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Effects of Direct Tabletting Agents on Drug Release Kinetics and Swelling Behavior of Hydrophilic Matrix Tablets

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Aims: This work focused on the effects of direct tabletting agents (DC-agents) (Microcel PH101®, Cellactose 80®, Ludipress LCE®, Pharmatose DCL11®) and hydroxypropyl-methylcellulose (HPMC) types (Methocel® K100LV, K15M, K100M) on release of Verapamil HCl from hydrophilic matrix tablets and swelling behaviors of these tablets.

Material and Methods: Tablets were prepared by direct compression method. In vitro dissolution and swelling degree tests were performed on the tablets. The release mechanisms of drug were evaluated by using Korsmeyer-Peppas model.

Results: While the increase in cellulose content of DC-agents contributed to the swelling of matrices and decreased the release rate of drug from the matrices, in contrast the increase in lactose content of DC-agents caused a faster hydration and erosion of the matrices and accelerated the release of drug. The increase in viscosity grade of HPMC resulted as a decrease in release rate of drug and Methocel K15M and K100M delayed the release of drug to the same extent. Drug release was mainly fitted to the non-Fickian transport mechanism and became diffusive by decreasing the R/F values of the matrices. Tablets containing Cellactose® 80 showed an equal contribution of diffusion and swelling with 3 types of HPMCs, according to their n values and R/F profiles. The FM1 formulation containing Microcel PH101® with Methocel K100LV and the reference product Isoptin®-KKH both showed a non-Fickian transport mechanism and they were found to be similar depending on the values of difference factor (f_1 = 9.4) and similarity factor (f_2 = 56.8).

Conclusions: An extended release tablet formulation can be prepared as a matrix tablet by using a cellulose based DC-agent and a low viscosity grade HPMC polymer as an alternative to film coated tablets.

Key Words: Hydroxypropyl-methylcellulose, Direct tabletting agents, Matrix tablet, Swelling degree, Verapamil hydrochloride

Doğrudan Tabletleme Ajanlarının Hidrofilik Matris Tabletlerin Şişme Davranışları ve Etkin Madde Salım Kinetikleri Üzerindeki Etkileri

Amaç: Bu çalışma, farklı doğrudan tabletleme ajanları (DT-ajanları) (Microcel PH101®, Cellactose 80®, Ludipress LCE®, Pharmatose DCL11®) ve hidroksipropilmetilselüloz (HPMC) türlerinin (Methocel® K100LV, K15M, K100M) doğrudan basım yöntemi ile hazırlanan hidrofilik matris tabletlerden Verapamil HCl salımı ve bu tabletlerin şişme davranışları üzerindeki etkilerine odaklanmıştır.

Yöntem ve Gereç: Tabletler doğrudan basım yöntemi ile hazırlanmıştır. Tabletlerde in vitro çözünme hızı ve şişme değeri testleri yapılmıştır. Etkin madde salım mekanizmaları Korsmeyer-Peppas modeli ile değerlendirilmiştir.

Bulgular: DT-ajanlarının selüloz içeriğindeki artış matrislerin şişmelerine katkıda bulunup matrislerden etkin madde salım hızını düşürmekteyken, aksine DT-ajanlarının laktoz içeriğindeki artış matrislerin hızlı hidratasyonuna ve erozyonuna neden olarak etkin maddenin salımını hızlandırmaktadır. HPMC`nin viskozitesindeki artış etkin maddenin salım hızında azalmaya neden olmakta ve Methocel K15M ve K100M etkin madde salımını aynı derecede geciktirmektedir. Etkin madde salımı temel olarak Fick difüzyonuna uymayan salım göstermekte ve matrislerin R/F değerindeki azalma ile difüzyon ağırlıklı hale gelmektedir. Cellactose® 80 içeren tabletler üç tür HPMC ile, n değerleri ve R/F profillerine göre, difüzyon ve şişmenin eşit katkılı olduğunu göstermektedir. Microcel PH101® ile Methocel K100LV içeren FM1 formülasyonu ve referans ürün Isoptin®-KKH`ın her ikisi Fick difüzyonuna uymayan salım göstermekte olup, fark faktörü (f_1 = 9.4) ve benzerlik faktörü (f_2 = 56.8) değerlerine bağlı olarak benzer bulunmuşlardır.

Sonuç: Uzatılmış salım yapan selüloz kökenli DT-ajanı ve düşük viskoziteye sahip HPMC polimeri içeren bir matris tablet formülasyonu film kaplı tabletlere alternatif olarak hazırlanabilmektedir.

Anahtar Sözcükler: Hidroksipropilmetilselüloz, Doğrudan tabletleme ajanları, Matris tablet, Şişme değeri, Verapamil hidroklorür

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Introduction

Verapamil HCl (VRP HCl) is a water-soluble phenyl-alkyl amine derivative, used widely in the treatment of hypertension, angina pectoris and arrhythmias (1).

Various types of oral extended-release (ER) dosage forms are currently in use, with coated beads, osmotic pumps and matrix tablets being some of the important classes (2). Among these classes, matrix tablets composed of drug and the release-retarding material (polymer) offer the simplest approach to designing an ER system. Hydrophilic polymers like HPMCs are commonly used in these systems as release-retarding materials (3). Several formulation variables such as HPMC concentration and viscosity grade, dosage size, excipient type and ratio have been used to modulate drug release from HPMC-based matrix tablets. According to different characteristics of the polymers and excipients used, these drug delivery systems exhibit different release kinetics and swelling behaviors. In these systems, drug release profiles are strongly influenced by the viscosity of the gel layer that forms on the tablet surface as a result of hydration of the constituent polymer and by the solubility of the excipient, which affects the formation of the gel layer and the hydrosolubility of the drug as well (4-7).

The goals of the present study were to assess the effect of different DC-agents including lactose (a soluble excipient) and cellulose derivatives (insoluble excipients) on the release of a soluble drug VRP HCl from hydrophilic matrix tablets containing different viscosity grade HPMCs and to investigate the swelling behaviors of these matrix tablets.

Materials and Methods

Materials

Verapamil HCl (Knoll AG, Ludwigshafen, Germany), hydroxypropylmethylcellulose Methocel® K100LV, K15M and K100M with nominal viscosities of 98 mPa.s, 7382 mPa.s and 18,243 mPa.s respectively, Dow Chemical Co., Stade, Germany), microcrystalline cellulose (Microcel® PH101, Blanver Farmaquimica Ltda, Sao Paulo, Brazil), α-lactose monohydrate 75%-cellulose powder 25% mixture (Cellactose® 80, Meggle GmbH, Wasserburg, Germany), α-lactose monohydrate 96.5%-Kollidon 30 3.5% mixture (Ludipress® LCE, BASF, Ludwigshafen, Germany) and α-lactose monohydrate-amorph lactose mixture (Pharmatose® DCL11, DMV International, Veghel, The Netherlands), Isoptin®-KKH film coated tablets (Knoll AG, Batch number: 156/96) were used. All other chemicals used were analytical grade.

Preparation of Tablets

Tablets were prepared by direct compression. The respective preweighed powders (drug, polymer and DC-agent) were blended using a spatula on a glass plate (the composition of each formula is presented in Table 1). Then the mixture was fed manually into the die of a hydraulic press (Ayaşlı Üçler, Ankara, Turkey) equipped with flat-faced punches of 8 mm diameter to produce tablets. The compaction force was kept constant at 255 MPa for 10 s.

In vitro Drug Release Studies

Drug release studies were carried out according to the method given for Delayed Release Articles in USP XXVII

Table 1. Composition of matrix tablets.

Content (mg)	FM1	FM2	FM3	FC1	FC2	FC3	FL1	FL2	FL3	FP1	FP2	FP3
VRP HCl	120	120	120	120	120	120	120	120	120	120	120	120
Microcel® PH101	120	120	120	-	-	-	-	-	-	-	-	-
Cellactose® 80	-	-	-	120	120	120	-	-	-	-	-	-
Ludipress® LCE	-	-	-	-	-	-	120	120	120	-	-	-
Pharmatose® DCL11	-	-	-	-	-	-	-	-	-	120	120	120
Methocel K100LV	40	-	-	40	-	-	40	-	-	40	-	-
Methocel K15M	-	40	-	-	40	-	-	40	-	-	40	-
Methocel K100M	-	-	40	-	-	40	-	-	40	-	-	40

by using the USP paddle (apparatus II) method with a dissolution tester (Aymes D96D, İstanbul, Turkey) at 50 rpm. pH 1.2 0.1 N HCl was used for the first 2 h and pH 6.8 phosphate buffer was used for the following 6 h as dissolution media. The amount of VRP HCl was determined spectrophotometrically (UV-1601 Shimadzu Spectrophotometer, Tokyo, Japan) at 278 nm. All the experiments were performed in triplicate. SPSS 9.0 for Windows was used for calculations.

Determination of Swelling Degree of Hydrated Matrix Tablets

The thickness of hydrated tablets was measured by an electrical device modified from that developed by Fatt (8) by Karatas and Baykara (9). The same conditions (volume of fluid, temperature, hydrodynamic conditions etc.) of release studies were obtained for swelling studies. Initially dehydrated tablet thickness was measured by this electrical device and recorded as h_0. Then the tablet was immersed in dissolution medium. At selected time intervals (the same as those in the release studies), the hydrated tablet was taken out of dissolution medium and its thickness was measured and then it was again immersed in dissolution medium. Each measuring was completed in 20 s and recorded as h_t. The swell change of each tablet was calculated as the normalized thickness (h_t/h_0) and plotted versus time. All the experiments were performed in triplicate. SPSS 9.0 for Windows was used for calculations.

Results and Discussion

In vitro Release and Swelling Studies

In hydrophilic matrices the release of drug is controlled by the rate of formation of a partially hydrated gel layer formed on the tablet surface upon contact with aqueous gastric media (10). In this study rapidly hydrating Methocel K series were used to prevent the probable dose dumping of highly soluble VRP HCl, and the level of HPMC in the tablets was kept lower than the manufacturers' suggestion (20%-40%) (11) to determine the effect of DC-agents on drug release.

Drug release profiles of the matrix tablets containing different DC-agents with Methocel K100LV are presented in Figure 1a. FP1 containing Pharmatose® DCL11 (lactose 100%) showed the fastest and FM1 containing Microcel® PH101 (MCC 100%) showed the slowest release of drug. FL1 containing Ludipress® LCE (lactose 96%-Kollidon 30 3.5%) and FC1 containing Cellactose® 80 (lactose 75%-cellulose powder 25%) gave release profiles nearer to that of FP1. However, the release of drug was faster from FL1 with respect to the FC1 formulation.

Being a soluble excipient, lactose increases the tablet porosity and stimulates the water penetration into the inner parts of the matrix, which results in a faster diffusion of drug and erosion of polymer, causing a rapid release of drug from the tablets (5,11). Thus the rapid release of drug from FP1, FL1 and FC1 formulations

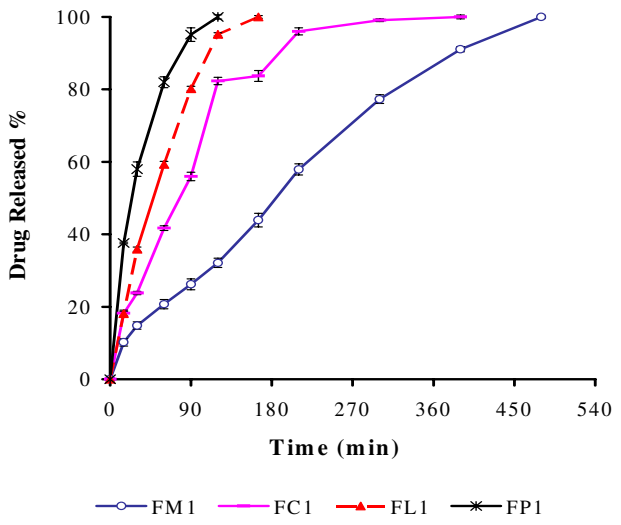

Figure 1a. Drug release profiles for different DC-agents with Methocel K100LV.

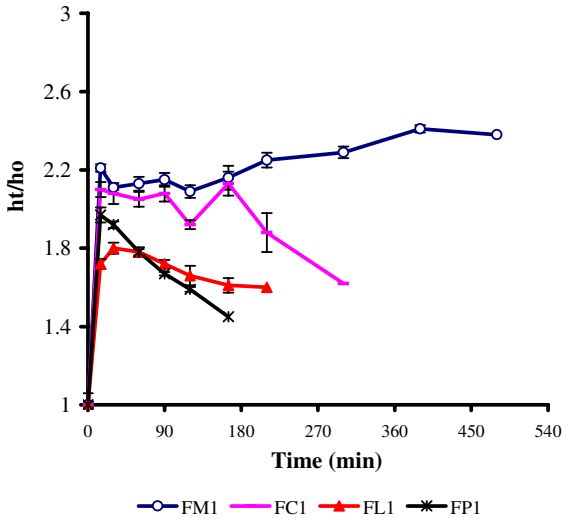

Figure 1b. Swelling profiles of matrix tablets for different DC-agents with Methocel K100LV.

could be explained by the lactose content of their DC-agents. These data are in accordance with some other studies (3-5,12-14).

On the other hand, MCC is an insoluble excipient and has a swelling property that contributes to the development of swelling of HPMC and the resistance of the gel layer. It is reported that the highest level (<10%) of MCC is most likely acting as a strong tablet binder to decrease tablet porosity and thus slows the release rate of drug from the tablet formulations (5,15). The MCC level was 41.5% (w/w) for Microcel® PH101 containing tablets in our study, and so the delay in drug release for FM1 could be attributed to the high MCC content of its DC-agent (3,5,13,14). However, the overall release of drug from FP1, FL1, FC1 and FM1 formulations was rapid due to the low viscosity grade of Methocel K100LV (3,6).

Drug release profiles of the matrices containing different DC-agents with Methocel K15M are presented in Figure 2a. FP2 containing Pharmatose® DCL11 showed the fastest and FM2 containing Microcel® PH101 showed the slowest release of drug due to their lactose and MCC content respectively (3,10,12). Drug release from FL2 was slower than expected. This could be attributed to the Kollidon 30 content of Ludipress® LCE and it could be inferred that incorporation of Kollidon 30 with high viscosity HPMC contributes to the increase in viscosity and resistance of the gel layer that forms on the tablet surface thus slows the drug release. The drug release profile of FC2 was between those of FP2 and FM2 formulations, as expected. The increase in viscosity grade of HPMC from 98 mPa.s to 7382 mPa.s resulted in a decrease in the release rate of drug from the formulations (Figure 1a and 2a) (3,10).

Drug release profiles of the matrices containing different DC-agents with Methocel K100M are shown in Figure 3a. As shown in Figure 2a and Figure 3a, an increase in the viscosity grade of HPMC from 7382 mPa.s to 18,243 mPa.s showed no marked decrease in the release rate of drug from the matrix tablets, which was also observed by some other investigators (16,17). In contrast, an unexpected increase in the release rate of drug was observed for the FC3 formulation containing Cellactose® 80 (Figure 3a).

Among all the formulations the release profile of FM1 containing Microcel® PH101 and Methocel K100LV showed closer values to the limits of VRP HCl ER Tablets monograph in USP XXVII, which was similar with the release of Isoptin®-KKH (Figure 4).

During the swelling process a general trend was observed in all formulations, namely a similar rapid swelling for the first 15 min (Figures 1b, 2b, 3b). As shown in Figure 1b, FM1 showed a distinct increase in gel layer thickness due to its high content of swellable MCC after 15 min. The fastest erosion was observed for FP1, which has the highest lactose content in this group of formulations. The surface erosion rate of FL1 was slower

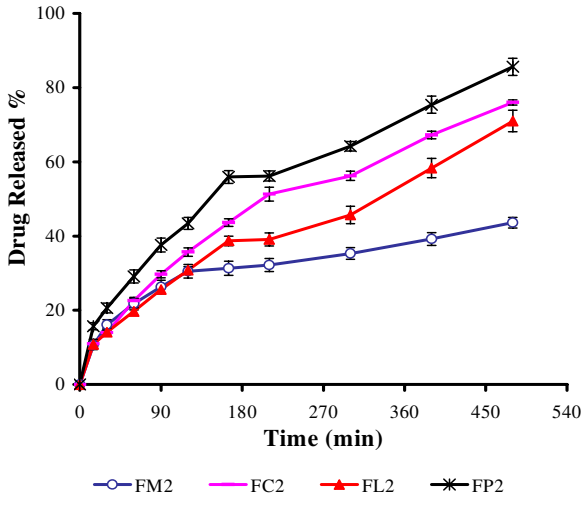

Figure 2a. Drug release profiles for different DC-agents with Methocel K15M.

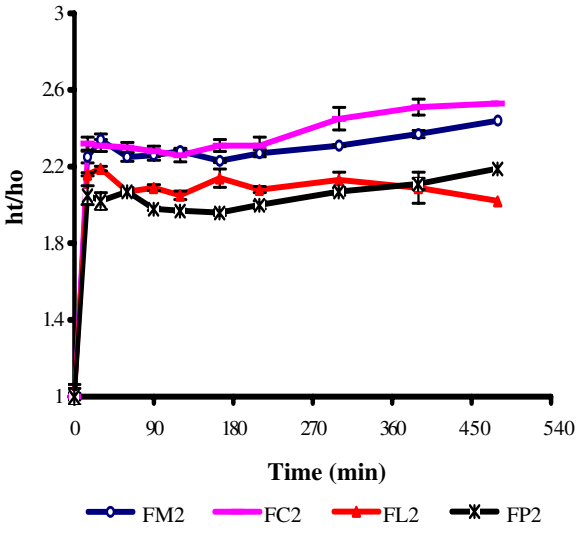

Figure 2b. Swelling profiles of matrix tablets for different DC-agents with Methocel K15M.

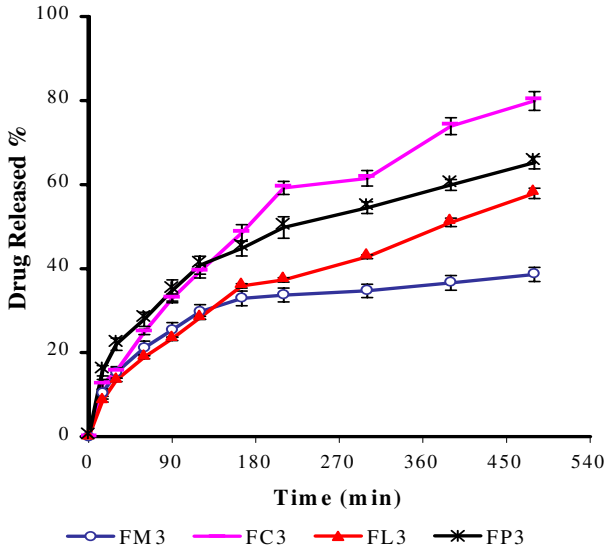

Figure 3a. Drug release profiles for different DC-agents with Methocel K100M.

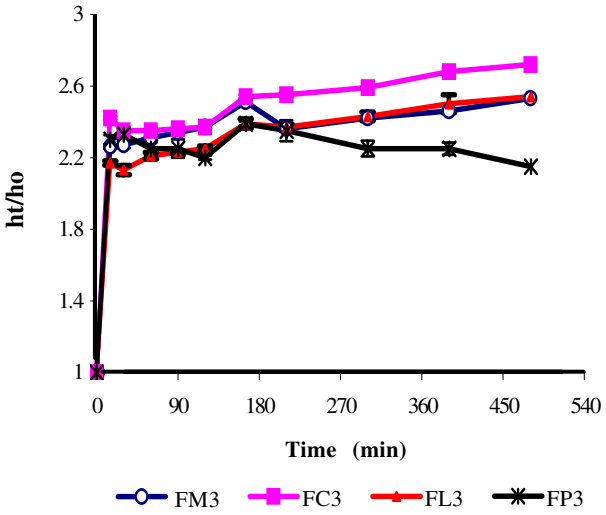

Figure 3b. Swelling profiles of matrix tablets for different DC-agents with Methocel K100M.

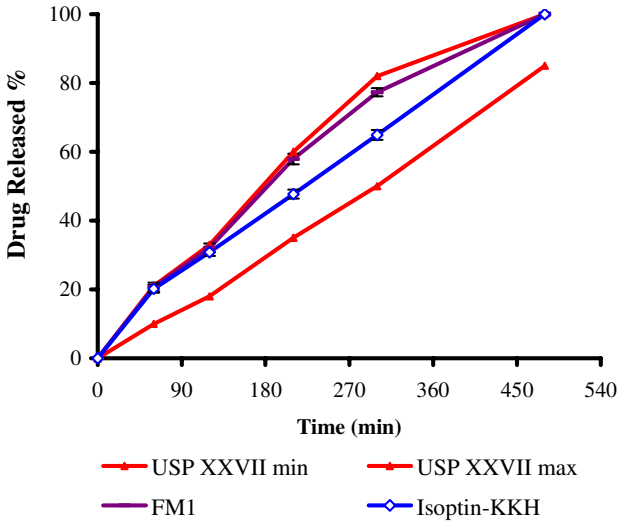

Figure 4. Dissolution profile of FM1 and pharmacopeial limits of VRP HCl ER tablets in USP XXVII.

than that of FP1, which could be attributed to the Kollidon 30 content of Ludipress® LCE, and it can be concluded that Kollidon 30 affected the resistance of the gel layer towards erosion because of its binding property. FC1 containing lactose and cellulose powder together gave swelling profiles between those of FM1 and FL1 formulations. A similarity was observed between the release and swelling profiles of these formulations' order (Figure 1a and 1b).

As shown in Figure 2b, the high viscosity grade HPMC exhibited extensive swelling with all DC-agents and no marked difference was found between the swelling profiles of formulations in this group. FM2 and FC2 including cellulose derivatives gave higher swelling values compared to FL2 and FP2 including lactose. It has been reported that low viscosity grade HPMCs are more erodible (18,19) and high viscosity grade HPMCs are more swellable (12,20). These data are in accordance with our results as shown in Figures 1b and 2b.

Swelling profiles of matrix tablets containing different DC-agents with Methocel K100M are presented in Figure 3b. FC3 containing Cellactose® 80 exhibited unexpectedly the highest degrees of swelling. FP3 containing Pharmatose® DCL11 gave the expected swelling and eroding profile. Despite the higher lactose content of FL3, almost the same swelling profiles were observed with FM3. This may be explained by the higher gel strength of the high viscosity grade HPMC counteracting erosion of the gel layer. However, the similarity between the swelling profiles of FL3 and FM3 was not observed in their drug release profiles (Figure 3a).

As a result, while cellulose contributed to the strength of the gel layer that forms on the surface of matrix tablets, lactose weakened the structure of this gel layer, which caused an increase in drug diffusion and gel layers' erosion, and so accelerated the release of drug from the matrices.

Kinetic Evaluation of Drug Release

Drug release mechanisms of the matrix tablets were evaluated by using the Korsmeyer-Peppas semi-empirical model (21). In this model, the value of n identifies the release mechanism of drug. For the case of cylindrical tablets, $0.45 \leq n$ corresponds to a Fickian diffusion mechanism, $0.45 < n \leq 0.89$ to non-Fickian transport, $n = 0.89$ to Case II (relaxational) transport, and $n > 0.89$ to super Case II transport (22,23). The values of release parameters n and k are inversely related. A higher value of k may suggest burst drug release from the matrix.

The calculated exponents (n) (Table 2) indicate that the n values of all formulations and Isoptin®-KKH are within the limits of the non-Fickian transport mechanism except FM2, FM3 and FP3 formulations. However, published data for cylindrical matrices containing HPMC polymers showed that typical values of n were approximately 0.6 (24), which is consistent with most of our data (Table 2). As mentioned above, the higher k value of FP1 was proved by rapid drug release from this formulation (Table 2, Figure 1a).

Calculation of the approximate contribution of the diffusional and relaxational mechanisms during the non-Fickian release process was carried out by fitting the data to the heuristic model proposed by Hopfenberg (25) and adapted to pharmaceutical problems by Peppas and Sahlin (26).

Table 2. Diffusion exponent (n) and kinetic constant (k) values of formulations and Isoptin®-KKH.

Formulation Code	Kinetic constant $k \times 10^{-2}$ (m-n)	Diffusion exponent n ± SD
FM1	1.66	0.635 ± 0.032
FM2	4.32	0.383 ± 0.021
FM3	4.27	0.375 ± 0.023
FC1	2.88	0.650 ± 0.037
FC2	2.11	0.589 ± 0.016
FC3	2.09	0.596 ± 0.024
FL1	1.82	0.858 ± 0.036
FL2	2.45	0.525 ± 0.020
FL3	2.04	0.541 ± 0.009
FP1	6.92	0.626 ± 0.051
FP2	3.63	0.517 ± 0.022
FP3	5.25	0.416 ± 0.016
Isoptin®-KKH.	0.01	0.689 ± 0.019

In this model, drug release from swellable matrices is described as a result of 2 transport mechanisms, i.e. diffusion across the gel layer (F) and relaxation of the polymeric chains (R). From fitting of the data to this equation the ratio of relaxational (R) and Fickian (F) contributions can be calculated by

$$R/F = k_2 / k_1 t^m \qquad \text{(Eqn)}$$

The release data of formulations were analyzed according to this equation. The R/F value of Isoptin®-KKH was not calculated because of its being a coated film tablet. The ratio of relaxational to diffusional contributions vs. fraction released of drug are presented in Figure 5. As shown in this figure, the contributions of the 2 mechanisms for the fractional release of drug seem to be almost equal for FC1, FC2, FM1 and FC3 formulations, corresponding to the non-Fickian transport mechanism. For the other formulations (FL3, FL2, FP2) the Fickian diffusion mechanism seems to be more effective on drug release as evident from their values of n (Table 2). Since a rapid release of drug occurred for FL1 and FP1 formulations (Figure 1a) (probably caused by a faster erosion rate of these formulations, Figure 1b), these formulations did not exhibit the R/F profiles as expected from their values of n. Lower n values of FM2 and FM3 formulations could be attributed to these formulations' extremely slow drug release rate after the first 2 h (Figures 2a and 3a).

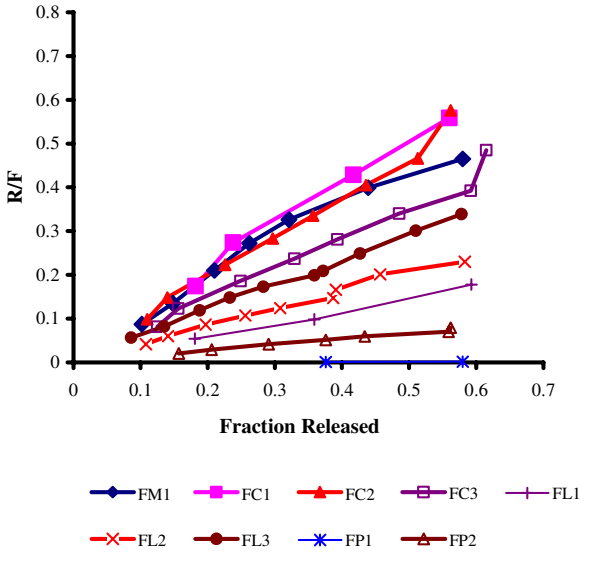

Figure 5. Ratio of relaxational and diffusional contributions to overall release vs. fractional VRP HCl release from matrix tablets.

Among the formulations that fitted the non-Fickian transport mechanism, FC1, FC2, FM1 and FC3 exhibited diffusion and swelling controlled mechanisms at almost equal ratios according to their R/F profiles, and the others showed that drug release is mainly diffusive and deviated from linearity. When DC-agents were evaluated from this point of view, Cellactose® 80 showed an equal contribution of diffusion and swelling with 3 types of HPMCs, thus giving more linear results.

Dissolution profiles of FM1 and Isoptin®-KKH were compared by f_1-difference and f_2-similarity factors. The values of 0-15 for f_1 and the values of 50-100 for f_2 are acceptable (27). f_1=9.4 and f_2=56.8 values showed the similarity of the release profiles of FM1 and Isoptin®-KKH.

Conclusion

An ER tablet formulation in agreement with USP pharmacopeial requirements can be prepared by direct compression as a matrix tablet using a microcrystalline cellulose based DC-agent and a low viscosity grade HPMC polymer as an alternative to film coated VRP HCl tablets.

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