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THE EFFECT OF CO-PROCESSED DRY BINDER WITH MICROCRYSTALLINE CELLULOSE ON RELEASE OF VERAPAMIL HYDROCHLORIDE FROM HYDROPHILIC MATRIX TABLETS

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Abstract: The aim of this study was to evaluate the use of co-processed dry binder MicroceLac®100 (lactose and microcrystalline cellulose in ratio 3 : 1) and Comprecel® 102 (pure microcrystalline cellulose) in formulations for the extended release of verapamil hydrochloride. Hydrophilic matrix tablets containing verapamil hydrochloride, hypromellose and dry binder were prepared by the direct compression method. Hypromelloses Methocel™ K4M Premium CR or Methocel™ K100M Premium CR were used as controlled release agents. Using scanning electron microscopy regular distribution of the active substance in the prepared tablets was confirmed. Release of verapamil hydrochloride from the prepared formulations was studied by the dissolution test method. The dissolution profiles were fitted to the first-order kinetic model, Higuchi diffusion model, Korsmeyer-Peppas and Weibull model and kinetic parameters as the first order release rate constant (k_1), release exponent (n) from Korsmeyer-Peppas model, Higuchi constant (K_H) and parameters of Weibull model (b, λ) were determined. Based on the results of non-linear regression analysis, the higher release rate constants were found for formulations containing co-processed dry binder MicroceLac®100 in comparison with formulations containing pure microcrystalline cellulose (Comprecel® 102). In addition, tablets swelling, erosion and disintegration during the dissolution test were monitored photographically.

Keywords: Verapamil hydrochloride, hypromellose, Comprecel® 102, MicroceLac®100, matrix tablets, dissolution kinetics

Matrix tablets are a prospective dosage form, which enables prolonged release of the drug in the organism. According to the character of the retarding component, they are divided into polymeric insoluble, hydrophilic gel, lipophilic and mixed matrix tablets (1, 2). The simplest method of preparation of matrix tablets is the method of direct compression. Direct compression requires a high quality of the excipients used, the principal excipients for direct compression being dry binders. In tableting materials, dry binders act both as fillers and binders. The principal requirements for these substances are the best flowability possible, compressibility, high dilution potential, and low lubricant sensitivity (3). An excellent dry binder for direct compression is microcrystalline cellulose. This substance possesses excellent compressibility, high dilution potential and, within certain size limits, it also shows good flowability. Its negative property is high sensitivity to lubricants, as it is compressed by the mechanism of plastic deformation (4). In addition, in higher concentrations in the tablet, it may prolong disintegration time (5). No dry binder shows all ideal properties, so it is advisable to combine two or more dry binders in tableting materials, usually with the mechanism of compression of plastic deformation and fragmentation (6). Dry binders can be combined either in the form of a physical mixture, or they can be also transferred by means of the so-called coprocessing into one product, which gives rise to co-processed dry binders (7), (8). Coprocessing is defined as a combination of two or more established

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excipients by a pharmaceutical process. The products so formed are physically modified such that they do not lose their chemical structure and stability. This means that excipients maintain their independent chemical properties; while, synergistically increase their functional performance (9, 10).

A very important combination is the combination of fragile α-lactose monohydrate with plastic microcrystalline cellulose (11). Examples of such excipients containing lactose and microcrystalline cellulose in a ratio of 3 : 1 are products MicroceLac® 100 (12) and the newer Disintequik MCC 25 (13). Lactose in these co-processed products fulfills the function of the filler, accelerating the disintegration of tablets due to its solubility and decreasing the sensitivity of microcrystalline cellulose to the added lubricant. Microcrystalline cellulose improves binding properties (11). The retarding component often used in matrix hydrophilic gel tablets is hypromellose. Its retarding effect depends on the degree of viscosity and concentration employed. The gel barrier which this substance produces on the surface of the tablet decelerates the release of the active ingredient which diffuses through this barrier (14-16). The dissolution profile of the drug formulation can be described by an appropriate mathematical model. Models based on the laws of chemical kinetics together with physical diffusion models are the most commonly used for evaluation and description of the processes of active substance release from various drug formulations (17, 18).

The aim of this study was to evaluate the use of co-processed dry binder MicroceLac®100 (lactose and microcrystalline cellulose in ratio 3 : 1) and Comprecel® 102 (pure microcrystalline cellulose) in formulations for the extended release of verapamil hydrochloride. Recently, co-processed dry binders are more often used for tablet production by direct compression method but their use in controlled drug release formulations has not been studied in detail.

EXPERIMENTAL

Materials

Verapamil hydrochloride (VH, European Pharmacopoeia Reference Standard, Sigma Aldrich Chemie GmbH, Germany) was used as the active substance. Hypromelloses Methocel™ K4M Premium CR (HPMC 1) or Methocel™ K100M Premium CR (HPMC 2) – both from Colorcon GmbH, Germany – were used as controlled release agents forming a hydrophilic matrix system. Comprecel® 102 (binder COM) from Mingtai Chemical CO., LTD., Taiwan and MicroceLac® 100 (binder ML) from MEGGLE PHARMA, Germany were used as dry binders. Magnesium stearate (Acros Organics, USA) was used as a lubricant.

For the preparation of dissolution media and standard solution of verapamil hydrochloride, redistilled water and chemicals of analytical grade (Lach-Ner s.r.o., Neratovice, Czech Republic) were used.

Preparation of tablets

The composition of the studied formulations is described in Table 1. Preparation of the tabletting materials is described in detail in (19). Tablets were prepared by direct compression using the material testing equipment T1-FRO 50 TH.A1K Zwick/Roell (Zwick GmbH&Co, Germany) by means of a special die with a lower and an upper punch. The rate of compaction was 40 mm/min, pre-load was 2 N, and the rate of pre-load 2 mm/s. The tablets were of cylindrical shape without facets of a diameter of 13 mm and weight of 0.5 ± 0.0010 g. Compression forces were adjusted in such a way that tablet strength ranged between 0.8 – 0.9 MPa. The content of VH in the tablet (10 randomly selected from each formulation) was confirmed.

For each dissolution, 6 tablets with the active ingredient and 1 tablet without the active ingredient as the blind sample were compressed. For blind samples, the amount of VH was replaced by the same amount of binder contained in the relevant formulation. In the same way, samples for the photographic observation of the swelling and erosion of the tablets were prepared.

Scanning electron microscopy (SEM)

A compact scanning electron microscope VEGA3 SBU (Tescan, Brno, Czech Republic) was used to investigate both the structure and homogeneity of excipients and active substances and mixtures prior to the compression and prepared tablets. Parameters set were an acceleration voltage of 20 kV, backscattered electron (BSE) detector and low vacuum mode (10 Pa, N_2). For individual compounds from which tableting materials for tablet compression were prepared, size and shape of particles were primarily investigated. For mixtures prior to compression, the uniformity of components mixing was evaluated, and for the tablets, surface and cut and fracture across tablets were studied. The cut was created by the breaking of the tablets and the cut surface was leveled using a sharp steel knife. The tablet surface and tablet fracture were not modified before the analysis.

In vitro dissolution tests

The release of VH from prepared drug formulations was studied by the dissolution test method according to the European Pharmacopoeia 9th (20) using basket apparatus (Sotax AT 7 Smart, Allschwil, Switzerland). The dissolution test was performed in two different dissolution media (acidic medium pH 1.2 and phosphate buffer pH 6.8) which were prepared according to the European Pharmacopoeia 9th (20). Six tablets containing 120 mg of VH and one blank tablet were placed in the baskets and immersed in the dissolution medium (900 mL). All tests were carried out for 24 h at a stirring rate of 125 rpm. The temperature was maintained at 37 ± 0.5°C. At predetermined times, 3 mL of the dissolution medium was automatically withdrawn and the same volume of fresh tempered medium was replaced. Consecutive samples were filtered and VH concentration was determined by UV VIS spectrometry. Each experiment was performed three times with six tablet samples and one blind tablet. The mean values of the released amount of VH with standard deviations were calculated.

VH content determination in solid part of F1 tablet after dissolution test

Tablets were withdrawn from the dissolution medium (pH = 1.2) at time intervals of 1, 2, 3, 4, 6, 8, 10 and 12 h and dried for 24 h in an oven at 37°C. A dried tablet was grounded in a mortar and the powder was quantitatively transferred into a 200 mL volumetric flask. Then 150 mL of 0.1 M HCl was added and an ultrasonic bath was used to assure total disintegration of the tablet (30 min approximately). After tablet disintegration, the solution was stirred for 1 h. Consequently, the sample volume was fulfilled to 200 mL with 0.1 M HCl. Then a portion of the solution was filtered using glass microfiber filter 0.45 µm (Whatman®) and diluted by deionized water to 0.01 M HCl. The amount of VH in sample solution was determined using UV VIS spectrometry.

Determination of VH using UV VIS spectrometry

The concentration of VH in samples of the dissolution medium was determined by UV VIS spectrometry (spectrophotometer HP Agilent 8453) at 272 nm using a corresponding blind solution. Three points background correction for peak evaluation was applied. To transform absorbance values into concentrations and percentage, the calibration curve method was used. The linear dependence of absorbance on VH concentration in the studied concentration range was confirmed and the potential interference of some excipients of drug formulation was also tested. The concentration of VH was recalculated to percentages of the released VH (the theoretical individual content of VH in a tablet was 120 mg, the exact content of VH confirmed with HPLC was 98.91 ± 0.35%).

Tablets swelling and erosion observation

In situ photographic observation of the swelling of VH tablets during dissolution testing was carried out using the paddle method (Sotax AT 7 Smart, Allschwil, Switzerland). The same dissolution media and conditions as were mentioned above were applied. Photographs were taken at zero time, 1, 2, 4 and 6 h using a Panasonic Lumix DMC-FZ18 digital camera.

Mathematical and statistical evaluation of the dissolution profiles

The dissolution profiles obtained were fitted to the first-order kinetic model ([Eq. 1, 2], (17, 18) and 21)), Higuchi diffusion model ([Eq. 3], (22)), Korsmeyer-Peppas model ([Eq. 4], (17, 18, 23, 24)) and Weibull model ([Eq. 5], (17)):

$$A_{t(l)} = A_{\infty}(1 - exp^{-k_1 t}) \quad (1)$$

$$A_{t(s)} = A_0 exp^{-k_1 t} \quad (2)$$

$$\frac{A_{t(l)}}{A_{\infty}} = K_H\sqrt{t} \quad (3)$$

$$\frac{A_{t(l)}}{A_{\infty}} = at^n \quad (4)$$

$$A_{t(l)} = A_{\infty}(1 - exp[-\ \lambda(t - T_i)^b]) \quad (5)$$

Table 1 Composition of tablets (%), tablet weight 500 mg.

Formulation	F1	F2	F3	F4	F5	F6
Binder ML	45	45			75	
Binder COM			45	45		75
HPMC 1	30		30			
HPMC 2		30		30		
Magnesium stearate	1	1	1	1	1	1
Verapamil hydrochloride	24	24	24	24	24	24

where $A_{t(l)}$ is the released amount of drug in time t, $A_{t(s)}$ is the amount of drug in solid drug formulation in time t, A_∞ represents the maximum releasable amount of drug in infinite time (it should be equal to the absolute amount of drug incorporated in solid drug formulation at time $t = 0$, A_0), k_l is the first order release rate constant in units of time^{-1}, K_H is the Higuchi dissolution constant, a is a constant incorporating structural and geometric characteristics of the dosage form and n is the release exponent indicative of the drug release mechanism, λ represents the reciprocal value of time-scale of the process, the location parameter T_i represents the lag time before the onset of the dissolution (in most case is zero) and b describes the shape of the dissolution curve progression.

By derivative of Eq. 1 (25) and by second-order approximation of the first derivative (26), the time dependence of the release rate can be obtained. All experimental data were mathematically processed and statistically evaluated by means of the computer programmes Graph Pad Prism and Origin 9 Pro. The coefficient of determination (R^2) and residual sum of squares (RSS) were used for comparison of used kinetic models. Statistical significance was tested using Student's t-test for unpaired samples, at a significance level of $p < 0.05$.

RESULTS AND DISCUSSION

Evaluation of tablet homogeneity by the SEM method

Representative SEM images of pure substances are presented in Figures 1, 2 and 3. Crystals of pure VH have the form of prisms from 10 to 20 μm high. Particle sizes of about 50 μm are also common. Rarely do platelet units in sizes above 100 μm occur (Fig. 1A). Binder COM and both types of hypromellose form irregular elongated grains extending from grain to rod shapes with sizes mostly between 50 and 200 μm, in the case of binder COM, individual particles may be twisted and possess a layered structure (Figs. 1B, C). The spherical porous particles of binder ML size of 100-200 μm resemble pieces of charcoal in structure (Fig. 1D). Magnesium stearate has a relatively uniform structure of spherical agglomerates having a diameter of about 10 μm (Fig. 1E).

In the tablet cuts it can be seen that the tablet cutting did not cause the particles to be torn or lifted from the cut surface but the particles themselves were cut, which indicates that the tablets have a relatively compact structure and good cohesion of the individual components (Figs. 2A, B, C, D).

At the transverse fracture of the tablets, a distinct layered structure caused by compression can be seen. Particles are preferably oriented in parallel with the upper and lower surface of the tablet (Fig. 3A). Significant rods and grains of HPMC (1 or 2) between which the pulp of binder COM or M can be observed at the tablet surface and tablet cut. Particles of magnesium stearate are not visually identifiable. The structure of the tablet binder ML is no different from tablets containing binder COM.

VH in the reflected light areas in the image are due to chloride contained in the VH molecule which increases the average atomic number and therefore the brightness of the area of the sample (using BSE detector) (Fig. 3A).

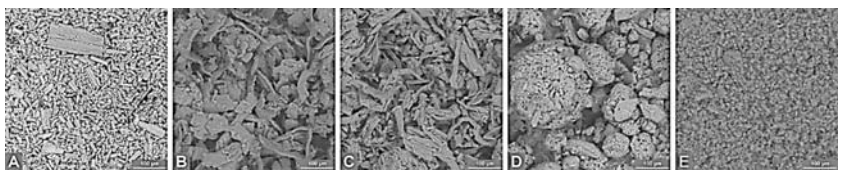

Figure 1. Representative SEM images of pure substances: VH (**A**), HPMC 2 (B), binder COM (C), binder ML (D) and magnesium stearate (E)

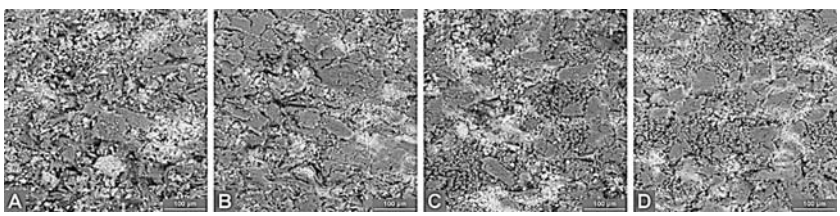

Figure 2. Representative SEM images of tablet cuts: F1 formulation (**A**), F2 formulation (B), F3 formulation (**C**), F4 formulation (D), width 0.5 mm

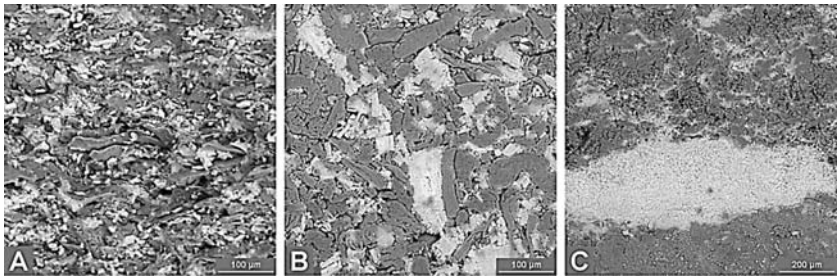

Figure 3. Representative SEM images: transverse fracture of F4 tablet (A), surface of F4 tablet (B), cut of F2 tablet (C), width 1 mm

Table 2A. Kinetic parameters of VH release in acidic dissolution medium (pH 1.2) - the first order and Weibull model.

Formulation	First-order				Weibull			
	$k_1 \pm SD$ (h^{-1})	$A_\infty \pm SD$ (%)	*RSS*	R^2	$\lambda \pm SD$	$b \pm SD$	*RSS*	R^2
F1	0.196 ± 0.003	102.2 ± 0.6	1455	0.9921	0.206 ± 0.004	0.94 ± 0.02	1348	0.9926
F2	0.136 ± 0.005	105.0 ± 1.7	5732	0.9665	0.147 ± 0.007	0.77 ± 0.03	4333	0.9746
F3	0.154 ± 0.005	102.5 ± 1.2	3916	0.9766	0.170 ± 0.005	0.76 ± 0.02	2229	0.9867
F4	0.118 ± 0.004	85.2 ± 1.3	2411	0.9766	0.104 ± 0.002	0.69 ± 0.02	9856	0.9904

Table 2B. Kinetic parameters of VH release in the dissolution medium of pH 6.8 - the first order and Weibull model.

Formulation	First-order				Weibull			
	$k_1 \pm SD$ (h^{-1})	$A_\infty \pm SD$ (%)	*RSS*	R^2	$\lambda \pm SD$	$b \pm SD$	*RSS*	R^2
F1	0.188 ± 0.009	94.7 ± 1.7	7421	0.9222	0.207 ± 0.015	0.67 ± 0.05	7735	0.9413
F2	0.138 ± 0.006	83.0 ± 1.6	1283	0.9787	0.139 ± 0.014	0.70 ± 0.04	4237	0.9603
F3	0.165 ± 0.007	91.4 ± 1.6	2110	0.9705	0.180 ± 0.012	0.70 ± 0.08	5883	0.9566
F4	0.123 ± 0.006	73.5 ± 9.5	1635	0.9673	0.119 ± 0.003	0.93 ± 0.02	7520	0.9973

k_1 is the first order release rate constant, A_∞ is the maximum releasable amount of drug in infinite time, λ is the reciprocal value of time scale of the process, T_i is the location parameter and b is the shape parameter, *RSS* is residual sum of squares, *SD* is the standard deviation and R^2 is the coefficient of determination

VH in the tablets is distributed fairly regularly, rarely sharply demarcated areas (diameter from 100 µm to 1 mm) with a significantly increased concentration of VH were found. These areas have a disc-shaped cross-section at the tablet cut (Fig. 3B) and tablet fracture, whilst at the tablet surface, they are approximately circular. In some cases, these areas may result from the disintegration of larger particles of VH during compression but their formation from originally spherical agglomerates of the active substance which can be observed in the mixture prior to compression, is probably more frequent. Although these clusters can be observed in all types of studied tablets regardless of their specific composition, it seems that their number and size is the fewest in the tablets containing binder COM.

Evaluation of verapamil hydrochloride release from F1 – F6 formulation

In order to describe and quantitatively evaluate the mechanism of VH release from studied tablets (F1-F4), the dissolution profiles were fitted to the first-order kinetic model (Eq. 1, 2), Higuchi diffusion model (Eq. 3), Korsmeyer-Peppas model (Eq. 4) and Weibull model (Eq. 5). Results obtained from the mathematical evaluation using regression analysis are listed in Table 2 A, B and Table 3 A, B.

In both dissolution media (pH 1.2 and 6.8), the formulations without retarding component (F5, F6) was found to be dissolved almost immediately and therefore their dissolution data were not evaluated by regression analysis. For these formulations, a marked increase in the amount of VH released was found at the beginning of the dissolution process and almost all the amount of the active substance incorporated in dosage form was released within 5 min after insertion of the tablet into the medium. The studied formulations F1 – F4 containing 30% of hypromellose (in two viscosity grades) as the retarding component showed a significant slowdown of VH release in comparison with F5 and F6 formulation. As is clear from Figure 4A (acidic medium), the highest release rate of VH was found for F1 formulation. In this medium, 50% of the drug from F1 is released in about 4 h and the dissolution profile of the formulation follows the first order kinetic model with high value of the coefficient of determination (R^2 = 0.9921, Table 2A). In the medium of pH 6.8 (Fig. 4B), the dissolution profiles of F1 and F3 overlap but from release rate constants obtained based on regression analysis (Table 2B) it follows that VH is released faster from F1 formulation in comparison with F3 formulation. However, the different values of release rate constants are affected by the higher value of RSS and lower value of R^2 for F1 formulation.

This higher release rate of VH from F1 formulation is probably due to the presence of lactose in the co-processed dry binder ML. Lactose contained in the dry binder increases the hydrophilic character of the tablets, therefore, a higher release rate of the active substance can be expected.

In the dissolution medium of pH 6.8, the lowest drug release rate was obtained for F4 formulation but the best fit for the first-order kinetic model was obtained for F2 formulation which is confirmed by the high value of R^2 (Table 2B).

As can be seen in Table 2A, in the acidic dissolution medium, the studied hydrophilic formulations also follow the Weibull model with high values of R^2. When the shape parameter b in (Eq. 5) is equal to one, the Weibull empiric model corresponds to the first order kinetic model and the parameter λ in (Eq. 5) corresponds to the first order release rate constant k_1. In the acidic medium for F1 formulation the value of b = 0.94 and in medium pH of 6.8 for F4 formulation the value of b = 0.93 were found which confirms the fact that these dissolution processes can be considered for the first-order kinetics.

Although in Figure 4A and 4B the increase of the drug released amount versus time can be seen, the actual drug release rate can be obtained only by a derivative of the dissolution profile. The derivative of the dissolution profile at any given point with respect to time (the independent variable) corresponds to the drug release rate. If the dissolution profile meets the first-order kinetic model, it is possible to make an analytical derivative (Rate Law), otherwise, it is necessary to perform a numerical derivative (e.g., a second-order approximation of the first derivative). The dependence of the drug release

Table 3A. Kinetic parameters of VH release in acidic dissolution medium (pH 1.2) - Korsmeyer-Peppas and Higuchi model.

Formulation	Korsmeyer-Peppas				Higuchi		
	$n \pm SD$	$a \pm SD$	*RSS*	R^2	$K_H \pm SD$	*RSS*	R^2
F1	0.709 ± 0.02	20.45 ± 0.48	853	0.9700	25.16 ± 0.41	2297	0.9191
F2	0.626 ± 0.02	18.46 ± 0.56	1365	0.9407	21.30 ± 0.33	1881	0.9183
F3	0.653 ± 0.02	19.44 ± 0.51	1120	0.9599	23.14 ± 0.34	2004	0.9282
F4	0.595 ± 0.01	14.33 ± 0.28	628	0.9826	16.95 ± 0.14	1162	0.9679

Table 3B. Kinetic parameters of VH release in acidic dissolution medium (pH 1.2) - Korsmeyer-Peppas and Higuchi model.

Formulation	Korsmeyer-Peppas				Higuchi		
	$n \pm SD$	$a \pm SD$	*RSS*	R^2	$K_H \pm SD$	*RSS*	R^2
F1	0.550 ± 0.03	21.57 ± 0.98	4686	0.8591	21.72 ± 0.24	11660	0.9162
F2	0.581 ± 0.02	15.78 ± 0.47	1576	0.9544	17.96 ± 0.16	4770	0.9553
F3	0.578 ± 0.02	19.62 ± 0.58	1638	0.9404	21.00 ± 0.19	7298	0.9461
F4	0.530 ± 0.02	12.78 ± 0.64	5008	0.8839	13.64 ± 0.20	7573	0.8853

a is the structural and geometric characteristics of the dosage form, n is the release rate exponent, K_H is the Higuchi dissolution constant, *RSS* is residual sum of squares, *SD* is the standard deviation, R^2 is the coefficient of determination

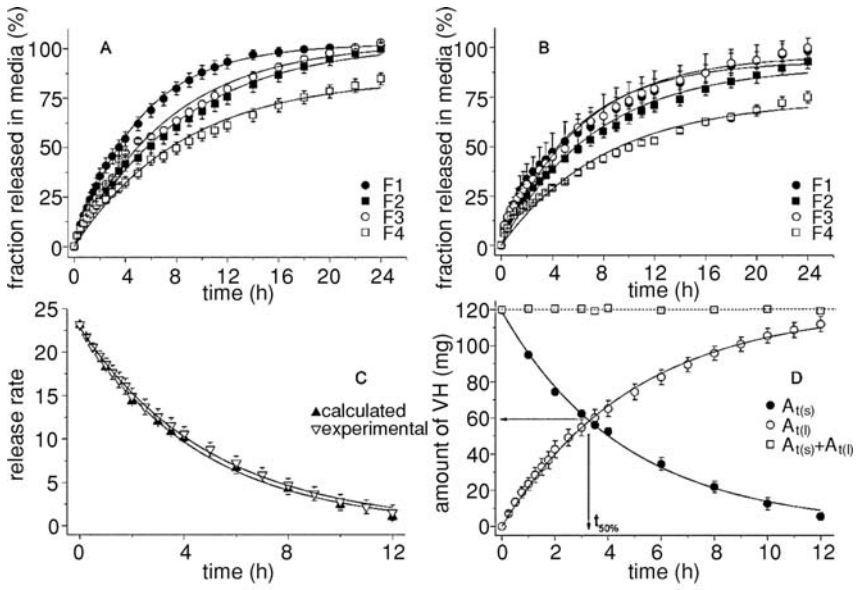

Figure 4. Dissolution profiles of F1-F4 formulations in dissolution medium of pH 1.2 (A) and 6.8 (B) fitted to the first order kinetic model; the dependence of the drug release rate with time for F1 formulation (C); the dependence of $A_{t(s)}$, $A_{t(l)}$ and total amount of VH vs. time for F1 formulation and graphical evaluation of $t_{50\%}$ (D)

rate with time for F1 formulation is shown in Figure 4C. It is clear that the time dependence of the release rate of VH is a monotone decreasing curve and after about 12 h from the beginning of the dissolution process, the drug release rate is almost zero. Figure 4C also shows a good concordance of the release rate obtained by the derivative of the dissolution profile with the release rate calculated based on Rate Law. A decrease in the amount of VH in solid drug form $A_{t(s)}$ (fitted to Eq. 2) and increase in the amount of VH in the dissolution medium $A_{t(l)}$ (fitted to Eq. 1) for F1 formulation is shown in Figure 4D. Intersection of both curves determines the half-life of drug release $t_{50\%}$. Assuming that the drug dissolution profile fulfills the first-order kinetic model, the value of $t_{50\%}$ can be also calculated from the equation, where k_1 is the first-order release rate constant with the unit of time^{-1}. The values of $t_{50\%}$ obtained by graphical method (Figure 4D) and calculated according to are comparable – 3.32 h graphically and 3.54 h calculated from k_1, which confirms the validity of the first order kinetic model.

The effect of the viscosity of HPMC and dry binder used is clearly visible in Table 2A, B. In both dissolution media the highest release rate constant was found for F1 formulation. The F1 and F2 tablets contain co-processed dry binder ML (lactose and microcrystalline cellulose in a ratio of 3 : 1). As was mentioned above, the addition of lactose increases the hydrophilic character of these matrix tablets and fast penetration of the acidic dissolution medium into the tablet allows faster release of good soluble VH in comparison with matrix tablets F3 and F4 containing pure microcrystalline cellulose (Fig. 2A). Quick release of VH from F1 tablets is also evident from the slope of the first part of the dissolution profile (Figs. 4A, B) and high release rate of VH at the beginning of the dissolution process is shown in Figure 4C. Approximately 4 h after insertion of the tablet into the medium the release rate of VH decreases almost linearly with time. The values of release rate constant also confirm the fact that a more viscous form of hypromellose (HPMC 2) slows down the release of VH more effectively.

Swelling and disintegration of studied formulations are shown in Figure 5. The swelling of the matrix tablets containing hypromellose (HPMC) is due to the disruption of the hydrogen bonding between the polymer chains. Water penetrates the solid HPMC and the forces between the chains diminish. As shown in Figure 5, during the dissolution test the swelling and disintegration of the studied tablets into particles were observed. As a result of these concurrent processes the dimensions and shape of the tablets were changed with time.

In order to evaluate the mechanism of VH release from studied formulations, the dissolution profiles were fitted to Korsmeyer-Peppas (Eq. 4) and Higuchi model (Eq. 3). Results of regression analysis are summarized in Table 3A and 3B. As clearly indicated by values of the release exponent *n* (0.595 – 0.709 in acidic medium, 0.530 – 0.581 in medium of pH 6.8), all studied formulations show anomalous transport – superposition of case-II transport and diffusion-controlled drug release mechanism. Case-II transport is the drug transport mechanism associated with stresses and state-transition in hydrophilic glassy polymers which swell in water or biological fluids (25). The studied drug formulations F1 – F4 contain water-soluble VH incorporated into a swellable HPMC matrix, therefore drug release controlled mainly by diffusion can be expected. But due to the fact that the diffusion coefficients of water and incorporated drug are strongly concentration dependent, the application of Korsmeyer-Peppas equation cannot give exact information about the drug release mechanism (27).

CONCLUSION

Hydrophilic matrix tablets containing microcrystalline cellulose in two forms: as co-processed dry binder ML (lactose and microcrystalline cellulose in ratio 3 : 1) or as pure microcrystalline cellulose (binder COM), were prepared using the direct compression method. HPMC in two viscosity grades was used as release retardant and VH was used as the active substance. Based on non-linear regression analysis of the dissolution profiles, the release kinetics of verapamil hydrochloride was evaluated. The higher release rate constants were found for formulations containing co-processed dry binder ML in comparison with formulations containing pure microcrystalline cellulose (binder COM). This fact can be explained by more hydrophilic character of the tablets containing binder ML. Furthermore, it was confirmed that the drug release rate is strongly influenced by the viscosity grade of HPMC used (HPMC 1 – higher release rate of VH).

Evaluation of microcrystalline cellulose in co-processed dry binder ML for extended release of VH in comparison with pure microcrystalline cellulose (binder COM) showed that the addition of lactose facilitates a faster release of VH from the tablet.

Declaration of interests

The authors declare that there is no conflict of interests.

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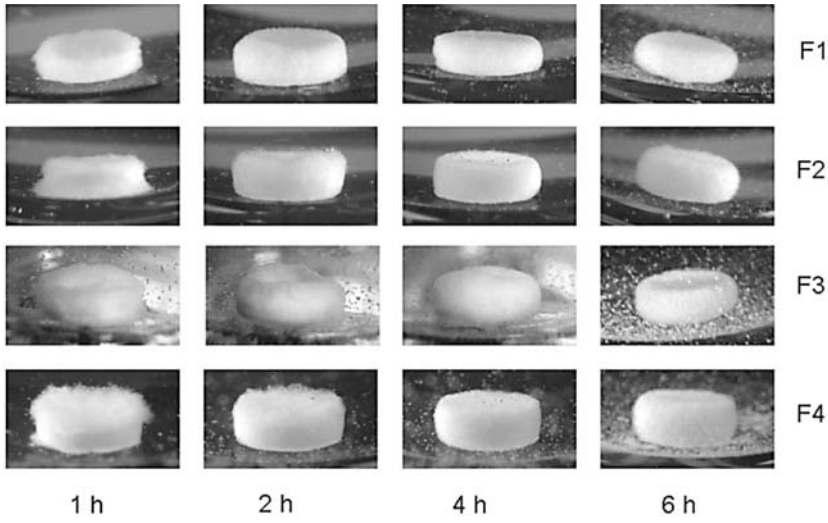

Figure 5. *In situ* photographic observation of the tablets during the dissolution test in acidic medium (pH 1.2)

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