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To Study the Effect of Hydroalcoholic Dissolution Media for Integrity of Sustained Release Polymer

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ABSTRACT

In July 2005, the FDA issued an alert for healthcare professionals regarding dissolution media effects on drug release from a SR dosage form not involving a hydrophilic matrix, i.e., alcohol-Palladone interaction[1.] Hence, the aim of present works was to check the effect of Hydro alcoholic dissolution media in sustained release polymer and investigate the influence of hydro-alcoholic media on drug release for metoprolol Succinate sustained release tablets. Metoprolol succinate is a drug used for Hypertension and it is suitable drug candidate for extended release due to its short Half-life. Combination of HPMC K4M and HPMC K100M, Carbopol 934 P, Chitosan, HPMC K100 M: Ethyl Cellulose (4:1), Sodium-Carboxyl Methyl Cellulose were used as a polymer matrix to control the release of Metoprolol succinate up to 12 hrs. The Sustained release tablets of Metoprolol succinate were prepared by Wet granulation method. All the tablets were evaluated for the Pre-compression and post Compression Parameter. *In-vitro* dissolution study was done in Normal Dissolution Media, Phosphate Buffer pH 6.8 and also in 10 %, 20 %, 30 % and 40% v/v ethanol solutions for up to 12 hrs. All HPMC, Chitosan, Sodium-CMC preparation did not fail in hydro-alcoholic media, while Carbopol 934 P preparation show highest differences compare to all other. The highest dissolution was found to be more than 80 % in 12 hours for 40 % v/v ethanol solution in Carbopol 934 P ,which was not comply with standard range of drug release by USFDA and show dose dumping of Formulation. Kinetic model application confirmed that the release of Metoprolol succinate follows zero order as well as Korsmeyer-Peppas model. From these studies it was concluded that Carbopol 934 P formulation indicated highest signs of a potential dose dumping compare with other formulation.

Keywords: Dose dumping, Sustained Release Polymer, Hydroalcoholic Dissolution Media.

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INTRODUCTION

Alcoholic beverages have been consumed for thousands of years, and a UK National Health Service survey indicated that 73% of men and 57% of women (aged 16 and over) had alcoholic drinks on at least one day per week. In another report, US statistical data showed that around 50% of the American population routinely consumed alcoholic beverages. The potential effect of alcoholic drinks in significantly accelerating drug release from SR oral formulations has been of some concern. It is known that alcohol has an influence on the absorption, metabolism and excretion of drugs, which can potentially lead to adverse side effects. Toxicity is most often associated with acute intake rather than longer-term consumption of alcohol, but both patterns can impact the toxic-kinetics of concomitantly administered medicines. Unintended, rapid drug release in a short period of time of the entire amount or a significant fraction of the drug contained in a modified release dosage form is often referred to as "dose dumping". Depending on the therapeutic indication and the therapeutic index of a drug, dose-dumping can pose a significant risk to patients, either due to safety issues or diminished efficacy or both. Generally dose-dumping is observed due to a compromise of the release-rate-controlling mechanism. The likelihood of dose-dumping for certain modified release products when administered with food has been recognized for about twenty years and a regulatory process established to address it [1-2].

Some modified-release oral dosage forms contain drugs and excipients that exhibit higher solubility in ethanolic solutions compared to water. Such products can be expected to exhibit a more rapid drug dissolution and release rate in the presence of ethanol. Therefore, in theory, concomitant consumption of alcoholic beverages along with these products might be expected to have the potential to induce dose dumping. This potential mechanism leading to dose-dumping from an oral modified-release dosage form has not previously attracted attention in the pharmaceutical science literature or in regulatory assessment process. There are many reasons this may not have previously been considered, amongst these reasons is that there may have existed a general assumption that a clinically insignificant difference in drug release rate would be expected with concomitant ethanol consumption in vivo. A study conducted over twenty years ago[1] and the absence of a clear post-marketing signal pointing to alcohol inducing dose dumping may have reinforced the latter assumption.

However, a recent observation of alcohol-induced dose dumping and the potential risk it posed[1] necessitates a re-examination of this issue. In July 2005, FDA concluded that the overall risk versus benefit profile of a hydromorphone modified-release drug product was unfavorable due to alcohol induced dose dumping. This decision was based, in part, on an a pharmacokinetic study in healthy subjects (utilizing a naltrexone block), which demonstrated

that co-ingestion of this product with 240 mL (8 ounces) of 40% (80 proof) alcohol resulted in an average peak hydromorphone concentration approximately six times greater than when taken with water. Furthermore, one subject in this study experienced a 16-fold increase when the drug was ingested with 40% alcohol compared with water. This study also showed that 8 ounces of 4% alcohol (equivalent to 2/3 of a typical serving of beer) could in some subjects result in almost twice the peak plasma hydromorphone concentration than when the drug was ingested with water.[1]

The FDA's recent finding of an unfavourable risk versus benefit profile of a hydromorphone product due to alcohol-induced dose dumping necessitates development of a general regulatory approach to address the issue of whether alcohol undermines the release characteristics of the drug for new drug applications and currently marketed products that utilize a controlled-release mechanism. The goal of the regulatory approach should be to minimize the risk of alcohol-induced dose dumping from modified-release dosage forms, irrespective of any warnings on product labelling and instructions by health care providers.

Concomitant alcohol use is warned against or contraindicated for many drugs due to the potential for pharmacokinetic (e.g., altered clearance) or Pharmacodynamic interactions (e.g., effects on the central nervous system). In these cases, product labels warn physicians and patients on the adverse consequence of alcohol consumption while on a drug regimen. For other drugs moieties, those that do not have a pharmacokinetic or Pharmacodynamic interaction with alcohol, a warning on the adverse consequence of alcohol consumption due to potential for dose dumping may not be included in the product label. However, especially for certain narrow therapeutic index drugs (including hydromorphone), it may be prudent to consider the consequences of concomitant alcohol use, even in the face of significant alcohol warnings in product labelling because alcohol use would still be likely.[2,3]

Pharmacokinetic studies in healthy subjects that involve co-administration of high alcohol loads (to emulate a "worst case" scenario) and a modified-release product may pose a risk, either due to the alcohol load itself and because of the potential for dose dumping in cases where the high exposure itself may be dangerous. For some drugs a pharmacologic antagonist can be used to reduce risks posed by dose dumping (e.g., for opiates, a naltrexone or naloxone block), however this approach may not be feasible or provide an adequate protection for most drugs. In case of food-induced dose dumping, the FDA guidance clearly recognizes that (unless the product is well designed) food effect studies can pose a risk to study subjects - "co-administration with food can result in dose dumping, in which the complete dose may be more rapidly released from the dosage form than intended, creating a potential safety risk for the study subjects".[(2)] One can, therefore, argue that the current food-

effect study requirements for modified release dosage forms are not primarily intended to assess dose-dumping; these studies have much broader utility in terms of how the information generated is used for clinical study design and dosing regimen recommendations. To be consistent with these FDA principles - intended to minimize risk to subjects – reliable alternate approaches to an in vivo evaluation are preferred.

The aim of present works is to check the effect of Hydro alcoholic dissolution media in sustained release polymer & evaluate their integrity on Metoprolol Succinate sustained release tablets. The Rational of Present Work is to Check the effect of Hydroalcoholic dissolution media in sustained release polymer for to minimize risks of alcohol leading to dose-dumping and to Patient's convenience and compliance could be improved.

MATERIALS AND METHOD

Metoprolol succinate was procured as a gift sample from Lincoln Pharmaceutical Pvt. Ltd., Khatraj and other polymers HPMC K 100M, HPMC K 4 M, Carbopol 934 P, Chitosan, Ethyl Cellulose, Na-CMC was procured from Chemdyes Corporation, Ahmedabad.

DRUG- EXCIPIENT COMPATIBILITY STUDIES[4, 5, 6, 7]:

The compatibility study was carried out using Fourier Transform Infrared Spectroscopy (FTIR) by pressed pellet technique using a KBr press. Potassium bromide was taken and kept in a hot air oven for two hours for the removal of any moisture if present. The drug powder sample was mixed with dried KBr crystals and the mixture was pressed to form pellets using KBr press. The prepared pellet was placed in the sample holder and kept in the instrument to record the IR peaks. The same process is repeated with the physical mixture sample of drug and polymers and IR peaks were recorded.

Preparation of Tablets using Wet Granulation Method:

Metoprolol succinate SR Tablets were prepared by Wet granulation method. Sifting: API, MCC pH 101, HPMC K100 M & HPMC K4 M was passed through 40#. Wet Granulation: HPC LH 21 was dissolved in IPA and above solution was used for preparation of granules.

Drying: Granules was dried in Hot air oven. (LOD: 1.5 – 2.0)

Sifting: Granules were passed through 20 #.

Blending and Lubrication: Blending Aerosil for 10 min and lubricated by Sodium Stearyle Fumarate for 5 min.

Compression: finally go for compression.

Formulation and Evaluation:

Polymers were selected and then lower & upper limit was determined. 3^2 factorial design was employed for Sustained Release Tablets. Design-Expert® 9 trial version software (Stat-Ease Inc., USA) was applied to obtained optimized batch. The independent and dependent

variables was selected as follows:

Table 1: Design matrix for 3^2 factorial designs

Sr. No.	Coded Value		Actual Value	
	Factor 1 Conc. of HPMC K 4 M (A)	Factor 2 Conc. of HPMC K 100 M (B)	Factor 1 Conc. of HPMC K 4 M (X_1)(mg)	Factor 2 Conc. of HPMC K 100 M (X_2)(mg)
1	1	1	80	96
2	0	1	64	96
3	-1	1	48	96
4	1	0	80	80
5	0	0	64	80
6	-1	0	48	80
7	1	-1	80	64
8	0	-1	64	64
9	-1	1	48	64

Table 2: Formulation Batches using 3^2 factorial designs

Ingredients	mg/Tablets								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Metoprolol Succinate	47.5	47.5	47.5	47.5	**47.5**	47.5	47.5	47.5	47.5
MCC pH 101	79.5	95.5	111.5	95.5	**111.5**	127.5	111.5	127.5	143.5
HPMC K4 M	80	64	48	80	**64**	48	80	64	48
HPMC K100 M	96	96	96	80	**80**	80	64	64	64
HPC LH 21	10	10	10	10	**10**	10	10	10	10
Isopropyl Alcohol	0	0	0	0	**0**	0	0	0	0
Colloidal Anhydrous Silica	3	3	3	3	**3**	3	3	3	3
Sodium Stearyl Fumarate	4	4	4	4	**4**	4	4	4	4
Avg weight	320	320	320	320	**320**	320	320	320	320

Optimization of formulation using 3^2 full factorial designs:

It is desirable to develop an acceptable pharmaceutical formulation in shortest possible time using minimum number of man-hours and raw materials. Traditionally pharmaceutical formulations after developed by changing one variable at a time approach. The method is time consuming in nature and requires a lot of imaginative efforts. Moreover, it may be difficult to develop an ideal formulation using this classical technique since the joint effects of independent variables are not considered. It is therefore very essential to understand the complexity of pharmaceutical formulations by using established statistical tools such as factorial design. In addition to the art of formulation, the technique of factorial design is an effective method of indicating the relative significance of a number of variables and their interactions.

The number of experiments required for these studies is dependent on the number of independent variables selected. The response (Y_i) is measured for each trial.

$$\mathbf{Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_1^2 + b_{22}X_2^2}$$

Where Y is the dependent variable, b_0 is the arithmetic mean response of the nine runs and b_i is the estimated coefficient for the factor X_1. The main effects (X_1 and X_2) represent the average result of changing one factor at a time from its low to high value. The interaction terms (X_1X_2) show how the response changes when two factors are simultaneously changed. Coefficients with one factor represents the effect of that particular factor while the coefficients with more than one factor and those with second order terms represents the interactions between those factors and the quadric nature of the phenomena respectively. Positive sign in the front of the terms indicates synergistic effect while negative sign indicates antagonistic effect of the factor.

Optimized batch using Design-Expert® 9 software:

Using Design-Expert® 9 software; F5 batch has been selected as optimized Formulation. According this formulation; other polymer batch was prepared and evaluated.

Table 3: Formulation Batches of other polymer according to optimized batch F5

Ingredients	**mg/Tablets**			
Batch	**CA1**	**CH1**	**HE1**	**SC1**
Metoprolol Succinate	47.5	47.5	47.5	47.5
MCC pH 101	111.5	111.5	111.5	111.5
HPMC K 100 M	--	--	115.2	--
Carbopol 934 P	**144**	--	--	--
Chitosan	--	**144**	--	--
Ethyl Cellulose	--	--	**28.8**	--
Sodium-Carboxyl Methyl Cellulose	--	--	--	**144**
HPC LH 21	10	10	10	10
Isopropyl Alcohol	q.s.	q.s.	q.s.	q.s.
Colloidal Anhydrous Silica	3	3	3	3
Sodium Stearyl Fumarate	4	4	4	4
Avg weight	320	320	320	320

RESULTS AND DISCUSSION

Table 4: Result of FT-IR study of Metoprolol Succinate + HPMC K4 + HPMC K100 M and Carbopol 934 P

Functional group	**IR Peak[46] (cm^{-1}) Pure drug**	**IR Peak (cm^{-1}) API**	**IR Peak (cm^{-1}) API +HPMC K100 M + HPMC K 4 M**	**IR Peak (cm^{-1}) API + Carbopol 934 P**	**Result**
C-O Str(1^{o} Alcohol)	1035.52	1053.17	1053.17	1053.17	Compatible
C-O Str inC-O-C	1110.06	1114.89	1114.89	1114.89	Compatible
C-O Str in C=C-O-C	1258.42	1242.20	1242.20	1242.20	Compatible
C=C Ring Str	1511.63	1562.39	1562.39	1562.39	Compatible
N-C Str	3145.67	3144.07	3151.79	3020.63	Compatible

Table 5: Result of FT-IR study of Metoprolol Succinate + Chitosan +HPMC K 100 M + Ethyl Cellulose + Na-CMC

Functional group	IR Peak (cm^{-1}) API + Chitosan	IR Peak (cm^{-1}) API + HPMC K 100 M+ Ethyl Cellulose	IR Peak (cm^{-1}) API +Na-CMC	Result
C-O Str(1º Alcohol)	1053.17	1053.17	1053.17	Compatible
C-O Str inC-O-C	1114.89	1114.89	1114.89	Compatible
C-O Str in C=C-O-C	1242.20	1242.20	1242.20	Compatible
C=C Ring Str	1562.39	1562.39	1562.39	Compatible
N-C Str	3144.07	3155.65	3147.94	Compatible

There was no significant difference in characteristic peak at wave numbers of the drug in presence of the excipient. So it was concluded that no interaction between Drug and polymers used in study**.**

Table 6: Post compression parameter of all batches

Batch	Weight variation*** (mg)	Hardness* (kg/cm^2)	% Friability**	Drug content*
F1	320.45±1.4270	8.5 ±1.159	0.171 ±0.041	99.75±0.173
F2	321.23±2.4989	9.0 ±1.313	0.211 ±0.054	97.75±0.173
F3	319.88±1.0809	11±1.214	0.182 ±0.025	98.16±0.051
F4	312.51±1.4692	9.0±1.132	0.233 ±0.016	99.41±0.259
F5	320.46±2.4198	10.5±1.162	0.357 ±0.019	99.50±0.219
F6	321.12±1.8578	11.5±1.102	0.144 ±0.064	98.83±0.161
F7	320.24±0.8849	10±1.003	0.261 ±0.053	98.56±0.234
F8	323.12±1.6212	12±1.630	0.128 ±0.071	97.91±0.179
F9	321.21±2.5011	10.5±1.001	0.241 ±0.102	97.33±0.315
CA1	320.45±1.053	10 ±1.132	0.81 ±0.028	99.76±0.069
CH1	319.45±1.053	9.7 ±1.432	0.67 ±0.016	101.76±0.087
HE1	321.20±0.894	9.34 ±0.019	0.69 ±0.017	100.45±0.32
SC1	320.90±0.72	8.5 ±0.018	0.345 ±0.041	100.18±0.32

All values are expressed as Mean± SD; * n=3; ** n=10, *** n=20

In Vitro Drug Release Studies: (in Phosphate Buffer pH 6.8)

HPMC K 100 M & HPMC K 4 M

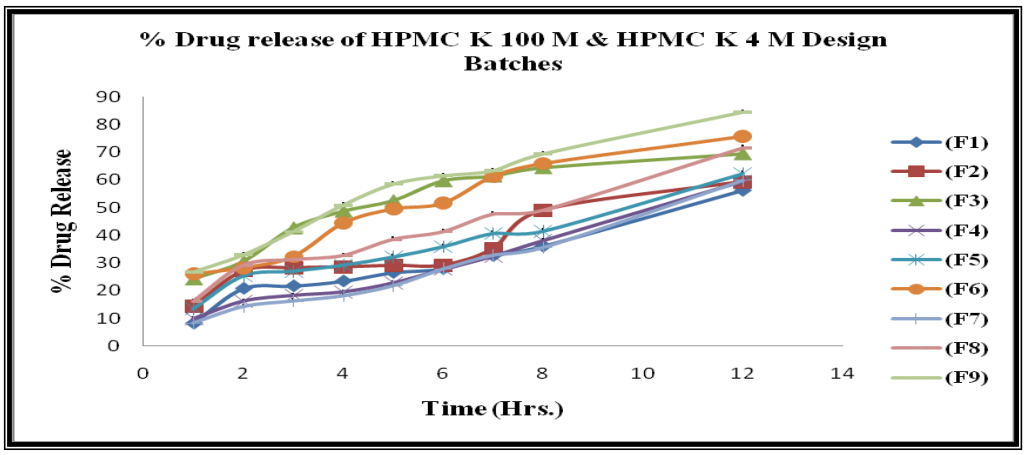

Figure 1: % Drug release in Phosphate Buffer pH 6.8 for HPMC K 100 M & HPMC K 4 M Design Batches

IN VITRO DRUG RELEASE STUDIES :(IN HYDROALCOHOLIC DISSOLUTION MEDIA)

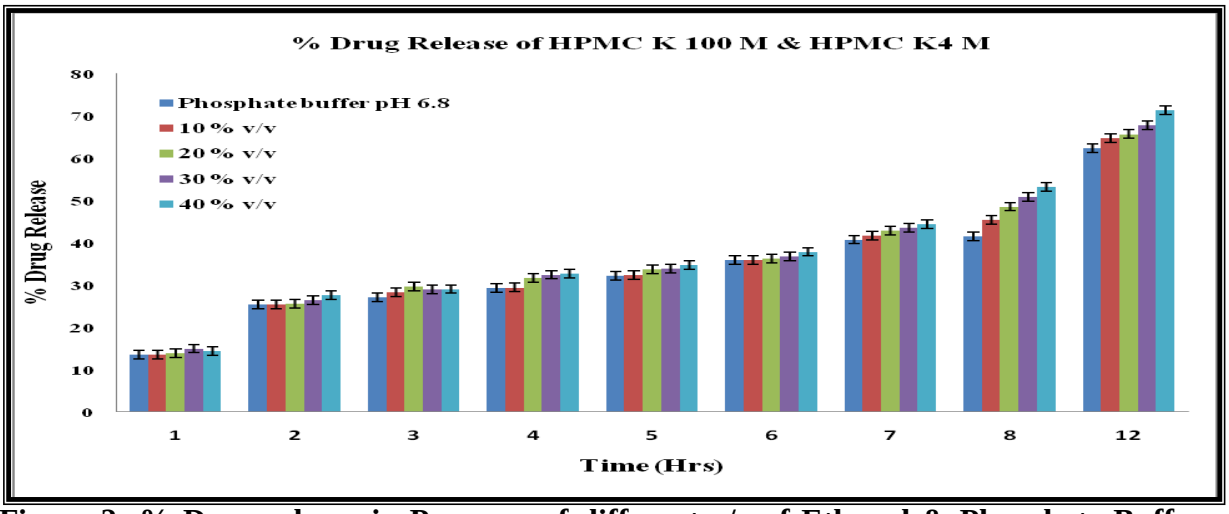

Figure 2: % Drug release in Presence of different v/v of Ethanol & Phosphate Buffer pH 6.8 for HPMC K 100 M & HPMC K 4 M

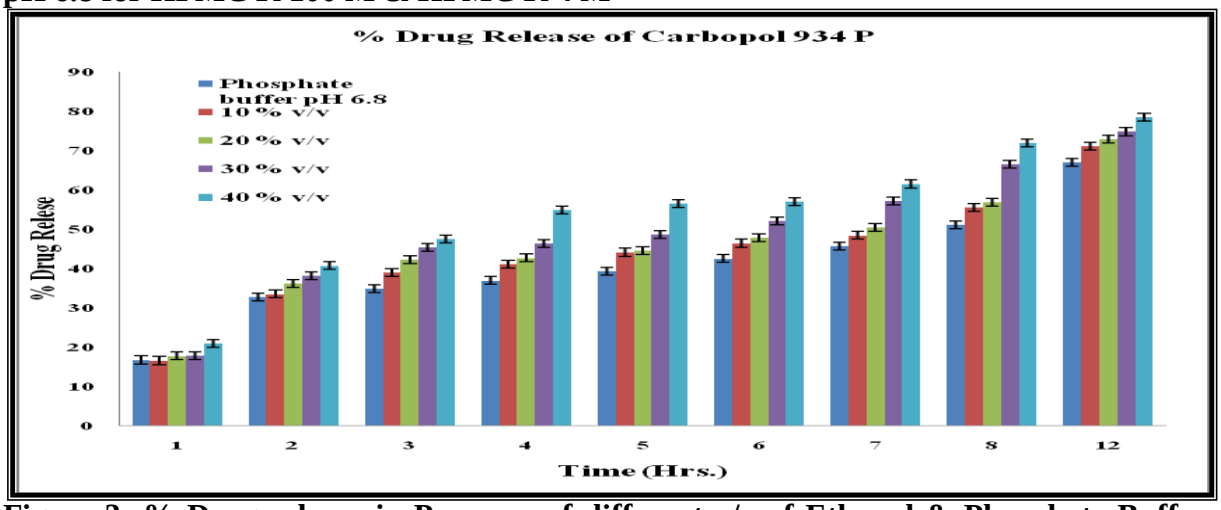

Figure 3: % Drug release in Presence of different v/v of Ethanol & Phosphate Buffer pH 6.8 for Carbopol 934 P

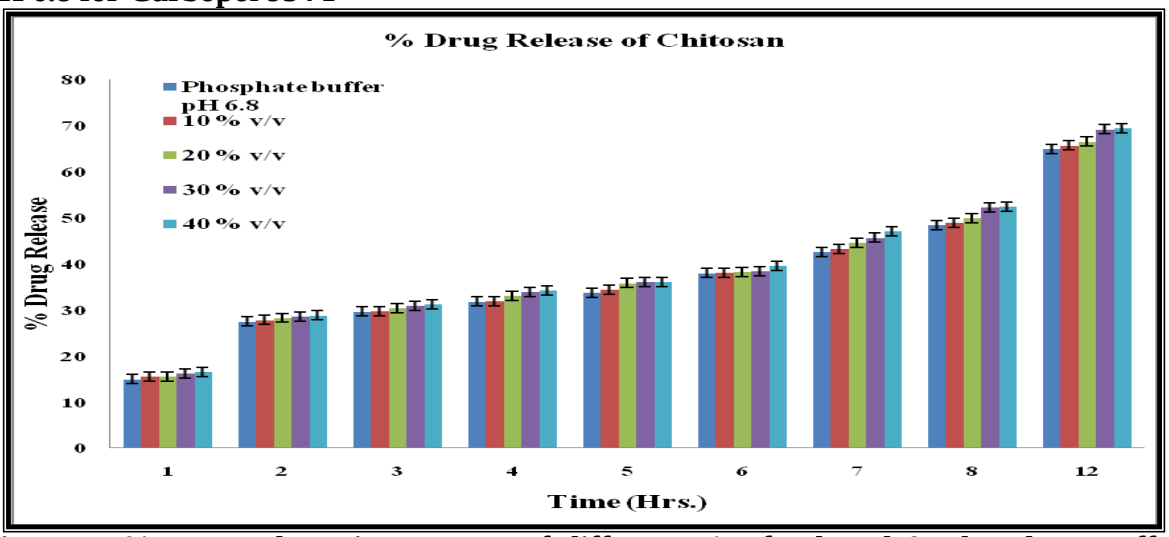

Figure 4: % Drug release in Presence of different v/v of Ethanol & Phosphate Buffer pH 6.8 for Chitosan

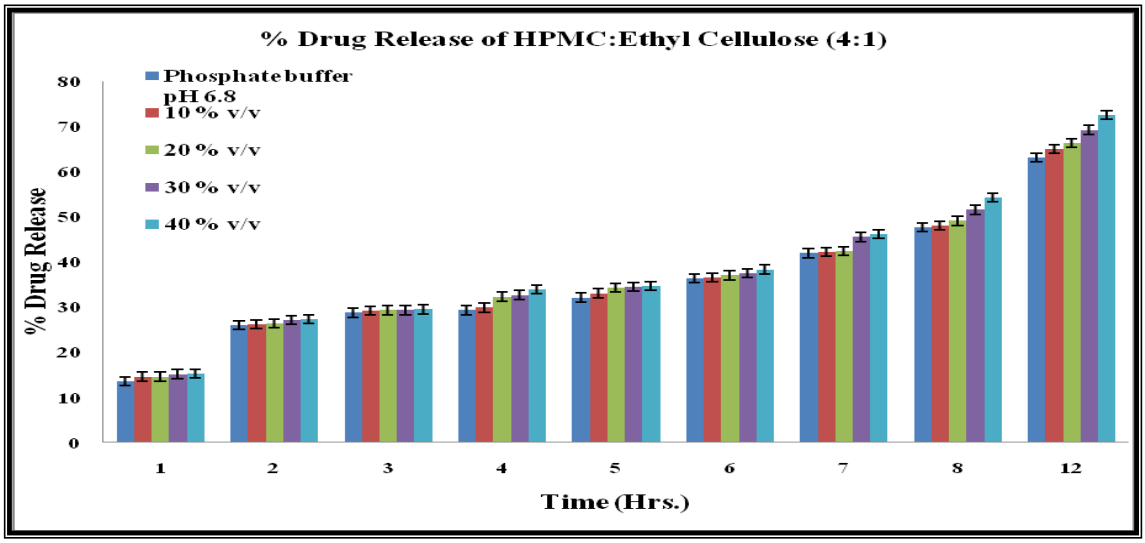

Figure 5: % Drug release in Presence of different v/v of Ethanol & Phosphate Buffer pH 6.8 for HPMC K 100 M: Ethyl Cellulose(4:1)

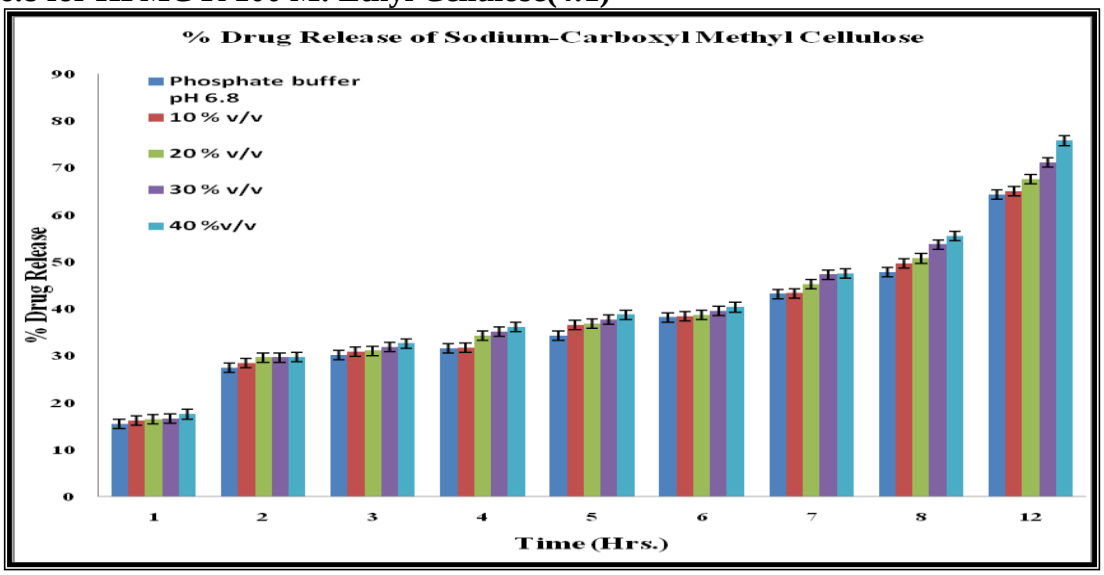

Figure 6: % Drug release in Presence of different v/v of Ethanol & Phosphate Buffer pH 6.8 for Sodium-Carboxyl Methyl Cellulose

DISSOLUTION COMPARITIVE STUDY:

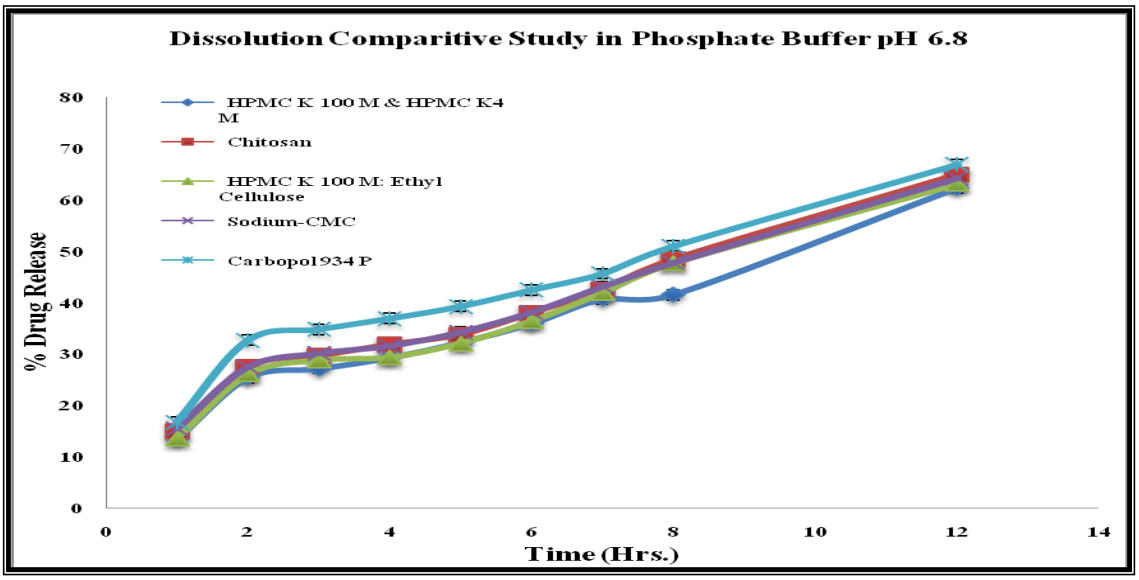

Figure 7: Dissolution Comparative study in Presence of Phosphate Buffer pH 6.8(In Normal Dissolution media (Phosphate Buffer pH 6.8) (900 ml)

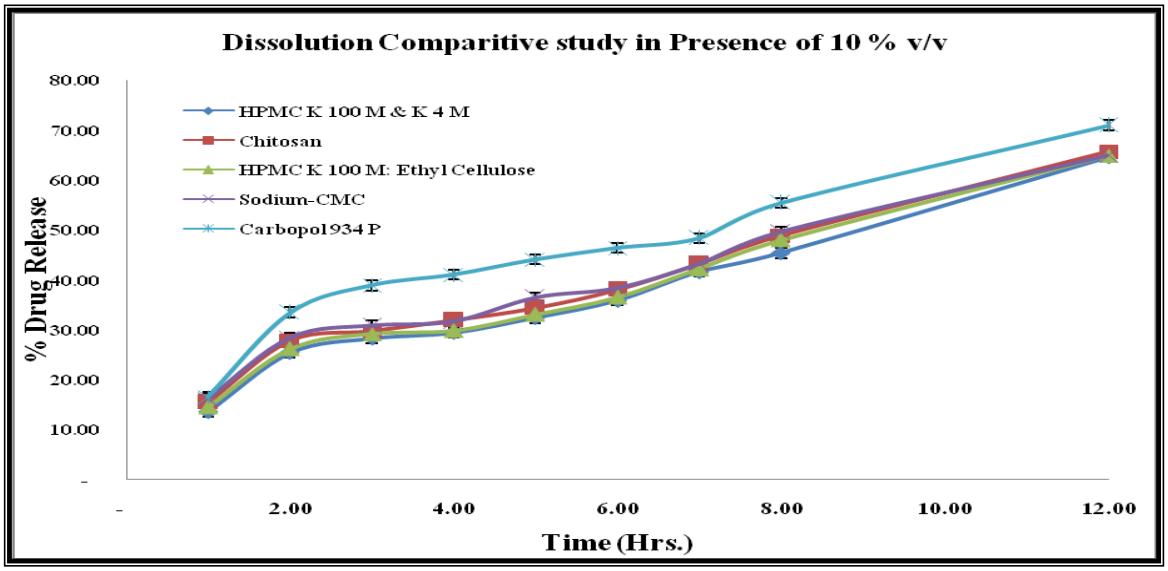

Figure 8: Dissolution Comparative study in Presence of 10 % v/v of Ethanol & Phosphate Buffer pH 6.8

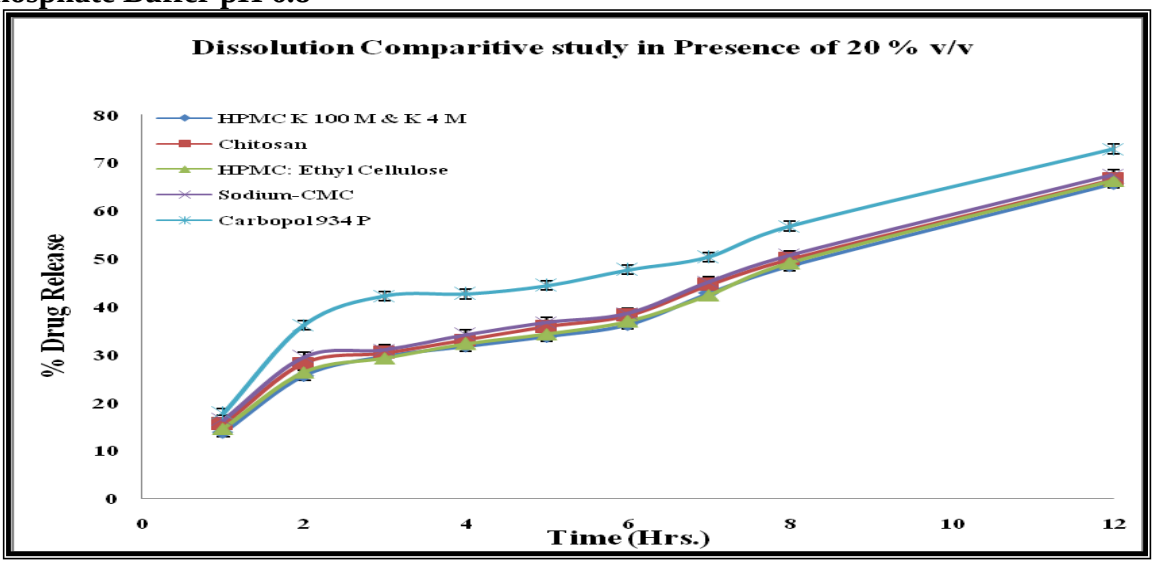

Figure 9: Dissolution Comparative study in Presence of 20 % v/v Ethanol & Phosphate Buffer pH 6.8

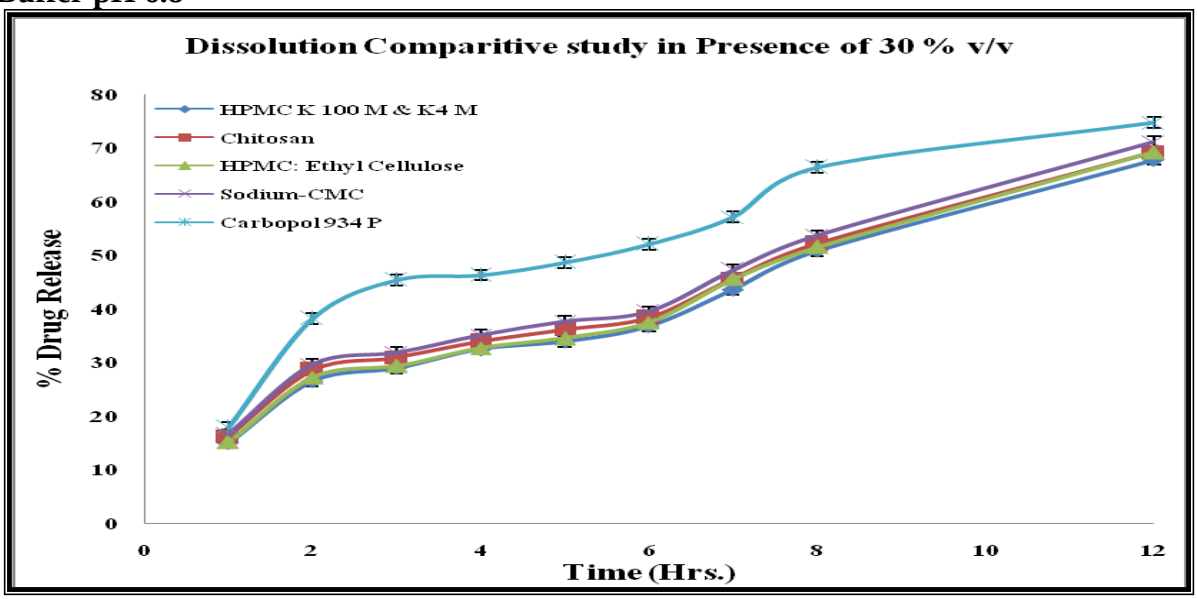

Figure 10: Dissolution Comparative study in Presence of 30 % v/v Ethanol & Phosphate Buffer pH 6.8

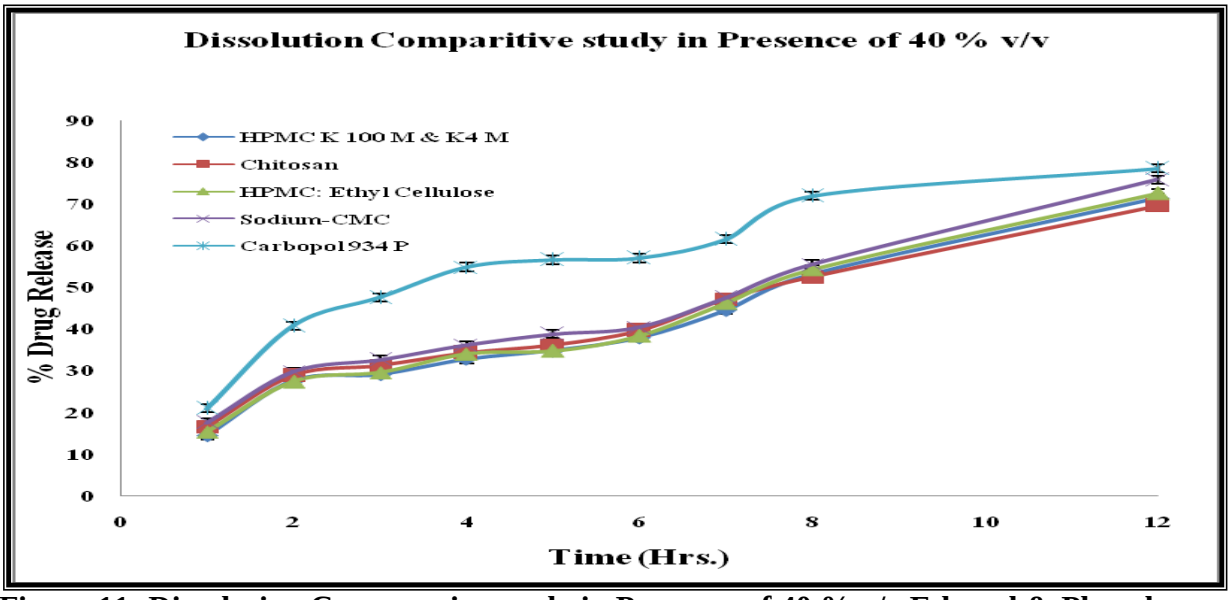

Figure 11: Dissolution Comparative study in Presence of 40 % v/v Ethanol & Phosphate Buffer pH 6.8

Where; Normal indicates 900 ml Phosphate Buffer pH 6.8

10 % v/v indicates 810 ml Phosphate Buffer pH 6.8 + 90 ml Ethanol

20 % v/v indicates 720 ml Phosphate Buffer pH 6.8 + 180 ml Ethanol

30 % v/v indicates 630 ml Phosphate Buffer pH 6.8 + 270 ml Ethanol

40 % v/v indicates 540 ml Phosphate Buffer pH 6.8 + 360 ml Ethanol

MODEL DEPENDED ANALYSIS:

Mean Dissolution Time [8,9,10]:

The mean dissolution time (MDT) represents the mean time for drug molecules to completely dissolve. It is used to characterize the drug release rate from a dosage form and indicates the drug release retarding efficiency of the Polymer.

MDT measure of the rate of the dissolution process was calculated using Eq. 1.

$$MDT = \frac{\sum_{i=1}^{i=n} t_{mid} \times \Delta M}{\sum_{i=1}^{i=n} \Delta M} \qquad (1)$$

Where,

'i' is the dissolution sample number;

'n' is the number of observation;

't_{mid}' is the midpoint time between 'i' and 'i-1' and

'ΔM' is the additional amount of drug dissolved between 'i' and 'i-1'.

The drug release rate and MDT are inversely related.

Table 7: Mean Dissolution Time different polymers in Presence of Ethanol & Phosphate Buffer pH 6.8

Batch	HPMC K 100 M & K 4 M	Carbopol 934 P	Chitosan	Sodium-Carboxyl Methyl Cellulose	HPMC K 100 M: Ethyl Cellulose
	Mean ± STDEV	Mean ± STDEV	Mean ± STDEV	Mean ± STDEV	Mean ± STDEV
Ph. Buffer pH 6.8	5.05 ± 0.02	4.39 ± 0.08	4.90 ± 0.03	4.97 ± 0.07	5.04 ± 0.01
10 % v/v Ethanol	4.99 ± 0.04	4.26 ± 0.02	4.82 ± 0.02	4.77 ± 0.01	4.95 ± 0.01
20 % v/v Ethanol	4.96 ± 0.04	4.18 ± 0.09	4.78 ± 0.02	4.73 ± 0.01	4.92 ± 0.01
30 % v/v Ethanol	4.93 ± 0.06	3.69 ± 0.07	4.74 ± 0.03	4.69 ± 0.04	4.87 ± 0.02
40 % v/v Ethanol	4..91 ± 0.02	3.39 ± 0.04	4.73 ± 0.02	4.6 ± 0.14	4.81 ± 0.08

To characterize the drug release rate from tablets, MDT was calculated for all the formulation in presence of ethanol. Formulations containing 144 mg of Carbopol 934 P a sustained release polymer showed low MDT values ranged from 3.390 to 4.393 when compared with other formulations. This indicates that increasing ethanol amount in tablet, increase drug release.

RESPONSE SURFACE ANALYSIS FOR OPTIMIZATION OF FINAL BATCH

Selected independent variable: Concentration of HPMC K4M (X1), Concentration of HPMC K100M (X2)

Selected dependent variable: % Drug release at 1Hrs. (Y1), % Drug release at 4Hrs. (Y2), % Drug release at 8 Hrs. (Y3), % Drug release at 12 Hrs. (Y4)

Table 8: Results of ANOVA study

Response model	F value	P value	R2 value	Adequate Precision
Y1	70.01	0.0026	0.991	19.98
Y2	40.58	0.0059	0.985	16.29
Y3	24.24	0.0125	0.975	12.25
Y4	41.35	0.0057	0.854	18.84

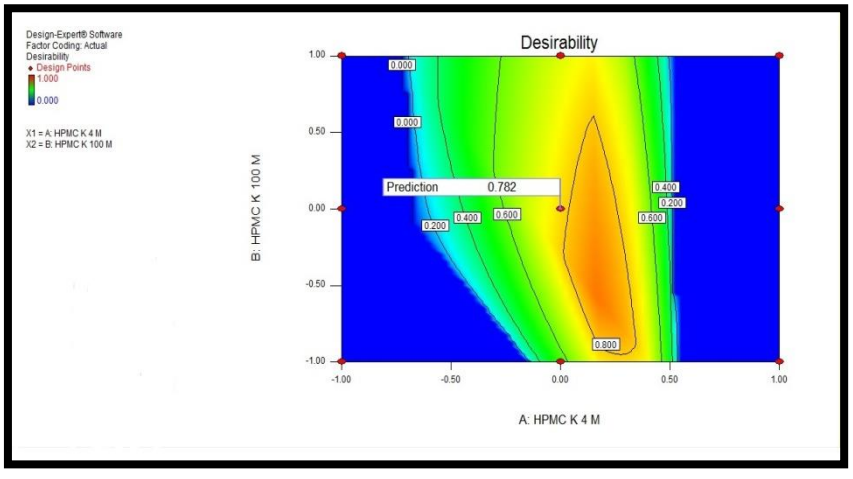

Figure 12: Contour plot for Desirability

➢ **RESPONSE MODEL FOR % DRUG RELEASE AT 1 HRS. (Y1)**

The Model F-value of 70.01 for Drug release at 1 hrs. implied the model was significant. Values of "Prob > F" was < 0.0026 which was less than 0.05 indicated model terms were significant. Adequate Precision measures the signal to noise ratio. A ratio greater than 4 is desirable. Ratio of 19.98 indicated an adequate signal. This model could be used to navigate the design space.

Polynomial equation

% Drug Release at 1 Hrs. (Y1) = + 16.30 + 8.46 X1 + 0.77 X2

In above equation coefficient of X1 showed positive sign, so increase in concentration of HPMC K 4M increases the % Drug Release at 1 Hrs. Coefficient of X2 shows positive sign, so increase in concentration of HPMC K 100 M increase % Drug Release at 1 Hrs.

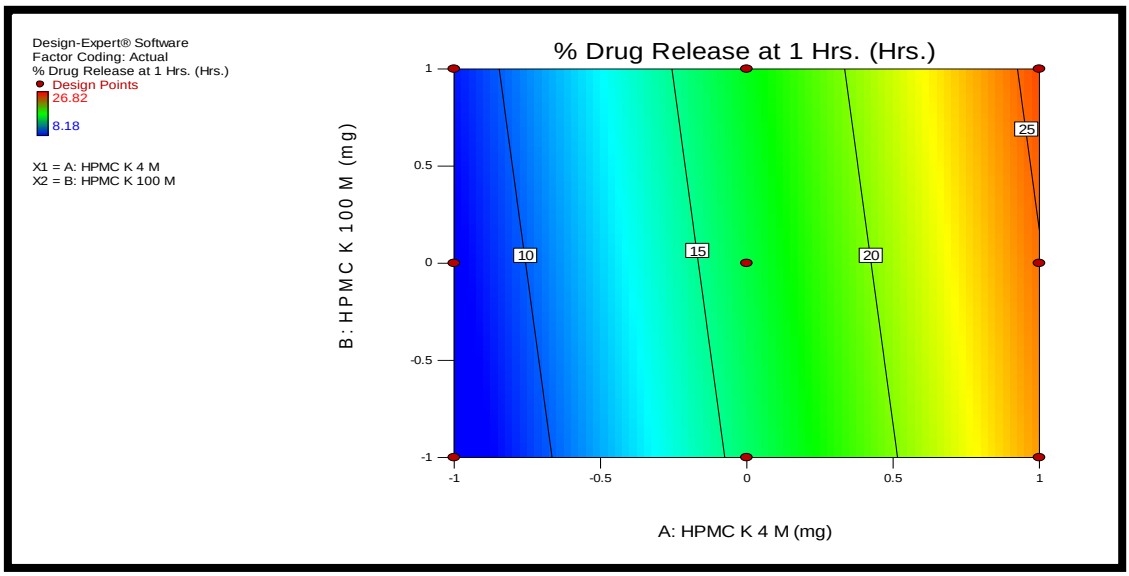

Figure 13: Contour plot for % Drug Release at 1 Hrs.

➢ **RESPONSE MODEL FOR % DRUG RELEASE AT 4 HRS. (Y2)**

The Model F-value of 40.58 for Tensile strength implied the model was significant. Values of "Prob > F" was 0.0059 which was less than 0.05 indicated model terms were significant. Adequate Precision measures the signal to noise ratio. A ratio greater than 4 is desirable. Ratio of 16.29 indicated an adequate signal. This model could be used to nevigate the design space.

Polynomial equation

% Drug Release at 4 Hrs. (Y2) = + 32.87 + 13.79 X1 + 0.20 X2

In above equation coefficient of X1 showed positive sign, so increase in concentration of HPMC K4M increases the % Drug Release at 4 Hrs. Coefficient of X2 shows positive sign, so increase in concentration of HPMC K 100M increases the % Drug Release at 4 Hrs.

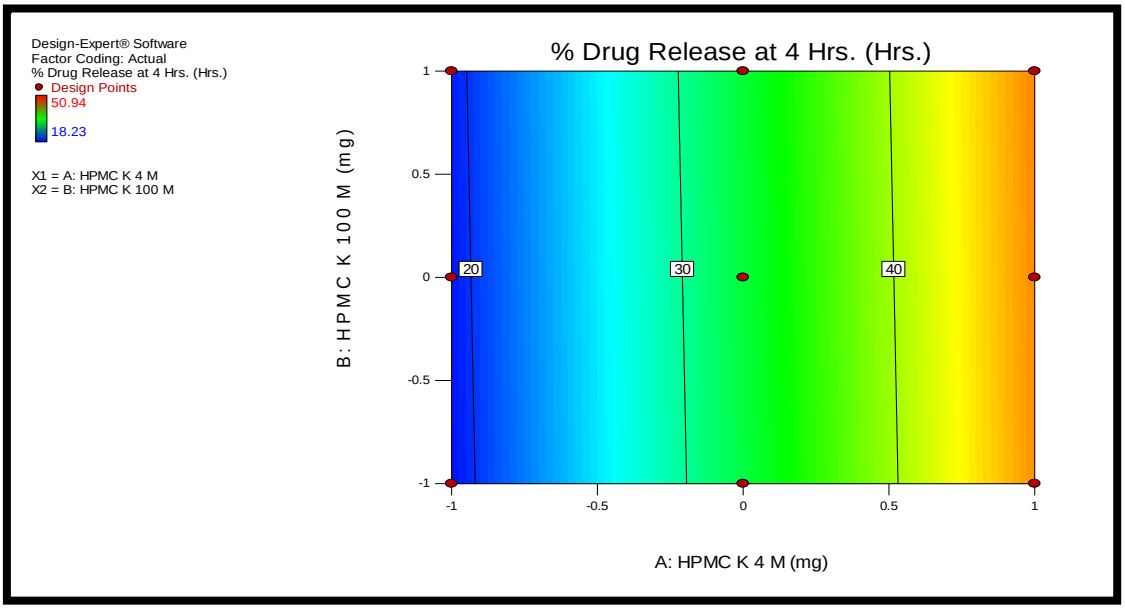

Figure 14: Contour plot for % Drug Release at 4 Hrs.

RESPONSE MODEL FOR % DRUG RELEASE AT 8 HRS. (Y3)

The Model F-value of 24.24 for % drug release implied the model was significant. Values of "Prob > F" was 0.0125 which was less than 0.05 indicated model terms were significant. Adequate Precision measures the signal to noise ratio. A ratio greater than 4 is desirable. Ratio of 12.25 indicated an adequate signal. This model could be used to navigate the design space.

Polynomial equation

% Drug Release at 8 Hrs. % Drug release (Y3) = + 49.88 + 14.97X1 + 0.76 X2

In above equation coefficient of X1 showed positive sign, so increase in concentration of HPMC K 4M increases the % Drug Release at 8 Hr. Coefficient of X2 shows positive sign, so increase in concentration of HPMC K 100M increases the % Drug Release at 8 Hrs.

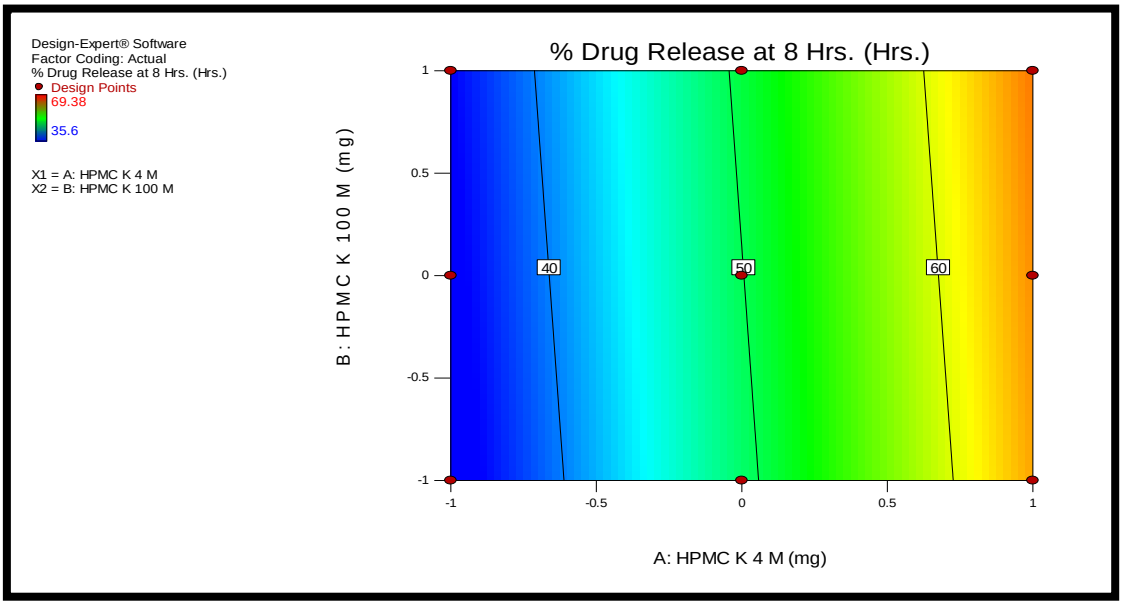

Figure 15: Contour plot for % Drug Release at 8 Hrs.

RESPONSE MODEL FOR % DRUG RELEASE AT 12 HRS. (Y4)

The Model F-value of 41.35 for % drug release implied the model was significant. Values of "Prob > F" was 0.0057 which was less than 0.05 indicated model terms were significant. Adequate Precision measures the signal to noise ratio. A ratio greater than 4 is desirable. Ratio of 18.84 indicated an adequate signal. This model could be used to navigate the design space.

Polynomial equation

% Drug Release at 12 Hrs. (Y4) = + 82.93 + 8.98 X1+ 5.13X2

In above equation coefficient of X1 showed positive sign, so increase in concentration of HPMC K4M increases the % Drug Release at 12 Hrs. Coefficient of X2 shows positive sign, so increase in concentration of HPMC K 100M increases the % Drug Release at 12 Hrs.

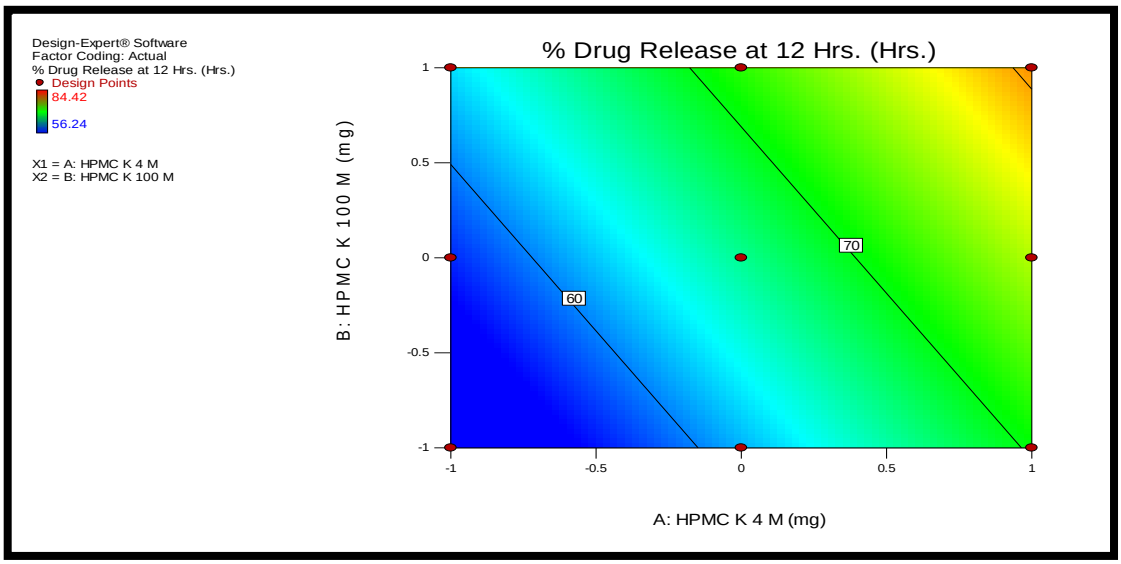

Figure 16: Contour plot for % Drug Release at 12 Hrs.

OPTIMIZATION OF FORMULA

After generating the polynomial equations relating the dependent and independent variables, Metoprolol succinate SR tablets were optimized for the responses % Drug Release at 1 Hrs. (Y1), % Drug Release at 4 Hrs.(Y2), % Drug Release at 8 Hrs. (Y3) and % Drug Release at 12 Hrs. (Y4). The desirable ranges of these responses were restricted to $0 \leq Y1 \leq 25$, $20 \leq Y2 \leq 40$, $40\ \% \leq Y3 \leq 60\ \%$ and $60\ \% \leq Y4 \leq 80\ \%$. The optimum values of the variables were obtained by graphical and numerical analyses using the Design-Expert software which are on criterion of desirability. The optimized formula was achieved with 20 mg of HPMC K 4 M and 25 mg of HPMC K 100 M concentration. Therefore, to verify the evolved models, the optimum formulation was prepared according the above values of the factors and evaluated for % Drug Release at 1 Hrs., % Drug Release at 4 Hrs., % Drug Release at 8 Hrs., and % Drug Release at 12 Hrs., As shown in table, it was demonstrating that the observed value of a new batch was quite closer to predicted value**.**

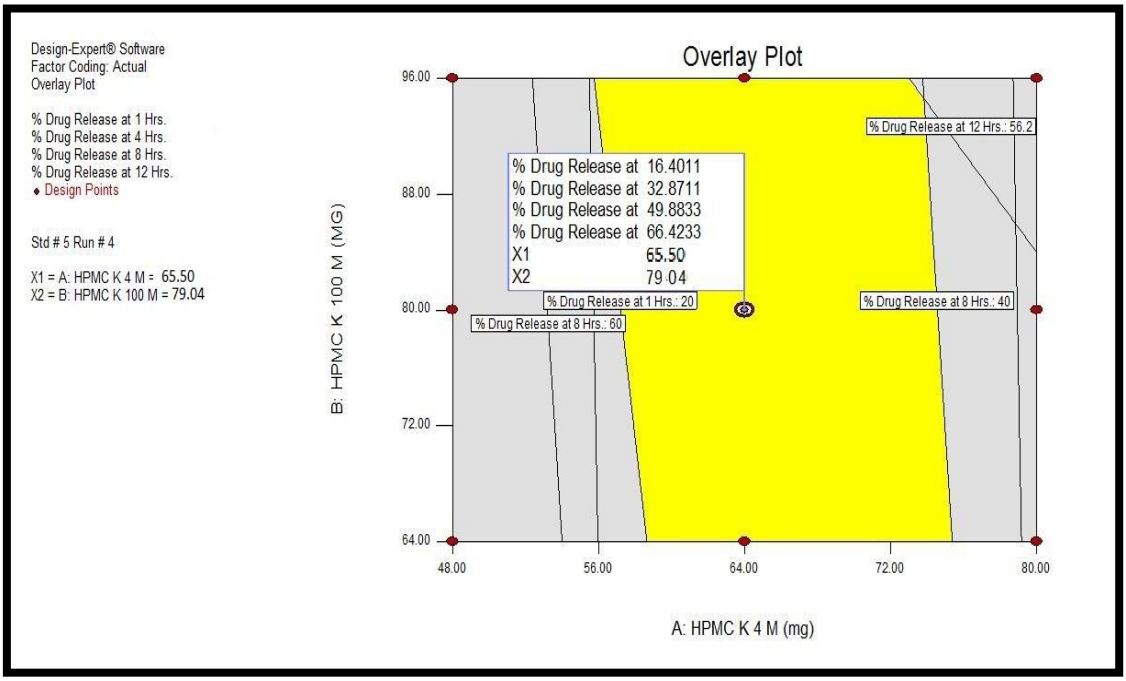

Figure 17: Overlay Plot of Design

Preparation and evaluation of Check point batch:

Table 9: Formulation of Metoprolol Succinate Check point batch

Ingredient	Quantity (mg)
Metoprolol Succinate	47.5
MCC pH 101	110.96
HPMC K 4 M	**65.50**
HPMC K 100 M	**79.04**
HPC LH 21	10
Isopropyl Alcohol	q.s.
Colloidal Anhydrous Silica	3
Sodium Stearyl Fumarate	4
Avg weight	320

Comparison of Experimental and predicted values of Check point batch:

After formulating a check point batch, it was evaluated for in-vitro drug release (% CDR) at 1, 4,8,12 Hrs. The results obtained by performing experiment were compared with the model's predicted values as shown in below table

Table 10: Comparative levels of predicted and observed responses for optimized Metoprolol succinate SR tablets

Response	Check point batch	
	Predicted	**Observed**
Y1	16.40	13.50
Y2	32.87	29.26
Y3	49.88	41.53
Y4	66.42	62.30

From the above statistical model application, the software suggested the optimized concentration for HPMC K 4 M was 65.50 mg and for HPMC K 100 M was 79.04 mg. So the formulation **F5** has been selected as optimized formulation.

Table 11: Kinetic analysis of All Batches

Batch		Zero Order	First Order	Higuchi model	Korsmeyer-Peppas	Hixson-Crowell
F1	R2	0.949	0.927	0.915	0.992	0.885
	Slope	3.790	-0.025	16.64	0.657	0.135
	Intercept	7.965	1.984	-8.39	0.987	2.250
F2	R2	0.881	0.874	0.835	0.846	0.855
	Slope	3.669	-0.026	16.02	0.481	0.114
	Intercept	13.83	1.957	-1.794	1.189	2.563
F3	R2	0.855	0.924	0.950	0.972	0.797
	Slope	4.212	-0.037	19.90	0.461	0.109
	Intercept	27.90	1.878	6.630	1.388	3.071
F4	R2	0.972	0.927	0.896	0.942	0.982
	Slope	4.326	-0.029	18.63	0.671	0.151
	Intercept	4.050	2.011	-13.81	0.955	2.114
F5	R2	0.962	0.945	0.937	0.950	0.918
	Slope	3.931	-0.029	17.37	0.537	0.122
	Intercept	13.25	1.963	-3.953	1.162	2.540
F6	R2	0.949	0.980	0.964	0.937	0.914
	Slope	4.972	-0.047	22.47	0.482	0.126
	Intercept	21.79	1.940	-1.064	1.352	2.920
F7	R2	0.975	0.927	0.900	0.955	0.983
	Slope	4.487	-0.030	19.34	0.740	0.162
	Intercept	2.219	2.020	-16.35	0.886	2.008
F8	R2	0.972	0.940	0.887	0.955	0.927
	Slope	4.542	-0.038	5.373	0.531	0.128
	Intercept	15.51	1.968	12.86	1.232	2.674
F9	R2	0.953	0.987	0.986	0.977	0.900
	Slope	5.622	-0.059	24.05	0.799	0.125
	Intercept	26.29	1.941	1.526	0.741	3.074
(CA1)	R2	0.940	0.951	0.945	1.00	0.859
	Slope	3.929	-0.031	17.66	-	0.112
	Intercept	19.73	1.954	1.876	-	2.799
(CH1)	R2	0.969	0.957	0.947	0.988	0.919
	Slope	4.118	-0.031	18.26	1.073	0.123
	Intercept	14.83	1.959	-3.312	-0.165	2.619
(HE1)	R2	0.967	0.960	0.945	0.987	0.911
	Slope	4.126	-0.031	18.30	1.133	0.127
	Intercept	13.40	1.964	-4.80	-0.280	2.551
	R2	0.972	0.961	0.951	0.987	0.922
(SC1)	Slope	4.030	-0.031	17.89	1.044	0.120
	Intercept	15.35	1.954	-2.449	-0.116	2.638

The kinetic investigations of the release profile gave us useful insight into the mechanism of drug release from the Metoprolol succinate Sustained release Tablets. Tablets depict the different release kinetic models for Metoprolol succinate sustained release tablets. From regression value it revealed that all formulations followed **Korsmeyer-Peppas and first order model**, which indicates that drug release follows constant release mechanism.

CONCLUSION

Metoprolol succinate, Beta 1- selective adrenergic receptor blocking agent used in the management of hypertension, angina pectoris, cardiac arrhythmias, myocardial infarction, heart failure, hyperthyroidism and in the prophylactic treatment of migraine. The half-life of drug is relatively short approximately 4-6 hrs., and in normal course of therapy drug administration is required every 4- 6 hrs., thus warrants the use of Extended release formulation for prolong action and to improve patient compliance. In the present study different polymers like HPMC K4M, HPMC K100M, Carbopol 934 P, Chitosan, Ethyl Cellulose were used to prepare Sustained release matrix tablet of Metoprolol succinate. Drug and polymers were subjected for compatibility study using FT-IR which suggest there was no interaction between drug and polymer. HPMC, Chitosan, Sodium-CMC tablets of Metoprolol Succinate 47.5 mg retained their hydrated structural integrity when exposed to 10%, 20%, 30% and 40% v/v ethanol solutions for up to 12 hours without any failure of the matrices resulting in dose-dumping.

Drug release profiles from these SR Metoprolol Succinate tablets using Carbopol 934 P was exposed to different 10%, 20%, 30% and 40% v/v ethanol solutions for 12 hours that were explained by changes in drug solubility and produce dose dumping, while other preparation using Chitosan, HPMC K100 M: Ethyl Cellulose, Na-CMC show lowest effect as compare to Carbopol 934 P tablet.

Exposure of compacts of five different Polymer to Phosphate Buffer pH 6.8 or hydro-alcoholic solutions had shown gradual swelling and gelation without any disruption to the tablet integrity. The In-vitro dissolution studied shows 60 to 68 % drug Release in Phosphate Buffer pH 6.8, while in 40 % v/v ethanol, carbopol 934 P indicate highest 80 % drug release in 12 hrs. and other Polymer preparations are in the range of 60-70 % drug release in 12 hrs.

This study clearly indicates that all polymers except Carbopol 934 P produces consistent drug release in water and in hydro-alcoholic media with no signs of a potential dose dumping, hence only Carbopol 934 P indicated signs of a potential dose dumping.

The Model depended parameter like Mean dissolution Time (MDT), are inversely towards the % drug release. MDT indicated increasing the % drug release, decreasing the value of MDT. The lowest value was observed in Carbopol 934 P SR tablet in 40% v/v ethanol. The results of in vitro dissolution study indicated that the drug release was in controlled fashion. To analyze the mechanism of drug release from the matrices, the In vitro drug release data were fitted to Korsmeyer-Peppas, first order. It was observed that the release of drug followed first order release in all the formulations and controlled by diffusion mechanism.

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