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Original Article

Influence of cetyl alcohol and enteric polymers on the release of water soluble drug in monolithic bilayered matrix tablet

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ABSTRACT

The enteric polymers Eudragit L 100 & Cellulose acetate phthalate was congealed using waxy polymer Cetyl alcohol and their retardant effect of release of diltiazem hydrochloride from the monolithic bilayer tabletwas studied using 2^3 factorial design. 8 bilayered tablet containing the various polymers at high and low levels were formulated and were evaluated for their physical properties. The influence of the various polymers on the diltiazem hydrochloride release indicated that cetyl alcohol was capable of retarding diltiazem hydrochloride to a higher extent when compared to the polymers Eudragit L 100 and Cellulose acetate phthalate. Further the release of diltiazem hydrochloride from the waxy monolithic matrix was found to have erosion mediated and concentration independent.

Key words: Eudragit L 100, Cellulose acetate phthalate, Cetyl alcohol, Waxy monolithic matrix tablet, Erosion mediated

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INTRODUCTION

The development of a monolithic matrix formulation for highly water-soluble drugs has been highly challenging in research compared to the membrane coated systems because the problems such as dose dumping, burst release, and difficulty in achieving 24-hour linear release profile are encountered for matrix systems in oral controlled release delivery for freely water-soluble drugs(1).Waxes are much more complicated system, both experimentally and theoretically, due to their various physical-chemical factors and properties not present in the plastic systems. For drugs with high water solubility, hydrophobic polymers (waxes) are suitable as matrix forming agents for developing sustained-release dosage forms(2). Wax matrix tablets are suitably prepared from the granules prepared from the congealed mixture and they tend to provide better retardation of drugs than directly compressed and wet granulated tablets (3). Enteric polymers when introduced in the matrix help to hinder the release of the drug in the acidic conditions while will help to accelerate the release in alkaline conditions. In this study it was aimed to study the extent of impact of the various components incorporated in the matrix, on drug release using 2^3 factorial design.

Diltiazem Hydrochloride, an orally active calcium channel blocker, is a drug of choice in the management of angina pectoris and for cardiac arrhythmia many decades (4). Diltiazem hydrochloride belongs to BCS Class I drug and possess high solubility and permeability (5).Nevertheless it is highly water soluble and is completely absorbed from the gastrointestinal tract, following an oral administration, it suffers extensive hepatic metabolism. It has acquired a biological half-life of 3.5 ± 1.2 hours. Despite its wide spread use and reproducible pharmacological capability, it suffers several inadequacies from patients point of view such as multiple daily dosing due to its petite biological half-life. These drawbacks create impetus for the development of sustained release dosage forms and hence in this study diltiazem hydrochloride was used as a model drug to study the release profile of water soluble drug from monolithic waxy matrix. Immediate release layer was compressed on the matrix as a bilayered tablet to produce immediate drug release.

Cardiac arrhythmia is an appalling clinical manifestation allied with pain and if left untreated result in death. As a consequence it is mandatory to acquire a drug delivery system, which upon controlled release of the drug, not only manages the syndrome effectively but also imparts quick relief, will yield a fruitful result. For gratifying these objectives, a bilayered tablet of Diltiazem Hydrochloride was designed with both the loading and maintenance dose using various enteric polymers like Hydroxy propyl methyl cellulose phthalate, Eudragit L-100, Cellulose acetate phthalate, Methyl cellulose and the wax, Cetyl alcohol.

MATERIALS AND METHODS

Diltiazem Hydrochloride was obtained as a gift sample from Microlabs, Hosur. Hydroxy propyl methyl cellulose phthalate was procured from Zydus Cadilla, Hyderabad. Eudragit L-100 was procured from Rohm pharma, Germany. Cellulose acetate phthalate was procured from Paris Dakner, Chennai. Cetyl alcohol was procured from Fischer Chemic Ltd, Chennai. Sodium carboxy methyl cellulose was procured from Paris Dakner, Chennai. Lactose was procured from Genuine chemicals, Mumbai. Magnesium stearate was procured from Nice chemicals, Nagpur. Talc was procured from Swestik pharmaceuticals, Mumbai.

Preparation of bilayered tablet*:* The immediate release layer contains 30 mg of Dilitizem Hydrochloride was prepared with fixed proportion of the excipients using wet granulation technique. The sustained release monolithic matrix contains 60 mg of Dilitiazem Hydrochloride along with varying proportions of the various enteric polymers and cetyl alcohol.

Formulation of immediate release layer granules*:* The immediate release layer was intended to release the loading dose (30mg)of the drug, was prepared by wet granulation method using Sodium carboxy methyl cellulose-20 mg, Lactose-46 mg per tablet as excipients and distilled water as granulating agent. After mixing the aforementioned additives, it was wet granulated by spraying distilled water over the mixture of drug and additives to yield a coherent mass. The resultant mass was passed through sieve no.40 and then dried in hot air oven for 15 minutes at 55^0C. Then the resultant granules were lubricated with talc and magnesium stearate and was added in the hopper of 21 station double-sided Rotary Tablet Press (Rimek, India). The bi layered tablets were compressed using 21 station double-sided Rotary Tablet Press (Rimek, India) at a pressure of 35 psi using 8 mm flat faced punch. Then the tablets were collected and used for evaluation.

Formulation of waxymonolithic matrix granules using experimental design: The sustained release matrix was intended to release 60 mg of Diltiazem Hydrochloride.2^3 (three-factor and two-level) full

factorial design was employed for optimization of the waxy monolithic matrix. The quantities required for the formulation of O1-O8 are represented in the Table no 1. Amount of Eudragit L-100 (X1, mg), Cellulose acetate phthalate (X2, mg) and Cetyl alcohol (X3, mg) were selected as independent variables (factors), which were varied at two levels (low and high). It was granulated with varying amounts of Cellulose acetate phthalate, EudragitL-100 and fixed amount of Hydroxy propyl methyl cellulose phthalate was incorporated as per the quantity given in table 1. It was granulated using water:ethanol (2:3)as the granulating agent, until a coherent mass was formed. Then the coherent mass was passed through sieve no. 20 and the wet granules were dried at ambient temperature for 20 minutes. Then the granules were coated with Cetyl alcohol as per the quantity given in the table 1 by congealing method. The congealed granules were lubricated with sufficient quantity of talc and were subjected to compression. The effect of the various polymers were studied using the basic polynomial equation (6).

$$Y=B_0+B_1(X_1)+B_2(X_2)+B_3(X_3)+B_{12}(X_1X_2)+B_{13}(X_1X_2)+B_{23}(X_2X_3)+B_{123}(X_1X_2X_3)$$

where Y is the dependent variable, while bo is the intercept, B_0, B_1, B_2, B_3, B_{12}, B_{13}, B_{23}, and $B_{123}$are regression coefficients; X_1, $X_2$and X_3 are undependable variables; X_1X_2, X_2X_3, and X_1X_3 are interaction between variables. The time taken for 90% drug release ($T_{90\%}$) was used as dependent variable (response). Design-Expert 10.0.3.0 software (Stat-Ease Inc., USA) trial version was used for generation and evaluation of the statistical experimental design. The matrix of the design including investigated factors and response are shown in Table 1. The validity of the derived polynomial equations for the dependent variables (dissolution parameters) was verified by designing and evaluating extra check point formulation. The variables are substituted in the polynomial equation and the $T_{90\%}$ value was predicted. The extra design check point formulation was formulated by calculating the transformed value to actual proportion. The extra design check point formulation was coded as C-1 and was evaluated by dissolution studies.

Evaluation of bilayered tablet:

Weight Variation: Weight variation of each batch was calculated by randomly selecting 20 tablets and individual weight of them were taken in analytical balance (Shimadzu TX-423L, Japan) and the test was performed according to the official method (7).

Thickness: Tablets were randomly sampled and thickness of 10 tablets was measured individually using digital Vernier caliper. Then mean ± standard deviation was calculated

Hardness: Hardness of 10 tablets was measured individually using Monsanto hardness tester. Then mean ± SD was calculated.

Friability: 20 tablets were weighed in a Shimadzu digital balance having readability of 1 mg. These tablets were transformed into Roche friabilator which was set to 100 revolutions. After the completion of revolution dust was removed completely, weighted again in the same balance and percentage loss was calculated.

Drug content: The prepared tablets were analysed for Diltiazem Hydrochloride content. Tablets were crushed into fine powder and Diltiazem Hydrochloride was extracted with water by shaking the crushed powder with water mechanically for two hours. The supernatant liquid was filtered, diluted suitably and estimated in Shimadzu UV Pharmaspec Double beam spectrophotometer (Shimadzu, Japan) at λmax 237nm (8).

In vitro drug release study: Release of Diltiazem was determined using a Lab India Disso 2000 (Labindia analytical instruments private limited, Thane, Maharashtra) at 100 rpm. The dissolution was studied using 900ml 0.1N hydrochloric acid for 2 h followed by 900 ml phosphate buffer saline (pH 7.4). The temperature was maintained at 37± 0.2°C. Samples of 5ml were withdrawn at appropriate time intervals throughout the dissolution study of 12 hrs and was taken for analysis. Samples were suitably diluted and analyzed for diltiazem hydrochloride content using Shimadzu UV Pharmaspec Double beam spectrophotometer (Shimadzu, Japan) at λmax 237nm. After each sampling 5 ml of the same buffer was added to the bowl to maintain sink conditions (9).

In vitro drug release kinetics: The rate and the mechanism of release of Diltiazem hydrochloride from the prepared matrix tablets were analysed by fitting the dissolution data into zero order equation(10).

$$Q = Q_0-K_0t,$$

where Q is the amount of drug released at time, t, and k_o is the release rate,
first order equation(11),

$$LnQ= LnQ_o -k_1t,$$

where k_1 is the release rate. The dissolution date was further analyzed to define the mechanism of

release by applying the dissolution date following the empirical equation(12),

$$Q = K_H t^{\frac{1}{2}}$$

where K_H is the Higuchi dissolution constant at time t.

The release of the drug was further evaluated using Hopfenberg model following the empirical formula for evaluating the heterogenous erosion of the device

$$\frac{M_t}{M_\infty} = 1 - \left[1 - \frac{K_0 t}{C_0 A_O}\right]^2$$

where M_t is the amount of drug dissolved in time t, M_∞ is the total amount of drug dissolved when the pharmaceutical dosage form is exhausted, M_t / M_∞ is the fraction of drug dissolved, K_0 is the erosion rate constant, C_0 is the initial concentration of drug in the matrix and A_0 is the initial radius for a sphere or cylinder or the half-thickness for a slab. The value of n is 1, 2 and 3 for a slab, cylinder and sphere respectively(13).

RESULTS AND DISCUSSION

Physical evaluation of tablets: The results of the physical evaluation of the tablets were depicted in table no 2. All the compressed tablets when evaluated for weight variation test were found to be within the limit of ± 5% (2.34 – 3.44%). The thickness of all the batches was found to be in between 4.302 – 4.425 mm. The hardness of all the batches was found to be 3.52 – 4.51 kg/cm^2. The % friability of all the batches was found to be in between 1.8 – 2.3%. The drug content in all the formulation was found to be in between 98.94 – 99.68%.

In-vitro drug release studies: Diltiazem hydrochloride is highly soluble and permeable and belongs to BCS class I category it was taken as a model drug to study the release of it from the waxy and enteric polymer matrix. The monolithic waxy matrix was prepared by incorporating the water soluble drug diltiazem along with enteric polymers and were microgranulated (Hydroxy propyl methyl cellulose phthalate, Eudragit L-100, Cellulose acetate phthalate) and while wax, cetyl alcohol, was used to coat the enteric granules, using congealing method. In order to study the extent of influence of each polymer and to control the magnitude of impact, either positive or negative in nature, the study was designed statistically using 2^3 factorial design. The eight formulations of optimization phase were categorized as four groups based on the level and number of variables. The groups are listed below:

Group 1: Formulation containing all variables at low level (O1)
Group 2: Formulation containing any one of the three variables at high level (O2,O3,O5)
Group 3: Formulation containing any two of the three variables at high level (O4, O6, and O7)
Group 4: Formulation containing all three variables at high level (O8)

The comparative analysis of each formulation was based on *in vitro* kinetic parameters which elucidate the release profile such as amount of drug release in acidic medium and basic medium separately, uniformity of drug release in basic medium and time taken by the delivery system to release 90% of the loaded drug. The group 1 formulation, O1, not only released 59.38% of the loaded drug in acidic medium but also found to be devoid of drug molecules within 10 hours. In group 2 formulations containing any one of the three variables at high level, the T90% values, the order of influence may be arranged in the descending order of Cetyl alcohol> Eudragit L-100>Cellulose acetate phthalate. Presence of cellulose acetate phthalate has not only exhibited least retardant effect, comparatively, but also revealed the ability to extend the release for stipulated 12 hours. This could be attributed to the high solubility of cellulose acetate phthalate, a substituted cellulose derivative having high solubility in phosphate buffer despite its insolubility in acidic medium(14), which might have mediated the drug release through pore diffusion rather than erosion mediated release, commonly observed pattern in waxy matrix(15). Nevertheless, the release pattern obeyed Hofbenberg's model (erosion plot) with fair linearity indicating the controlled release. Eudragit L-100, methacrylic anionic copolymer having dissolving property above a pH of 6 (16), was found to have retardant effect higher than that of Cellulose acetate pthalate. As mentioned above, Cetyl alcohol, waxy retardant used in the coating of enteric granules exhibited maximum influence to retard the release. This might be due to both its insolubility in both acidic and basic medium and its presence in the outer coating that controls the amount of dissolution medium entering into the granules thereby initializes and controls the release.

CONCLUSION

The study revealed that cetyl alcohol was capable of retarding the water soluble diltiazem hydrochloride than the enteric polymers Eudragit L 100 and Cellulose acetate phthalate which was evident from the higher % contribution value. The drug release from all the formulations was found to be erosion mediated and concentration independent. Cetyl alcohol is capable of retarding the water soluble drug diltiazem hydrochloride.

Table 1: Composition of sustained release layer of diltiazem HCl bilayered tablet with observed response values for diltiazem bilayered tablet

Batch code	Eudragit L-100 in mg	Cellulose acetate phthalate in mg	Cetyl alcohol in mg	Hydroxy propyl methyl cellulose phthalate in mg	$T_{90\%}$ in min (Mean ± S.D) (n=3)
O1	20 (-1)	15 (-1)	55 (-1)	10	508.92 ± 8.62 (Y1)
O2	30 (+1)	15 (-1)	55 (-1)	10	643.83 ± 10.22 (Y2)
O3	20 (-1)	30 (+1)	55 (-1)	10	531.33 ± 9.64 (Y3)
O4	30 (+1)	30 (+1)	55 (-1)	10	601.02 ± 7.55 (Y4)
O5	20 (-1)	15 (-1)	75 (+1)	10	654.87 ± 9.88 (Y5)
O6	30 (+1)	15 (-1)	75 (+1)	10	708.98 ± 8.42 (Y6)
O7	20 (-1)	30 (+1)	75 (+1)	10	683.55 ± 12.02 (Y7)
O8	30 (+1)	30 (+1)	75 (+1)	10	827.89 ± 6.26 (Y8)

(+1) = higher values and (−1) = lower values

Table 2: Physical Properties of the Compressed Tablets

Batch Code	Deviation in Weight Variation Test (%)	Thickness (mm)	Hardness (Kg/cm^2)	% Friability	Drug content uniformity
O-1	3.44 ± 0.25	4.302 ± 0.012	3.52 ± 0.01	2 ± 0.1	99.15± 0.14
O-2	3.25 ± 0.31	4.363 ± 0.021	3.81 ± 0.02	2.3 ± 0.2	99.67 ± 0.08
O-3	3.12 ± 0.45	4.372 ± 0.013	4.21 ± 0.01	2.1± 0.2	99.14 ± 0.07
O-4	2.94 ± 0.69	4.391 ± 0.03	4.51 ± 0.03	1.9 ± 0.1	99.03 ± 0.09
O-5	2.65 ± 0.66	4.402 ± 0.015	3.82 ± 0.04	1.8 ± 0.3	99.76 ± 0.14
O-6	3.12 ± 0.29	4.410 ± 0.016	4.21 ± 0.01	2.4 ± 0.2	99.68 ± 0.16
O-7	2.65 ± 0.38	4.419 ± 0.001	4.31 ± 0.02	2.2 ± 0.1	98.98 ± 0.19
O-8	2.34 ± 0.54	4.425 ± 0.02	4.22 ± 0.01	2.2 ± 0.1	98.94 ± 0.15

All values are expressed as mean ± SE

Table 3: Regression values of in vitro kinetic models

Invitro Kinetic model Regression values	Batch code							
	O1	O2	O3	O4	O5	O6	O7	O8
Zero order	0.9907	0.9942	0.9986	0.9869	0.9971	0.9965	0.9965	0.9976
First order	0.7058	0.8321	0.6608	0.9668	0.9548	0.9947	0.9322	0.9893
Highuchi model	0.9259	0.9569	0.938	0.9768	0.9571	0.9596	0.9541	0.9653
Hopfenberg model	-0.9464	-0.938	-0.9316	-0.9857	-0.9713	-0.9707	-0.9648	-0.9951

Table No 4 Main effects and interaction of Eudragit L 100, Cellulose acetate phthalate and Cetyl alcohol on drug dissolution in bilayered tablets

Main effects and interaction	Standardized effect	Sum of squares	% contribution
A-Eudragit L 100	100.7625	20306.2	28.0085
B-Cellulose acetate phthalate	31.7975	2022.16	2.78919
C-Cetyl alcohol	147.5475	43540.5	60.056
AB	6.2525	78.1875	0.10784
AC	-1.5375	4.72781	0.00652
BC	41.9975	3527.58	4.86563
ABC	38.8625	3020.59	4.16633

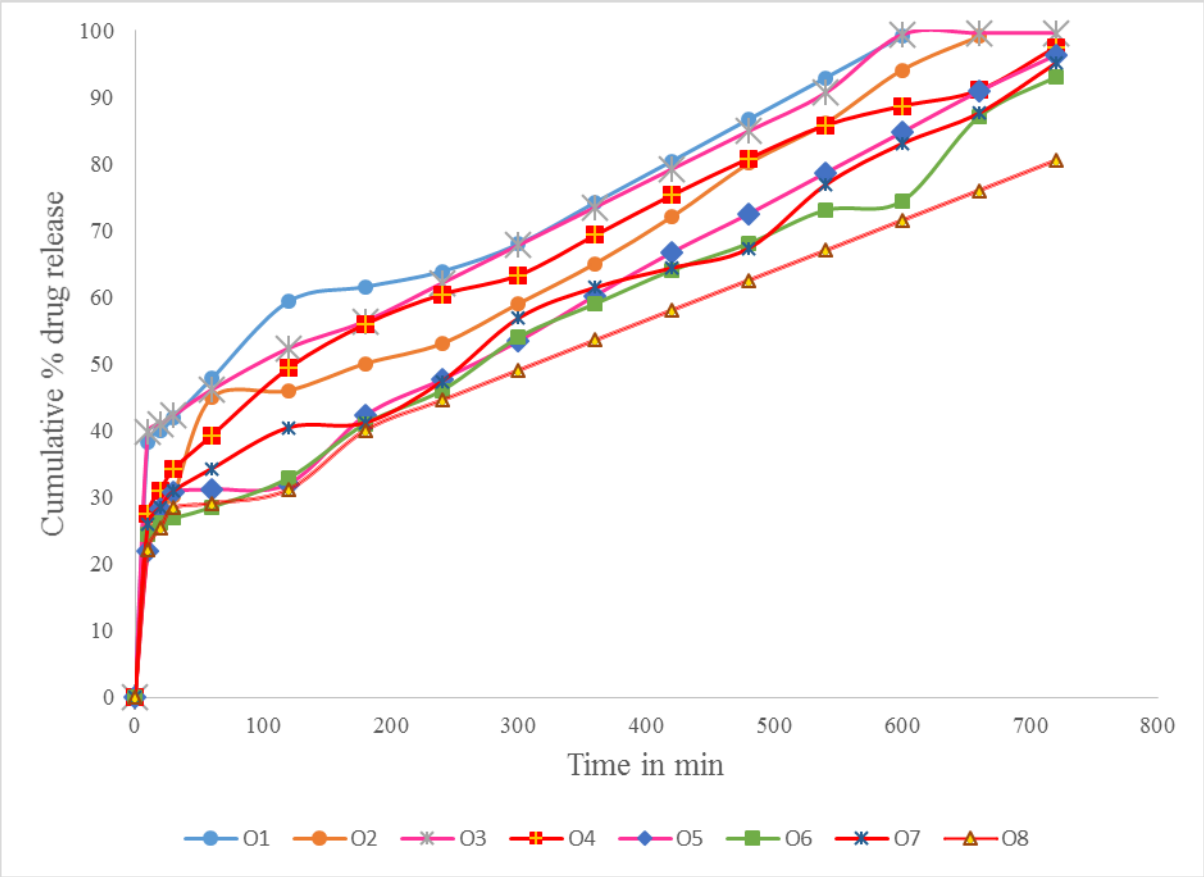

Figure 1: In vitro drug release data of formulated bilayer tablets

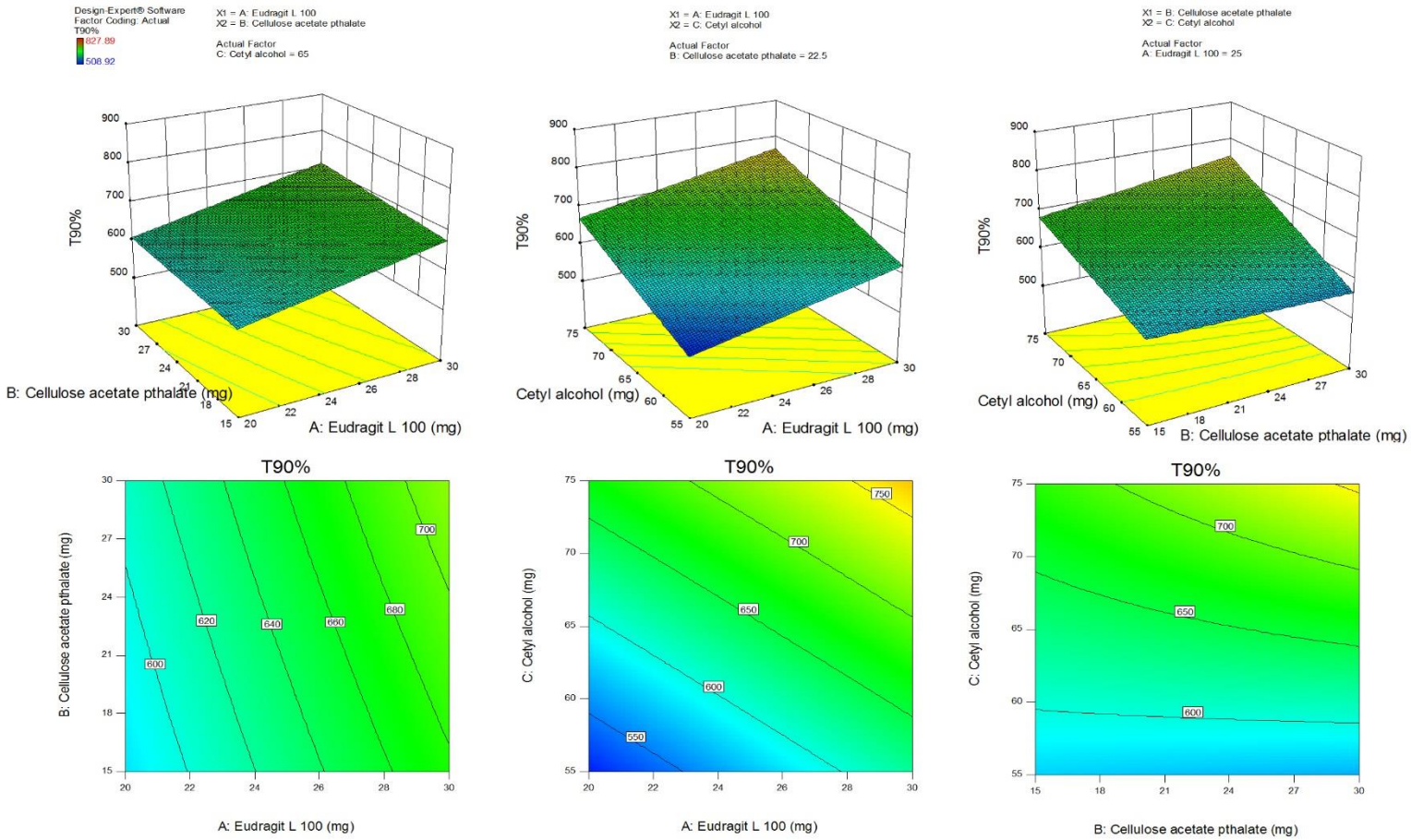

Figure 2: Response surface plots showing the influence of Cellulose acetate phthalate, Eudragit L 100 and Cetyl alcohol on $T_{90\%}$

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