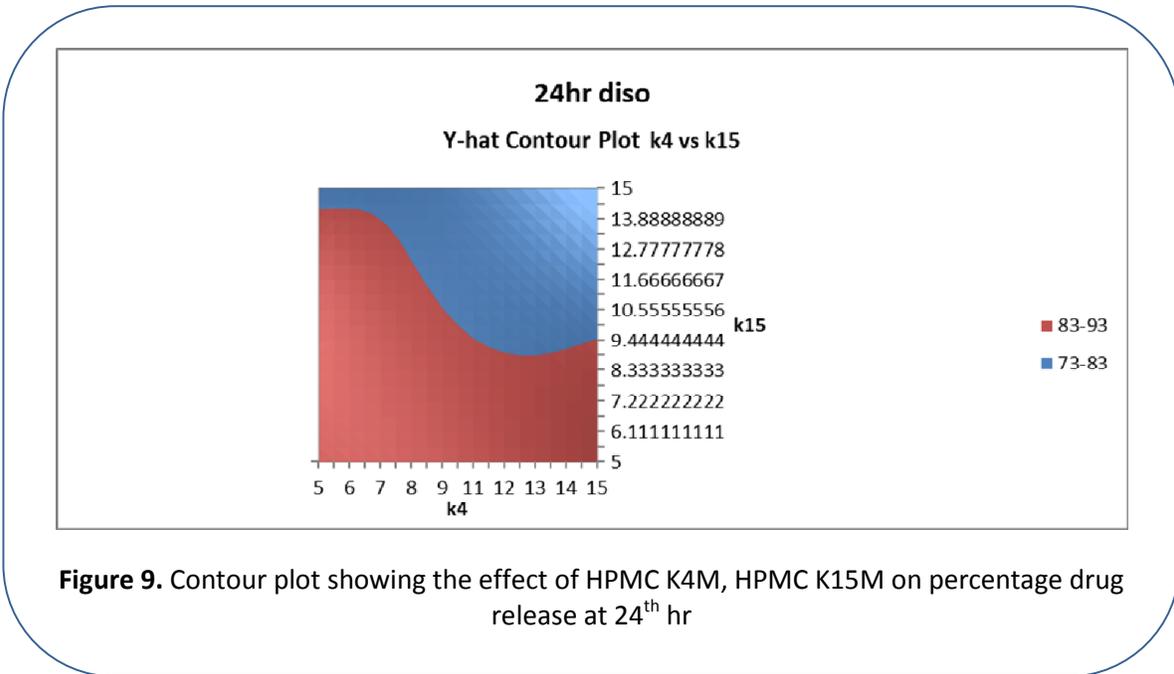**Figure 8.** Contour plot showing the effect of HPMC K4M, HPMC K15M on percentage drug release at 5th hr

Figure 9. Contour plot showing the effect of HPMC K4M, HPMC K15M on percentage drug release at 24th hr