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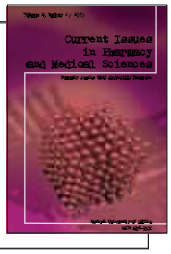

Effect of bioadhesive agents on physico-chemical properties of suppositories

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ABSTRACT

Dissolution rate of an active substance from suppositories may be altered by the qualitative and quantitative selection of suitable excipients. Thus, the accelerated-release or sustained-release suppositories can be manufactured. The objective of our study was to prepare the suppositories containing paracetamol in Novata BD and Novata BCF bases by the fusion method as well as to evaluate the influence of addition of the bioadhesive substances, namely: hydroxypropyl methyl cellulose (HPMC) and methylcellulose (MC) at concentrations of 5, 10, 15 and 20%, on the physico-chemical properties of suppositories. Assessment of the preparations were based on the outcomes of the following tests: uniformity of mass, uniformity of content of active substance, hardness of suppositories, softening time determination and the disintegration time of suppositories. Release of the active substance into the phosphate buffer at pH 7.2 was also performed. Content of the active substance was determined spectrophotometrically at 243 nm. On the basis of the obtained results it may be concluded that the addition of MC at concentrations of 15%, 20% and HPMC at concentrations of 5%, 10%,15%, 20% delays the release of active substance from suppositories. The physical properties of the prepared suppositories met the requirements of the Polish Pharmacopoeia, 9th edition.

Keywords: suppository bases, surfactants, paracetamol

INTRODUCTION

Paracetamol, also known as acetaminophen belongs to the class of non-opioid analgesics and antipyretics that are available without prescription. Unlike the analgesics from the non-steroidal anti-inflammatory drugs, it exerts only a slight anti-inflammatory effect. Thanks to its favorable safety profile as well as a high therapeutic index, paracetamol is commonly administered to pediatric and geriatric patients [11]. Being an agent significantly and slowly absorbed through the rectal mucosa, it is frequently used in a convenient suppository form, suitable for a wide range of patients [12]. The release of an active substance from a suppository as well as its absorption into the bloodstream depend on several factors, i.e. selection of a suppository base, addition of surfactants and other excipients, dissolution of an active ingredient in the applied vehicle [2,9,13]. Introduction of surfactants into the suppository base considerably influences the process of active substance release from the drug form. It may both modify the release rate and increase or reduce the amount of the released active ingredient [5]. There are number of research papers focused on the relationship between the surfactant addition (and its concentration) and the amount of a drug substance released from a preparation. Surfactants are the compounds that lower the surface tension of a suppository base, expanding the contact area between the applied active ingredient and vehicle [6]. Amongst the bioadhesive surfactants that are able to modify the process of active substance release from a suppository, methylcellulose and its derivatives are mentioned. The main objective of our study was to evaluate the influence of addition of methylcellulose and hydroxypropyl methyl cellulose on the physicochemical properties of rectal suppositories as well as on the release of the active substance from this pharmaceutical form. When using this type of bioadhesive substances, the slow release of an active substance from the suppositories should be expected. Such suppositories are applied in order to lower a drug dose, improve bioavailability, increase patient compliance and reduce the dosing frequency. This is especially important in case of young children.

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MATERIAL AND METHODS

Paracetamol (SRI, Krishna Pharmaceuticals LTD, India), Novata BD, Novata BCF (Cognis GmbH), Methylcellulose (400 cP, Sigma Aldrich), Hydroxypropyl methyl cellulose (80-120 cP Sigma).

Formulation of paracetamol suppositories. Suppositories (1g), containing 250 mg of paracetamol were prepared by the fusion method using Novata BD, Novata BCF with or without adjuvants. As adjuvants, methylcellulose and hydroxypropyl methyl cellulose were added in different concentrations i.e. 5, 10, 15, 20% w/w.

The suppository base was precisely weighted and melted in a water bath. Then, paracetamol and bioadhesives were added and the ingredients were mixed. After complete melting, the suppository mass was poured into suppository forms of 1 g. Suppositories were stored in a refrigerator at a temp. of 4°C.

Table 1. Physico-chemical characterization of the formulation

Suppository composition	Formula	Mass mean ±SD (g) n=20	Hardness mean (g) n=10	Softening time ±SD (min) n=3	Disintegration time±SD (min) n=3	Content uniformity ±SD (%) n=10
Novata BD	F 1	1.057 (0.007)	3900	7.30 (1.176)	15.25 (0.987)	98.3 (4.008)
Novata BD+ MC 5%	F2	0.934 (0.013)	3900	10.40 (2.580)	18.24 (2.609)	95.3 (4.169)
Novata BD + MC 10%	F3	1.019 (0.201)	4000	12.45 (0.478)	22.45 (1.885)	102.3 (3.699)
Novata BD + MC 15%	F4	1.024 (0.031)	4200	13.25 (1.2420	26.50 (3.144)	100.3 (2.427)
Novata BD + MC 20%	F5	1.059 (0.027)	4200	14.15 (1.457)	29.15 (2.106)	99.46 (2.903)
Novata BD + HPMC 5%	F6	0.992 (0.024	3800	8.20 (1.107)	18.55 (2.241)	98.78 (2.916)
Novata BD + HPMC 10%	F7	1.223 (0.032)	3900	9.30 (2.915)	23.30 (1.568)	100.3 (3.082)
Novata BD + HPMC 15%	F8	1.199 (0.040)	3600	14.2 (0.985)	27.24 (1.614)	101.4 (3.45)
Novata BD + HPMC 20%	F9	1.291 (0.063)	3400	14.9 (0.458)	29.46 (0.531)	102.5 (4.259)
Novata BCF	F10	1.064 (0.026)	3500	8.15 (1.015)	14.40 (2.007)	100.6 (3.635)
Novata BCF + MC 5%	F11	0.997 (0.028)	3600	9.30 (0.985)	17.46 (1.819)	102.1 (2.530)
Novata BCF + MC 10%	F12	1.125 (0.040)	3800	10.50 (1.336)	23.27 (0.275)	99.3 (3.763)
Novata BCF + MC 15%	F13	1.165 (0.040)	3700	11.45 (0.976)	25.55 (1.174)	99.68 (2.772)
Novata BCF + MC 20%	F14	1.154 (0.041)	3700	13.24 (0.251)	29.58 (1.794)	100.67 (2.871)
Novata BCF + HMC 5%	F15	1.147 (0.040)	3300	10.23 (0.990)	19.47 (1.357)	100.34 (4.059)
Novata BCF + HMC 10%	F16	1.256 (0.043)	3000	12.23 (3.258)	24.34 (1.680)	101.2 (4.191)
Novata BCF + HMC 15%	F17	1.258 (0.171)	2800	14.8 (0.20)	26.52 (1.433)	100.8 (1.909)
Novata BCF + HMC 20%	F18	1.212 (0.032)	2800	14.9 (0.656)	29.55 (0.709)	100.23 (2.123)

Evaluation of physical properties of suppositories

Uniformity of mass. Twenty suppositories of each formulation were individually weighed and their average mass was determined.

Hardness of the suppositories. The Erweka hardnes tester (Erweka, GmbH, Germany) was used to measure the resistance of the suppositories to crushing.

Softening time determination. The softening time was determined using apparatus described in the Polish Pharmacopoeia 9th edition (FP 9th) [10].

Disintegration time. This test was performed in water maintained at 37°C ± 0,5°C using the FP 9th disintegration apparatus. Three suppositories were put into a disintegration apparatus and the disintegration time was measured.

Standard calibration curve of paracetamol. The standard solutions of paracetamol were prepared in phosphate buffer (pH 7.2) at the concentrations of 2-12 µg/ml and the absorbances were measured spectrophotometrically at λ=243 nm. The linear regression equation of the calibration curve was Y = 0.0618x – 0.010. The calibration curve parameters, slope, intercept and SD of slope, SD of intercept are presented in Table 2.

Uniformity of content. Ten suppositories of each formulation were chosen randomly. The suppositories were transferred individually into 1000 ml volumetric flask and dissolved in 100 ml of phosphate buffer (pH 7.2) by shaking. After dilution and filtration, the absorbance was assayed spectrometrically (Helios Omega UV-Vis, SpectroLab, Warszawa) at a wavelength of 243 nm. Corresponding suppositories without drug substance were used as a control.

In vitro drug release. The in vitro release of paracetamol from suppositories was carried out in a dissolution apparatus [4]. Each suppository was placed in a beaker containing 500 ml of phosphate buffer solution (pH 7.2), maintained at 37 ± 0.5°C. The stirrer was rotated at the constant speed of 100 rpm.

Table 2. Statistical parameters for calibration curve

Parameter	Value
Correlation coefficient	0.9996
Slope	0.0618
Intercept	0.010
SD of slope	0.000564
SD of intercept	0.004394

Samples, each of 5 ml were taken at the predetermined time intervals and filtered. The volume withdrawn at each time interval was replaced by the same quantity of fresh dissolution medium maintained at 37 ± 0.5°C. After suitable dilution, the samples were analyzed for drug release by measuring the absorbance at 243 nm, using a spectrophotometer after suitable dilution.

Statistical analysis. Results are expressed as the mean ± SEM of five experiments. In order to determine the statistically significant differences between the tested groups the analysis of variance Anova with post-hoc Tukey test was used.

RESULTS AND DISSCUSSION

Rectal suppositories of paracetamol were prepared by the fusion method using Novata BD, Novata BCF bases with and without adjuvants. As adjuvants, methylcellulose and hydroxypropyl methyl cellulose at concentrations of 5, 10, 15, 20% were used.

The results of an average mass, softening time, distintegration time, hardness, drug content uniformity were found satisfactory and listed in Table 1.

All suppositories were free from pits, fissures and cracks.

The average suppository mass was ranged between 0.934 and 1.291 g with no statistical differences between the obtained values ($p>0.05$). The percent deviation from the mean mass of all batches were found within the limits (mean mass ± 5%) given by the Polish Pharmacopoeia 9th edition (FP 9th) [10]. Also, the mean drug content for all suppositories was found to meet the requirement of the FP 9th for the uniformity of content. None of the suppositories had less than 85% and none of them had more than 115% of the expected paracetamol content.

Hardness was determined using a hardness tester (Erweka). The fracture point of the prepared suppositories was between 2.8 and 4.2 kg.

In most cases, the addition of MC and HPMC to suppositories prepared on Novata BD and Novata BCF in most cases caused an increase in hardness.

Softening time of all tested suppositories was found to be within the acceptable limits given by the Polish Pharmacopoeia 9th edition (i.e. less than 15 min for lipophilic base).

Investigating the influence of the addition of adjuvants on the softening time, it was found in each case, the addition of bioadhesive substances caused extending of the deformation time in comparison with formulation without excipients.

The disintegration time of all tested suppositories was up to 30 minutes. The disintegration time for the suppositories prepared on the Novata BD and Novata BCF bases without adjuvants was: 15.25 and 14.40 min, respectively.

The addition of MC and HPMC into Novata BD and Novata BCF bases caused an extension of the disintegration time of suppositories, this effect may have been observed due to an increase in concentration of adjuvants. Disintegration time is an important parameter determining the dissolution of a suppository. The addition of excipients enables to control the disintegration rate, and thus facilitates preparation of either fast or slowly disintegrating suppositories.

The release of paracetamol into a buffer at pH 7.2 was carried out at 37 °C and the obtained results are shown in Figure 1-4. The amount of active ingredient released after 60 min from Novata BD (F1) and Novata BCF (F10) bases was 85.62% and 80.6%, respectively.

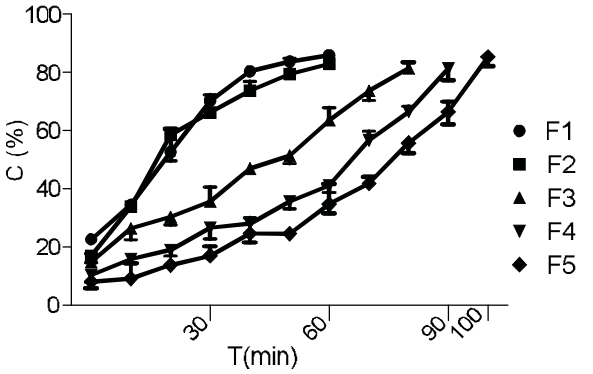

Fig. 1. The effect of MC on the release profile of paracetamol from Novata BD. Each value represents the mean of five experiments

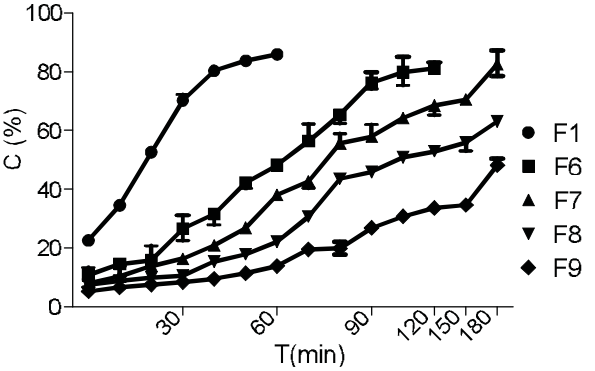

Fig. 2. The effect of HPMC on the release profile of paracetamol from Novata BD. Each value represents the mean of five experiments

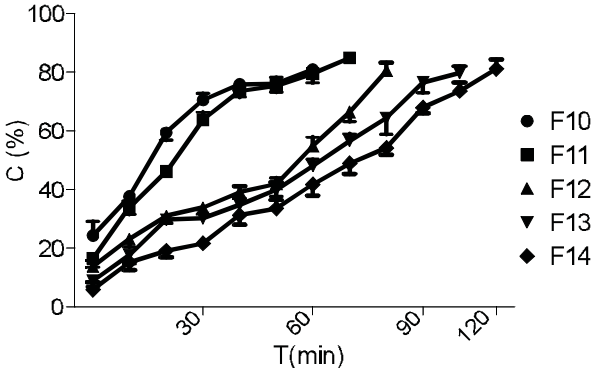

Fig. 3. The effect of MC on the release profile of paracetamol from Novata BCF. Each value represents the mean of five experiments

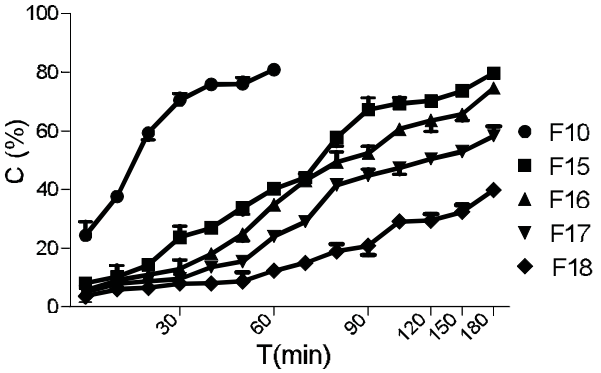

Fig. 4. The effect of HPMC on the release profile of paracetamol from Novata BCF. Each value represents the mean of five experiments

The influence of the addition of MC and HPMC to the suppositories on active substance release was evaluated. Supplementation of F2, F3, F11 and F12 formulation with MC at the concentrations of 5% and 10% did not indicate any significant changes in the release profiles after 60 min when compared with control ($p>0.05$); the amounts of the released active substance were: 83.4, 82.1, 84.6, 81.4%, respectively. MC at a concentration of 15% (F13) considerably decreased the amount of the released drug to 48.7% ($p<0.05$). In case of F4, F5 and F14 formulations, a reduction in the amount of the released active ingredient was also noticed (40.4, 35.8, 40.6% respectively) ($p<0.01$). Inclusion of HPMC to a suppository mass caused a significant extension of drug release time, which was recorded for all formulations ($p<0.001$).

Time needed for 20%, 40% and 80% drug release ($t_{20\%}$, $t_{40\%}$, $t_{80\%}$) was calculated theoretically, using the modified Higuchi's equation ($M_t = K_o(\sqrt{t} - \sqrt{T_D})$, where M_t is the quality of released substance and K is the release rate constant [3]. According to the obtained data, 80% of active substance released within 60 min from the suppositories without addition of the bioadhesive substances (F1, F10). It means that the release of active ingredient was fast.

As shown in Table 3, in case of formulations containing MC, 80% of the active substance released after 50.3 min to 108.36 min and after 57.15 min to 120.56 min for F2-F5 and F11-F14, respectively. In case of suppositories with HPMC, the release of 80% of paracetamol was observed after 115.1 min to 407.2 min and after 158.15 min to 568.26 min for F6-F9 and F15-F18, respectively. It is easy to observe that T values soar with the simultaneous increase of MC and HPMC concentrations, e.g. the time needed for release of 40% of paracetamol was prolonged from 12.53 min to 51.12 min (F1-F5) and from 40.16 min to 155 min (F6-F9), when the concentration of these excipients was raised from 5% to 20%. Comparing $t_{20\%}$, $t_{40\%}$, $t_{80\%}$ obtained for formulations supplemented with MC and formulations containing HPMC, a significant extension of paracetamol release time was indicated for the latter. On the basis of the results presented in Table 1 and 3, for all types of suppositories supplemented with the excipients, the $t_{80\%}$ values are higher than the corresponding disintegration time. Thus, the disintegration time of a suppository is not dependent on the release time [7]. It may also suggest that the dissolving time of a suppository does not necessarily exactly correspond with the changes of the dissolution rate. The values of drug release rate constant (K) decrease gradually with the increase of HPMC concentration, which suggests the reduction of drug release rate. However, such a correlation was not noticed for formulations containing MC. As mentioned above, this type of extension of the release time may be considered as the sustained release [8]. It may be caused by the modification of the viscosity of suppository base [1].

Table 3. Parameters of release profiles

Formula	K	$T_{20\%}$	$T_{40\%}$	$T_{80\%}$
F2	28.12	3.13	12.53	50.30
F3	27.54	12.32	28.44	80.48
F4	29.04	23.34	42.38	99.00
F5	30.71	30.47	51.12	108.36
F6	23.20	18.37	40.16	115.10
F7	22.59	36.36	69.29	160.52
F8	17.99	48.14	94.26	189.00
F9	12.96	74.19	155.0	407.20
F11	26.76	4.24	14.59	57.15
F12	28.87	16.00	33.23	85.04
F13	25.01	18.29	39.21	105.05
F14	24.56	24.11	48.14	120.56
F15	18.89	21.34	59.25	158.15
F16	18.32	30.10	67.31	186.00
F17	14.45	39.18	95.02	277.22
F18	9.84	74.18	187.29	568.26

K – release rate constant (mg $min^{-0.5}$), $T_{20\%}$, $T_{40\%}$, $T_{80\%}$ -time for 20%, 40%,80% release (min)

Thanks to their bioadhesive properties, HPMC and MC may be used for preparation of the sustained release suppositories.

CONCLUSION

The suppositories were manufactured on Novata BD or Novata BCF bases with addition of MC or HPMC. The prepared formulations met the requirements of the Polish Pharmacopoeia 9th edition in relation to the following tests: uniformity of mass, softening time, disintegration time, uniformity of content (of active ingredient). On the basis of the obtained results, it can be confirmed that MC at the concentrations of 15 and 20% and HPMC at the concentrations of 5, 10, 15 and 20% significantly extend the drug release time.

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