



## INTERNATIONAL JOURNAL OF PHARMACY &amp; LIFE SCIENCES

**Valsartan release from sustained release matrix tablet and effect of cellulose derivatives**

P. Mahajan, S.C.Mahajan and D.K.Mishra

Department of Pharmaceutics, Mahakal Institute of Pharmaceutical Studies, Ujjain, (M.P.) - India

**Abstract**

The present study was aimed to develop antihypertensive sustained release matrix tablets of valsartan Angiotensin II receptor antagonist, using hydroxypropylmethylcellulose alone and in combination with ethyl cellulose as the matrix material in different proportion by wet granulation method. The granules were evaluated for angle of repose, bulk density and Compressibility index. The tablets were subjected to weight variation test, drug content, hardness, friability, and in vitro release studies. The granules showed satisfactory flow properties, compressibility, and all the tablet formulations showed acceptable pharmacotechnical properties. The formulated tablets also compared with a marketed product. In vitro dissolution studies indicate that EC significantly reduced the rate of drug release compared to HPMC. But no significant difference was observed in the release profile of matrix tablets made by higher percentage of EC. The result of dissolution study indicate that the formulation prepared by low viscosity grade HPMC (H1 and H2) showed maximum drug release up to 8 hrs and high viscosity grade HPMC and EC formulation (H3 to H6) showed upto 12 hrs. In case of formulation containing combination of HPMC and EC (F1 to F4) prepared using factorial design, showed drug release up to 24 hrs, whereas marketed product was found to be release up to only 3 hrs. Mathematical treatment of the *in vitro* drug release data suggest that, optimized formulation F3 fitted in to Korsmeyer and Peppas release kinetic shows  $R^2$  value 0.9930. Drug release from the matrix occurred by combination of two mechanism, diffusion and erosion of tablet.

**Key-Words:** Valsartan, HPMC, EC, Sustained Release, Matrix Tablet**Introduction**

Valsartan is an angiotensin II receptor antagonist that is used for the treatment of hypertension. It treats the hypertension by blocking the vasoconstrictor and aldosterone secreting effect of angiotensin II selectively by blocking the binding of angiotensin II and angiotensin I receptor in many tissues. The most preferred route for this drug is oral delivery in form of tablets. Valsartan has poor water solubility, low bioavailability (approximately 20-25%), and shorter half-life (nearly 6 hours)<sup>1,2</sup>. Oral drug delivery has been known for decades as the most widely utilized route of administration among all the routes that have been explored for the systemic delivery of drugs via various pharmaceutical products of different dosage forms. The reason that the oral route achieved such popularity may be in part attributed to its ease of administration as well as the traditional belief that by oral administration the drug is as well absorbed as the food stuffs that are ingested daily<sup>3</sup>.

The conventional dosage form such as tablets and capsules are the major oral preparations. Conventional dosage forms have wide acceptance up to 50-60% of total dosage forms. Solid dosage forms are popular because of ease of administration, accurate dosage, self-medication, pain avoidance and most importantly the patient compliance. In last two decades the drug delivery technology has been developed rapidly and many novel oral drug delivery systems have been invented<sup>4</sup>.

Oral drug delivery has been the most widely utilized route of administration among all routes because of certain advantages such as unit dosage form, low cost, cheapest for packaging etc. apart from these advantages this route suffers from certain drawbacks like patient noncompliance, multiple dosing, therapeutic failure that limits its use. In order to overcome these drawbacks of conventional drug delivery there is a need of development of new drug delivery system or modified drug delivery system<sup>3</sup>.

Sustained release system is a type of modified drug delivery system that can be used as an alternative to conventional drug delivery system. These systems

**\* Corresponding Author**

sustain the release of drug and maintain the plasma drug concentration in therapeutic window except any fluctuation and increase the therapeutic efficacy of drug. They show their action by avoiding peak and trough in dosing and show constant plasma drug concentration in therapeutic window. Sustained release system have benefits like patient compliance, avoid multiple dosing, increase the plasma drug concentration, avoid side effects and overcome the problems associated with conventional system<sup>5</sup>.

### Material and Methods

Valsartan was a gift sample from Torrent pharmaceutical pvt. Ltd. Ahmedabad. HPMC K15M and HPMC K100M were purchased from S.Kant.Healthcare ltd Vapi, Gujarat. Ethyl cellulose was purchased from Coax Bioremedies Pvt. Ltd., Hisar. Other ingredient lactose was obtained from Qualigens Fine Chemicals, Mumbai, magnesium stearate from S. D Fine Chem. Ltd., Mumbai and talc was obtained from Nice Chemicals Pvt. Ltd., Cochin. The other entire chemical used was of high analytical grade.

### Drug excipients interaction

Compatibility of the drug with excipients was determined by differential scanning calorimeter (Parkinlanmer, USA). This study was carried out to detect any change on chemical constitution of the drug after combination with the excipients. The samples were taken for DSC study- Valsartan (Val), Val: HPMC K15M (1:1), Val: HPMC K100M (1:1) DRUG: EC (1:1), DRUG: HPMC K15M: HPMC K100M: EC (1:1:1).

### Preparation of matrix tablet

Initially, valsartan tablets with different concentration of hydrophilic and lipophilic polymer were prepared by wet granulation technique. Required quantities of all ingredients were weighed individually on electronic balance (citizen India). All ingredients were first sieved and mixed for 5 min. Isopropyl alcohol was added drop wise till suitable mass for granulation was obtained. The wet mass granulated through sieve 8#. The granules were dried at 60°C for 1 hour in an oven (lab tech India). The dried granules were passed through sieve 10# and fractions of granules retained on the sieve were discarded then blended with talc and magnesium stearate for lubrication of granules which were then compressed on single punch tablet machine using circular 4 mm punch (cadmech Ahmadabad India) the weight of tablet adjusted to 300 mg, each tablet containing 20 mg valsartan and other excipients listed in table 1 and 2<sup>6</sup>.

### Evaluation of granules<sup>1</sup>

#### Angle of repose

The angle of repose of granules was determined by the funnel method. The accurately weighed granules were taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the granules. The granules were allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation:

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

Where, h and r are the height and radius of the powder cone.

#### Bulk density

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. A quantity of 2 g of powder from each formula, previously lightly shaken to break any agglomerates formed, was introduced into a 10-mL measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2-second intervals. The tapping was continued until no further change in volume was noted. LBD and TBD were calculated using the following formulas

$$\text{LBD} = \frac{\text{weight of the powder}}{\text{volume of the packing}}$$

$$\text{TBD} = \frac{\text{weight of the powder}}{\text{tapped volume of the packing}}$$

#### Compressibility index

The compressibility index of the granules was determined by Carr's compressibility index

$$\text{Carr's index (\%)} = \frac{[(\text{TBD} - \text{LBD}) \times 100]}{\text{TBD}}$$

### Evaluation of tablets

#### Weight variation test<sup>1</sup>

To study weight variation, 20 tablets of each formulation were weighed using an electronic balance (Citizen, India), and the test was performed according to the official method

#### Hardness and friability<sup>5</sup>

For each formulation, the hardness and friability of 6 tablets were determined using the Hardness tester (lab tech, India) and the friabilator (Veego Friabilator India), respectively

#### In Vitro release studies<sup>7-8</sup>

Release of the prepared tablets was determined up to 24 hour using U.S.P type II paddle type dissolution rate test apparatus (Veego, India). 900 ml of 0.1 N HCl was used as dissolution medium for first 2 hrs and (pH 6.8) phosphate buffers for the test of the period as dissolution medium. The paddle was adjusted at 50 rpm and the temperature of 37±1°C was maintained throughout the experiment. Samples of 10 ml were withdrawn at known time intervals and were replaced



with same volume of fresh dissolution media after each withdrawal. The samples were analyzed for drug contents by measuring absorbances at 251 nm using UV-VIS Pharmaspec spectrophotometer shimadzu 1700 Japan.

#### Drug content<sup>8</sup>

Three tablets were selected randomly from each batch, powdered separately and then taken into three volumetric flasks of 100 ml. In each flask 100 ml of phosphate buffer pH 6.8 was poured and kept for 24 hrs. After filtering the solution and making suitable dilutions, the absorbance of the filtrate was measured at 251nm using UV-VIS Pharmaspec spectrophotometer shimadzu 1700 Japan. From this absorbance, drug content was determined. Drug content was determined according to the following formula

$$\text{Drug content} = (\text{Actual drug content} / \text{theoretical drug content}) \times 100$$

#### Swelling index<sup>9</sup>

Measurement of the swelling index was carried out to gain an insight into the phenomenon of polymer hydration and to evaluate the extent of media penetration within the tablets. The swelling index was determined by equilibrium weight gain method the study was carried out in the USP dissolution apparatus type 1. The tablets were accurately weighed, placed in dissolution basket, immersed in phosphate buffer (pH 6.8) and maintained at  $37 \pm 0.5^\circ\text{C}$  in the dissolution vessel. At regular intervals of 2, 4, 6, 8, 10 up to 24 hrs. The weighted basket matrix system was withdrawn from the dissolution vessel, lightly blotted with the tissue paper to remove excess test liquid and re-weighed. The swelling index (SI) of each tablet was calculated according to the following equation.

$$\text{S.I.} = \{(W_t - W_0) / W_0\} \times 100 \text{ Where- } W_0 = \text{initial weight, } W_t = \text{final weight}$$

#### Release kinetics<sup>10-12</sup>

In order to examine the release mechanism of drug sample from the prepared matrix tablets of the optimized formulation (F3), the results of the dissolution study was examined in accordance to the kinetic models such as zero-order, first order, Higuchi equation, Korsemeyer-Pappas equation and Hixson-Crowell equation.

#### Stability study<sup>13</sup>

Stability of a drug can be defined as the time from the date of manufacture and the packaging of the formulation, until its chemical or biological activity is not less than a predetermined level of labeled potency and its physical characteristics have not changed appreciably or deleteriously. The selected formulations were packed in yellow-color PVDC/ALU, Blister. They were then stored at  $40^\circ\text{C} / 75\% \text{ RH}$  for 3 months and evaluated.

## Results and Conclusion

### Drug excipient interaction

DSC thermogram showed endothermic and exothermic peaks. Endothermic peaks were observed at  $117^\circ\text{C}$  due to melting of drug and at  $116^\circ\text{C}$  due to melting of polymer HPMC K15M. Exothermic peaks were observed at  $215^\circ\text{C}$  and  $164^\circ\text{C}$  due to polymer HPMC K100M and EC respectively. Drug and polymer displayed their characteristic individual melting trends without any appreciable deviation. From this it is observed that there is no interaction between drug and polymer DSC curve are shown in fig 1 to fig 6

### Evaluation of granules

Formulation of granules is the key factor in the production of tablet dosage form involving sustained release of drug from matrix type particle. The granules of different formulation were evaluated for LBD, TBD, compressibility index, angle of repose (Table 3A & 3B). The result of granules of formulation H1 to H4 where LBD, TBD and angle of repose value ranging from  $0.45 \pm 0.01$  to  $0.50 \pm 0.01$ ,  $0.51 \pm 0.01$  to  $0.56 \pm 0.01$ ,  $10.20 \pm 0.92$  to  $11.90 \pm 0.70$ ,  $27.34 \pm 2.49$  to  $30.85 \pm 0.87$  respectively, formulation H5 and H6 results  $0.46 \pm 0.20$  and  $0.48 \pm 0.20$ ,  $0.57 \pm 0.17$  and  $0.54 \pm 0.02$ ,  $10.97 \pm 0.90$  and  $11.05 \pm 0.35$ ,  $30.04 \pm 0.74$  and  $30.48 \pm 0.32$  respectively and formulation F1 to F4 values ranging from  $0.45 \pm 0.12$  to  $0.46 \pm 0.20$ ,  $0.50 \pm 0.22$  to  $0.52 \pm 0.17$ ,  $10.52 \pm 0.90$  to  $11.26 \pm 0.37$ ,  $32.44 \pm 0.48$  to  $33.66 \pm 0.19$ . Generally compressibility index values upto 15% result in good to excellent flow properties but reading above 25% indicates poor flow properties and angle of repose rarely less than  $20^\circ$  and value up to  $40^\circ$  indicate reasonable flow properties. All these result indicate that the formulated granules possess satisfactory flow property and compressibility.

### Evaluation of tablet

#### Physical parameter

The tablets of different formulation were evaluated for hardness, weight variation, friability, drug content and thickness (table 4A & 4B). The result of tablets of formulation H1 to H4 where weight variation, thickness, hardness, friability, drug content values ranging from  $299.42 \pm 1.80$  to  $300.13 \pm 2.05$ ,  $3.03 \pm 0.06$  to  $3.20 \pm 0.10$ ,  $4.67 \pm 0.24$  to  $5.17 \pm 0.24$ ,  $0.38 \pm 0.02$  to  $0.42 \pm 0.02$ ,  $97.7 \pm 0.85$  to  $99.66 \pm 0.05$  respectively. Formulation H5 and H6 results  $300.00 \pm 1.68$  and  $300.27 \pm 1.57$ ,  $4.83 \pm 0.24$  and  $4.73 \pm 0.21$ ,  $0.41 \pm 0.10$  and  $0.39 \pm 0.01$ ,  $98.90 \pm 0.13$  and  $99.13 \pm 0.26$ . The result of tablets of formulation F1 to F4 where weight variation, thickness, hardness, friability, drug content values ranging from  $300.00 \pm 1.36$  to  $300.22 \pm 1.42$ ,  $3.03 \pm 0.06$  to  $3.13 \pm 0.10$ ,  $5.00 \pm 0.41$  to  $5.17 \pm 0.24$ ,  $0.38 \pm 0.01$  to  $0.40 \pm 0.01$ ,  $98.67 \pm 0.34$  to  $99.97 \pm 0.41$ . The result was

concluded that the all the parameter with in acceptant range.

#### Drug release study

Drug release studies was concluded that with increase in concentration of low viscosity grade polymer HPMC K15M, there was an increase in time of cumulative % release of drug, upto 8 hours and in the case of high viscosity grade HPMC K100M also increase in time of cumulative % release of drug up to 12 hours. In EC polymer increase in concentration there was a minimum effect on increase in time of cumulative % release of drug, up to 12 hours. So low viscosity grade polymer select from optimization study and it is combined with EC in optimization study. From the optimization studies (2 level and 2 factor factorial design) it was concluded that with increase in concentration of HPMC K15M, there was an increase in time of cumulative % release of drug, but increased concentration of EC does not seem to influence the release profile of drug .F1 and F2 fail to extend the release of drug therefore formulation F3 was selected as optimized formulation which showed the release of drug up to 24 hours. F4 formulation also shows the release of drug up to 24 hour same as F3 but used EC in high conc. as compared to F3. Drug release data and comparison of drug release curve of formulation H1 to H6 and F1 to F4 are shows in table 5 and fig 7A and 7B respectively.

#### Swelling index

Measurement of the swelling index was carried out to gain an insight into the phenomenon of polymer hydration and to evaluate the extent of media penetration within the tablets. Formulation F3 was showed  $195.73 \pm 0.79$  % swelling index and result concluded that formulation F3 showed good swelling index property.

#### Release kinetics

Release kinetic was showed that *in vitro* release curve fitted under Korsmeyer and Peppas model which show  $R^2$  value 0.9930 is highest as compared to other models. The regression coefficient  $R^2$  value nearer to 1 indicated the model fitting of the release mechanism.  $R^2$  value and curve of different model are shows in table 7 and fig 9 to 13 respectively

#### Stability studies

Stability studies were carried out at  $40^\circ\text{C}$  / 75 % RH for the selected formulation for the period of 3 months there was slightly acceptable changes was observed in physical and chemical parameter and slightly acceptable changes in drug release. F3 formulation was showed  $98.46 \pm 0.16$ ,  $97.48 \pm 0.06$  and  $97.48 \pm 0.22$  up to 24 hrs in 1 month, 2 month, and 3 month respectively. Result was concluded that formulation was stable under specific temperature and humidity condition.

#### *In Vitro* drug release of marketed tablet

The *in-vitro* drug release was performed by marketed tablet, Valzaar-40 mg (Torrent Pharmaceutical Ltd. India) and data was shown on table. *In-vitro* drug release of marketed drug was found to be  $97.87 \pm 0.33$  up to 3 hour which shows the less drug release as compared to the F3 formulation. And t-value was found to be 2.574.

The present study was carried out to perform the formulation and optimization study of valsartan pure drug. The physicochemical compatibility of the drug with polymers was established through DSC. The study indicated that the drug had good compatibility with polymers. Optimization result was showed that polymer HPMC K15M good for formulation of sustained release matrix tablet. From results it was concluded that formulation of sustained release tablet of valsartan containing HPMC K15M and ethyl cellulose batch F3 can be taken as an ideal or optimized formulation which show the release up to 24 hour. . *In-vitro* drug release of marketed drug was showed the less drug release as compared to the F3 formulation. All the physical and chemical parameters were found to be in acceptable rang and fulfill all the requirements for sustained release matrix tablet.

#### References

1. United States Pharmacopeia (2007). 30/NF25, Rockville M D: United State Pharmacopoeia Convention Inc., 616, 1174.
2. www.Rxlist.com
3. Chien Y.W. (1992). *Novel Drug Delivery Systems*, 2<sup>nd</sup> edition. Expanded Marcel Dekker 2: 118,140-155.
4. Vyas S.P. and Khar R.K. (2005). *Controlled Drug Delivery and Advances*. 1<sup>st</sup> edition. Delhi, Vallabh Prakashan,155-195.
5. Lachman L., Liberman H.A. and Kanig J.L. (2008). *The Theory and Practice of Industries Pharmacy*, 3<sup>rd</sup> edition. Varghese publishing house, 296-303, 430-456
6. Rahman N.U., Sarfaraz M.K. and Mohsin S. (2006). Naproxen release from sustained release matrix system and effect of cellulose derivatives. *Pak. J. Pharm. Sci.*, **19**(3): 244-251.
7. Venkatesh D.N., Jawahar N., Ganesh G.N.K., Kumar R.S., Senthil V., Samanta M.K., Sankar S. and Elango K. (2009). Development and *In Vitro* evaluation of sustained release matrix tablet of theophylline using hydrophilic polymer as release retardant. *Int. J. Pharm. Sci. Nano.*, **2**(1): 34-38.
8. Mridanga R.R., Bose S.K. and Sengupta K. (2008). Design, Development and *in vitro*



- evolution of directly compressed sustained release matrix tablet of famotidine. *Research J. Pharm. and Tech.*, **1(3)**: 175-178.
9. Hingmire L.P., Deshmukh V.N. and Sakarkar D.M. (2008). Development and evaluation of sustained release matrix tablet using natural polymer as release modifier. *Research J. Pharm. Tech.*, **1(3)**: 123.
  10. Debjit M., Chandira M., Chiranjib, Kumudhavalli and Jayakar B. (2009). Formulation, design and development of buccoadhesive tablets of verapamil hydrochloride. *Int. J. Pharm. Tech. Research* **1(4)**: 1663-1677.
  11. Karasulua E., Karasulub H., Ertanb G., Kirilmaza L. and Tamer G. (2003). Extended release lipophilic indomethacin microspheres: formulation factors and mathematical equations fitted drug release rates. *Europe J. Pharm. Sci.*, **19**:9-104.
  12. Shahi S.R., Shinde N.V., Agrawal G.R., Shaikh S.A., Shaikh S.S., Somani V.G., Kale, M.A., Shamkuwar P.B. and Padalkar A.N. (2008). Statistical optimization of gastric floating system for oral controlled delivery of clarithromycin. *Rasayan J. Chem.*, **1(2)**:367-377.
  13. International Conference on Harmonization (ICH), Harmonized Tripartite guideline for stability testing of new drugs substances and products Q1A (R2) 2003; Feb 6.

**Tablet 1: Formulation with Single matrix material**

Ingredients	Quantity of Ingredients/Tablet (mg)					
	H1	H2	H3	H4	H5	H6
Valsartan	20	20	20	20	20	20
HPMC K15M	60 20%	120 40%	-	-	-	-
HPMC K100M	-	-	60 20%	120 40%	-	-
EC	-	-	-	-	30 10%	60 20%
Mg. Stearate	1.5	1.5	1.5	1.5	1.5	1.5
Talc	1.5	1.5	1.5	1.5	1.5	1.5
Lactose	217	157	217	157	247	217

**Tablet 2: Formulation with combined matrix material of HPMC K15M and EC**

Ingredients	Quantity of Ingredients/Tablet (mg)			
	F1	F2	F3	F4
Valsartan	20	20	20	20
HPMC K15M	60 20%	60 20%	120 40%	120 40%
EC	30 10%	60 20%	30 10%	60 20%
Mg. Stearate	1.5	1.5	1.5	1.5
Talc	1.5	1.5	1.5	1.5
Lactose	187	157	127	97

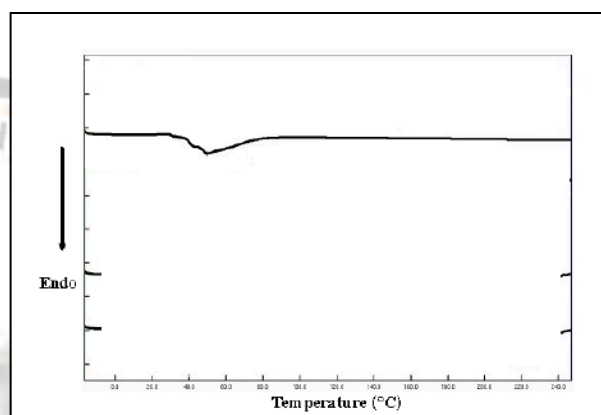
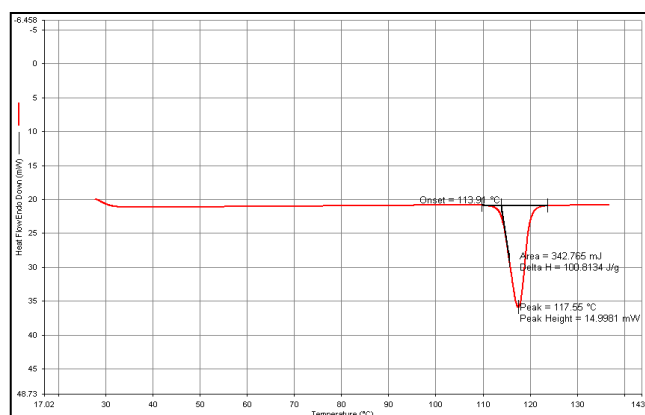


Fig. 1 &amp; 2 DSC tharmogram of Drug sample and HPMC

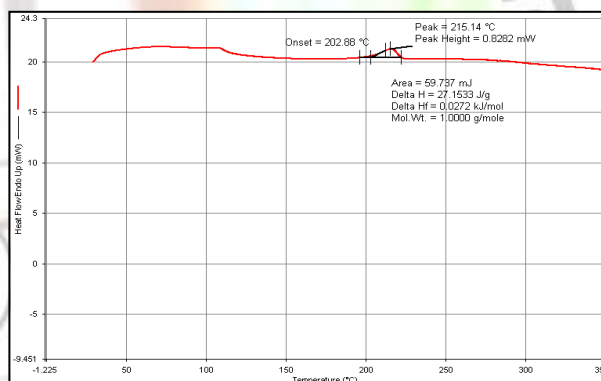
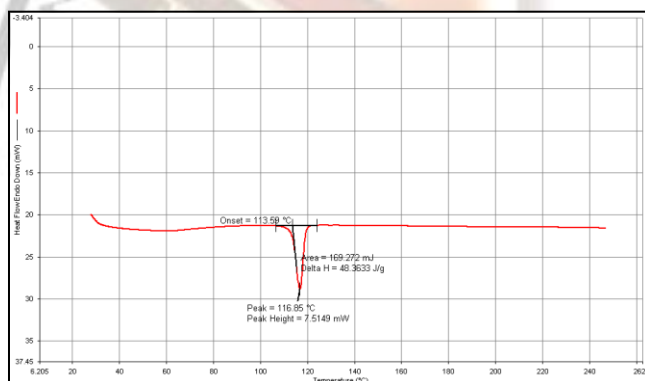


Fig. 3 &amp; 4 DSC tharmogram of Drug sample with HPMC K15M and HPMC K100M

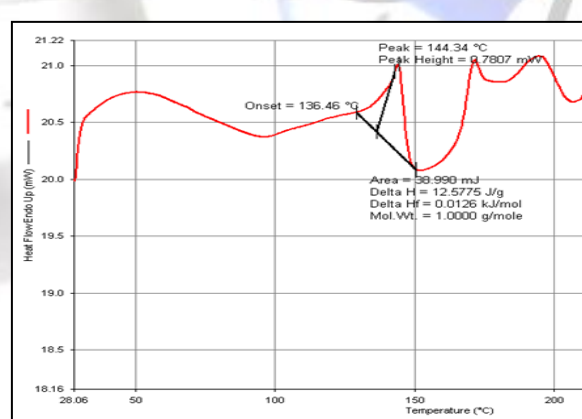
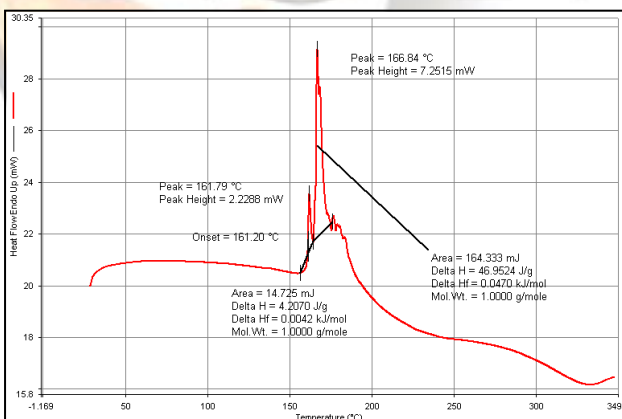


Fig. 5 &amp; 6 DSC tharmogram of Drug sample with EC and Mixture (HPMC+EC+DRUG)

Table 3A: Pre-compression parameters of granules of formulation H5 to H6

Tests	H1	H2	H3	H4	H5	H6
Bulk density (gm/ml)	0.45±0.01	0.47±0.01	0.47±0.02	0.50±0.01	0.46±0.20	0.48±0.20
Tapped density (gm/ml)	0.51±0.01	0.52±0.01	0.53±0.02	0.56±0.01	0.57±0.17	0.54±0.02
Hausner ratio	1.13±0.03	1.11±0.12	1.13±0.02	1.14±0.01	1.12±0.11	1.12±0.01
Carr's index (%)	11.11±0.09	10.20±0.92	11.31±1.34	11.90±0.70	10.97±0.90	11.05±0.35
Angle of Repose(Degree)	27.34±2.49	27.63±0.88	30.36±0.47	30.85±0.87	30.04±0.74	30.48±0.32

Table 3B: Pre-compression parameters of granules of formulation F1 to F4

Tests	F1	F2	F3	F4
Bulk density (gm/ml)	0.46±0.20	0.45±0.12	0.46±0.17	0.45±0.21
Tapped density (gm/ml)	0.52±0.10	0.51±0.15	0.52±0.17	0.50±0.22
Hausner ratio	1.12±0.01	1.12±0.01	1.12±0.10	1.13±0.01
Carr's index (%)	10.89±0.72	10.52±0.90	10.96±0.73	11.26±0.37
Angle of Repose(Degree)	32.44±0.48	32.54±0.42	33.66±0.19	33.64±0.21

Table 4A: Evaluation of Formulated Tablets of formulation F1 to F4

Tests	H1	H2	H3	H4	H5	H6
% Wt variation	300.12±1.21	299.99±1.91	300.13±2.05	299.42±1.80	300.00±1.68	300.27±1.57
Thickness (mm)	3.13±0.15	3.17±0.06	3.20±0.10	3.03±0.06	3.03±0.06	3.10±0.10
Hardness (kg/cm <sup>2</sup> )	4.67±0.24	4.83±0.24	5.0±0.41	5.17±0.24	4.83±0.24	4.73±0.21
Friability (%)	0.42±0.02	0.410±0.05	0.41±0.03	0.38±0.02	0.41±0.10	0.39±0.01
Drug content (%)	99.66±0.05	99.8±0.01	97.7±0.85	98.8±0.12	98.90±0.13	99.13±0.26

Table 4B: Evaluation of Formulated Tablets of formulation F1 to F4

S.No.	Batch Code	% Wt variation	Thickness (mm)	Hardness (kg/cm <sup>2</sup> )	Friability (%)	Drug content (%)
1	F1	300.22±1.42	3.03±0.06	5.00±0.41	0.40±0.01	99.67±0.62
2	F2	300.00±1.36	3.13±0.10	5.00±0.41	0.39±0.01	98.67±0.34
3	F3	300.00±1.43	3.03±0.12	5.17±0.24	0.38±0.01	99.97±0.41
4	F4	300.02±1.66	3.13±0.06	5.00±0.41	0.38±0.02	99.43±0.66

Table 5: Drug release data from formulation H1 to H6

S.No.	Batch Code	Drug Release (up to hrs.)
1.	H1	99.42±0.86 (5)
2.	H2	98.46±0.36 (8)
3.	H3	96.51±0.65 (9)
4.	H4	97.48±0.38 (12)
5.	H5	97.08±0.74 (11)
6.	H6	99.43±0.41 (12)
7.	F1	99.43±0.24 (13)
8.	F2	96.51±0.28 (13)
9.	F3	98.46±0.18 (24)
10.	F4	97.48±0.03 (24)

Fig. 7A: Comparison of % cumulative release curve of HPMC formulation

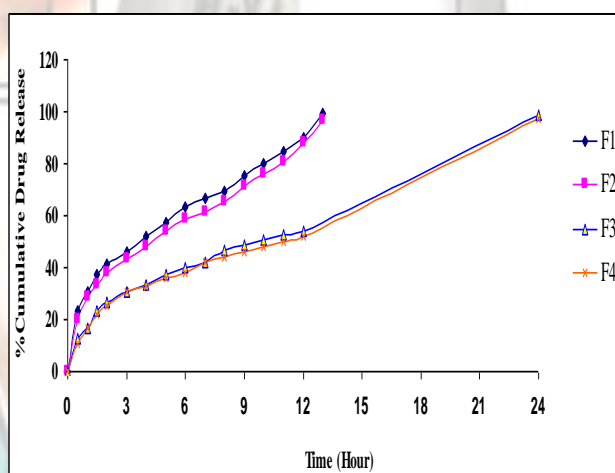
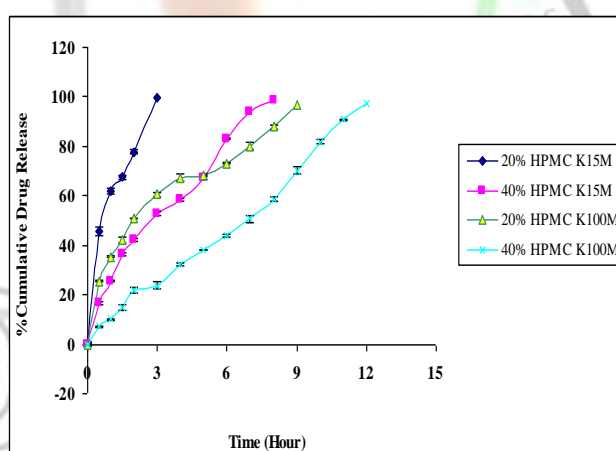


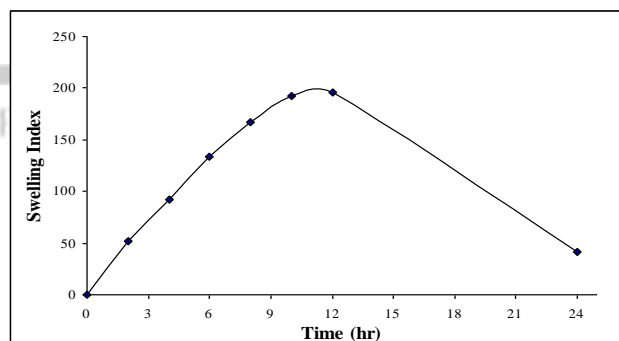
Fig. 7B % Cumulative release curve of formulation F1 to F4



Table 6: Swelling index of optimized formulation (F3)

Time Interval (hr)	Swelling Index (%)
0	0.00±0.00
2	52.03±0.24
4	92.07±0.54
6	133.53±0.25
8	167.17±0.19
10	192.87±1.13
12	195.73±0.79
24	41.03±0.76

Fig. 8 Swelling index curve of formulation F3

Table 7: R<sup>2</sup> value of drug release kinetic models

S. No.	Model	R <sup>2</sup>
1	Zero Order	0.9798
2	First Order	0.8026
3	Higuchi	0.9600
4	Hixson-Crowell	0.9061
5	Korsmeyer and Peppas	0.9930

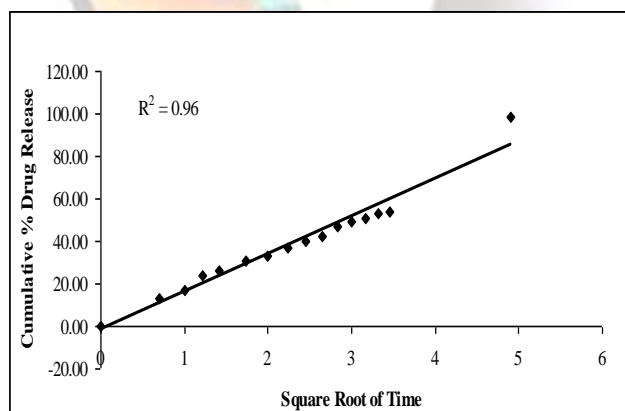
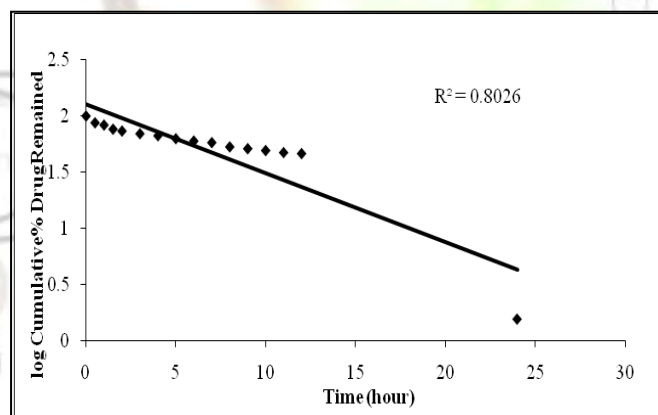
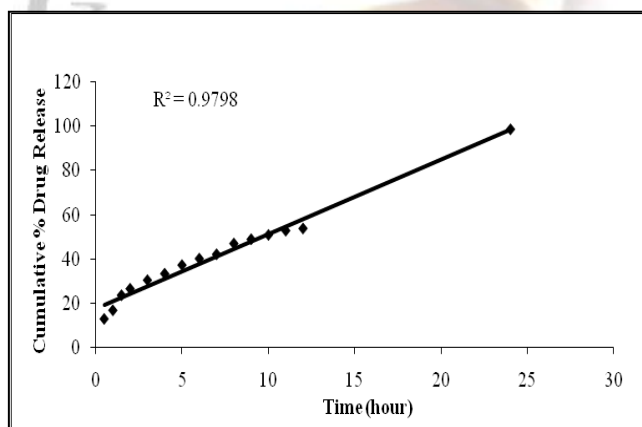


Fig. 12 Hixson-Crowell model

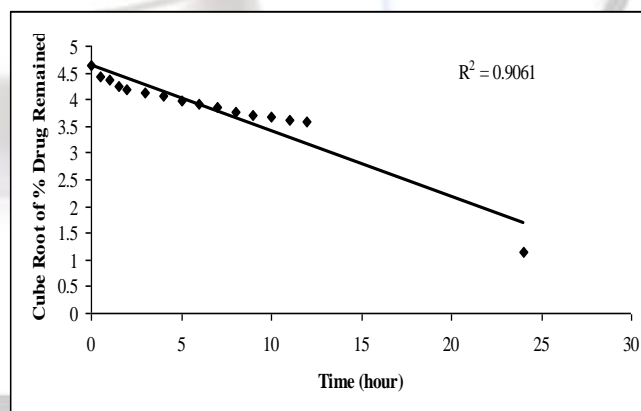


Fig. 11 Higuchi model

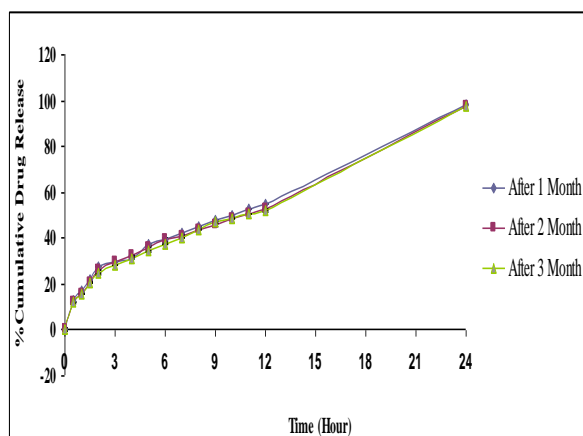


Fig. 13 Korsmeyer and Peppas

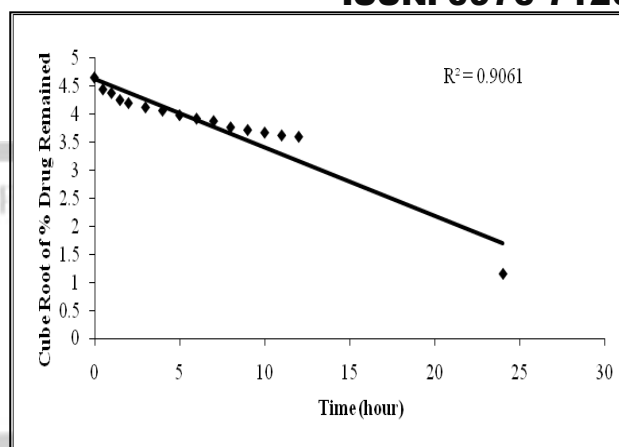


Fig. 14 % cumulative drug release curve of F3 after stability study

Table 8: Optimized formulation after stability study Table 8 *In vitro* drug release of marketed tablet

Parameter	After 1 month	After 2 month	After 3 month
Weight variation	300.43±0.76	301.00±0.46	301.03±0.52
Thickness	3.29±0.22	3.25±0.22	3.25±0.32
Hardness	5.17±0.24	5.17±0.24	5.17±0.24
Friability	0.39±0.78	0.40±0.58	0.40±0.72
Drug content (%)	99.76±0.41	99.86±0.21	99.85±0.41
% Drug Release (up to 24 hrs)	98.46±0.16	97.48±0.06	97.48±0.22

Time (Hour)	% Drug release
0.5	53.03±2.08
1	68.84±1.93
1.5	75.55±0.59
2.0	83.28±0.88
2.5	91.20±0.86
3.0	97.87±0.33

Where All Values are mean  $\pm$  S.D for n=3

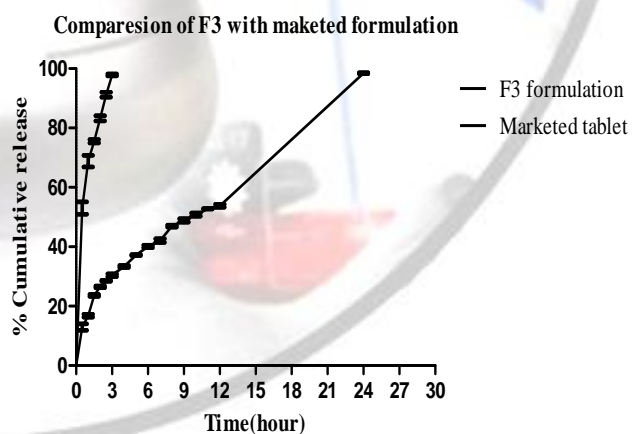


Fig. 14 &amp; 15 % Cumulative release curve of marketed formulation and comparison with F3 formulation