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## Formulation Development and Evaluation of Sustained Release Matrix Pellets of Tizanidine Hydrochloride

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### ABSTRACT:

Aim of this study is to prepare matrix pellets of muscular spasticity drug [Tizanidine Hydrochloride] by extrusion – spheronization technique and formulating the sustained release matrix pellets using hydrophobic and hydrophilic matrix forming polymer like Ethyl cellulose and HPMC K15M Drug -polymer interaction was studied by FTIR. Different preliminary batches were performed binder solution water: alcohol(8:2). Speed of spheronization was 1500 rpm for 10 minutes and HPMC K 15M as hydrophilic and ethyl cellulose hydrophobic polymer were selected. From that polymers in the ratio 30% HPMC K 15M and 45 % ethyl cellulose batch (F3) pellets have good morphological properties and desire drug release. A 32 factorial design was used to determine the effects of the dependent and independent variables. It was concluded that significant effects were exerted by the concentration of hydrophobic and concentration of hydrophilic polymer. Friability, flow properties, Content uniformity determined and in vitro drug release characteristics was studied by UV spectroscopy and optimized batch surface morphology and particle size analysis was done by optical SEM. Selection and optimization was carried by using Design-Expert® Software V10 software and kinetics of drug release determined by DDSolver.

**Key words:** Tizanidine hydrochloride, Extrusion-spheronization, HPMC K15 M, Ethylcellulose, SR Matrix pellets.

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### INTRODUCTION:

Sustained release systems involve such drug delivery system that provides slow release of drug over an extended period of time. If the system is significant in maintaining persistent drug levels in the blood or target tissue, it is call as a controlled-release system. For sustained release systems the oral route of administration has greater important for the reason that more flexibility in dosage form design. The design of oral sustained release delivery systems is considered to several interrelated variables of viable importance like as the disease being treated, the patient, type of delivery system, and the length of therapy and the properties of the drug <sup>(1, 2)</sup>.

Pellets for pharmaceutical applications are defined as small, spherical, free-flowing granules with a narrow size distribution, typically varying in diameter between 500 to 1500 µm, in which the active pharmaceutical ingredient (API) is present as a number of small independent subunits. To deliver the recommended total dose, these subunits are filled into a sachet or encapsulated or compressed into a tablet. Pellets disperse freely in the GIT. It maximizes drug absorption; minimize local irritation of mucosa by certain irritant drugs. Reduce variations in gastric emptying rates, flexibility in dosage form design, ease

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to coat; these are advantages of pellets over tablet<sup>(4, 5, 6)</sup>.

Extrusion-Spheronization technique is most advance technique of pelletization. The process of extrusion spheronization includes. **Dry mixing:** The material is dried, mixed to achieve homogeneous powder dispersion. **Wet granulation:** With the help of a suitable granulating fluid, powder mixture is transformed into a plastic wet mass. **Extrusion:** The wet mass obtained is extruded to produce rod-shaped particles of uniform diameter that is charged into a spheronizer. **Spheronization:** The extrudates are

rounded off into spherical particles using a spheronizer. **Drying and Screening:** The spherical particles were then dried to achieve the desired moisture content and optionally screened to achieve a targeted size distribution. Drying is achieved by tray drying or room temperature, the specific requirements for a wetted mass to be suitable for extrusion and spheronization. Ethylcellulose is a hydrophobic matrix forming polymer shows drug release retardation. During dissolution, the HPMC pellets absorb water and producing a viscous gel matrix which controlled the drug release by diffusion or erosion<sup>(7, 8)</sup>.

Tizanidine is a short-acting drug for the management of muscular spasticity. Tizanidine is an agonist at  $\alpha_2$ -adrenergic receptor site and presumably reduces spasticity by increasing presynaptic inhibition of motor neurons. Tizanidine is approved by the food and drug Administration in 1996, is often used as antispastic agent when oral treatment is indicated<sup>(10, 11)</sup>.

#### MATERIALS AND METHOD:

Tizanidine Hydrochloride drug obtained as gift sample from SUN Pharmaceutical industries Ltd. Vadodara, India. HPMC K15M other HPMC grades and Etylcellulose obtained as gift sample from torrent research center, Ahmedabad, India. Diluent- Microcrystalline cellulose PH10, binder- alcohol and distilled water were used in the preparation of matrix pellets.

#### Preparation of Pellets:

The pellets are prepared by pelletization technique using extrusion-spheronization. Drug, HPMC K 15M, EC and MCC are passed through sieve No. 60 prior to pelletization. The binder water:alcohol (8:2) solution is added drop wise to the mixture and mixed for few minute. The obtained dough mass is extruded using a simple Ram extruder (1 mm orifice). The extrudates are immediately spheronized for optimized time at optimized rotational speed. The pellets are dried overnight at room temperature and in a tray dryer.

**FTIR:** FTIR was carried out in the scanning range 4000-400  $\text{cm}^{-1}$ . The FTIR spectra of Tizanidine hydrochloride (figure:1) and drug with excipients spectra were recorded(figure:2). **Differential scanning calorimetry (DSC):** the thermal behavior of tizanidine hydrochloride was studied using DSC (figure:3).

#### Evaluation Parameters of the pellets:

**Determination of particles size:** The size of pellets was determined by particle size distribution, mean particle, mean diameter, geometric mean diameter, and length. Particle size analysis carried out by a simple sieve analysis. Simply sieve analysis done for pellets size of pellets are consider as average of that sieve size can be measured.

**Bulk Density ( $D_b$ ):** Bulk density defined as the ratio of total mass of powder to the bulk volume of powder. It is expressed in g/ml and is given by

$$D_b = M / V_b$$

Where,

M is the mass of powder

$V_b$  is the bulk volume of the powder.

**Tapped Density ( $D_t$ ):** Tapped density is the ratio of total mass of the powder to the tapped volume of the powder. Volume was measured by tapping the powder for 750 times (in a bulk density apparatus). It is expressed in g/ml and is given by

$$D_t = M / V_t$$

Where,

M is the mass of powder

$V_t$  is the tapped volume of the powder.

**Angle of Repose:** The angle of repose was determined using funnel method. Radius of the

heap (r) was measured and the angle of repose (q) was calculated using the formula.

$$\tan\theta = h/r$$

$$\text{Therefore, } \theta = \tan^{-1} h/r$$

Where,  $\theta$  = Angle of repose

**Hausner Ratio:** Hausner ratio is an indirect index of ease of powder flow. It is calculated by the following formula is as under given,

$$\text{Hausner ratio} = D_t/D_b \text{ Where, } D_t = \text{tapped density}$$

$$D_b = \text{bulk density.}$$

Lower Hausner ratio (<1.25) indicates better flow properties than higher ones (>1.25)

**Sphericity:** Sphericity is most important characteristic of pellets. Several methods are used to determine sphericity. One of them is visual inspection of pellets, but it is not an accurate method to determine the sphericity. Another method is a plan critical stability; it is the angle to which a plan has to be tilted before pellet begins to roll. But now days, to determine sphericity, aspect ratio is widely used, feret diameter is required for this purpose.

**% yield:** All the batches of sustained release pellets prepared by extrusion spheronization were evaluated for percentage yield of the pellets. The actual percentage yields of pellets were calculated by using the following formula:

$$\% \text{ yield of pellets} = \frac{\text{Practical yield of pellets}}{\text{Theoretical yield of pellets}} \times 100$$

**Friability:** Accurately weighed quantity of pellets (3 gm) were taken from final batch of pellets and placed in a friabilator and tumbled for 100 revolutions at 25 RPM. Twelve steel balls (weighing 0.445 gm each) were used as an attrition agent. Subsequently, the pellets were sieved through sieve no. 20. The weight loss (%) is calculated as:

$$\% F = (W_i - W_r / W_i) 100$$

Where,

$W_i$  is initial weight of pellets before friability testing,

$W_r$  is the weight of pellets retained above the sieve after friability testing.

**Drug Content:** Accurately weighed pellets equivalent 100 mg drug were crushed in a dried mortar- pestle. Powder of the pellets was dissolved in up to 100 ml phosphate buffer pH 7.4. It was stirred for 15 min and filtered. Appropriate dilutions of solution were prepared subsequently from it and were analyzed by UV-VIS spectrophotometer (UV-1700, Pharmaspec, Shimadzu Ltd, and Japan).

**In Vitro Drug Release Studies:** The in vitro release of the drug from pellets of all formulation batches were performed using USP apparatus Type I (Basket) Electro lab, India. The dissolution medium consisted of 900 ml of 0.1 N Hydrochloric acid for 2 hour than phosphate buffer pH 6.8. The medium was replenished with same amount of fresh dissolution media each time. The filtered samples were analyzed by UV-VIS spectrophotometer (UV-1700, Shimadzu Ltd, Japan)

#### Factorial Design:

In order to optimize Tizanidine HCl sustained release matrix pellets two independent variables were selected, concentration of HPMC K 15M and concentration of ethyl cellulose. In the present work, the  $3^2$  full factorial design (**table: 1**) was adopted to find out the optimum combination of independent variables. The desired values of responses selected by studying drug release profile of marketed preparation:

Independent variables are:

$X_1$  = concentration of HPMC K15M at 25 %, 30 % and 35 %

$X_2$  = concentration of ethylcellulose at 35%, 40 % and 45 %

Responses,

- 1) % Drug release at 2 hr ( $Y_1$ ) between 28 % to 32
- 2) % Drug release at 6 hr ( $Y_2$ ) between 55 % to 61%
- 3) % Drug release at 12 hr ( $Y_3$ ) not less than 95 %

Drug release kinetics was studied using DDSolver and comparison is done with marketed product.

## RESULT AND DISCUSSION:

Drug excipients interaction was carried out by FTIR (**figure:2**) and DSC thermogram (**figure:3**) which indicates that there is absence of any interaction between drug and excipients. *In vitro* drug release study of all formulation batches (F1-F9) were performed in triplicate using USP apparatus Type-I (Basket), 100rpm and distilled water as dissolution medium. The batch F4 and F5 shows  $97.93 \pm 0.63$  % and  $98.86 \pm 0.87$  % drug release respectively in the 10 hrs. F4 and F5 batch cannot sustained the release up to 12 hrs. The batch F6 shows  $98.80 \pm 0.48$  drug release in 11 hour. The other batches F1, F2, F3, F7, F8, F9 were able to sustained the drug release up to 12hrs. Among these batches F1, F3, F7 and F8 shows that  $96.94 \pm 0.131$  %  $93.41 \pm 1.06$  %,  $89.13 \pm 1.15$  % and  $94.27 \pm 0.56$  drug release at 12 hrs respectively. The Batches F3 and F9 shows better drug release and it was within the acceptance range as per dependent variable range. The result of percentage of drug release (%) of all formulation batches was shown in (**figure: 4**).

Response  $Y_1$  (countour plot **figure:5** and 3D surface plot **figure: 6**) % Drug release at 2 hr was set to less than 28.5-31.5 % and  $Y_2$  (countour plot **figure:7** and 3D surface plot **figure: 8**) % Drug release at 6 hr in the range 55.1-60.9 %,  $Y_3$  ( countour plot **figure:9** and 3D surface plot **figure:10** % Drug release at 12 hr values not less than of 95 %. These specifications satisfy the requirements of sustained release matrix tablet in terms of release profile. It can be concluded that by adopting a systematic formulation approach, one can reach to an optimum point in the shortest time with minimum efforts. From the overlay plot of the responses generates area batch F3 was found in the region of optimized area (**figure: 11**).

Statistical analysis From the ANOVA study of percent drug release at 2 hour, percentage drug release at 6 hour and percentage of drug release at 12 hour it is found that of p value for percent drug release at 2 hr and percentage drug release 6 hr were found to be less than 0.05 indicate that model was significant, and best fit model for response surface design was linear model. This study carried by using design expert software. The

percentage drug release 12 hr it was found p value for less than 0.05 indicate model was significant, and fit model for response surface design was quadratic model. It observed that as the change in the concentration of polymer namely Ethylcellulose (A) and HPMC K15M (B), it affects the percent drug release at 2, 6 and 12 hr.

Kinetics of drug release of optimized batch was evaluated by model dependent method using DDSolver software and model the higher correlation coefficient was considered to be best model. The result showed that korsmayer peppas followed by matrix pellets order of kinetics and the release is by ficknian diffusion mechanism (**table: 5**).

While comparing the release profile of formulated dosage form and marketed preparation, the f value was found to be 76.39, which indicates that there was no significant change in release profile. Upon comparison, the formulated preparation (pellets) showed good drug release in terms of concentration fluctuation. The comparison shown in (**figure: 12**).

While comparing the release profile of optimized batch at initial stage and after 4 weeks, the optimized batch was found to be 82.64 which indicate that there is no significant change in release profile ( **figure: 13**).

## CONCLUSION:

The results of this study showed that combination of EC as hydrophobic and HPMC K15 M as hydrophilic matrix forming polymer were 45 % and 30 % respectively and useful for sustaining the Drug release to treat muscle spasm. The resultant optimum formulation F3 was selected from the factorial batches on the basis of *in-vitro* drug released studies it showed at 2 hour 30.66 % , at 6 hour 56.96 % and drug release at 12 hour 97.92 % and have within acceptance limit. The drug release kinetics can be concluded that the Korsmeyer and Peppas model fits to optimized and non Fickian diffusion process. Comparing the release profile of formulated dosage form and marketed preparation, the f2 was found to be 76.39 means no significant changes in formulation. This study resolved the extrusion spheronization technique as

a promising approach for formulation of sustained release matrix pellets of Tizanidine Hydrochloride without coating.

#### ACKNOWLEDGEMENT:

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**Table: 1 Formulation of batches of 3<sup>2</sup> factorial design**

Formulation Ingredient	F1	F2	F3	F4	F5	F6	F7	F8	F9
Tizanidine HCl (%)	20	20	20	20	20	20	20	20	20
HPMC K 15M (%)	35	25	30	25	30	30	35	35	25
Ethyl cellulose (%)	45	45	45	35	35	40	40	35	40
MCC PH 101 (%)	00	10	05	20	15	10	05	10	15
Binder (water:alcohol)	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

**Table: 2 Evaluation of flow properties of F1-F9**

Batche no.	Angle of repose (°)	Bulk density (gm/cm <sup>3</sup> )	Tapped density (gm/cm <sup>3</sup> )	Carr's Index (%)	Housner's Ratio
F1	22.13±0.42	0.75±0.003	0.83±0.004	10.48±0.32	1.10±0.023
F2	23.13±1.09	0.82±0.004	0.85±0.002	3.52±0.42	1.03±0.003

<b>F3</b>	22.65±0.30	0.82±0.004	0.88±0.008	10.12±0.42	1.07±0.005
<b>F4</b>	24.43±0.42	0.80±0.004	0.85±0.003	5.88±0.15	1.06±0.001
<b>F5</b>	22.13±0.28	0.74±0.005	0.78±0.003	5.18±0.027	1.05±0.001
<b>F6</b>	23.39±0.56	0.78±0.008	0.87±0.005	6.81±0.49	1.06±0.006
<b>F7</b>	22.65±0.30	0.72±0.006	0.81±0.007	9.36±0.46	1.12±0.006
<b>F8</b>	23.18±0.32	0.75±0.004	0.86±0.006	11.92±0.46	1.16±0.005
<b>F9</b>	25.76±0.36	0.82±0.005	0.89±0.004	5.80±0.73	1.06±0.005

**Table: 3 Morphological characteristics of pellets F1- F9**

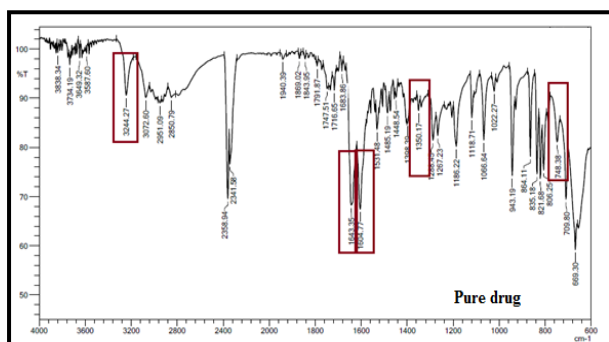
Batches	Shape	Aspect Ratio	Roundness %
<b>F1</b>	Spherical+ oval	1.00-1.23	82.17
<b>F2</b>	Spherical + oval	1.00-1.15	87.38
<b>F3</b>	Spherical +oval	1.00-1.22	89.57
<b>F4</b>	Spherical + dumbbell	1.06-1.32	81.27
<b>F5</b>	Spherical + oval	1.01-1.21	83.27
<b>F6</b>	Spherical + dumbbell	1.03-1.39	76.30
<b>F7</b>	Spherical + dumbbell	1.05-1.38	77.38
<b>F8</b>	Spherical + dumbbell	1.04-1.36	79.85
<b>F9</b>	Spherical + oval	1.01-1.24	82.31

**Table: 4 Evaluation parameter of pellets F1 – F9**

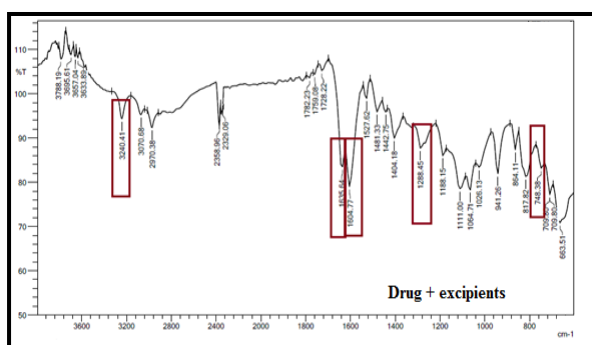
Batches	Content uniformity (%)	% yield	Friability	Particle size distributions
<b>F1</b>	97.36	82.54	0.23±0.02	1125
<b>F2</b>	98.24	87.62	0.22±0.05	1205
<b>F3</b>	98.49	88.26	0.25±0.01	1095
<b>F4</b>	96.46	86.59	0.24±0.01	1125
<b>F5</b>	97.73	84.96	0.28±0.06	1205
<b>F6</b>	98.62	86.35	0.24±0.01	1125
<b>F7</b>	98.34	85.42	0.23±0.05	1095
<b>F8</b>	96.76	87.89	0.26±0.05	1125
<b>F9</b>	96.43	85.12	0.25±0.01	1095

**Table : 5 Kinetic Model Analysis  $r^2$  and n value by DDSolver**

KINETIC MODEL	K0	R2	MSE	AIC	MSC	N
<b>Zero order</b>	7.716	0.9895	27.86	44.95	2.99	0.689
<b>First order</b>	0.172	0.9736	30.68	44.95	2.99	
<b>Higuchi</b>	25.87	0.9670	38.39	46.75	2.77	
<b>Korsmeyer and Peppas</b>	17.54	0.9980	2.69	26.26	5.33	
<b>Hixson crowell</b>	0.046	0.9838	18.87	41.83	3.38	



**Figure: 1 Fourier transform Infrared spectrum of Tizanidine HCl**



**Figure: 2 FTIR spectra of Tizanidine HCl with EC**

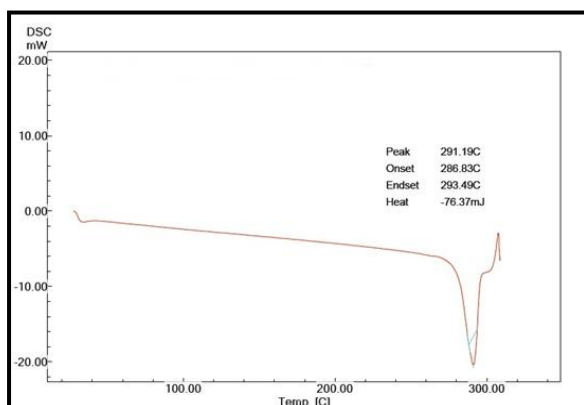
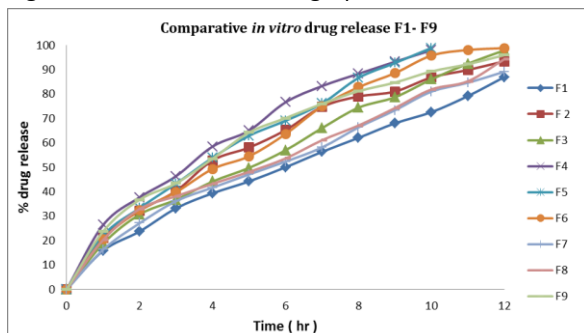


Figure: 3 DSC thermograph of Tizanidine HCl



**Figure: 5 Comparative *in vitro* drug release F1- F9**

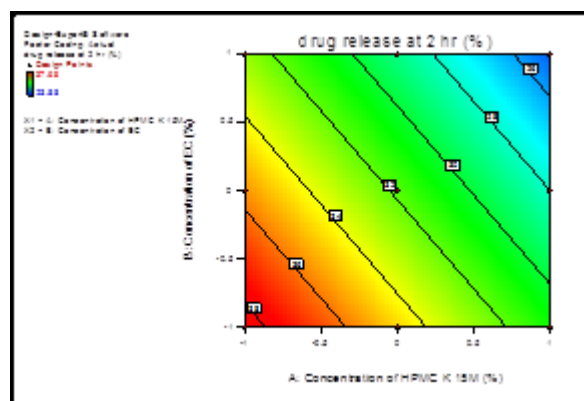


Figure: 5 contour plot of response  $Y_1$

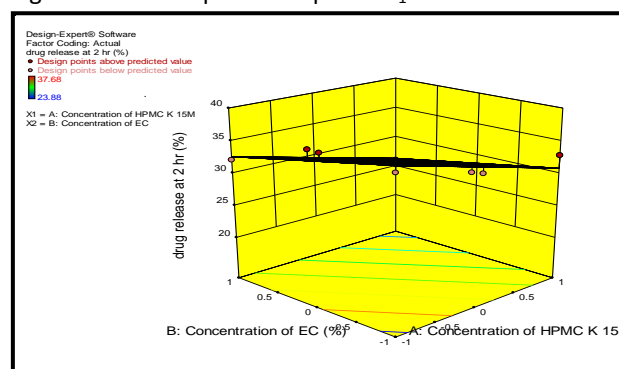


Figure: 6 3D surface plot of response  $Y_1$

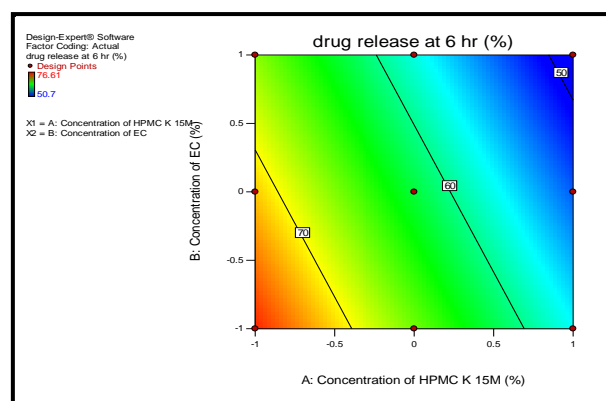


Figure: 7 contour plot of response  $Y_2$

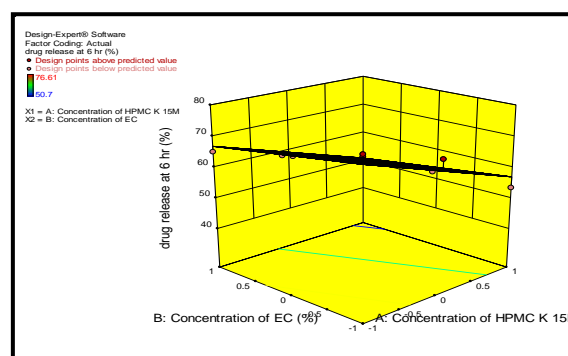


Figure: 8 3D surface plot of response  $Y_2$

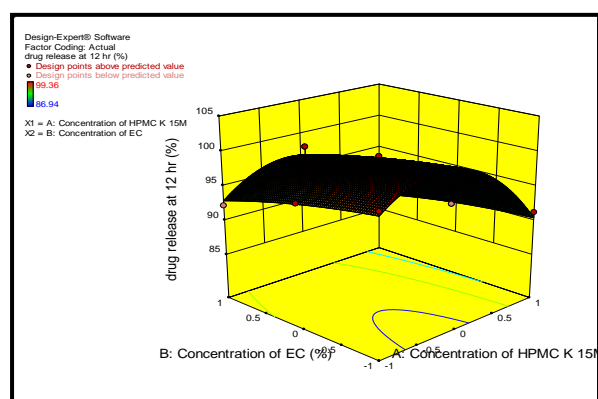
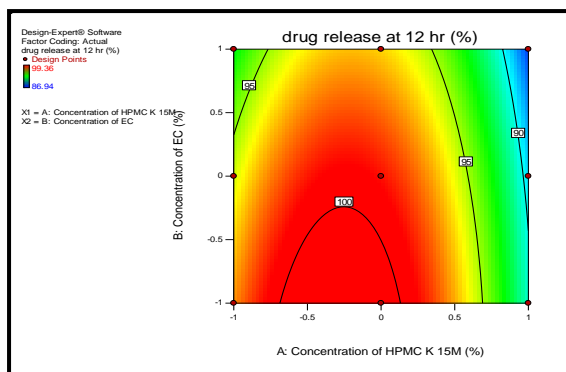
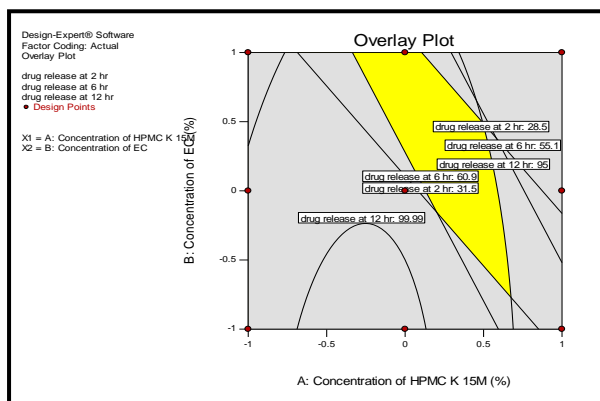
Figure 9 contour plot of response  $Y_3$ Figure 10 3D surface plot of response  $Y_3$ 

Figure 11 Overlay Plot of Response Variables

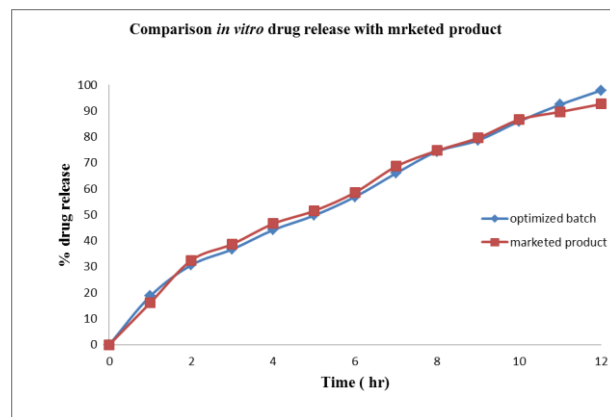
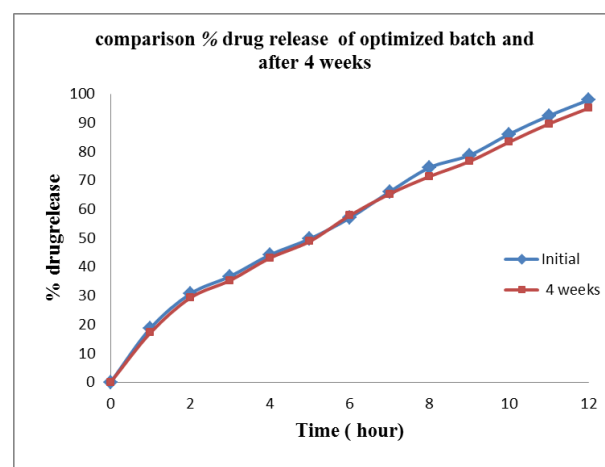
Figure 12 Comparison of *in vitro* drug release with marketed product

Figure 13 comparison % drug release of optimized batch and after 4 weeks

