American Journal of Advanced Drug Delivery

www.ajadd.co.uk

Original Article

Effect of Combination of Methocel K4M, K15M And K100M on the *In Vitro* Release of Aripiprazole from Controlled Release Tablets Using Full Factorial Design of Experiments

Vinay Umesh Rao*, E. Sangeetha, M. Sudhakar

Malla Reddy College of Pharmacy, Secunderabad, India

Date of Receipt- 31/05/2013
Date of Revision- 06/06/2013
Date of Acceptance- 10/06/2013

Address for Correspondence
Malla Reddy College of Pharmacy, Secunderabad, India

E-mail:
vinayrao68@gmail.com

ABSTRACT

The effect of three different viscosity grades on the in vitro dissolution profile of Aripiprazole controlled release tablets was studied. The study was carried out using full factorial design of experiments. The release rate of 5 to 6 mg%/ hour was targeted and the effect of the polymers on drug release over 24 hours was evaluated at the total polymer level between 30% and 45%. The DOE experiments have shown that when the combination of polymer is used, the total polymer concentration should be in a narrow range of 32.4% w/w to 37.5% w/w in order to achieve the target dissolution profile.

Keywords: Aripiprazole, Once a week formulation, Design of Experiments (DOE), Release rate kinetics

INTRODUCTION

Aripiprazole [1-3] is a newer generation atypical anti psychotic drug belonging to the chemical class of benzoxazole derivative. It is available in different dosage forms in the strength of 10 mg, 20 mg, and 40 mg tablets, orally disintegrating tablets and long acting parental depot preparations. The aim of the present work was to study the effect of three viscosity grades of HPMC polymers on the release rate kinetics of oral controlled release matrix type formulation of Aripiprazole. The target dissolution profile (Table 1) for a 24 hour release preparation was fixed between 5 to 6 % per hour and the effect of three levels of each of the three polymers was evaluated by measuring the in vitro dissolution in 0.1N HCl using a 3^3 full factorial design of experiments[4].

Aripiprazole is a typical BCS Class II drug with a strong blood level dependent adverse effect profile. The aim of the sustained release formulation[5] was to reduce the adverse effect intensity by bringing the drug slowly into the blood stream and at the same time to prolong the effect. The pharmacokinetics and pharmacodynamic profiles of the drug indicates that it is available for action at the receptor site for a

period as long as 72 hours from an immediate release formulation[6]. Hence the aim of this work was to try and develop a 24 hours release drug product which would have a potential for drug effect for one week.

MATERIALS AND METHODS

Chemicals and Reagents

Aripiprazole USP (EMCO Industries), HPMC K4M, HPMC K15M and HPMC k100M (Methocel, Dow Chemical's), Microcrystalline Cellulose USP (Avicel PH 102, FMC), Magnesium stearate USP (Ferro) were used. All other chemicals and reagents used were of Analytical Reagent grade and were used as such without further purification. Purified water USP was used where ever required.

Experimental

Tablets of 500 mg weight were prepared by the direct compression method[9]. The DOE levels are indicated in Table 2 and the formulation composition details are given in Table 3.

The tablets were compressed on 10.5 mm circular biconvex die/punch set using Rimek MiniPress rotary compression machine. The compression force was set in such a way that all formulations were compressed at hardness of 4 to 6 kg/cm^2. All batches were evaluated for physical parameters, assay and uniformity of content. Each batch (at n=3) was subjected to 24 hours dissolution profile in 0.1N HCl using USP Type II apparatus at 100 rpm[11]. Samples were withdrawn at 1, 2, 4, 8, 12, 16 and 20 hours interval and analyzed for % drug dissolved using UV spectrophotometric method. The release rate kinetics was calculated using the standard equations. The comparative values of dissolution at 1 hr (D1), 8 hours (D8) and 20 hours (D20) along with the rate kinetic values (%/hour) are shown in fig 2 & 3.

RESULTS & DISCUSSION

The physical properties for all batches were within acceptable values of average weight, weight variation, hardness and friability. The content uniformity and assay values were also within the range of 96.5% to 98.3%. The release rate order kinetics for each formulation was calculated and shown in Fig 1[7]. The formulations could be classified in three distinct release rates (Table 4).

The level of K4M and K100M seem to be primarily defining the rate kinetics of these formulations. In order to compare the rate and extent of the dissolution across all formulations, the drug release at 1 hr, (D1), 8 hours (D8) and 20 hours (D20) are shown in Fig 2.

The effect of viscosity grades of hydrophilic HPMC polymers when used in combination was evaluated in this study using 3^3 full factorial designs of experiments[8-12]. The D1, D8 and d20 values were fed into the DOE Pro Excel software. Sample interaction plots and the surface response plots are shown in Fig 3 to 8. The interaction plot shows a strong interaction between the polymers up to 8 hours of release. However, at 20 hours time point no apparent interaction between the three polymers is observed. The surface response plots were used to find out the range for each of the polymer within which the formulations would always meet the dissolution profile. The optimized range is given in Table 5.

This indicates that for achieving the target product profile for Aripiprazole, the three polymers have to be used in a very narrow range of between 32.4% to 37.5% total polymer content. The DOE method thus provides a very simple experimental tool to optimize the polymer range for a targeted release rate of 5 to 6 % hour. Combination of polymers of different viscosity grade help in keeping the total polymer requirement within narrow use levels.

CONCLUSION

The 3^3 design of experiments provides a simple tool for studying how the three grades of HPMC polymers affect the release rate of a poorly soluble drug like Aripiprazole. A design space has been established within which the formulation would always comply with the dissolution specifications set for a 24 hours release formulation. It has been postulated that for Aripiprazole, such a release profile would result in once a week formulation of the drug substance. Further in vivo studies to substantiate these findings are under progress in our laboratory.

REFERENCES

1. Bachmann CJ, Rieger-Gies A, Heinzel-Gutenbrunner M, Hiemke C, Remschmidt H, Theisen FM. Large variability of Aripiprazole and dehydroaripiprazole serum concentrations in adolescent patients with schizophrenia. *Therapeutic Drug Monitoring*. 2008; 30(4):462–6. [PubMed]
2. Bachmann CJ, Nicksch B, de Lange D, Theisen FM, Remschmidt H. Repeated creatine kinase elevation under treatment with quetiapine, clozapine, and aripiprazole in an adolescent. *Journal of Clinical Psychopharmacology*. 2007; 27(6):710–711. [PubMed]
3. Barrett E, Blonde L, Clement S, Davis J, Devlin J, Kane J, *et al*. Consensus development conference on antipsychotic drugs and obesity and diabetes. *Diabetes Care*. 2004; 27:596–601. [PubMed]
4. Design of experiments (doe) tutorialwww.agilent.com/find/eesof-doe.
5. Chien YW. “Controlled and modulated release drug delivery system”; In: Swarbrick J, Balyan JC. Encyclopedia of Pharmaceutical Technology; 1990; Marcel Dekker, New York, 281-313.
6. www.rxlist.com/abilify
7. Xiang A, McHugh A J. A generalized diffusion–dissolution model for drug release from rigid polymer membrane matrices *MembrSci* 2011; 366:104–115
8. Maderuelo C, Zarzuelo A, Lanao J M. Critical factors in the release of drugs from sustained Release hydrophilic matrices. *J Control Release*, 2011; 154: 2–19.
9. Hemnani M, Patel U, Patel G, Daslaniya D, Shah A, Bhimani B. Matrix tablet: A tool of Controlled drug delivery. *American Journal of Pharm Tech Research*, 2011; 1(4):127-143.
10. Barakat N A S, Elbagory I M, Almurshedi A S. Controlled-Release Carbamazepine Granules and Tablets Comprising Lipophilic and Hydrophilic Matrix Components. *AAPS PharmSciTech* 2008; 9 (4): 1054-1062.
11. Das N G and Das. Controlled-Release of Oral Dosage Forms, Formulation, Fill & Finish, 2003. Available fromhttp://www.pharmtech.com.
12. Tiara S B, Rajabi-Siahboomi A R. In: M. Kewal, K. Jain editors, *Drug Delivery Systems*; 2008; 217–243.

 ISSN-2321-547X

Table 1. Target product profile

TIME(HOURS)	MEAN % DRUG DISSOLVED
1	0-10%
2	8-15%
4	18-30%
8	50-65%
12	60-80%
20	90-100%

Table 2. DOE levels

HPMC GRADE	LOW LEVEL (30% OF TABLET WT)	MEDIUM LEVEL (37.5% OF TABLET WT)	HIGH LEVEL (45% OF TABLET WT)
HPMC-K4M	10%	12.5%	15%
HPMC-K15M	10%	12.5%	15%
HPMC-K100M	10%	12.5%	15%

Table 3. Unit Composition Formula

FORMULATION	ARIPIPRAZOLE (mg)	HPMC K4M (mg)	HPMC K15M (mg)	HPMC K100M (mg)	AVICEL PH102 (mg)	MAGNESIUM STEARATE (mg)
F1(HHH)	10	75	75	75	260	5
F2(HHM)	10	75	75	62.5	272.5	5
F3(HHL)	10	75	75	50	285	5
F4(HMH)	10	75	62.5	75	272.5	5
F5(HMM)	10	75	62.5	62.5	285	5
F6(HML)	10	75	62.5	50	297.5	5
F7(HLH)	10	75	50	75	285	5
F8(HLM)	10	75	50	62.5	297	5
F9(HLL)	10	75	50	50	310	5
F10(MHH)	10	62.5	75	75	272.5	5
F11(MHM)	10	62.5	75	62.5	285	5
F12(MHL)	10	62.5	75	50	297.5	5
F13(MMH)	10	62.5	62.5	75	285	5
F14(MMM)	10	62.5	62.5	62.5	297.5	5
F15(MML)	10	62.5	62.5	50	310	5
F16(MLH)	10	62.5	50	75	297.5	5
F17(MLM)	10	62.5	50	62.5	310	5
F18(MLL)	10	62.5	50	50	322.5	5
F19(LHH)	10	50	75	75	285	5
F20(LHM)	10	50	75	62.5	297.5	5
F21(LHL)	10	50	75	50	310	5
F22(LMH)	10	50	62.5	75	297.5	5
F23(LMM)	10	50	62.5	62.5	310	5
F24(LML)	10	50	62.5	50	322.5	5
F25(LLH)	10	50	50	75	310	5
F26(LLM)	10	50	50	62.5	322.5	5
F27(LLL)	10	50	50	50	335	5

Abbreviations-

HHH-High High High,
HHM-High High Medium,
HHL-High High Low,
HMH-High Medium High,
HMM-High Medium Medium,
HML-High Medium Low,
HLH-High Low High,
HLM-High Low Medium,
HLL-High Low Low,
MHH-Medium High High,
MHM-Medium High Medium,
MHL-Medium High Low,
MMH-Medium Medium High,
MMM-Medium Medium Medium,
MML-Medium Medium Low,
MLH-Medium Low High,
MLM-Medium Low Medium,
MLL-Medium Low Low,
LHH-Low High High,
LHM-Low High Medium,
LHL-Low High Low,
LMH-Low Medium High,
LMM-Low Medium Medium,
LML-Low Medium Low,
LLH-Low Low High,
LLM-Low Low Medium,
LLL-Low Low Low.

Table 4. Classification of Formulations based on Release rates (%/hour)

Release rate 1 (2.2-4.9%/hour)	Release rate 2 (5.0to 6.0 % /hour)	Release rate 3 (>6.0%/hour)
HHH	MMM	LLL
HHM	MML	
HMH	LML	
HHL	LLM	
HMM	LMM	
HLH		
HML		
HLL		
MHM		
MHL		
MMH		
MLH		
LHM		
LHL		
LMH		
LLH		
HLM		
MHH		
MLM		
MLL		
LHH		

Table 5. Optimized Range of Polymers

HPMC Grade	Low Level	High Level
K4M	10.8	12.5
K15M	10.8	12.5
K100M	10.8	12.5

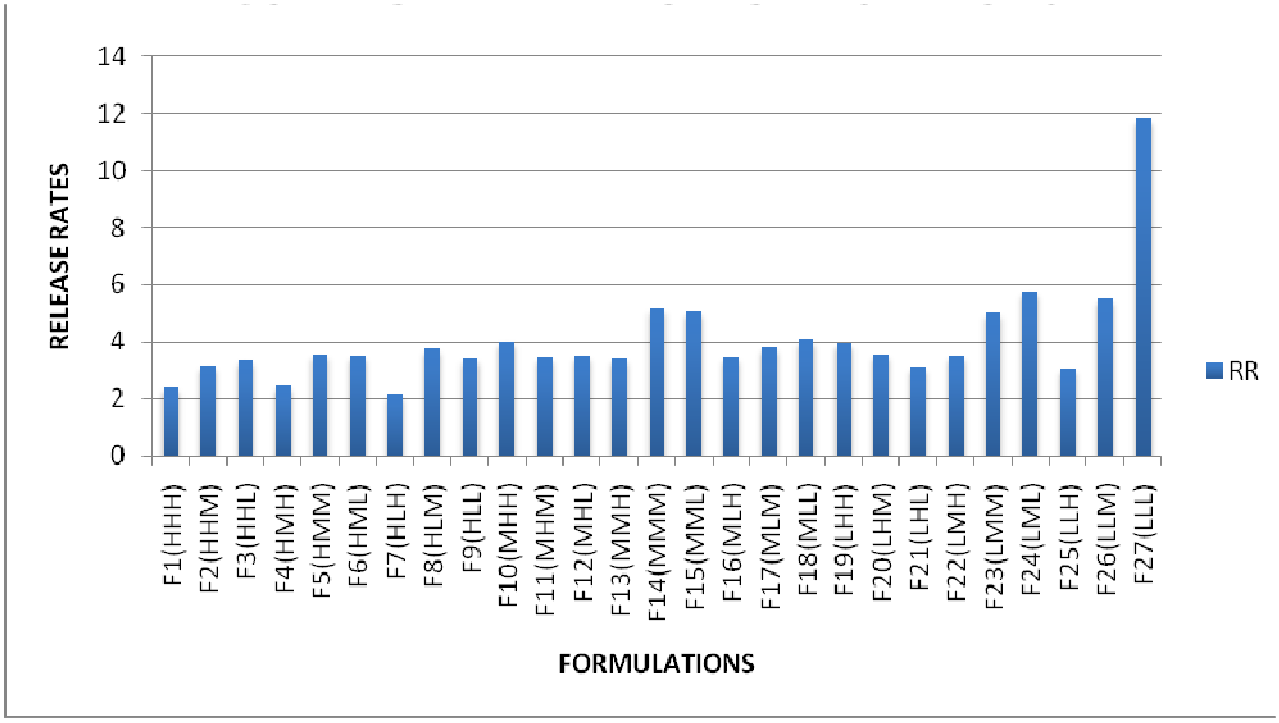

Figure.1. Release rate values (%/hour) for Aripiprazole Controlled Release Tablets

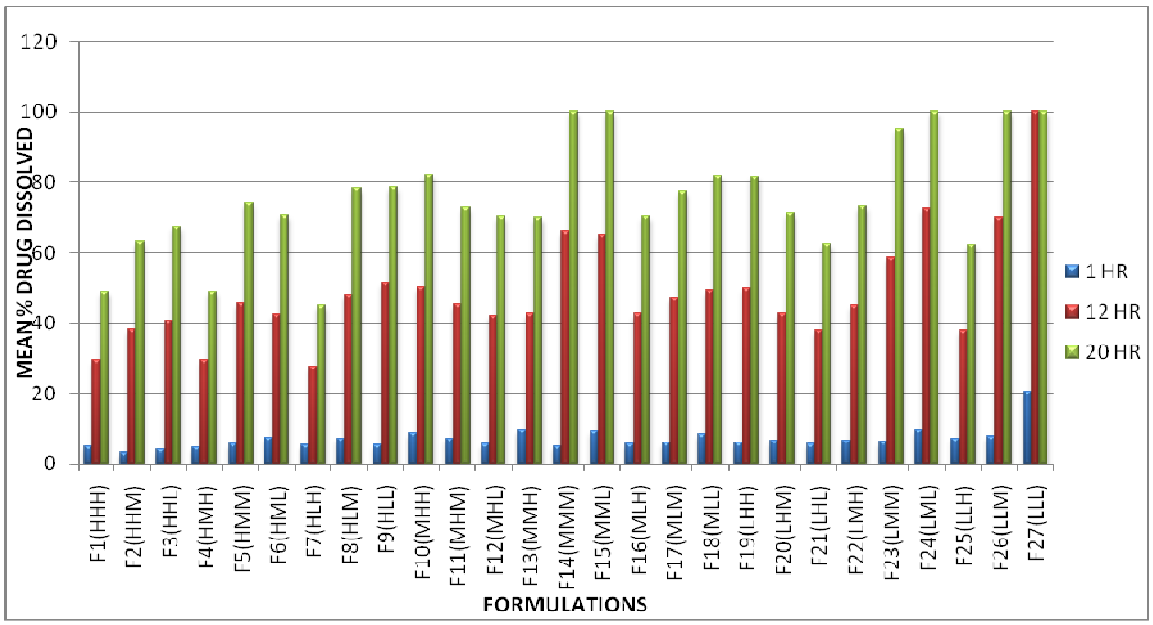

Figure.2. Comparative values of dissolution at 1 hr (D1), 8 hr (D8), 20 hr (D20).

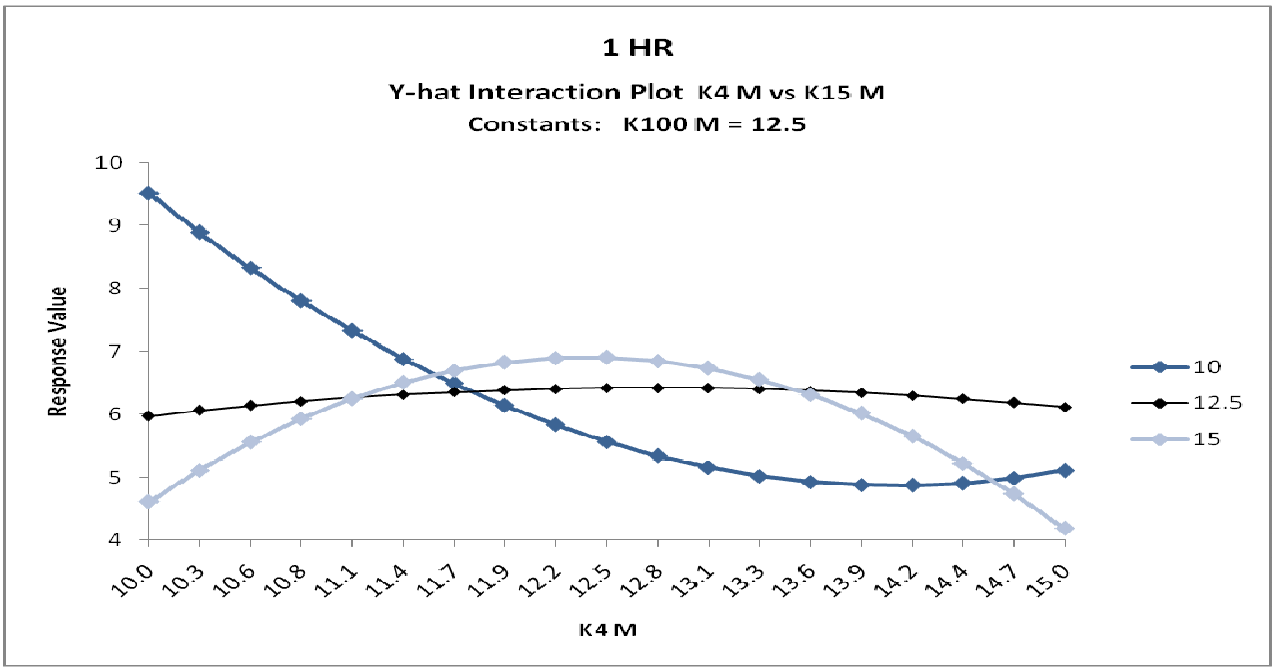

Figure.3. Interaction plot at 1 hr

 ISSN-2321-547X

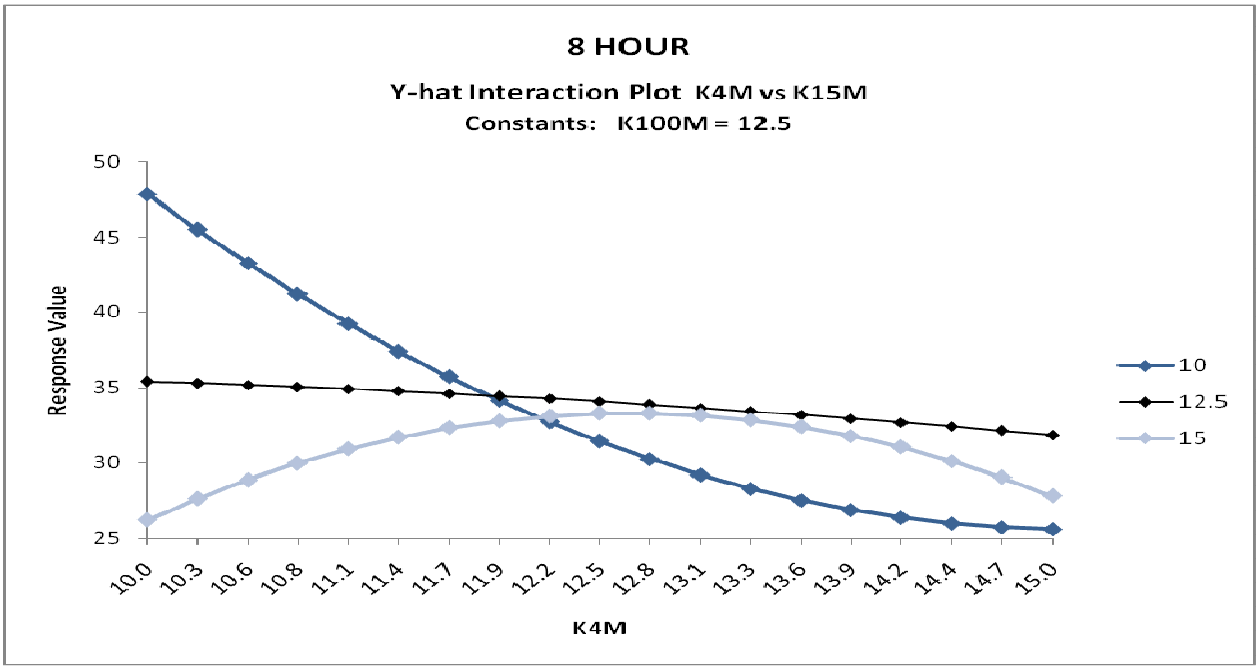

Figure.4. Interaction plots at 8 hrs

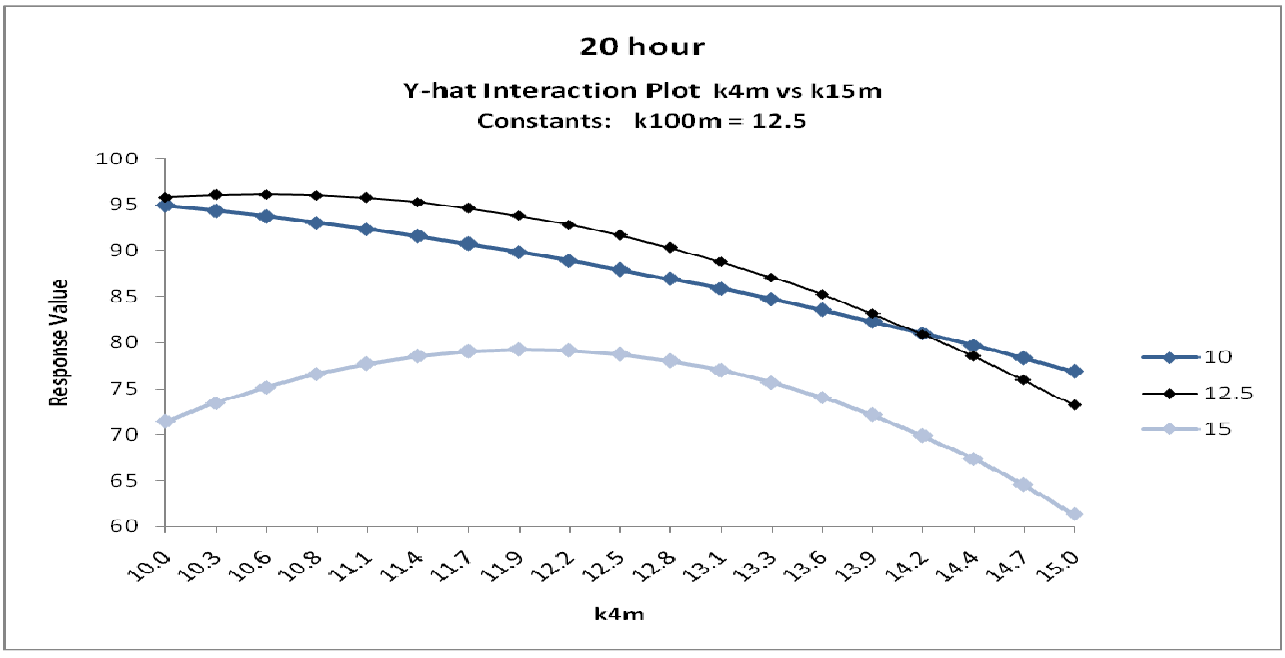

Figure.5. Interaction plots at 20 hrs

 ISSN-2321-547X

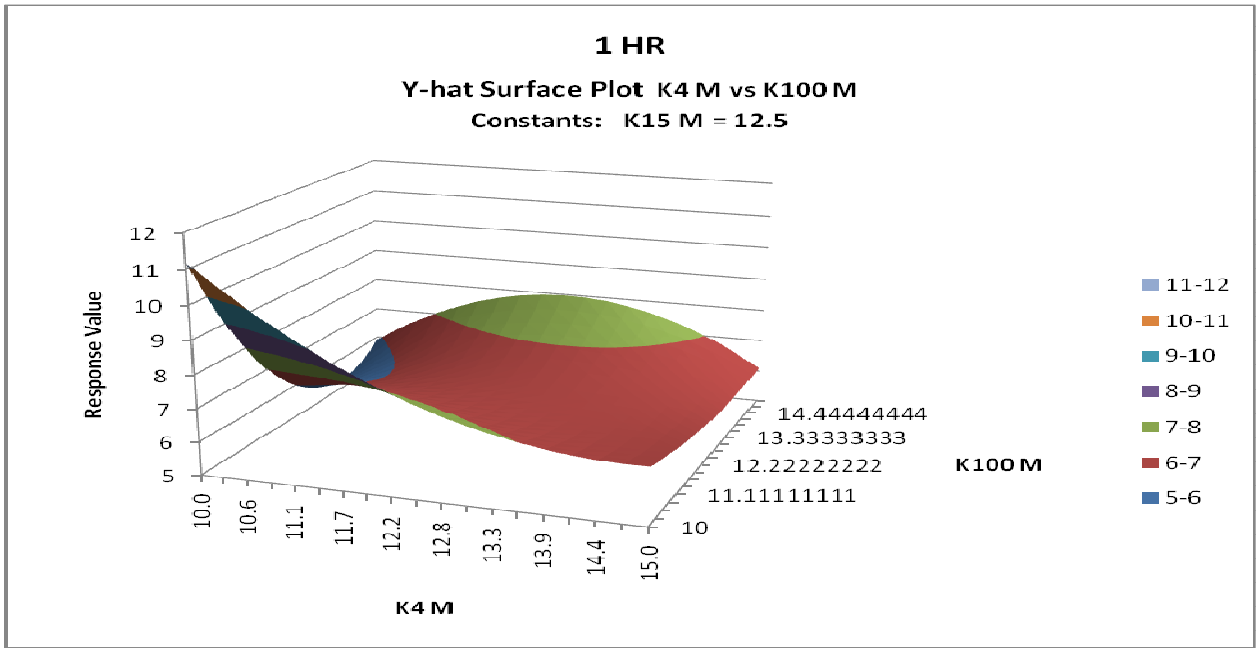

Figure.6. Surface response plots at 1 hr

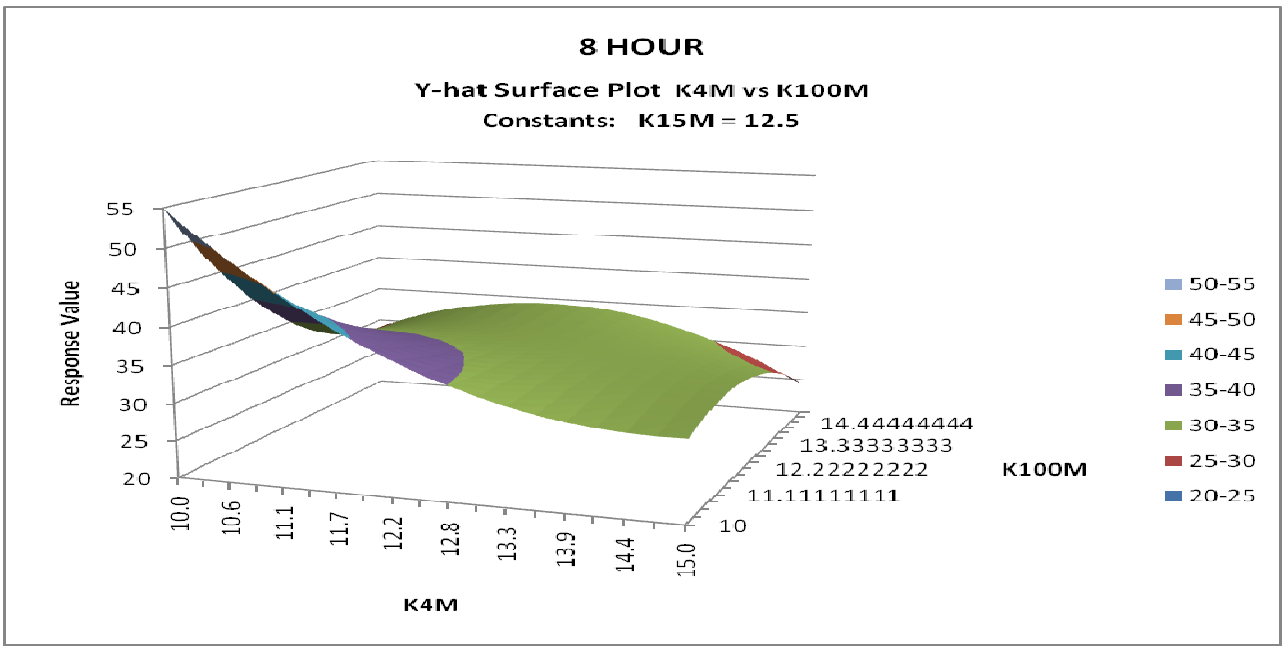

Figure.7. Surface response plots at 8 hrs when k15M is constant

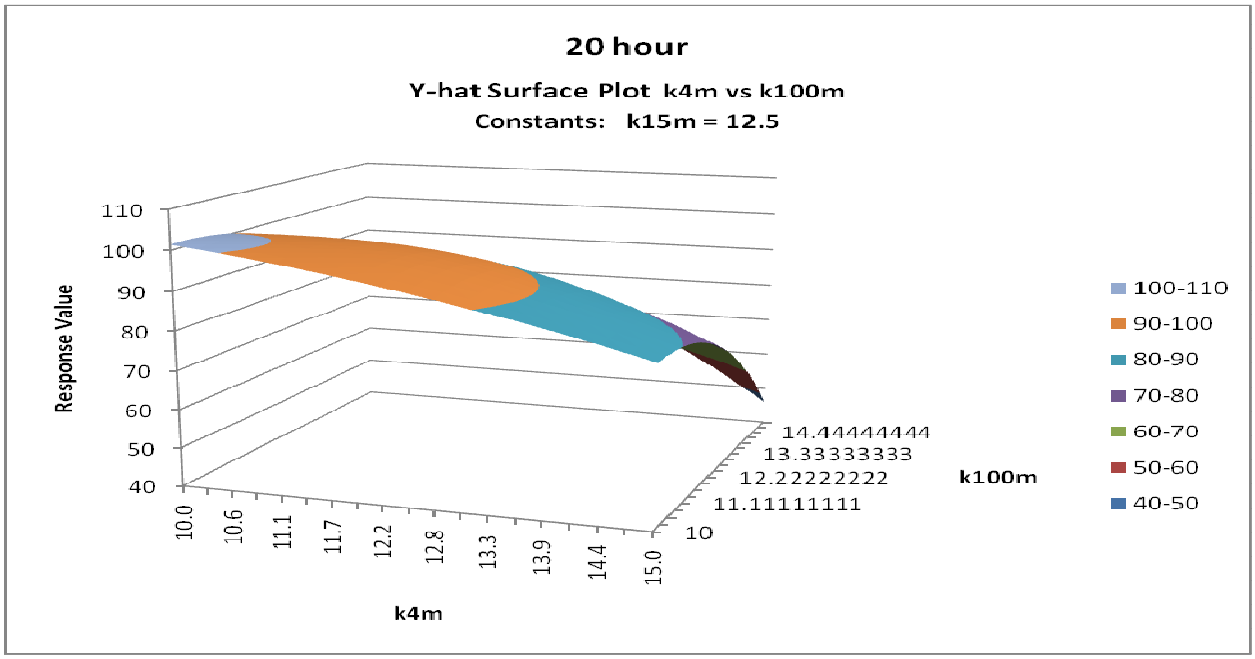

Figure.8. Surface response plots at 20 hrs when k15M is constant