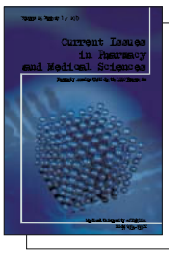

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Effect of nonionic surfactants on the release of paracetamol from suppositories

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ABSTRACT

The preparation suppositories contain 250 mg of paracetamol on different bases using Novata BD, Novata BCF and composition of Novata BCF/BD (1:1). Suppositories were prepared by the fusion method. The prepared formulations with or without surfactants (Tween 80, Span 60) at concentrations of 2% and 4% (w/w) were tested for hardness, total time of deformation, disintegration time, content uniformity and release of the drug. The release of the drug was carried in the apparatus with the stirrer shade in phosphate buffer (pH 7.2) at 100 rpm. The physical properties of the prepared suppositories were according with the requirement of Polish Pharmacopoeia 9th edition. Addition of 4 % Tween 80 to suppository bases significantly increased the drug release from all the investigated formulations. However, incorporation of Span 60 did not result in improvement of the drug release significantly.

Keywords: suppository bases, surfactants, paracetamol

INTRODUCTION

Paracetamol suppositories are used for reducing fever and treating minor aches and pains. Children who have difficulty taking oral medications may find the suppositories helpful. This product, which is available over-the-counter (OTC), is generally inserted into the rectum every four to six hours as needed. Paracetamol is well absorbed through the rectum [11]. The relative bioavailability is 80 % to that of oral administration [12].

A major role in the release of drug from suppositories is played both by drug solubility in the base and surfactants characteristics. The release rate depends on the solubility of the drug in vehicle, e.g. higher drug solubility in the vehicle results in slower drug release from suppositories. This is due to the tendency of the drug to be retained in the base [1, 8]. The incorporation of surfactants into different suppository bases may result in an increase or decrease of drug release depending on nature and concentration of surfactants [15, 3, 10].

Tensides give suppositories the required structural and mechanical properties and act as emulsifiers and activators for drug assimilation [14, 6].

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The interaction between a drug and an organism passes through many stages. With respect to suppositories, the first step involves their softening, release of drug from the base, and its dissolution in the biological fluid. This stage as a whole has a substantial influence on the rate and completeness of assimilation of drugs [7].

Therefore, the aim of this study was to evaluate the influence of various non-ionic surfactants on the release profiles of the paracetamol from suppositories and to study their physicochemical properties.

MATERIAL AND METHODS

Materials

Paracetamol was obtained as a gift from SRI, Krishna Pharmaceuticals LTD, Indie, Novata BD, Novata BCF (Cognis GmbH), Span 60 (Fluka, Chemika), Tween 80 (Fluka, Chemika).

Methods

Formulation of Paracetamol suppositories. Suppositories, each containing 250 mg of paracetamol, were prepared using different fatty bases: Novata BD, Novata BCF and composition of the base containing of Novata BCF and Novata BD (1:1). Suppositories were formulated by fusion method with and without a nonionic surfactant (Tween

80, Span 60) at concentrations of 2%, 4% w/w. The melted mass was poured into the appropriate suppository mould of capacity 1 g. All the suppositories were stored at temperature of 4°C to avoid the development of cracking.

Evaluation of the prepared paracetamol suppositories

Weight variation.. Twenty suppositories were individually weighed from each formulation. The average weight and standard deviation (SD) was calculated.

Hardness of fracture point. This was carried out using hardnes tester (Erveka, SBT Germany).

Total time of deformation. The total of deformation time was determined using apparatus according to Polish Pharmacopoeia 9th edition (FP 9th) [9].

Disintegration time. This test was performed in water maintained at 37°C ± 0.5°C using FP 9th disintegration apparatus. Disintegration criteria (FP 9th) were followed to calculate the disintegration time of the test suppository.

The mean weight, hardnes, total time of deformation and disintegration time ± SD are shown in Table 1.

After filtration and suitable dilution the absorbance was assayed spectrophotometrically (Helios Omega UV-Vis, SpectroLab, Warszawa) at a wavelenght of 243 nm against the blank prepared using respective suppository without drug. The mean contents of drug ± SD were calculated and given in Table 1.

In vitro drug release. The in vitro release of paracetamol from suppositories was carried in the dissolution apparatus [2]. The release was done for 60 min in 500 ml phospate buffer solution (pH 7.2) at temperature of 37±0.5°C. The stirrer was rotated at the constant speed of 100 rpm.

Samples, each of 5 ml were withdrawn from the dissolution medium at appropriate time intervals and filtered. The dissolution medium was replaced by 5 ml of fresh buffer to maintain a constant volume.

Filtered samples were suitably diluted and assayed spectrophotometrically at 243 nm against a phosphate buffer. Results are expressed as the mean of five determinations.

Statistical analysis. For statistical evaluations, data of profiles release were analyzed by ANOVA with post-hoc Tukey test.

Table 1. Composition and evaluation of paracetamol suppositories

Suppository composition	Formula	Weight mean ±SD (g) n=20	Hardnes mean ±SD (g) n=10	Total time of deformation ±SD (min) n=3	Distintegration time±SD (min) n=3	Drug content mean ±SD (%) n=5
Novata BCF	F 1	**1.057 (0.08)**	**3600 (5.2)**	**7.46 (1.34)**	**13.50 (1.33)**	100.3 (2.21)
Novata BCF + Tween 80 (2%)	F2	**1.069 (0.48)**	**3000 (5.8)**	**11.55 (0.98)**	**13.15 (1.56)**	101.8 (1.35)
Novata BCF + Tween 80 (4%)	F3	**1.074 (0.12)**	**2600 (5.8)**	**9.35 (0.97)**	**12.38 (0.98)**	101.9 (1.2)
Novata BCF + Span 60 (2%)	F4	**1.064 (0.09)**	**4200 (5.1)**	**12.20 (0.9)**	**18.47 (1.43)**	100.6 (1.45)
Novata BCF + Span 60 (4%)	F5	**1.063 (0.53)**	**3200 (5.8)**	**11.45 (1.58)**	**11.15 (1.1)**	101.2 (2.01)
Novata BD	F6	**1.058 (0.24)**	**3860 (5.1)**	**10.12 (0.89)**	**17.50 (1.12)**	104.1 (1.46)
Novata BD + Tween 80 (2%)	F7	**1.068 (0.51)**	**3200 (5.8)**	**11.55 (1.89)**	**16.52 (1.56)**	100.2 (1.24)
Novata BD + Tween 80 (4%)	F8	**1.073 (0.64)**	**2800 (5.1)**	**10.15 (0.99)**	**12.52 (1.78)**	101.6 (2.02)
Novata BD + Span 60 (2%)	F9	**1.071 (0.52)**	**4200 (5.1)**	**13.40 (0.87)**	**10.58 (1.45)**	102.2 (1.12)
Novata BD + Span 60 (4%)	F10	**1.064 (0.09)**	**4600 (5.8)**	**13.19 (1.56)**	**6.40 (1.23)**	100.4 (1.56)
Composition of Novata BCF/BD (1:1)	F11	**1.148 (0.08)**	**5400 (5.8)**	**8.10 (0.96)**	**11.30 (1.24)**	103.4 (1.89)
Composition of Novata BCF/BD (1:1)+ Tween 80 (2%)	F12	**1.148 (0.13)**	**3400 (5.1)**	**10.10 (0.76)**	**7.0 (0.98)**	102.4 (2.1)
Composition of Novata BCF/BD (1:1)+ Tween 80 (4%)	F13	**1.155 (0.49)**	**2600 (5.8)**	**10.06 (1.12)**	**5.5 (0.89)**	100.6 (1.14)
Composition of Novata BCF/BD (1:1)+ Span 60 (2%)	F14	**1.130 (0.61)**	**5400 (5.1)**	**13.25 (1.24)**	**13.15 (0.78)**	100.8 (1.44)
Composition of Novata BCF/BD (1:1)+ Span 60 (4%)	F15	**1.147 (0.72)**	**4400 (5.8)**	**11.15 (1.62)**	**20.10 (0.76)**	100.2 (1.12)

Standard calibration curve of Paracetamol

The standard solutions of Paracetamol in phosphate buffer (pH 7.2) of concentration 2-12 µg/ml were prepared and the absorbances were measured spectrophotometrically at λ=243 nm. The linear regression equation of the calibration curve was $Y = 0.062x - 0.012$. The calibration curve parameters, slope, intercept and SD of slope, SD of intercept are presented in Table 2.

Content uniformity. Five suppositories were randomly selected from each formula. The suppository was individually placed in 1000 ml standard flask containing 100 ml of phosphate buffer pH 7.2 and heated. The flask was shaken for desired period of time to dissolve the drug from suppository.

Table 2. Statistical parameters for calibration curve

Parameter	Value
Correlation coefficient	0.9996
Slope	0.062
Intercept	0.012
SD of slope	0.0005477
SD of intercept	0.004266

RESULTS AND DISSCUSSION

Suppositories of paracetamol at a dose of 250 mg were prepared by fusion method using Novata BD, Novata BCF and Novata BCF/ BD (1:1) with and without emulsifiers. As emulsifiers were used Span 60, Tween 80 at concentration of 2% and 4%.

Parameters of suppositories, such as weight, total time of deformation, distintegration time, the hardness, the percentage of drug substance and the process of in vitro release were determined. The results of the physical properties are shown in Table 1.

The average weight of all tested suppositories conformed with the Polish Pharmacopoeia 9th edition for each formula.

The average weight of suppositories prepared on the Novata BD, BCF and Novata BCF/BD was 1.058 g, 1.057 g, 1.148 g respectively.

Hardness was determined using a hardness tester (Erweka). For formulation prepared on the Novata BD, BCF and Novata BCF / BD was 3860 g, 3600 g, 5400 g respectively.

Addition of Span 60 to Novata BD caused an increase in hardness in proportion to the concentration, and the addition of Tween 80 at a concentration of 2% and 4% caused decrease in hardness.

In the case of formulations prepared on Novata BCF addition of 2% Span 60 caused increase in hardness, while 4% Span 60 and Tween 80 at concentration of 2% and 4% showed a reduction in hardness.

The reduction of hardness was obtained by the incorporation of 4% Span 60, 2% and 4% Tween 80 into composition of Novata BCF / BD suppository base. The addition of 2% Span 60 did not show changes of hardness.

Deformation time of all tested suppositories was found to be within acceptable values of Polish Pharmacopoeia 9th (less than 15 min for lipophilic base).

The influence of the addition of emulsifiers on deformation time was investigated and found that in each case, the addition of emulsifiers caused extending of deformation time in comparison with formulation without addition of emulsifier.

The disintegration time of all tested suppositories was up to 30 minutes. The disintegration time for the suppositories prepared on the Novata BD, BCF and Novata BCF/BD without excipients was: 17.50, 13.50, 11.30 min. respectively. Addition of 2% and 4% Span 60 into Novata BCF/ BD and only 2% Span 60 into Novata BCF caused shortening of distintegration time of a suppository, the rest of the excipients caused excendinig of distintegration time.

Disintegration is an important parameter to determine the dissolution of the suppository. Suppository dissolves quickly and allows for the rapid spread of the drug in the rectum.

By addition of excipients disintegration rate can be controlled, and thus disintegrating of the suppository can be created quickly or slowly. Hosney and colleagues [5] also showed that addition of Tween 80 into the suppositories significantly increased the dissolution of the suppository by indicating the wetting effect of that additive.

The release of paracetamol was carried out at 37°C into a buffer at pH 7.2. The pH of the dissolution medium reflects the pH of the fluid in the rectum (pH about 7.2-7.4). In this study, the possibility of increasing the release of paracetamol from suppositories was evaluated by incorporation of nonionic surfactants at concentration of 2%, 4% with different HLB values into Novata BD, Novata BCF, Novata BCF/BD.

Dissolution profiles are shown in Fig. 1-6 and analysis of variance (ANOVA) are presented in Figure 7. A suppository base of Novata BD, BCF, BCF/BD without nonionic surfactant was regarded as the control during the

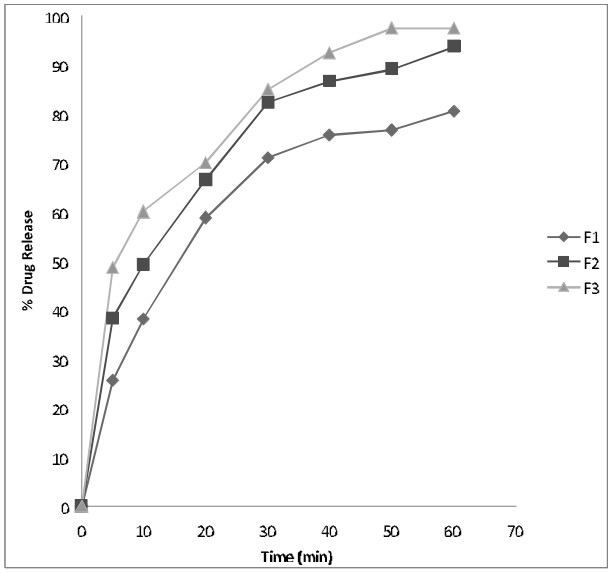

Fig. 1. The effect of Tween 80 on the release of paracetamol from Novata BCF

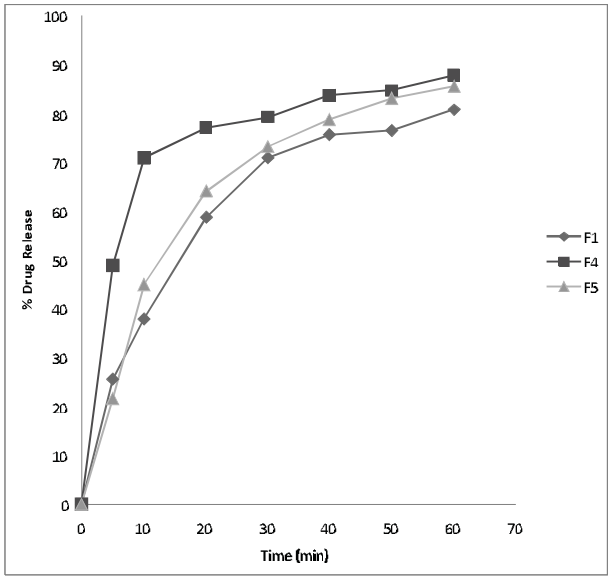

Fig. 2. The effect of Span 60 on the release of paracetamol from Novata BCF

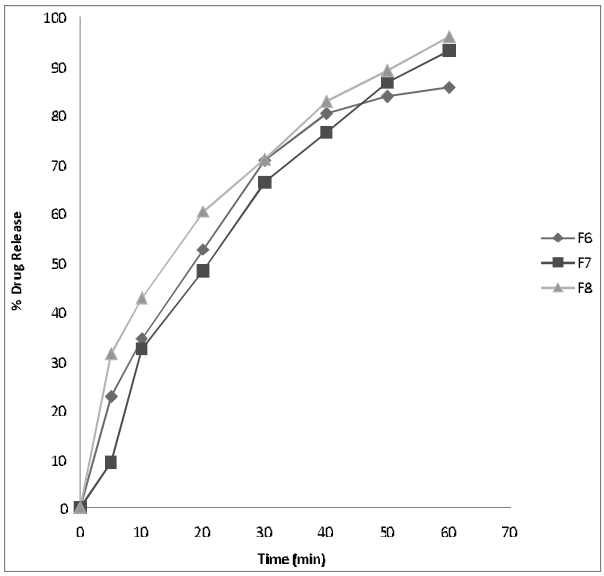

Fig. 3. The effect of Tween 80 on the release of paracetamol from Novata BD

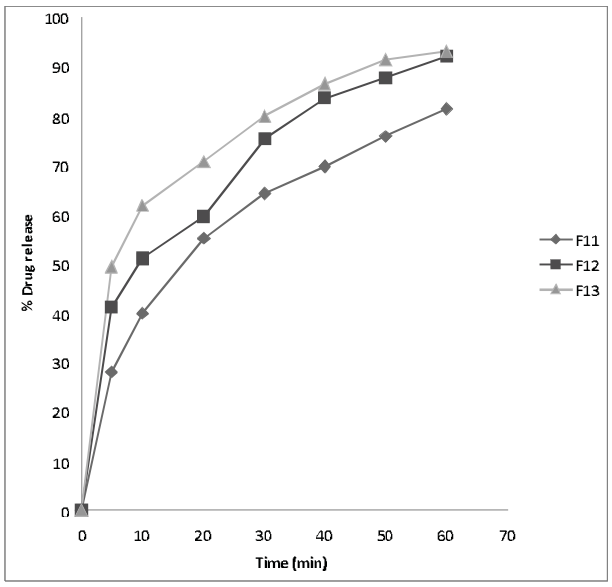

Fig. 5. The effect of Tween 80 on the release of paracetamol from composition of Novata BCF/Novata BD

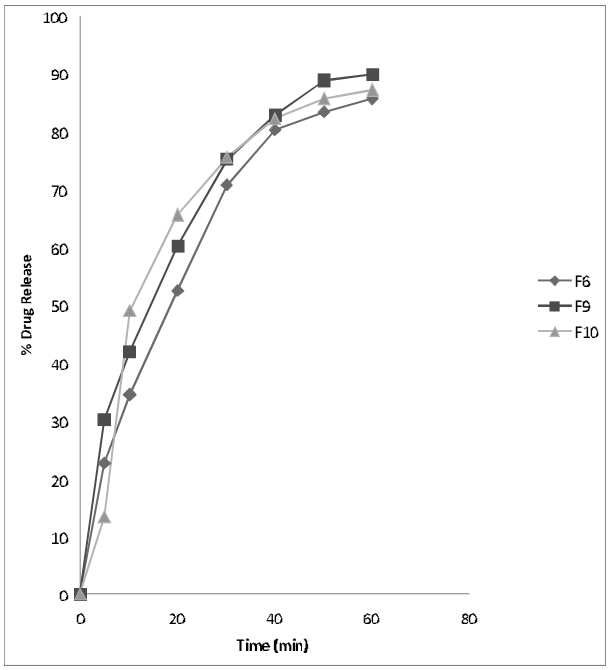

Fig. 4. The effect of Span 60 on the release of paracetamol from Novata BD

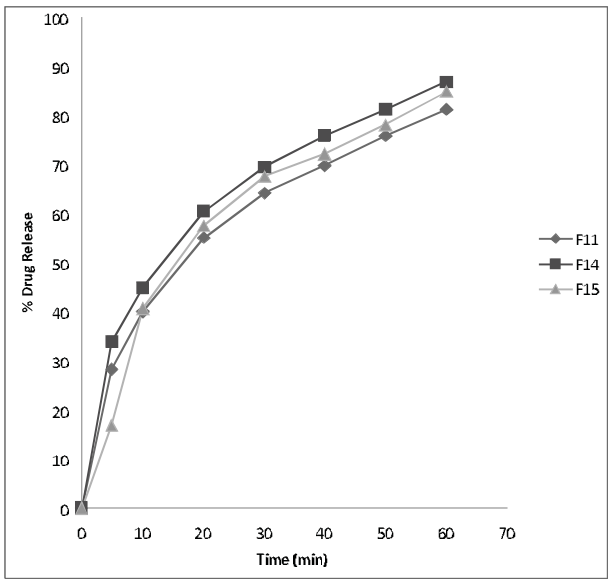

Fig. 6. The effect of Span 60 on the release of paracetamol from composition of Novata BCF/Novata BD

experiments. It was found that addition of 2% Tween 80 to the suppository base significantly increases the release of paracetamol in case of Novata BCF ($p<0.001$) and Novata BCF/BD ($p<0.05$). As for Novata BD an increase was not significant ($p<0.05$). The effect of adjuvant was shown to be concentration dependent [4]. The addition of 4% Tween 80 to suppository bases caused improvement of the paracetamol release in contrast to 2% Tween 80. Higher concentration of Tween 80 caused a significant increase in drug release in case of Novata BCF ($p<0.001$), Novata BCF/BD ($p<0.01$), and Novata BD ($p<0.05$) versus control. It can be assumed that the surfactants may decrease the interfacial tension between the drug and the dissolution medium with resultant improvement of drug solubility and release of the drug.

The addition of Span 60 (HLB =4.7) caused improvement of the paracetamol release, but less in comparison to Tween 80, which may be explained by a lower ability to dissolve the drug, and thus a lower rate of release. Furthermore, it was noted that lower concentration of Span 60 (2%) is more effective in enhancing drug release than higher concentrations 4%.

The decrease in drug release at higher concentration of excipient is likely attributable to micellar entrapment of the drug resulting in retardation of the drug release [13].

However, when the results of the paracetamol release from the three suppository bases with Span 60 were ana-

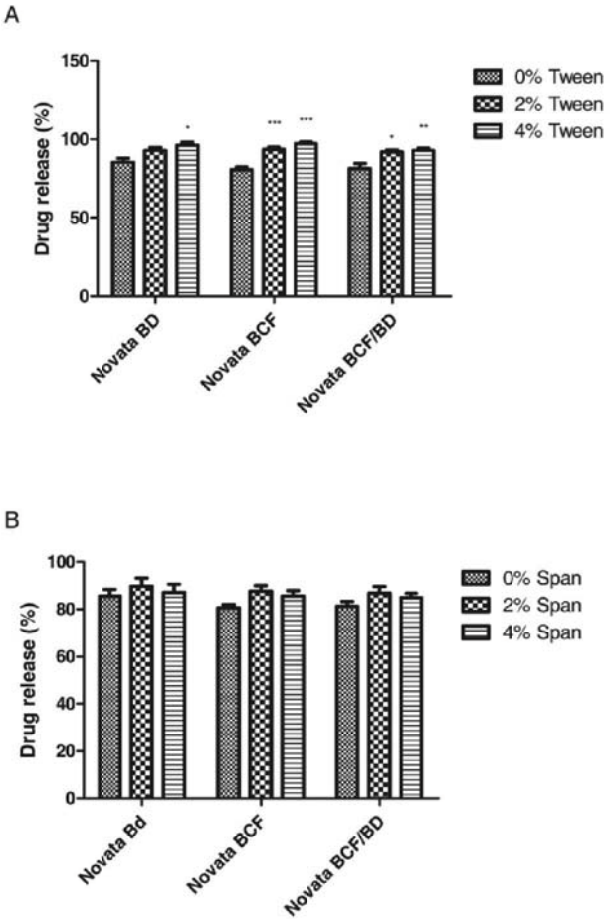

Fig. 7. (a) Influence of Tween 80 on paracetamol release after 60 min. (b) Influence of Span 60 on paracetamol release after 60 min. The data are average of the results of five experiments (±SEM) (*p<0.05, **p<0.01,*** p<0.001) versus control, analysis of one-way ANOVA with post-hoc Tukey test

lysed using one–way Anova test, the differences appeared to be not significant.

The increase of paracetamol release was greater by addition of Tween 80 than by addition of Span 60. This may be attributed to the much higher hydroxyl value of Tween 80 (HLB=15) relative to Span 60 (HLB=4.7), which may increase the ability of surfactant in wetting the bases.

In conclusion, the prepared formulations showed acceptable physical characteristics with respect to hardness, total deformation time, distintegration time and uniformity of drug content. Addition of 4 % Tween 80 significantly increased the drug release from all investigated formulations. However incorporation of Span 60 did not result in improvement of the drug release significantly.

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