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STUDY ON THE EFFECT OF ISOPROPYL ALCOHOL AS GRANULATING FLUID ON DRUG RELEASE FROM ETHYLCELLULOSE MATRIX TABLET

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ABSTRACT

A study was performed to check the effect of variation in the amount of ethylcellulose (EC), crospovidone (CP) and isopropyl alcohol (IPA) on drug release profile by designing an oral matrix tablet using partial factorial design on fifteen formulations (F1-F15). On the basis of theoretical aspect EC as a hydrophobic polymer retards the drug release, CP as a hydrating agent enhances water uptake and increases dissolution profile, whereas, IPA as a granulating fluid interacts with EC to form gel and effectively entrap the dispersed drug particles on drying. The study that we conducted showed similar results. Decrease in drug release profile was observed with the increase in the amount of EC. Increase in the amount in the drug release profile was seen with increase in amount of CP. Besides, the drug release profile decreased with the increase in the amount of IPA upto a certain point and on further increment, the released profile increased. The release pattern can be attributed to the individual and interacting effects of EC, CP and IPA. The formulation may be optimized to use for many water sensitive drugs by the use of hydrophobic polymers like ethylcellulose.

Keywords: Ethylcellulose, Crospovidone, Isopropyl Alcohol, Matrix Tablet

INTRODUCTION

Peroral sustained release dosage forms are modified dosage forms meant to be administered orally. They are designed to maintain a predetermined constant plasma

concentration of drug. Matrix tablets are sustained release dosage forms considered a breakthrough for novel drug delivery system (NDDS) **[1]**.

Ethylcellulose has been varied for investigation from use as a dry binder to wet granulating mixture by dissolving in the non-aqueous solvent isopropyl alcohol. Furthermore, the effect of a pore-forming agent viz. crospovidone has been evaluated in the research.

MATERIALS AND METHODS

Materials

Salicylic acid was used as a model drug. Isopropyl alcohol, crospovidone and ethylcellulose were the subject excipents. Besides, Povidone, Dibasic calcium phosphate and Magnesium stearate were also used in the formulation.

Methods

Experimental Design

Partial factorial design was used for designing of experiment. The three independent factors considered were ethylcellulose (X1), crospovidone (X2) and isopropyl alcohol (X3) at three level i.e. +1, 0 and -1. The formulation were evaluated with four response variables viz: percentage of drug release in the first hour (Y1), second (Y2), fourth (Y4) and eighth (Y8) hour. A total of 15 formulations were prepared (F1 to F15) by Box Behnken experimental design using STATGRAPHICS Centurion XV. The independent factors along with their levels are given in **Table 1**.

Calibration Curve and assay

A stock solution (100 µg/ml) of salicylic acid was prepared in water. 5, 10, 12.5, 20 and 30 µg/ml solutions were prepared from stock solution. The absorbance of each solution was measured at 295 nm taking distilled water as a blank.

Powder equivalent to 100 mg salicylic acid was weighed and dissolved in approximately 5 ml of ethanol using sonicator. The solution was appropriately diluted with distilled water. The prepared solution was finally filtered. The drug content was calculated using formula given by calibration curve,

$$X = \frac{Y - 0.001}{0.026}$$

Where: X=Concentration (µg/ml);
Y=Absorbance

In-Vitro Dissolution Study

Dissolution study of Salicylic acid tablet was performed with six stage dissolution test apparatus (USP Type 1) at 75 rpm using 900 ml water as dissolution medium maintained at 37±0.5 °C. Sample (10ml) was withdrawn in an hourly interval for 8 hour. The samples were replaced by an equal volume of dissolution medium to maintain the sink condition. The samples were filtered and

analyzed for the drug content using UV spectrophotometer at 295 nm after suitable dilution.

RESULT

The prepared dosage forms were evaluated for various physicochemical properties.

The experimental runs for 15 formulations are given in **Table 2.** The obtained regression relationship is in the form (Y= b0+ b1X1 + b2X2 + b3X3 + b1b2X1X3 + b2b3X2X3) **Equation 1**. The adjusted R^2 statistic was used for comparing and selecting best fit model for each response variable including or excluding different estimates for main and interacting factors. Selected mathematical models for the response variables are given in **Table 3**.

Analysis of variance (ANOVA) of estimate for each of the factors on response variable (**Table 4)** shows that among the six different factors i.e. three individual (X1, X2 and X3) and three interacting (X1X2, X1X3 and X2X3), estimate for X3, X1X3 and X2X3 were significant for response Y1; X1, X2, X3, X1X3 and X2X3 were significant for response Y2; X1, X3, and X1X3 were significant for response Y4; and X1, X3, and X1X3 were significant for response Y8. A positive sign of estimate **(Table 4)** represent a positive effects i.e. increase in response value with increase in independent factor while a negative sign indicates vice versa.

DISCUSSION

The variation in the drug release profile of various formulations is shown in the **Figure 1.** The variation in the drug release profile can be attributed to varying amount of ethyl cellulose, crospovidone, isopropyl alcohol and their interacting effects.

Effect of Formulation Variable on Release Property (Y1, Y2, Y4 and Y8)

Effect of EC (X1)

Analysis of variance (ANOVA) of estimate for factor X1 on response variable Y1 to Y8 shows that it has significant effect on the responses Y2 to Y8 (**Table 4**). The negative value of the estimate for X1 in responses Y2 to Y8 implies that drug release decreases with increase in amount of X1 from -1 to +1 level (0 mg to 10 mg) which are shown in (**Figure 2**). This decrease in drug release can be related to the hydrophobic nature of EC. Since, EC is a hydrophobic polymer it prevents penetration of water inside the matrix and hence retards the drug dissolution. **[2]** Furthermore, EC also increases inter particulate bonding during compaction of granules, thus preventing erosion of tablets. **[3]**. The insignificant role of EC on controlling the drug release at first hour may be related to the drug molecules at the surface

of tablet i.e. the drug molecules that are not entrapped in matrix of EC. These drugs when come in contact to dissolution medium release easily without any significant controlling effect of EC. **[4]** Thus, the amount of drug released in first hour depends merely on amount of the drug that is found at the surface of the tablet.

Effect of CP (X2)

ANOVA of estimate for the factor X2 on response variable Y1 to Y8 shows that it has significant effect on the response Y2 (**Table 4**). The positive value of the estimate for X2 in response Y2 implies that drug release increases with increase in the amount of X2 from -1 to +1 (0 mg to 7.5 mg) which is shown in (**Figure 2)**. The increase in the drug release profile can be attributed to the property of CP that CP is a water insoluble polymer which exhibits swelling property, high capillary activity and pronounced hydration capacity. Increased concentration of CP results in increased drug release rate due to increase in water uptake which can result in increased driving force of drug release. **[5]**

Effect of IPA (X3)

ANOVA of estimate for the factor X3 on response variable Y1 to Y8 shows that it has significant effect on the response Y1 to Y8 (**Table 4**). The negative value of the estimate for X3 in response Y1 to Y8 implies that drug release decreases with increase in the amount of X3 from -1 to +1 (0ml to 5ml) which are shown in (**Figure 2)**. This can be explained by the property of Isopropyl alcohol that it is a non polar solvent and has been used as a granulating fluid. In the process of granulation, there are 4 phases: pendular, funicular, capillary and suspension/droplet. These stages vary with the amount of granulating fluid being added. The most stable granules are formed at capillary stage where the arrangement of particles is most compact. Upon increasing the granulating fluid, the compactness is lost as spaces between particles are replaced by fluid itself. Compactness of granules remains intact when dried at capillary stage but in suspension stage when the fluid is evaporated, it leaves behind the larger inter particulate voids. Larger surface area will be available for the penetration of water due to larger voids which results in more drug release. **[6, 7]**

Interacting Effect of EC (X1) With Varying Range of IPA (X3)

ANOVA of estimate for interacting factors on response variable Y1 to Y8 shows that it has significant effect on X1X3 (EC and IPA) (**Table 4**). The negative value of the estimate for the interacting effect X1X3 in responses Y1 to Y8 implies that drug release decreases due to the interaction of EC and IPA. The

interacting effect between EC and IPA in first hour, second hour, fourth hour and eighth hour are shown in **(Figure 3)**.

As shown in **Figure 3**, in the first hour, when the amount of IPA is low, increase in the amount of EC didn't contribute significantly on the drug release profile. This may be explained by the property that the EC can entrap the drug particles only when the drug particles are granulated in gel form of EC and subsequently dried. **[8]** EC forms the gel after interaction with IPA. If drug particles are dispersed in the gel and dried, the drug particles can effectively be entrapped within the matrix. When the amount of IPA is low, EC will not have sufficient amount of granulating fluid to interact and form gel. So, even though the dispersion is dried the drug particles are not effectively entrapped. Due to this reason, the drug particles which are not entrapped are released and the effect of increase in the amount of EC cannot be seen in the drug release profile.

Likewise, from **Figure 3** when the amount of IPA is higher, increase in EC caused significant decrease in the drug release profile in different hours. This can be explained by the property that EC with sufficient amount of IPA can interact properly to form gel and thus entrap the dispersed drug particles in the optimal drying. **[8]** At higher amount of IPA, EC can interact with IPA and form gel. When the drug particles granulated with formed gel are dried at optimal temperature and time, the drug molecules can effectively be entrapped within the hydrophobic matrix of EC. Also, the increase in amount of EC content in sufficient amount of IPA provides a more tortuous pathway and a less porous tablet. **[9]** The decrease in the drug release profile with incorporation of higher amount of EC can be attributed to the decreased penetration of the solvent molecules in the presence of hydrophobic polymer leading to decreased diffusion of the drug from the matrix. **[4]**

Interacting of CP (X2) with Varying Range of IPA (X3)

ANOVA of estimate for interacting factor X2X3 (CP and IPA) on response variable Y1 to Y8 shows that it has significant effect on the response Y1 and Y2 (**Table 4**). The negative value of the estimate for the interacting effect X2X3 in responses Y1 and Y2 implies that drug release decreases due to the interaction of CP and IPA. The interacting effect between CP and IPA in first hour, and second hour are shown in contour plot **Figure 4**.

From the **Figure 4** when the amount of IPA is kept at low level, gradual increase in the amount of CP caused slight increase in drug release profile. This can be explained with the

help of property of CP. It shows rapid capillary activity and pronounced hydration with little tendency to gel formation. In addition, with increase in the amount of CP there is decrease in the wetting time leading to higher dissolution rate owing to fast hydration of tablet. **[10]** This contributes in forming the path way for the penetration of water to the inner matrix of the tablet. Thus, as CP comes in contact with the dissolution medium it rapidly uptakes the water. The dissolution medium rapidly dissolves the drug particles and contributes to the higher amount of drug release.

From the **Figure 3,** on the other hand, at the intermediate amount of IPA, the drug release was constant even when CP was increased. At higher amount of IPA, gradual decrease in drug release was seen with increase in amount of CP. These might be because amount of CP may have exceeded the optimal point.

No significant interacting effect of IPA and CP was found in 3rd to 8th hour.

Interacting effect of IPA (X3) with varying range of EC (X1)

ANOVA of estimate for interacting factor X3X1 (IPA and EC) on response variable Y1 to Y8 shows that it has significant effect (**Table 4**). The negative value of the estimate for the interacting effect X1X3 in responses Y1 to Y8 implies that drug release decrease due to the interaction of EC and IPA. The interacting effect between EC and IPA in first hour, second hour, fourth hour and eighth hour are shown in contour plot **Figure 3**.

As shown in the **Figure 3**, when the amount of EC is low, slight increases in IPA amount caused rapid decrease in the drug release profile. Further increase in the amount of IPA at the same low amount of EC resulted in the constant drug release profile. As the amount of IPA is further increased, increase in the drug release profile was seen.

This can be explained by the interacting effect of EC and IPA that wet granulation with IPA results in formation of granules which are coated with EC. As the IPA amount is gradually increased, interaction between the EC and IPA results in the gel formation. On drying, the dispersed drug particles are entrapped within the gel resulting in formation of granules. The capillary stage of the granule is the most stable stage resulting into its maximum strength. This results in the decrease in the drug release profile. **[6, 7]**

Constant release of drug, even with increasing amount of IPA (at intermediate level) at low amount of EC can be explained by the property of IPA that, optimal point of IPA that can be used for the wet granulation may have reached i.e capillary stage have reached.

On further increase in the amount IPA (at higher level) with EC still at low amount, increase in the drug release is seen. It can be explained by the property of IPA that, excess use of the granulating fluid shifts the granules from capillary stage to suspension stage. So drying the suspension phase of granules leads to formation of larger inter particulate voids. Dissolution medium can easily penetrate through the void present; dissolve the drug, resulting in higher drug release profile**. [6, 7]**

Whereas from **Figure 3**, as the amount of EC is fixed higher, increase in the amount of IPA value caused significant decrease in the drug release profile. Sufficient amount of EC interacts with IPA to form effective hydrophobic matrix tablet when dried and compressed. The presence of the hydrophobic matrix attributes to decreased penetration of the solvent. Retardation of the penetration of dissolution medium leads to decreased diffusion of the drug from the matrix. **[11]**

CONCLUSION

From the study, it can be concluded that different drug release profile from the core of the tablet can be obtained by varying the amount of EC as hydrophobic polymer, IPA as granulating fluid and CP as a dissolution agent.

Increase in the amount of EC, showed a retarded drug release by decreasing the penetration of solvent molecule due to its hydrophobic nature. In case of IPA, when IPA used was higher (F1, F4, F6, F12), the dissolution rate is slow than in which IPA used is low (F3, F8, F9, F15). Optimum IPA concentration used can form stable granules of capillary stage and control the release. CP is used as a wetting agent so that wetting of drug is enhanced, increasing the drug dissolution. Thus, the individual effect and properties of EC, CP and IPA can be optimized for the formulation and control release of hydrophobic matrix drug.

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REFERENCES

[1] Uttam Mandal VG, Formulation and Optimization of Sustained Release Matrix Tablet of Metformin HCL 500 mg Using Response Surface Methodology, Kolkata, India: Bioequivalence Study Centre, Department of Pharmaceutical Technology, 2007.

[2] Garekani HA, Sadeghi R and Sadeghi F, Comparision of Ethylcellulose Matrix Characteristics Prepared By Solid Dispersion Technique or Physical Mixing,

Mashhad, Iran: School of Pharmacy,Mashhad University of Medical Sciences.

[3] Mortazavi SA, Guilani TB and Tabandeh H, Preparation of Sustained Release Matrix Tablets of Aspirin with Ethylcellulose, Eudragit Rs.*100* and Eudragit S*100* and Studying the Release Profiles and their Sensitivity to Tablet Hardness, Tehran,Iran: School of Pharmacy, Shaheed Beheshti University of Medical sciences and Health Services.

[4] Jain P, Chaudhari S, Shear R and Chavanpatil PVM, Development of sustained release gastroretentive drug delivery system for ofloxacin:In vitro and in vivo evaluation, Matunga,Mumbai: Mumbai University Institute Of Chemical Technology, Pharmaceutical Sciences Division, 2005.

[5] Tiwari SB, Murthy TK, Pai MR, Mehta PR and Chowdary PB, Controlled Release Formulation of Tramadol Hydrochloride Using Hydrophilic and Hydrophobic Matrix System, AAPS. PharmSci. Tech., 2003

[6] Prasad DVK, Gupta VRM, and Setty CM, Development of Fast Dispersible Aceclofenac Tablets: Effect of Functionality of Superdisintegrants, Raichur-584 103, India: Department of Pharmaceutics, N.E.T Pharmacy College, 2008.

[7] Ethyl Cellulose: Physical and Chemical Properties, North Market Street, USA: Hercules Incorporated, 2008.

[8] Mahadlek J and Phaechamud T and Darunkaisorn W, Selection of Suitable Granulating Fluid, Nakhon Pathom, 73000, Thailand: Department of Pharmaceutical Technology, Faculty of Pharmacy.

[9] Fabrication of Controlled Release Metoprolol Succinate Matrix Tablet: Influence of Some Hydrophilic Polymers on the Release Rate and In Vitro Evaluation, Ajay L. Barhate, Santosh N. Shinde, Monali S. Sali, Kunal D. Ingale, Vishnu P.Choudhari, Bhanudas S.Kuchekar, Kothrud, Pune, India: Maharashtra Institute of Pharmacy.

[10] Anjali M Agrawal, Steven H Neau and Peter L Bonate , Wet *granulation fine particle ethylcellulose tablet*, Division of Pharmaceutical Sciences, School of Pharmacy, University of Missouri-Kansas City, Kansas City, MO- 64110

[11] Paul J Sheskey and Marian E Quinn Raymomd C Rowe, Handbook of Pharmaceutical Excipients:6^{th} Ed., Pharmaceutical Press, 2009, 208-210.

Table 1: Independent Variables and With Their Levels andResponse Variables

Independent Variable		High	+1	Low	-1
			%		%
Ethyl cellulose	X1	10 mg	2.85	0 mg	0
Crospovidone	X2	7.5 mg	2.14	0 mg	0
Isopropyl alcohol	X3	5 ml/50 tab	.028	0 ml	0

Table 2: Composition of Matrix Release Tablets

Ingredients	EC (mg/per tablet)	IPA (ml/ 50 tablets)	CP (mg/per tablet)
F1	0	5	5
F2	10	2.5	0
F3	5	0	0
F4	5	5	7.5
F5	5	2.5	5
F6	10	5	5
F7	0	2.5	0
F8	5	0	7.5
F9	10	0	5
F10	5	2.5	5
F11	10	2.5	7.5
F12	5	5	0
F13	5	2.5	5
F14	0	2.5	7.5
F15	0	0	5

NOTE: EC = Ethylcellulose; IPA = Isopropyl alcohol; CP = Crospovidone

Table 3 Regression Coefficients and their estimates of regression model for responses Y1 to Y8

Regression Model	R^2	R^2 (adjusted)
Y1 = 44.9685 + 3.25855X1 + 4.73054X2 - 19.3005X3 - 0.16388X1X2 - 1.0576X1X3 - 1.16509X2X3 + 3.76245X32	97.4363	95.5135
Y2 = 64.4008 + 0.568123X1 + 1.36397X2 - 20.3261X3 + 0.256417X12 - 0.152295X1X2 - 1.4942X1X3 + 0.3341X22 - 0.724632X2X3 + 4.19847X32	99.0459	97.3285
Y4 = 95.9658 - 1.99458X1 - 2.7065X2 - 24.3322X3 + 0.366033X12 – 1.5964X1X3 + 0.468867 X22 + 4.82493 X32	96.0134	92.0268
Y8 = 94.3 - 0.31175 X1 - 2.99658 X2 - 11.457 X3 + 0.163 X12 - 1.2558X1 X3 + 0.559767 X22 + 2.4564 X32	92.1138	84.2276

Table 4: Estimated Effects and Interaction for Response Variable Y1- Y8

Source	X1	X2	X3	X1X1	X1X2	X1X3	X2X2	X2X3	X3X3
Y1	-	-	- 50.7266 (.0001)	-	-	- 26.44 (.0099)	-	-21.8455 (.0186)	47.6233 (.0009)
Y2	-11.7432 (0.0134)	9.725 (0.0246)	- 47.6105 (0.0000)	12.8208 (0.0360)	-	- 37.355 (0.0003)	-	- 13.5868 (0.0233)	52.4808 (0.0001)
Y4	-23.2525 (.0034)	-	- 40.9475 (0.0001)	-	-	- 39.91 (0.0012)	-	-	60.3117 (0.0001)
Y8	-18.2125 (0.0091)	-	-1487.31 (0.0011)	-	-	- 31.395 (0.0034)	-	-	30.705 (0.0047)

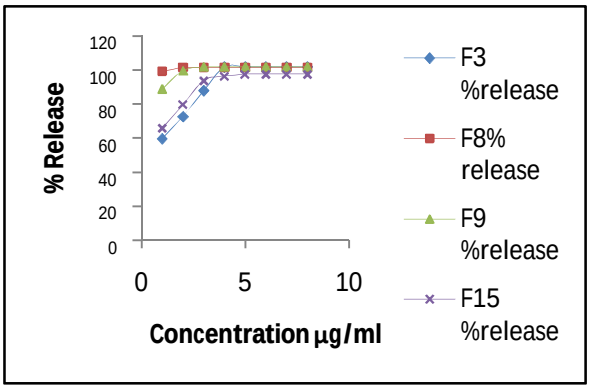

Figure 1.1: Drug Release Profile of Formulations Prepared Using 0 ml of IPA (F3, F8, F9 and F15)

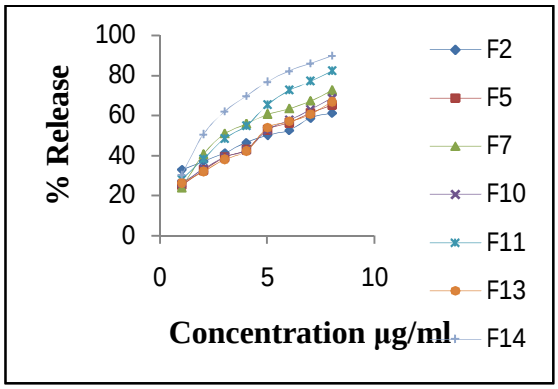

Figure 1.2: Drug Release Profile of Formulations Prepared Using 2.5 ml of IPA (F2, F5, F7, F10, F11, F13 and F14)

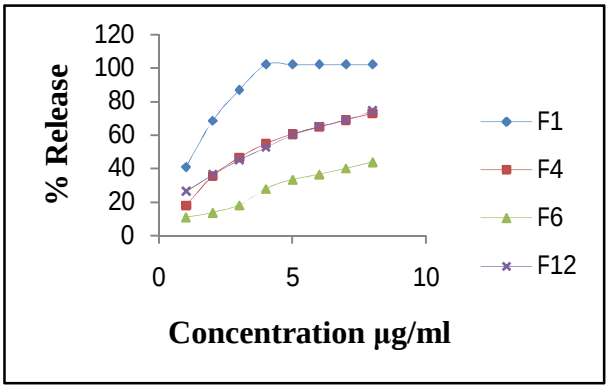

Figure 1.3: Drug Release Profile of Formulations Prepared Using 5 ml of IPA (F1, F4, F6 and F12)

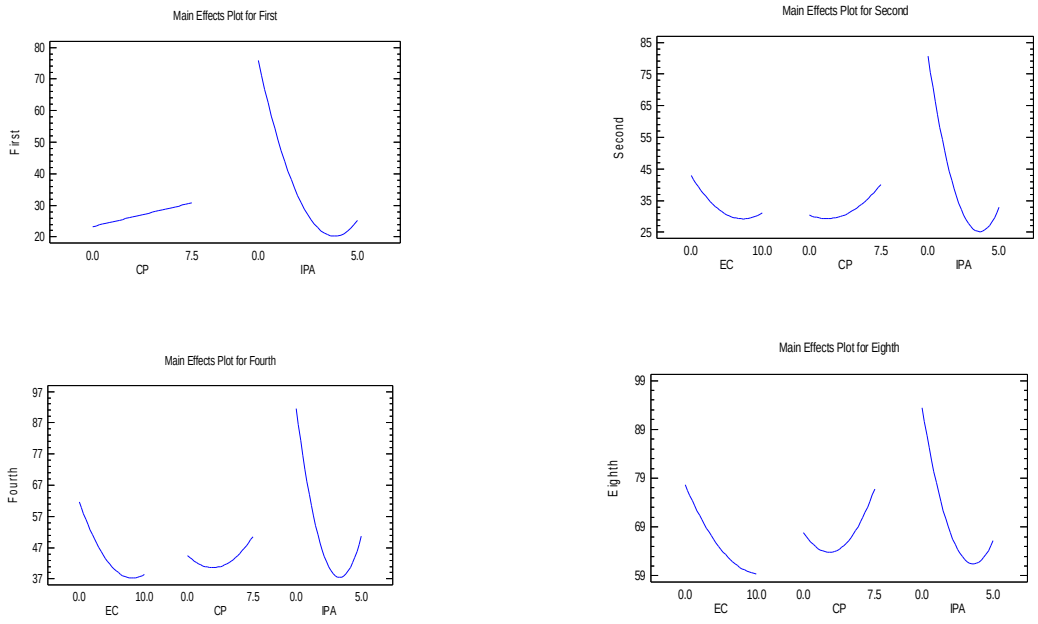

Figure 2: Main Effect Plot Showing the Effect of EC (X1), CP (X2) and IPA (X3) From First Hour (Y1) to Eighth Hour (Y8)

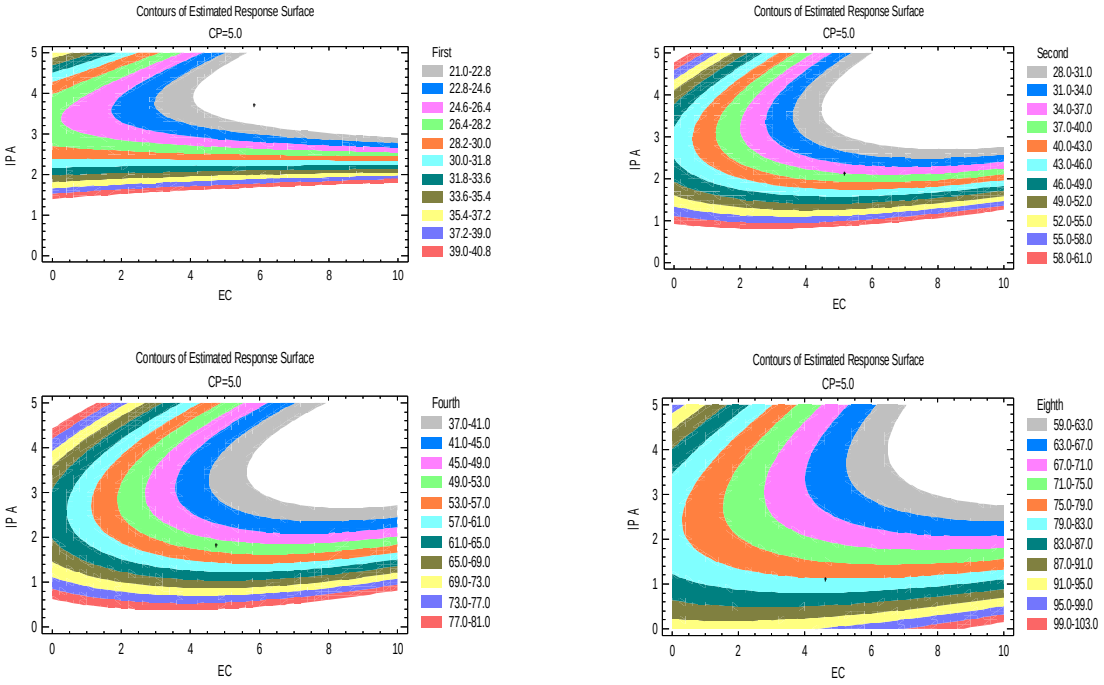

Figure 3: Contour Plots Showing the Effect of Amount of Polymer EC (X1) at Varying Amount of IPA (X3) and at Constant CP (X2) of 5 mg on Percentage Release at First, Second, Fourth and Eighth Hour Respectively

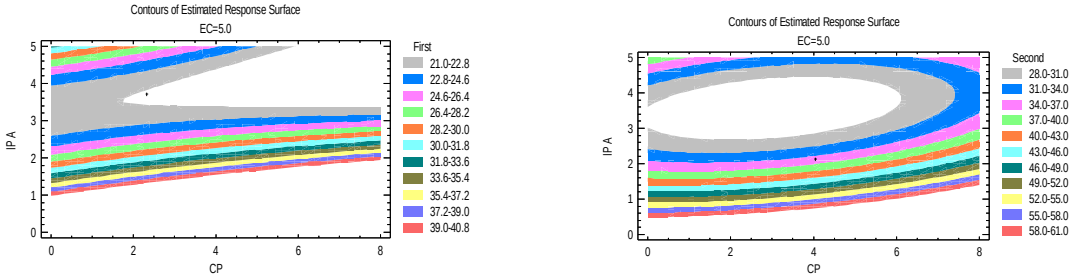

Figure 4: Contour Plots Showing the Effect of Amount of CP (X2) at Varying Amount of IPA (X3) and at Constant of Polymer EC (X1) 5 mg on Percentage Release at First and Second Hour Respectively