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The preparation of suppositories by various methods and evaluation of physicochemical properties

Przygotowanie czopków różnymi metodami i ocena właściwości fizykochemicznych

INTRODUCTION

Release of active substance from suppositories depend on many factors namely: the physicochemical properties of the drug, suppository base and excipient characteristics [1,6,12]. It has been shown that higher drug solubility in the vehicle results in slower drug release and reduced drug absorption from the dosage form. This is attributed to the tendency of the drug to be retained in the base [2]. The rate at which suppositories dissolve may also be dependent on the dose size, with smaller doses dissolving more quickly [11].

Formulation of a suppository with good biovailability reqiures a suitable base which melts at temperature well below the body temperature and spreads readily in the anorectal region or dissolves in the fluids present in the rectum [5,7]. The drug release rate from the suppository is mainly conditioned by excipient characteristic: temperature and fusion rate, viscosity, hydro-lipophilic characteristics. The same drug dose is therefore able to produce different therapeutic responses when vehicled in base with excipients with different characteristics [9, 10].

Therefore, the aim of this study was to evaluate the influence of various bases with or without surfactants on the release profiles of the drug from suppositories prepared by various methods and to study their physicochemical properties.

MATERIAL AND METHODS

M a t e r i a l s. Paracetamol powder was received as gift from SRI, Krishna Pharmaceuticals LTD, Indie, Novata BD, Novata BCF and Tween 60 were received as gift from Cognis GmbH, Cocoa butter (Pharma Cosmetic, Kraków), Span 80 (Fluka, Chemika).

P r e p a r a t i o n o f t h e s u p p o s i t o r i e s. The formulations of paracetamol suppositories used in this study are shown in Table 1.

Table 1. Constituents of suppositories

Base	Formula	Adjuvant	Method of preparation
Cocoa butter	F1 F2 F3	- - -	press melting method unguator
Cocoa butter	F4 F5 F6	Tween 60 Tween 60 Tween 60	press melting method unguator
Cocoa butter	F7 F8 F9	Span 80 Span 80 Span 80	press melting method unguator
Novata BCF	F10 F11 F12	- Tween 60 Span 80	melting method
Novata BD	F13 F14 F15	- Tween 60 Span 80	melting method
Mixture of Novata BCF and Novata BD (1:1)	F16 F17 F18	- Tween 60 Span 80	melting method

Suppositories weighing 1 g each, containing 250 mg of paracetamol were prepared from different bases namely: Cocoa butter, Novata BD, Novata BCF and mixture of Novata BCF and BD (1:1). Suppositories containg bases Cocoa butter were prepared by the melting method, in the press and in the unguator. Suppositories containing bases Novata BD, BCF and mixture of Novata BCF and BD (1:1) were prepared by the melting method.

The method of preparation of suppositories in the unguator: the base was melted and then a drug with or without a nonionic surfactant (Tween 60, Span 80) at concentration of 5% w/w was added. Next, the solution was transferred into a container, homogenisated and then was poured into a plastic suppository mold. In the case of the melting method, the base was melted, a drug with or without was added and poured at once into a plastic form.

In the case of the press, a drug with and without a surfactant was added to the base, mixed and transfered to the press. The prepared suppositories were wrapped in aluminum foil. All the suppositories were stored at temperature of 4^{o}C.

Evaluation of paracetamol suppositories.

Weight variation: The prepared suppositories were weighed and average weight was calculated. Then all the suppositories were individually weighed and the variation from the average was calculated.

Hardnes of fracture point: This was carried out using hardnes tester (Erveka, SBT Germany). Melting time: The melting time was determined using apparatus according to Polish Pharmacopoeia 8th edition.

The mean weight, hardnes, and the melting time ± standard deviation (SD) are shown in Table 2.

Content uniformity. Randomly selected suppository was taken 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. After dilution and filtration the absorbance was assayed

spectrometrically (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 are given in Table 2

I n v i t r o r e l e a s e s t u d y. Release of paracetamol from suppositories was carried in the apparatus with the stirrer shade [3]. Each suppository was placed in the beaker and a stirrer was lowered on the heigh 1-2 mm from the bottom of the beaker. The stirrer was rotated at the constant speed of 100 rpm and poured 500 ml phospate buffer solution (pH 7.2) at temperature of 37 +0.5°C. Next 5 ml of samples were withdrawn at appropriate time intervals and filtered. The dissolution medium was replaced by 5 ml of fresh dissolution fluid 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 ± SD of five determinations.

RESULTS AND DISSCUSSION

The results of weight variations, hardness, melting time, content uniformity, are given in Table 2 and the results of release profiles of paracetamol from suppositories are shown in Fig. 1-6.

Table 2. Physicochemical properties of paracetamol suppositories

Formula	Weight mean ±SD (g) n=20	Hardnes mean ±SD (g) n=10	Melting time mean ±SD (min) n=3	Drug content mean ±SD (%) n=5
1	1.0499 (0.089)	670 (5.1)	5.28 (0.348)	101.2 (3.3)
2	1.134 (0.0870	680 (5.1)	1.09 (0.972)	104.4 (1.56)
3	0.96 (0.035)	1280 (1.9)	1.26 (0.456)	96.0 (2.0)
4	1.0384 (0.106)	700 (5.1)	4.18 (0.111)	100.8 (2.01)
5	1.148 (0.006)	1060 (5.8)	0.57 (0.26)	104.0 (1.02)
6	1.0393 (0.077)	1660 (5.8)	1.05 (0.599)	100.4 (2.02)
7	1.0851 (0.044)	680 (5.8)	3.07 (0.491)	100.4 (1.13)
8	1.1528 (0.086)	920 (5.1)	1.09 (0.551)	103.2 (0.64)
9	1.0857 (0.613)	1540 (5.8)	2.14 (0.054)	100.0 (1.5)
10	1.1482 (0.072)	3400 (5.1)	6.36 (1.447)	103.6 (1.01)
11	1.155 (0.005)	4900 (5.1)	6.21 (0.054)	104.8 (1.9)
12	1.148 (0.085)	5200 (5.8)	7.01 (0.513)	103.2 (1.40)
13	1.134 (0.063)	3720 (5.1)	6.12 (0.168)	101.2 (1.35)
14	1.1484 (0.066)	5100 (5.8)	6.1 (0.161)	101.6 (1.05)
15	1.1357 (0.051)	3860 (10.2)	6.18 (0.593)	100.8 (1.02)
16	1.1473 (0.067)	5400 (5.1)	7.27 (0.524)	106.4 (2.0)
17	1.147 (0.012)	5200 (10.2)	7.09 (0.478)	105.2 (2.01)
18	1.1349 (0.051)	3040.6 (8.5)	7.3 (0.795)	103.6 (1.2)

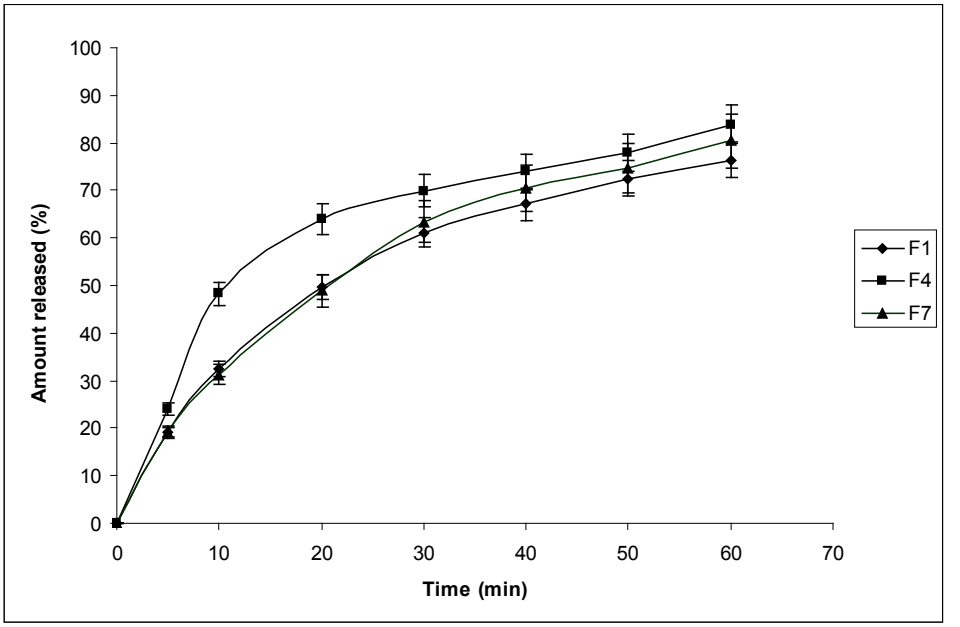

Fig. 1. The effect of surfactants on the release profile of paracetamol from suppositories with Cocoa butter prepared in the press

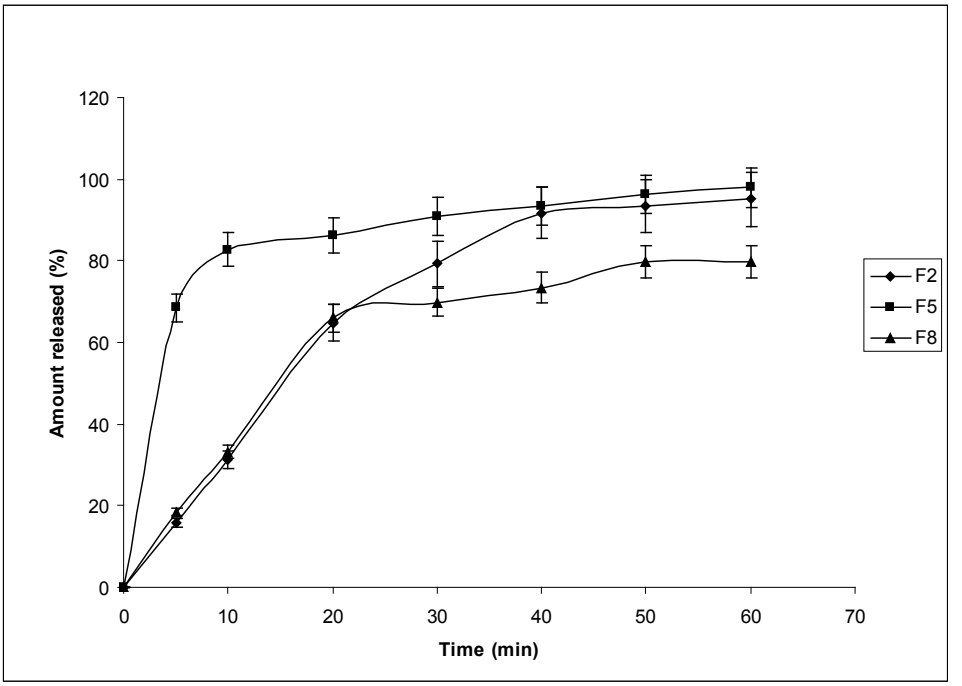

Fig. 2. The effect of surfactants on the release profile of paracetamol from suppositories with Cocoa butter prepared by the melting method

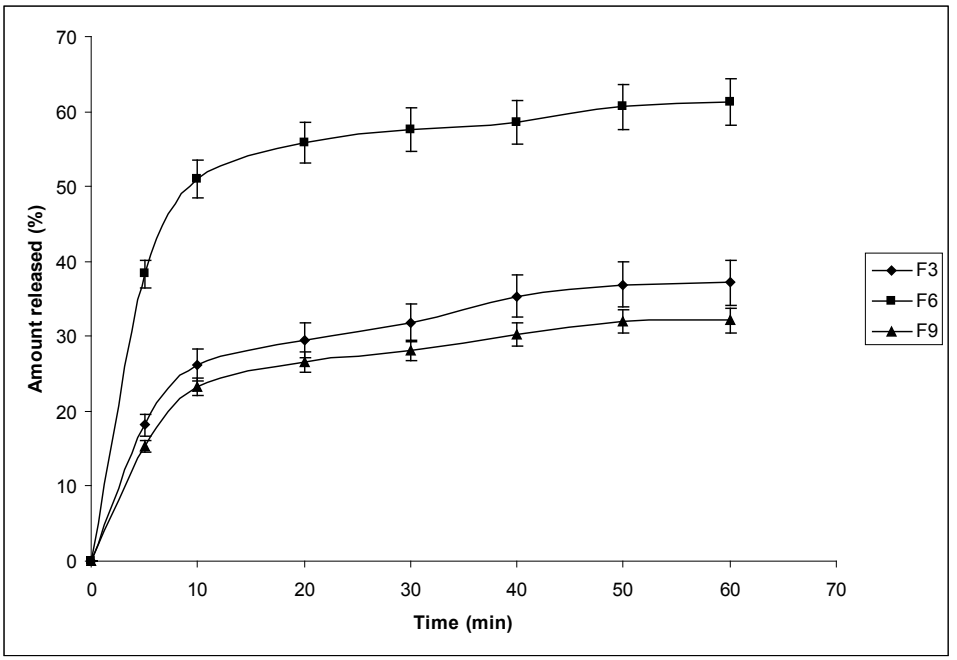

Fig. 3. The effect of surfactants on the release profile of paracetamol from suppositories with Cocoa butter prepared in the unguator

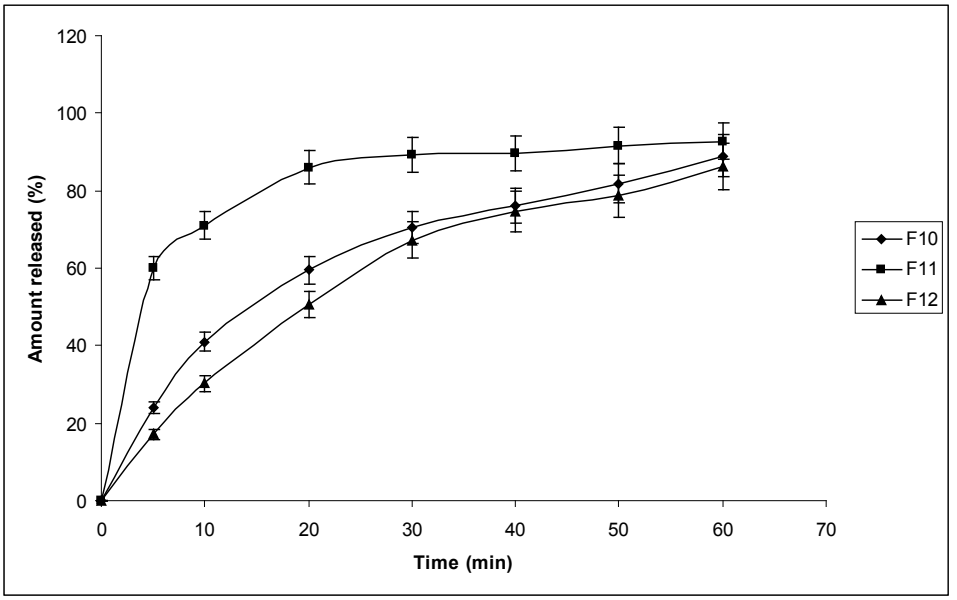

Fig. 4. The effect of surfactants on the release profile of paracetamol from suppositories with Novata BCF prepared by the melting method

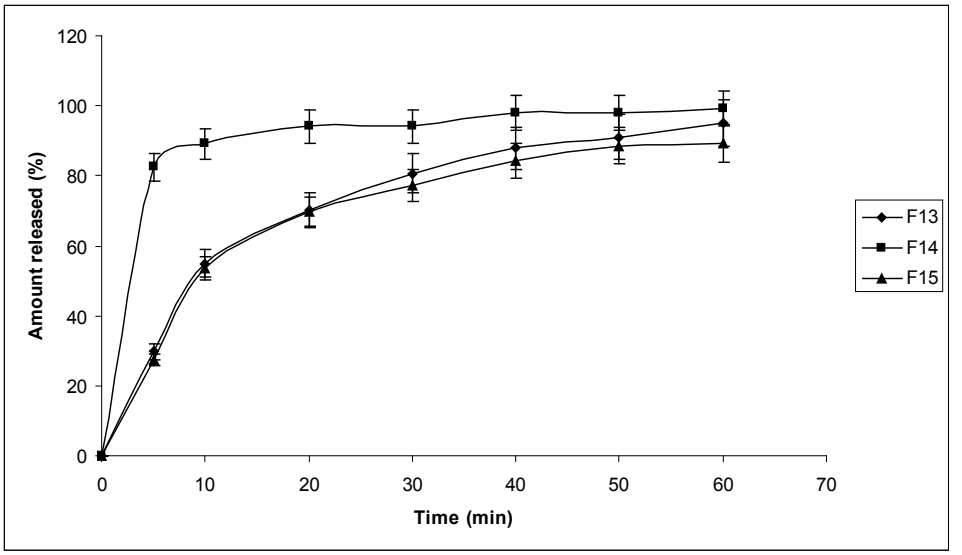

Fig. 5. The effect of surfactants on the release profile of paracetamol from suppositories with Novata BD prepared by the melting method

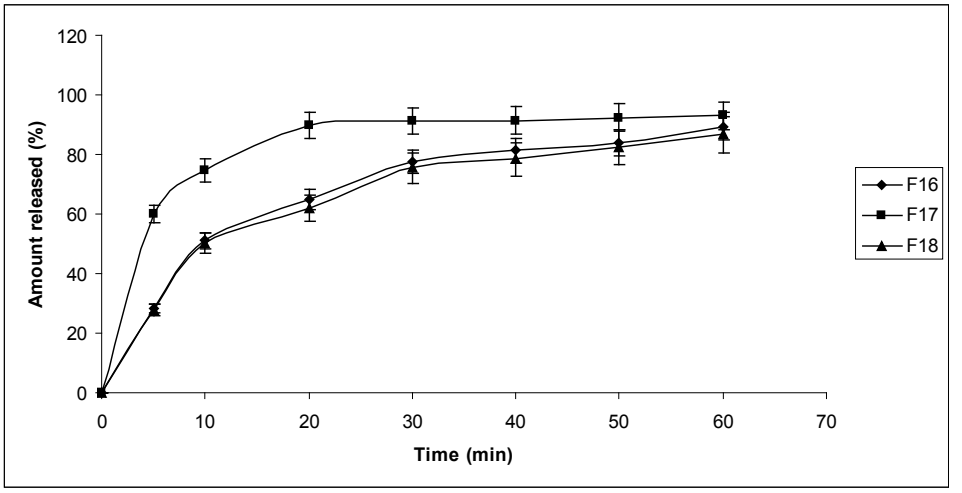

Fig. 6. The effect of surfactants on the release profile of paracetamol from suppositories with mixture of Novata BCF and Novata BD prepared by the melting method

Carried out studies shown that the physical parameters of suppositories were complied with Polish Pharmacopoeia 8 th edition [7] for each formulation independently on the method of preparation.

The hardness ranged from 670 g to 5400 g, melting time from 0.57 min to 7.3 min and drug content from 96% to 106.4%.

In the case of formulation prepared with Cocoa butter, addition surfactants decreased melting time but in the case of formulations with Novata BD, BCF and the mixture had not significant influence.

Addition of 5% Tween 60 or Span 80 induced an increase in hardness of prepared formulations with Cocoa butter (F4-F9) independently on the method of preparation as well as formulations with Novata BCF, BD (F11, F12, F14, F15) except from the mixture (F17, F18), when the addition of these surfactants caused a decrease in hardness.

From the obtained data, we conclude that the smallest release of paracetamol (32.12%) from formulations F 9 prepared in the unguator, when the added surfactant was Span 80 (surfactant with low value HLB=4.3). From formulations F3 without surfactant the released drug was 37.14%, however, addition of Tween 60 (surfactant with high value HLB=15.6) clearly increased the amount of drug released to 61.30%.

In the case of Tween 60 this may be due to its ability to improve the wettability of the base matrix and thus enhance diffusion of the embedded drug molecules [3].

Direction of prepared formulations from Cocoa butter by the melting method and in the press (F1, F2) occurred the most accepted to enhance the release of paracetamol from alone base, where after hour release was 95.08 % (F2) and 76.43% (F1). Addition of Tween 60 increased the amount of drug released to 98.01% (F5) and 83.92% (F4) respectively as well as addition of Span 80 in the case of formulations prepared in the press to 80.45% (F 7).

However regarding formulations prepared by the melting method (F8) Span showed unfavorable surfactant because not increased the amount of paracetamol released and after 30 min caused significantly delay of release.

This indicates that lipophilicity and hydrophilicity of surfactant has the main role in release rate of paracetamol from suppositories. This reduction in the release rate could be explained by being insolubilty and lipohility of the surfactant (HLB = 4.3) in dissolution medium [3].

From the obtained results, we concluded that the amount of released paracetamol from formulations on the base Novata BD (F14) was highest (99.26%), when the added surfactant was Tween 60 in comparison to formulations prepared on the base without surfactant (F13), when the amount of drug released was 94.94%. Addition of Span 80 in this case had not significant effects on the release profile (Fig.5) and the amount of released paracetamol was 89.33%.

The effect surfactants on release in the case of formulations prepared with Novata BCF (F11, F12) and mixture BCF and BD (F17, F18) was similar to the release profiles of formulations prepared with Novata BD (F14, F15) with tendency to decreasing of amount of substance released.

In conclusion, the prepared formulations showed acceptable physical characteristics with respect to hardness, melting time and uniformity of drug content. The smallest amount of paracetamol was released from formulations with Cocoa butter prepared method in the unguator and the highest amount was released from formulations with Novata BD prepared by the melting method. Addition of Tween 60 increased the drug of release from all investigated formalae independently of the method of preparation, but addition of Span 80 did not show influence on release profiles.

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SUMMARY

The preparation suppositories containing 250 mg of paracetamol on different bases using Cocoa butter, Novata BD, Novata BCF and mixture of Novata BCF: BD (1:1). Suppositories containing base Cocoa butter were prepared by the melting method, in the press and in the unguator. Suppositories containg bases Novata BD, BCF and mixture were prepared by the melting method. The prepared formulations with or without surfactants (Tween 60, Span 80) at concentrations of 5% (w/w) were tested for hardness, metting time, content uniformity and release of the drug. The relase 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 responded to requirements Polish Pharmacopoeia 8 th edition. The results showed that addition of 5 % Tween 60 increased the the drug of release from all the investigated formulae independently of the method of preparation.Whereas addition of Span 80 had not significant effect on the release profiles.

Keywords: suppository bases, surfactants, paracetamol

STRESZCZENIE

Przygotowano czopki zawierające 250 mg paracetamolu na różnych podłożach używając masła kakaowego, Novata BD, Novata BCF i mieszaniny Novata BCF: Novata BD: (1:1).

Czopki zawierające masło kakaowe przygotowano metodą wylewania, w prasie i w unguatorze. Z kolei czopki zawierające podłoże Novata BD, BCF i mieszaninę przygotowano metodą wylewania. Przygotowane formulacje z oraz bez surfaktantów (Tween 60, Span 80) w stężeniu 5% (w/w) badano na twardość, czas topnienia, zawartość jednolitości i uwalnianie leku. Uwalnianie leku przeprowadzono w aparacie kloszowym w buforze fosforanowym (pH 7.2) przy szybkości 100 obrotów. Właściwości fizyczne sporządzonych czopków odpowiadały normom wg Polskiej Farmakopeii VIII. Wyniki wykazały, iż dodatek Tweenu 60 zwiększa uwalnianie leku w każdym przypadku niezależnie od metody wykonania. Natomiast dodatek Spanu 80 nie miał istotnego wpływu na profile uwalniania.

Słowa kluczowe: podłoża czopkowe, surfaktanty, paracetamol