

**EFFECTS OF POLYMER TYPE, POLYMER:DIRECT TABLETTING  
AGENT RATIO AND TABLETTING METHOD ON VERAPAMIL  
HYDROCHLORIDE EXTENDED RELEASE FROM  
HYDROXYPROPYLMETHYLCELLULOSE MATRIX TABLETS**

POLİMER TİPİNİN, POLİMER:DOĞRUDAN TABLETLEME AJANI ORANININ VE  
TABLETLEME YÖNTEMİNİN HİDROKSİPROPİL METİLSELÜLOZ YAPILI  
MATRİS TABLETLERDEN VERAPAMİL HİDROKLORÜR'ÜN  
UZATILMIŞ SALIMI ÜZERİNE ETKİLERİ

**Evren ALĞIN, Müge KILIÇARSLAN, Ayşegül KARATAŞ,  
Nilüfer YÜKSEL, Tamer BAYKARA**

Ankara University, Faculty of Pharmacy, Department of Pharmaceutical Technology,  
06100 Tandoğan-Ankara, TURKEY

**ABSTRACT**

*This work has focused on the effects of different hydroxypropylmethylcellulose (HPMC) types and HPMC:direct tableting agent (DC-agent) ratio on Verapamil Hydrochloride (VRP HCl) release from monolayered and three-layered matrix tablets. Investigated polymers were Methocel K100LV, K15M, K100M and DC-agent was Ludipress® LCE. Eight formulations were prepared as monolayered matrix tablets while four formulations were prepared as three-layered matrix tablets by direct compression method. Drug release studies were carried out according to the method given for Delayed Release Articles in USP XXVII. HPMC types and ratios were found to be effective on drug release. Increasing amount and viscosity grade of HPMC resulted in a decrease in release of drug from the matrices. Tablets containing low viscosity grade HPMC at inner and outer layers presented release profiles close to or within the limits of pharmacopeia. Release data of three-layered matrix tablet (F12) and the reference product (Isoptin® -KKH) which were in agreement with USP XXVII criteria, were evaluated by mathematical models (zero order, first order, Higuchi, Hixson-Crowell, Korsmeyer-Peppas), difference factor ( $f_1$ ) and similarity factor ( $f_2$ ). The kinetics of VRP HCl release from F12 showed best fit to Higuchi model and Isoptin® -KKH well fitted to zero order kinetic model. F12 and Isoptin® -KKH were both show Anomalous transport mechanism*

according to their  $n$  exponent values. Depending on the results of  $f_1$  (5.2) and  $f_2$  (71.4) values, F12 and Isoptin<sup>®</sup>-KKH were found to be similar with regard to release kinetics.

**Key words:** Verapamil HCl, HPMC, Multi-layered tablets, Direct compression method, Similarity factor.

## ÖZET

Bu çalışma farklı hidroksipropilmetilselüloz (HPMC) tiplerinin ve HPMC:doğrudan tabletleme ajanı (dta) oranının, tek tabakalı ve üç tabakalı matris tabletlerden Verapamil Hidroklorür'ün (VRP HCl) salımı üzerindeki etkilerine odaklanmıştır. İncelenen polimerler Methocel K100LV, K15M, K100M ve dta Ludipress<sup>®</sup> LCE'dir. Sekiz adet tek tabakalı ve dört adet üç tabakalı matris tablet doğrudan basım yöntemi kullanılarak hazırlanmıştır. Etkin madde salım çalışmaları USP XXVII'de yer alan uzatılmış salım yapan ilaç şekillerine ait makaleler prosedürüne uygun olarak yapılmıştır. HPMC tipi ve oranının etkin madde salımı üzerine etkili olduğu saptanmıştır. HPMC miktarı ve viskozluğundaki artışın, matrislerden etkin madde salımının yavaşlamasına neden olduğu tespit edilmiştir. İç ve dış tabakalarda düşük viskozluğa sahip HPMC içeren tabletler, farmakope limitlerine yakın veya limitler içinde salım profilleri vermişlerdir. USP XXVII kriterlerine uyan üç tabakalı matris tablet (F12) ve referans ürüne (Isoptin<sup>®</sup>-KKH) ait salım verileri matematiksel modeller (sıfır derece, birinci derece, Higuchi, Hixson-Crowell, Korsmeyer-Peppas), fark faktörü ( $f_1$ ) ve benzerlik faktörü ( $f_2$ ) kullanılarak değerlendirilmiştir. VRP HCl'in salım kinetikleri F12 için en iyi Higuchi modeline, Isoptin<sup>®</sup>-KKH için sıfır derece kinetik modeline uyum göstermiştir. F12 ve Isoptin<sup>®</sup>-KKH'in her ikisi de  $n$  katsayılarına göre Anomali durumu göstermiştir.  $f_1$  (5.2) ve  $f_2$  (71.4) değerlerine göre F12 ile Isoptin<sup>®</sup>-KKH benzer kabul edilmiştir.

**Anahtar kelimeler:** Verapamil HCl, HPMC, Çok tabakalı tablet, Doğrudan basım yöntemi, Benzerlik faktörü.

## INTRODUCTION

Verapamil HCl (VRP HCl) is a water-soluble phenyl-alkyl amine derivative, which has been used widely in the treatment of the hypertension, angina pectoris and arrhythmias (1,2). Hydrophilic matrix tablets offer precise modulation of drug release through manipulation of a small number of formulation factors (3). Hydroxypropylmethylcellulose (HPMC), is a hydrophilic polymer which is used to control drug release from several pharmaceutical systems because of its non-toxic nature, easy compression, swelling properties and accommodation for high levels of drug. In HPMC matrix systems, drug release profiles are strongly influenced by the kind of polymer, its proportion in the formulation and its viscosity grade (4). However, fillers which are used in these systems play a significant role on drug release. While the addition of a soluble filler (*i.e.* lactose) to HPMC matrix systems increases porosity which leads to rapid diffusion of drug and also increases the rate of the polymer erosion which results in acceleration of drug release, the

addition of an insoluble filler (*i.e.* calcium phosphate dihydrate) can inversely effect the release of drug from these systems dependent on its level (5). HPMC and lactose combinations to form an erodible hydrophilic gel matrix system have previously been used successfully to produce controlled release preparations (6). However, swollen hydrophilic matrix systems have generally showed a nearly first order drug release profile. In hydrophilic matrix systems, the dissolution of the drug present at the surface of the matrix causes an initially high release rate of drug, followed by a rapidly declining drug release rate due to swelling and consequent increasing of the dissolution path-length of the matrix (7-11). To overcome this undesirable behavior, various matrix geometries have been recommended to achieve an almost constant release rate of drug with time. One of these techniques relies on the use of multi-layered matrix tablets as a drug delivery device (12). Multi-layered matrix tablet is a drug delivery device, which comprises a matrix core containing the active solute and one, or more barriers (modulating layers) incorporated during the tableting process. A three-layered matrix tablet consists of drug core layer sandwiched by the external modulating layers. The modulating layers which contain a hydrophilic polymer, usually HPMC (13), delay the interaction of active solute with dissolution medium, by limiting the surface available for the solute release and at the same time controlling solvent penetration rate (14-16). Thus burst effect can be smoothened and the release can be maintained at a relatively constant level during the barrier layers' swelling and erosion process. When the swollen barriers are erosion dominated the surface available for drug release slowly increases (15). By this way, combining a time-dependent control of the hydration rate of the device with the reduction of tablet surface exposed to the dissolution medium, it is feasible to achieve a linear drug release profile. Some of the advantages of three-layered matrix systems include the maximum flexibility in drug release patterns, ease of manufacturing, total system solubility and total release of drug (12, 17,18).

The objective of this work was to prepare VRP HCl extended release tablet formulations by altering the type of HPMC, the ratio of HPMC:DC-agent and tableting method.

## **MATERIALS AND METHODS**

### **Materials**

Verapamil HCl (Knoll AG), Methocel<sup>®</sup> K100LV, K15M and K100M (hydroxypropyl-methylcellulose with viscosities of 98 mPa.s, 7382 mPa.s and 18243 mPa.s, respectively) (Dow Chemical Co.), Ludipress<sup>®</sup> LCE (96% alpha-lactose monohydrate + 3.5% Kollidon 30 physical mixture) (BASF), Isoptin<sup>®</sup>-KKH film coated tablets (Knoll AG) (Batch number: 156/96) were used.

### Preparation of Matrix Tablets

Matrix tablet formulations were prepared by direct compression method and compressed in a hydraulic press using a flat-faced punches of 8 mm diameter, at a compaction force of 255 MPa. The pressure was kept at 255 MPa for 20 seconds. First group of formulations (F1-F8) were prepared as monolayered homogenous matrix tablets and the second group of formulations (F9-F12) were prepared as three-layered matrix tablets (Table 1). To prepare monolayered matrix tablets, the die cavity was accurately and manually filled with preweighed and mixed matrix content then compressed with 255 MPa compaction force. HPMC polymers (Methocel K100LV, 15M, 100M) were used as matrix and polymer layer materials. The same types of the polymers were used for the bottom and top layers of each formulation. To prepare three-layered matrix tablets, initially the volume of the die cavity was adjusted, then preweighed amount of polymer equivalent to bottom layer was manually filled into the die cavity and slightly compressed for uniform spreading. The upper punch was lifted up, and mixture of the preweighed drug layer content was manually filled over the bottom layer in the die cavity and again slightly compressed for uniform spreading. The remaining volume of the die cavity was filled with the preweighed amount of polymer equivalent to top layer and compressed with 255 MPa force of compaction.

**Table 1.** Composition of matrix tablets

Content (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
VRP HCl	120	120	120	120	120	120	120	120	120	120	120	120
Methocel K100 LV	40	-	-	60	-	-	80	90	90	90	90	90
Methocel K15M	-	40	-	-	30	-	-	-	-	-	-	-
Methocel K100M	-	-	40	-	-	25	-	-	-	-	-	-
Ludipress LCE	120	120	120	100	130	135	80	70	70	70	70	70
Contents of bottom and top layers (mg)												
Methocel K100 LV	-	-	-	-	-	-	-	-	10x2	-	-	20x2
Methocel K15M	-	-	-	-	-	-	-	-	-	10x2	-	-
Methocel K100M	-	-	-	-	-	-	-	-	-	-	10x2	-
Total weight (mg)	280	280	280	280	280	280	280	280	300	300	300	320

### *In vitro* Release Studies

Drug release studies were carried out according to the method given for Delayed Release Articles in USP XXVII. pH 1.2 0.1N HCl was used for the first two hours and pH 6.8 phosphate

buffer was used for the following six hours as dissolution media. USP XXVII-Apparatus II was used at 50 rpm. The amount of VRP HCl was determined spectrophotometrically (UV) at 278 nm.

To prove the analytical process validation of *in vitro* dissolution studies, linearity and range, accuracy and precision tests were carried out.

For linearity and range, two different stock solutions of VRP HCl with 0.1 mg/ml concentration were prepared by using pH 1.2 0.1N HCl and pH 6.8 phosphate buffer solutions. Ten different dilutions (0.005 mg/ml-0.050 mg/ml) from each stock solution were prepared and amount of VRP HCl in the dilutions was determined at 278 nm. Then equation of calibration line, confidence intervals of regression, standart deviation of residuals from line, linear regression sum of squares, residual sum of squares and residual mean square of each calibration line belong to different dissolution media were calculated.

For accuracy, two different stock solutions of VRP HCl with 0.1 mg/ml concentration were prepared by using pH 1.2 0.1N HCl and pH 6.8 phosphate buffer solutions. Six different dilutions (0.015 mg/ml-0.045 mg/ml) from each stock solution were prepared. The recovery values of dilutions for each pH medium were determined by spectrophotometry. For pH 1.2 medium, the mean recovery value was calculated as 101.0% and the value of relative standart deviation % (RSD%) was calculated as 0.973%. For pH 6.8 medium, the mean recovery value and RSD% were calculated as 100.8% and 1.16% respectively.

For precision, reproducibility and repeatability tests were done. For reproducibility (n=6) at pH 1.2 0.1N HCl medium the value of RSD% was calculated as 0.00876%, at pH 6.8 phosphate buffer medium the value of RSD% was calculated as 0.0106%. For repeatability, difference between the results of the tests (n=6) which were done by two different analysts was not significant at  $t=0.05$  probability level according to  $p<2.57$  value.

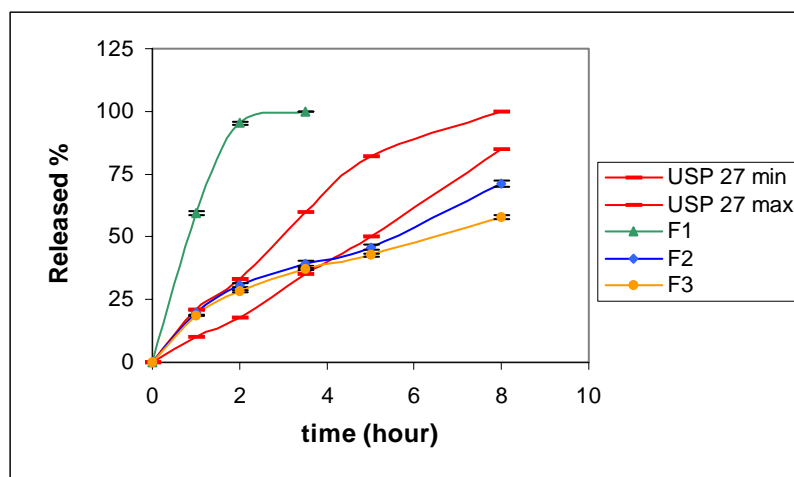
Drug release data of F12 and Isoptin<sup>®</sup>-KKH were evaluated by mathematical models (zero order, first order, Higuchi, Hixson-Crowell, Korsmeyer-Peppas) (19) and dissolution profiles were compared by  $f_1$ -difference and  $f_2$ -similarity factors (20). SPSS 9.0 computer program was used for calculations.

## RESULTS AND DISCUSSION

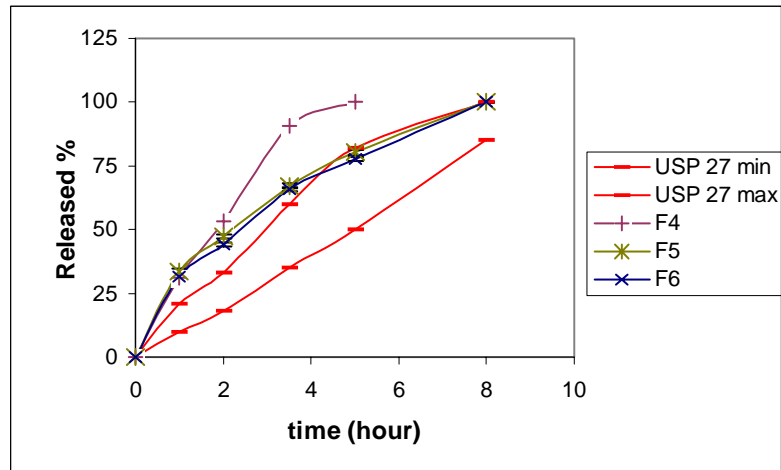
Release profiles of drug from F1-F3 formulations are given in Figure 1. In these formulations, the polymer:DC-agent ratios were kept constant (Table 1); only the type of HPMC used in formulations differed. F1 containing Methocel K100LV showed the most rapid release probably due to the low viscosity grade of the polymer. F2 and F3 containing Methocel K15M and

K100M showed very slow and similar release profiles as expected (21). Difference between viscosity grades of the polymers does not seem to be effective on the drug release profiles. These data are in accordance with some other studies (22,23). It was reported that the release of drug was affected by polymer concentration but there was no dependence on HPMC viscosity grade above 4000 cP, for the drugs with high and moderate solubility (22). As seen in Figure 1 none of the formulations (F1, F2, F3) presented a release profile within the limits of pharmacopeia during the test period (8 hours).

The polymer:DC-agent ratios were changed in F4, F5 and F6 formulations to obtain the desired drug release profile (Table 1). The amount of low viscosity grade polymer was increased and the soluble DC-agent was decreased in F4 formulation to delay the release of drug from the matrix tablet. This modification has resulted in slower release of drug from F4 formulation (Figure 2). Decrease in high viscosity grade polymers (Methocel K15M and K100M) and increase in the soluble Ludipress® LCE resulted in an increase in drug release from F5 and F6 formulations. These results are in accordance with some other studies (5,24), but this group of formulations were also unable to give a release profile within the limits of pharmacopeia (Figure 2).

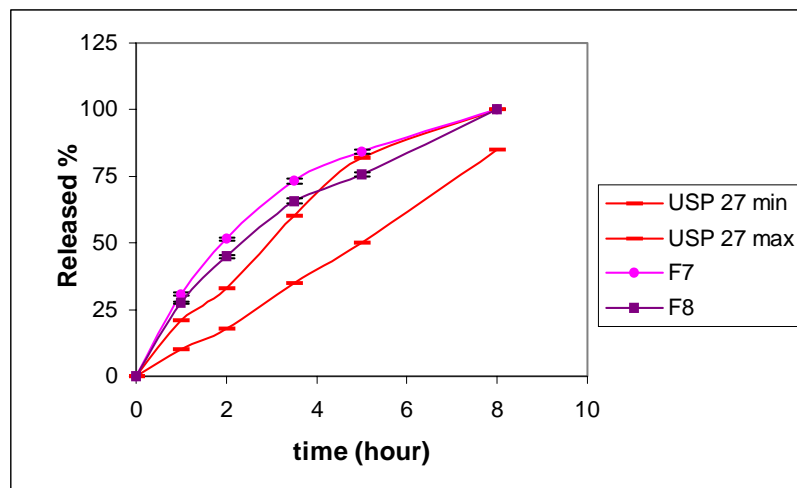


**Figure 1.** Dissolution profiles of F1, F2, F3 and pharmacopeial limits.



**Figure 2.** Dissolution profiles of F4,F5, F6 and pharmacopeial limits.

With formulations prepared using Methocel K15M and K100M (F2, F3, F5, F6), it was not possible to obtain the drug release profile between the limits of pharmacopeia. Release profiles of the first group of formulations (F2, F3) were within the limits only for the first four hours, while those of the second group (F5, F6) were within the limits for the last four hours of the test period. Therefore, F4 formulation was preferred for further modification and F7 and F8 formulations (Table 1) were prepared by changing the amounts of polymer and DC-agent.

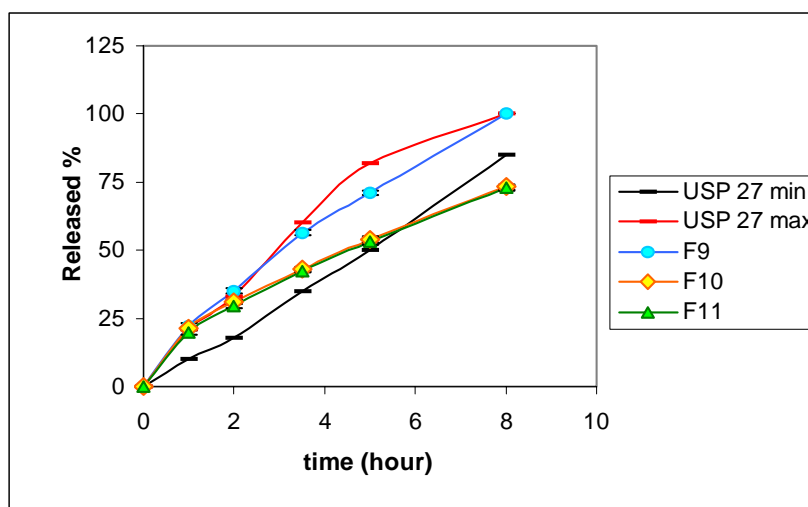


**Figure 3.** Dissolution profiles of F7, F8 and pharmacopeial limits.

F7 and F8 gave slower drug release compared to F4 and showed close release profiles to the upper limits of pharmacopeia and release profile of F8 was within the limits for the last four hours (Figure 3). At the beginning of the test period, the water-soluble drug easily passed through the

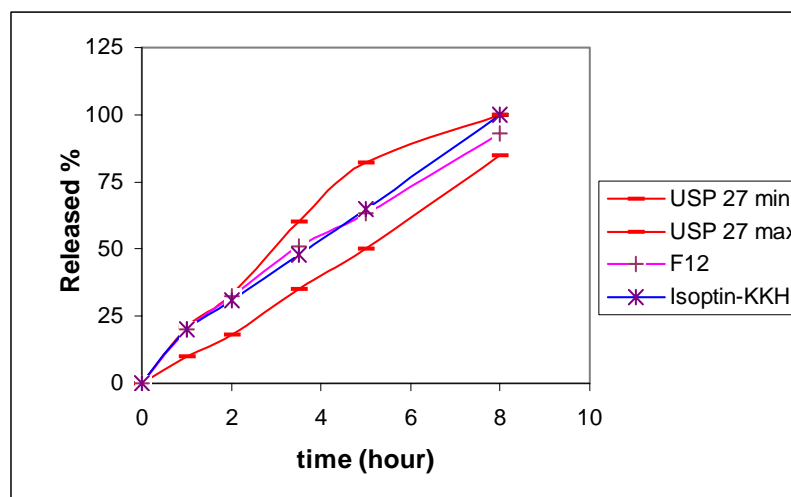
dissolution medium until formation of a gel layer on the tablet surface. After formation of the gel barrier on the surface, release of drug was delayed due to the increase in diffusion pathway to the dissolution medium. This was the reason for the initial rapid release in the first four hours (7-11). In order to delay the release of drug in the first four hours, F8 was modified by adding the same type of polymer layer to each face of the tablet, thus F9, F10 and F11 were prepared as three-layered matrix tablets (Table 1) (14,15,16,25). Among them, release profile of F9 which was layered with low viscosity grade polymer was found to be similar to pharmacopeial profiles (Figure 4).

To obtain the desired release of drug from F9 formulation, the amount of polymer (Methocel K100LV) on the layers was increased and F12 was thus prepared (Table 1). It was reported that HPMC used in the barrier formulations, is generally efficient in controlling drug release rate in three-layered matrix systems which also in accordance with our data (26). As seen in Figure 5, F12 and Isoptin®-KKH have given similar release profiles which were both within the pharmacopeial limits.



**Figure 4.** Dissolution profiles of F9,F10, F11 and pharmacopeial limits.





**Figure 5.** Dissolution profiles of F12, Isoptin<sup>®</sup>-KKH and pharmacopeial limits.

Drug release data of F12 and Isoptin<sup>®</sup>-KKH were evaluated using mathematical models (zero order, first order, Higuchi, Hixson-Crowell, Korsmeyer-Peppas). The values of kinetic model parameters are summarized in Table 2. According to the highest determination coefficient and the lowest residual mean square values, F12 fits well to Higuchi model and zero order model. For hydrophilic matrix tablets, *in vitro* drug release of water-soluble drugs is controlled by diffusion through the gel layer (27). In accordance with the Higuchi model suggesting a release mechanism controlled by diffusion, F12 being a matrix tablet fits to Higuchi model (18). Coated systems generally show zero order release kinetics. Polymer layers at the top and bottom of F12 can be accepted as a half coating of the tablet. Therefore, F12 and Isoptin<sup>®</sup>-KKH fit well to zero order kinetic model. Drug release mechanisms of F12 and Isoptin<sup>®</sup>-KKH were evaluated by using a drug release model proposed by Korsmeyer and Peppas. In this model, value of exponent  $n$  identifies the release mechanism of drug. As a geometrical evaluation tablets are accepted as cylinder shape dosage forms whose values of  $n$  can range between 0.45 and 0.89. Value of  $n=0.45$  indicates Fickian diffusion mechanism, values of  $0.45 < n < 0.89$  indicate Anomalous (non-Fickian or coupled diffusion/relaxation) transport and value of  $n=0.89$  indicates Case II transport mechanism (28,29). Values of  $n=0.7518$  and  $n=0.6893$  for F12 and Isoptin<sup>®</sup>-KKH respectively, both indicate Anomalous transport mechanism. And it was reported that, Colombo and co-workers (30) had also

found Anomalous transport mechanism for a soluble drug from HPMC-based matrix tablets, which supports our data.

**Table 2.** Kinetic data of F12 formulation and Isoptin<sup>®</sup>-KKH

Kinetic Model		F12	Isoptin <sup>®</sup> -KKH
Zero Order	r <sup>2</sup>	0.9820	0.9940
	RMS	23.932	9.9640
	k	0.1860	0.2010
	SE	0.0120	0.0080
First Order	r <sup>2</sup>	0.9280	0.9900
	RMS	0.0832	0.0022
	k	0.0053	0.0034
	SE	0.0010	0.0000
Higuchi	r <sup>2</sup>	0.9910	0.9740
	RMS	9.1210	34.329
	k	5.1350	5.6360
	SE	0.2750	0.5330
Hixson-Crowell	r <sup>2</sup>	0.9720	0.8750
	RMS	0.0331	0.5230
	k	0.0056	0.0100
	SE	0.0010	0.0020
Korsmeyer-Peppas	r <sup>2</sup>	0.9980	0.9950
	RMS	0.0001	0.0004
	k	0.0091	0.0118
	SE	0.0623	0.1049
	n	0.7518	0.6893
	SE	0.0301	0.0506

r<sup>2</sup> : Determination coefficient  
 RMS : Residual mean square  
 k : Dissolution rate constant  
 SE : Standard error of model parameter  
 n : Diffusion exponent

For the comparison of dissolution profiles of F12 and Isoptin<sup>®</sup>-KKH, f<sub>1</sub>-difference and f<sub>2</sub>-similarity factors were used. The values of 0-15 for f<sub>1</sub> and the values of 50-100 for f<sub>2</sub> are acceptable (20). f<sub>1</sub> (5.2) and f<sub>2</sub> (71.4) values showed the similarity of the release profiles of F12 and Isoptin<sup>®</sup>-KKH.

## CONCLUSION

It is found that an extended release tablet formulation which is in agreement with USP pharmacopeial requirements can be prepared as multi-layered tablets by using low viscosity grade HPMC polymers as an alternative to film coated VRP HCl tablets.

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