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STUDY OF DUAL MATRIX TABLETS CONTAINING HYPROMELLOSE OF DIFFERENT VISCOSITY DEGREE AND GLYCERYL DIBEHENATE

JITKA MUŽÍKOVÁ[1]*, KATEŘINA HOLUBOVÁ[1], ALENA KOMERSOVÁ[2] and VÁCLAV LOCHAŘ[2]

[1]Department of Pharmaceutical Technology, Charles University in Prague,
Faculty of Pharmacy in Hradec Králové, Heyrovského 1203, 500 05 Hradec Králové, Czech Republic
[2]Department of Physical Chemistry, University of Pardubice, Faculty of Chemical Technology,
Czech Republic

Abstract: Studies are described on the compressibility of directly compressible tableting materials containing two viscosity types of hypromellose in two concentrations and tableting materials containing additional glyceryl dibehenate, also in two concentrations. Compressibility is evaluated by means of the energy profile of the compression process and determination of tensile strength of tablets. Dissolution test examines the rate of release of the active ingredient from matrix tablets, which is subsequently evaluated mathematically. Increased concentrations of both hypromelloses and an addition of glyceryl dibehenate into tablets with both types of hypromellose improved compressibility. The rate of drug release was decreased with increasing viscosity degree of hypromellose and its increasing concentration. An addition of glyceryl dibehenate exerted the same influence on release as increased concentrations of the pertinent hypromellose.

Keywords: hypromellose, glyceryl dibehenate, dual matrix tablets, energy profile of compression, tensile strength of tablets, release kinetics.

Dual matrix tablets represent one type of matrix tablets used as systems with prolonged release of the active ingredient. These tablets contain both a hydrophilic gel component and a lipophilic one (1). A very frequently employed hydrophilic polymer in matrix tablets is hypromellose, which ensures decelerated release of the active ingredient just by forming a gel through which the drug passes by diffusion or possibly also erosion. The rate of release of the drug significantly depends on the employed viscosity degree of hypromellose and its concentration (2). The lipophilic substance which can be used for the preparation of matrix tablets is glyceryl dibehenate (COM). This excipient in concentrations up to 3% is used as a lubricant; in order to prolong the release it is necessary to increase its concentration above 10% (3). The releasing mechanism of the active ingredient from the matrices with COM is prevalently diffusion, an advantage is independence of drug release on pH (4), which has been reported also for hypromellose (5). The present paper aimed to evaluate compressibility of directly compressible tableting materials containing two types of hypromellose in two concentrations and tableting materials containing additional COM also in two concentrations. Compressibility was evaluated by means of the energy profile of compression process and determination of tensile strength of tablets. Another aim was to compare the rate of release of the active ingredient from matrix tablets.

EXPERIMENTAL

Materials

Spray-dried lactose FlowLac® 100 was supplied by the Meggle Pharma (Germany), hypromellose (Methocel™ K4M Premium CR, Methocel™ K100M Premium CR) by Colorcon GmbH (Germany). Glyceryl dibehenate (Compritol® 888 ATO) was obtained from Gattefossé (France) and sodium stearyl fumarate (Lubripharm® SSF) from SPI Pharma (France). Salicylic acid was from JQC (Huayin) Pharmaceutical Co., Ltd. (China).

Preparation of tableting materials

A set of 8 tableting materials was prepared, the composition of which is presented in Table 1. The

* Corresponding author: e-mail: muzikova@faf.cuni.cz

Table 1. Composition of tableting materials (%).

Tableting material	FlowLac 100	Methocel K4M	Methocel K100M	Compritol 888ATO	Salicylic acid	Lubripharm SSF
F1	54	20			25	1
F2	44	30			25	1
F3	54		20		25	1
F4	44		30		25	1
F5	44	20		10	25	1
F6	34	20		20	25	1
F7	44		20	10	25	1
F8	34		20	20	25	1

substances were mixed stepwise in a mixing cube KB 15S (Erweka GmbH, Germany). First, the pertinent hypromellose was mixed with spray-dried lactose for 5 min, then COM, if included, was added for another 5 min of mixing. Then, salicylic acid was added, with which the mixture was mixed for another 5 min. Finally, the lubricant was added and the material was mixed for additional 2.5 min. Altogether 30 g of each mixture was prepared. The rate of rotations of the mixing cube was 17 rev/min.

Preparation of tablets and energy evaluation of compression process

Tablets were compressed on a material testing equipment T1-FRO 50 TH.A1K Zwick/Roell (Zwick GmbH & Co., Ulm, Germany) in a special matrix of a diameter of 13 mm. Compression velocity was 40 mm/min. The tablets were of a cylindrical shape without facets with a weight of 0.5 ± 0.0010 g. From all tableting materials always 10 tablets, by means of which compressibility was tested, were compacted at compression forces of 4, 6 and 8 kN. The computer program testXpert V 9.01 simultaneously recorded the energy process of compression by means of the "force-displacement" record and numerically evaluated the energy balance of compression, i.e., the energy consumed for friction E_1, the energy accumulated by the tablet after compression E_2, and the energy released during decompression E_3, the total energy E_{max}, which is the sum total of all energies, and plasticity (6). From each tableting material another 6 tablets were compressed for dissolution in such a way that their final strength ranged between 0.71–0.88 MPa. For tableting materials with 20% hypromellose without COM a compression force of 8 kN, for the same tableting materials with 30% hypromellose and for the tableting materials with 20% hypromellose and 10% COM a compression force of 6 kN were used. In compression of tableting materials with 20% hypromellose and 20% COM a compression force of 4 kN was employed.

Measurement of tensile strength of tablets

Tensile strength of tablets was measured in 10 tablets no sooner than 24 h after compression. Measurements were performed using a Schleuniger apparatus (Dr. Schleuniger Pharmatron AG, Switzerland), which measures the diameter and height of tablets with a precision of 0.01 mm and destruction force in N. Tensile strength of tablets was subsequently calculated according to the following equation [Eq.1] (7):

$$P = 2 \times F/(\delta \times d \times h) \quad (1)$$

where P is tensile strength of tablets in MPa, F is destruction force in N, d is diameter of tablets in mm, h is height of tablets in mm.

Dissolution testing

The rate of release of salicylic acid was evaluated in 6 tablets from each tableting material. The method of the rotating basket according to the European Pharmacopoeia 7 (8) performed on a dissolution unit Sotax AT 7 *smart* (Sotax AG Basel, Switzerland) served for the assay. Dissolution medium was 900 mL of purified water at 37°C. The rate of rotation of the basket was 100 rpm and at one hour intervals samples in an amount of 3 mL were withdrawn, and subsequently this volume was replaced with a pure medium. The content of salicylic acid was determined spectrophotometrically at the wavelength of 270 nm by means of a spectrophotometer Specord 205 (Analytic Jena, Germany) and the program WinAspect. Absorbance was measured *versus* a blind sample which was obtained by dissolution of tablets of the correspon-

ding composition without salicylic acid. The amount of the released active ingredient was determined by means of the calibration curve of salicylic acid.

Mathematical and statistical processing of results

The values of the energy profile of compression were statistically processed by the computer programme testXpert V 9.01 directly during compaction. The results of tensile strengths were statistically processed by means of the computer programmes Excel. Elementary data analysis yielded the mean values with standard deviations. In the cases of unclear significance of differences in the values, unpaired t-test at a level of significance of 0.05 was employed.

The dissolution kinetics of investigated formulations was tested by dissolution study *in vitro*. As the concentration of the active substance (salicylic acid) in the dissolution medium was monitored, the generally known equation for the first order kinetics (9) had to be transformed into the time dependence of the released amount of drug:

$$A_{t(l)} = A_{\infty}(1 - e^{-k_1 t}) \quad (2)$$

where $A_{t(l)}$ is the released amount of the drug (active substance) in dissolution medium in time t, A_{∞} is the maximum releasable amount of the drug in infinite time (the initial amount of the drug in a solid drug formulation), and k_1 is the first order rate constant expressed in units of time $^{-1}$. Eq. 2 expresses the first order kinetics as time dependence of active substance amount (concentration) released into dissolution medium. All obtained experimental data from the dissolution test were fitted by Eq. 2 and the first order kinetics was verified by the N-order kinetic model (10, 11). For non-linear regression analysis and statistical evaluation, the computer programmes

Table 2. Values of energy profile of compression (means ± SD, n = 10).

Tableting material	CF (kN)	E_{max} (J)	E_1 (J)	E_2 (J)	E_3 (J)	PI (%)
F1	4	5.91 ± 0.13	3.31 ± 0.12	2.21 ± 0.02	0.39 ± 0.00	85.06 ± 0.14
	6	9.60 ± 0.17	5.76 ± 0.17	3.07 ± 0.03	0.77 ± 0.01	79.86 ± 0.16
	8	13.22 ± 0.29	8.07 ± 0.28	3.87 ± 0.04	1.29 ± 0.02	74.98 ± 0.27
F2	4	6.12 ± 0.18	3.41 ± 0.17	2.31 ± 0.01	0.40 ± 0.00	85.27 ± 0.15
	6	10.01 ± 0.15	5.97 ± 0.16	3.26 ± 0.03	0.78 ± 0.01	80.64 ± 0.23
	8	13.87 ± 0.30	8.49 ± 0.28	4.07 ± 0.04	1.30 ± 0.01	75.74 ± 0.19
F3	4	5.55 ± 0.09	2.89 ± 0.10	2.26 ± 0.02	0.40 ± 0.02	84.88 ± 0.54
	6	9.00 ± 0.14	5.06 ± 0.14	3.16 ± 0.02	0.78 ± 0.01	80.24 ± 0.19
	8	12.86 ± 0.23	7.58 ± 0.23	3.98 ± 0.02	1.30 ± 0.01	75.39 ± 0.14
F4	4	9.33 ± 0.20	6.55 ± 0.20	2.36 ± 0.02	0.42 ± 0.01	84.90 ± 0.27
	6	15.10 ± 0.46	11.02 ± 0.48	3.28 ± 0.03	0.80 ± 0.01	80.43 ± 0.14
	8	20.96 ± 1.82	15.56 ± 1.82	4.08 ± 0.06	1.32 ± 0.01	75.62 ± 0.29
F5	4	5.91 ± 0.20	3.40 ± 0.20	2.11 ± 0.02	0.41 ± 0.00	83.77 ± 0.21
	6	9.84 ± 0.32	6.14 ± 0.32	2.89 ± 0.03	0.81 ± 0.01	78.13 ± 0.21
	8	13.61 ± 0.52	8.78 ± 0.50	3.50 ± 0.03	1.33 ± 0.01	72.50 ± 0.18
F6	4	6.08 ± 0.27	3.70 ± 0.26	1.96 ± 0.02	0.42 ± 0.00	82.52 ± 0.16
	6	9.81 ± 0.32	6.42 ± 0.31	2.56 ± 0.02	0.83 ± 0.01	75.63 ± 0.18
	8	13.73 ± 0.32	9.32 ± 0.32	3.04 ± 0.03	1.38 ± 0.01	68.79 ± 0.29
F7	4	5.87 ± 0.19	3.37 ± 0.18	2.09 ± 0.01	0.41 ± 0.01	83.71 ± 0.34
	6	9.46 ± 0.33	5.82 ± 0.31	2.84 ± 0.03	0.80 ± 0.01	77.98 ± 0.21
	8	13.47 ± 0.25	8.71 ± 0.24	3.44 ± 0.02	1.33 ± 0.01	72.18 ± 0.20
F8	4	6.12 ± 0.21	3.77 ± 0.20	1.94 ± 0.01	0.41 ± 0.00	82.60 ± 0.16
	6	10.17 ± 0.35	6.81 ± 0.34	2.53 ± 0.02	0.83 ± 0.01	75.44 ± 0.25
	8	14.16 ± 0.13	9.75 ± 0.12	3.03 ± 0.03	1.38 ± 0.01	68.69 ± 0.25

Explanations: CF – compression force; E_{max} - total energy; E_1 – energy of friction; E_2 – energy accumulated by the tablet; E_3 – energy of decompression; Pl – plasticity; SD – standard deviation.

Table 3. Statistical evaluation of dissolution profiles by the first order kinetic model (means ± SD, n = 6).

Tableting material	k_1 (h^{-1})	A_∞ (%)	R^2	SSR
F1	0.3545 ± 0.0180	103.81 ± 1.58	0.9942	58.115
F2	0.1438 ± 0.0027	100.85 ± 0.69	0.9984	26.438
F3	0.1071 ± 0.0025	85.43 ± 0.83	0.9980	24.980
F4	0.0797 ± 0.0020	87.43 ± 1.11	0.9984	17.655
F5	0.1458 ± 0.0039	98.96 ± 0.90	0.9962	68.716
F6	0.1344 ± 0.0046	98.93 ± 1.21	0.9945	100.783
F7	0.0705 ± 0.0042	91.81 ± 2.98	0.9927	84.340
F8	0.0771 ± 0.0034	88.26 ± 2.02	0.9955	52.410

Explanations: k_1 - the first order release rate constant; A_∞ - maximum releasable amount of the drug in infinite time; R^2 - the coefficient of determination; SSR - the sum of squares of residues.

GraphPad Prism and Origin 9 Pro were used. Regression coefficient R^2 and the sum of squares of residues (SSR) were used for comparison of dissolution profiles. Statistical significance was tested using Student's *t*-test for unpaired samples, at a significance level of $p < 0.05$.

RESULTS AND DISCUSSION

The paper aimed to compare compressibility of directly compressible tableting materials containing either hypromellose alone in different viscosity degrees, or the added lipophilic component COM. Hypromelloses Methocel K4M and K100M were used in concentrations of 20 and 30 %. Tableting materials with hypromelloses of a concentration of 20% were supplemented with COM in concentrations of 10 and 20%. Compression forces of 4, 6 and 8 kN were selected in such a way that the final strength of most tablets ranged within the optimal range of tensile strength of tablets, which is 0.56-1.12 MPa (12). Compressibility of tableting materials was evaluated by means of the energy profile of compression process and by means of the test of tensile strength of tablets. Another aim was to compare the rate of release of the active ingredient from tablets. Tablets for dissolution tests were prepared in such a way so that their strength ranged in the same range, i.e., 0.71–0.88 MPa.

Evaluation of compressibility of tablets

Energy profile of compression process

The values describing the energy profile of all tableting materials are listed in Table 2. The total energy of compression E_{max} increases with compression force. If its values for tableting materials without COM are compared, their increase with increased concentrations of both hypromelloses is observed. In tableting materials with Methocel K4M this increase in the values is very low, but in the case of Methocel K100M it is marked. It is also of interest that with increasing viscosity degrees in 20% hypromellose concentration there occurs a tendency to decrease E_{max}, whereas in 30% concentration, on the other hand, an increase in E_{max} is observed. It can be also stated that the above-mentioned dependences of total energy of compression are due to the values of the energy for friction E_1, which in the sum total with the energy accumulated by the tablet E_2 and the energy of decompression E_3 participates in the total energy, for there are no more significant differences for the pertinent tableting materials between the values of the energy accumulated by the tablet and the energy of decompression. After addition of COM to 20% Methocel K4M concentration there is no significant change in the values of total energy of compression, and there is no statistically significant difference between the values. This result is based on the fact that the component of the total energy of compression accumulated by the tablet E_2 is decreased due to an addition of COM, but on the other hand, the component of the energy for friction E_1 is slightly increased for the same reason, and there is no more significant difference between the values of the energy of decompression E_3. After addition of COM to Methocel K100M there occurs a very slight increase in the values of total energy of compression. The dependences of other energies are the same as in the previous case. The values of plasticity are decreased with compression force due to a decreasing number of pores in the compact. In tableting materials with Methocel K4M, the values of plasticity are slightly increased with its increased concentration, in the case of the tableting

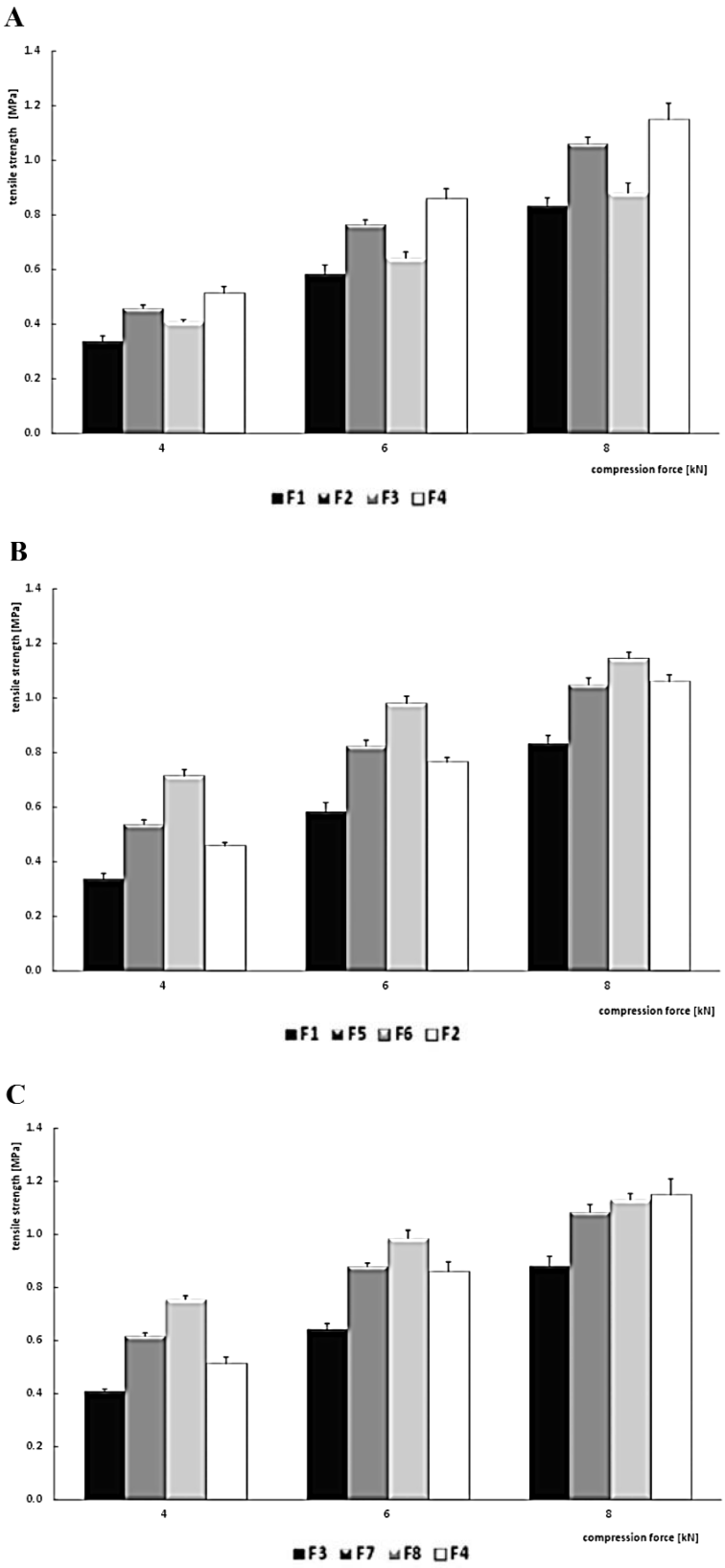

Fig. 1 A, B, C. Tensile strength of tablets in function of compression force. A. Tableting materials without Compritol 888 ATO. B. Tableting materials with Methocel K4M and Compritol 888 ATO. C. Tableting materials with Methocel K100M and Compritol 888ATO

materials with Methocel K100M there is no significant difference between the values within the range of the concentration used. An addition of COM to tableting materials with both types of Methocel produces a decrease in plasticity, which is decreased with its increasing concentration.

Tensile strength of tablets

Tensile strength of tablets in dependence on compression force is represented in Figures 1 A, B and C. Strength of tablets for tableting materials only with hypromellose in two viscosity degrees is shown in Figure 1 A. The strength increases with compression force as well as with increasing concentrations of both Methocels. Higher values are observed in the tablets containing hypromellose of a higher viscosity degree, i.e., with Methocel K100M. Nokhodchi et al. (13), on the other hand, describe the opposite effect of viscosity grade on tablet strength. Figures 1 B and C represent the dependences of strength on compression force for tableting materials with Methocels and COM. It is clear from the Figures that a presence of the wax-like substance COM increases tensile strength of tablets. The strength is increased with its increasing concentration. The presence of wax thus means an increase of binding capacity (14). For the sake of comparison, the Figures also show the value for the tablets with the pertinent Methocel in a concentration of 30% alone. The value of tensile strength of these tablets is closest to the value of the strength of tables which contain the pertinent Methocel in of 20% and 10% COM concentrations. An exception is the value of the strength of tablets with 30% Methocel K100M at 8 kN (Fig. 1 C), where this value is closest to the strength of tablets with 20% of the pertinent Methocel and 20% of COM.

Evaluation of the dissolution test

Fitting of dissolution profiles by first order and N-order kinetic models

The non-linear regression analysis of untransformed dissolution data was used to characterize and evaluate the kinetic profiles of the drug formulations. All dissolution profiles were fitted by the first order kinetic model (Eq. 2) and statistically evaluated. Based on regression analysis results, it was proved that the process of active substance release from the drug formulation follows first order kinetics. The values of R^2 for all the formulations studied were found in the range of 0.9927-0.9984 and the values of SSR in the range of 17.655-100.783 (Table 3). Validity of the first order kinetic model was also verified by fitting of the dissolution data by the N-order model. The values of R^2 for the N-order model were found in the range of 0.9856-0.9984, which is slightly lower in comparison with first order kinetics. However, the parameter N in the N-order model, representing the actual order of the dissolution process, was found for all formulations under study in the range of 0.9993-1.003, which corresponds with first order kinetics.

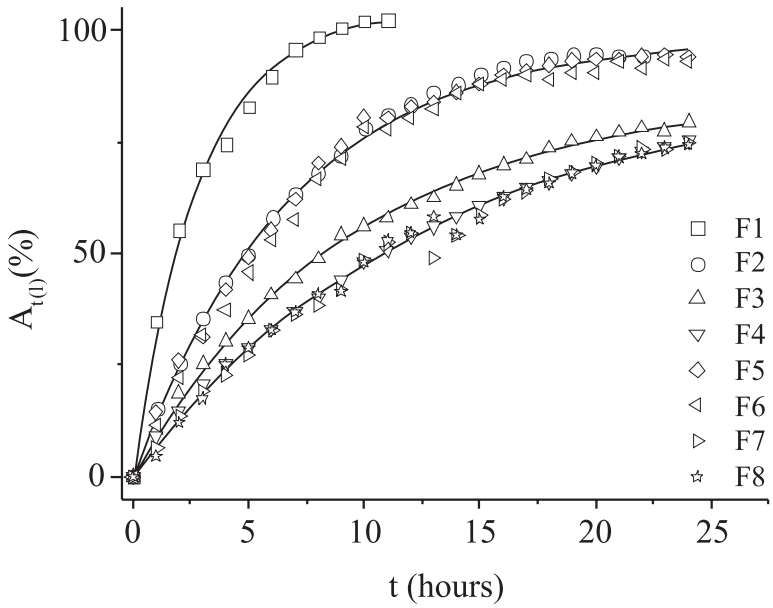

Figure 2. Regression analysis of dissolution profiles by the first order kinetic model

Effect of Methocel K4M and K100M

Based on non-linear regression analysis, the first order release rate constants of salicylic acid from all formulations were found (Table 3). The values in the range of 0.0705-0.3545 h^{-1} show that the active substance release is influenced by composition of the matrix.

The active substance (salicylic acid) releases the most quickly from formulation F1 containing 20% of Methocel K4M as the matrix agent. An addition of 10% of Methocel K4M in formulation F2 causes a strong decline of the release rate constant to the value of 0.1438 h^{-1}, which represents a reduction of the release rate constant value by more than 50%. When Methocel K100M (F3 and F4) was used as the matrix forming agent, the decline of the release rate constant value with an addition of 10% of Methocel K100M is not so strong in comparison with formulations F1 and F2. It follows from the values of the release rate constant presented in Table 3 that the cellulose type (Methocel K4M or Methocel K100M) is an important parameter affecting salicylic acid release from the formulations under study. A difference in the composition between formulations F1-F3 and F2-F4 occurs only in the cellulose type (see composition in Table 1), therefore it can be assumed that the decline of the release rate constant of F3 in comparison with F1, and F4 in comparison with F2 is caused by the viscosity of the gel layer which is formed around the matrix. The viscosity grade of the cellulose used influences also the value of A_∞, as is shown in Table 3. For investigated formulations containing Methocel K100M without COM (F3 and F4), lower A_∞ values (85.43 and 87.43%) were found in comparison with formulations F1 and F2 formed by Methocel K4M cellulose without COM (103.81 and 100.8 %).

Effect of glyceryl dibehenate addition

Formulations F5-F8 contained 20% of hypromellose (Methocel K4M or Methocel K100M) and addition of COM (10 or 20%). On the basis of non-linear regression analysis, it was found that the addition of COM does not influence the mechanism of drug release – all investigated dissolution profiles fulfill the first order kinetic model with R^2 in the range of 0.9927-0.9962. It is clear from the obtained values of the release rate constant (Table 3) that an addition of 10% of COM into formulation F1 exerts the same effect on active substance release rate as an addition of 10% of Methocel K4M – in both cases the release rate constants were found in about 0.14 $hours^{-1}$ (overlapping curves F2 and F5 in Figure 2). The following increase in the COM content in the formulation with 20% of Methocel K4M (F6) causes only a low decline of the release rate constant, as is presented in Table 3 and Figure 2. When Methocel K100M cellulose was used as the matrix forming agent, an addition of 10% of COM (F7) decreased the value of the release rate constant by more than 30% in comparison with F3 formulation containing pure Methocel K100M as the matrix. The following increase in the COM content (F8) by 10% caused a slight increase in the release rate constant value (Table 3). The release rate of the active substance from formulations F7 and F8 is comparable with formulation F4 containing only pure Methocel K100M (30%) as the matrix agent (Fig. 2). COM influences also the maximum releasable amount of the drug. It was demonstrated that an addition of COM (10 or 20%) into the matrix formed by Methocel K4M (formulation F5 and F6) slightly decreases A_∞ value – for F5 and F6 formulation A_∞ = 99% was found. But an addition of COM (10 or 20%) into the formulations containing Methocel K100M cellulose shows an opposite effect than in Methocel K4M formulations – the obtained values of A_∞ for F7 and F8 (containing 10 and 20% COM) are higher in comparison with F3 formulations (20% Methocel K100M without COM).

CONCLUSION

In conclusion, it can be stated that higher concentrations of both hypromelloses and the presence of COM in the tableting materials with both types of hypromelloses increase compressibility as there occurs an increase in tensile strength of tablets. From the viewpoint of the release of salicylic acid it is clear that the viscosity grade of employed cellulose as the matrix forming agent does not influence the release mechanism but strongly influences the release rate constant of salicylic acid. In formulations with Methocel K4M, a more important effect of cellulose content was found in comparison with Methocel K100M formulations. An addition of COM does not influence the release mechanism but it influences the values of k_1 and A_∞. As mentioned above, an addition of 10% of COM into the formulation containing 20% of Methocel K4M shows the same effect on release rate as an addition of 10% of Methocel K4M. When formulations with Methocel K100M and COM were studied, similar results were found.

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