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Physical and Release Properties of Metronidazole Suppositories

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Abstract

Purpose: A study was made of the effects of some bases and adjuvants on the physical and release properties of metronidazole suppositories with a view to providing more information for the optimization of the rectal formulation of metronidazole.Method: Suppositories (1g) containing 200mg of metronidazole each were prepared in witepsol (H15 and E75) and polyethylene glycol (PEG 2850 and 4650) bases, using different concentrations of Tween 80, sodium salicylate and methylcellulose as adjuvants. The setting time, solidification point and melting range of the suppositories were determined, along with their crushing strength, disintegration time and the time for 80% of metronidazole to be released from the suppositories (t80).Results: The ranking of setting time for the suppositories was witepsol H15 > PEG 2850 > witepsol E75 > PEG 4650, while the ranking of solidification point, melting range, crushing strength, disintegration time and the time for 80% of metronidazole to be released from the suppositories (t80) was the reverse of that for setting time. Optimal concentrations of Tween 80 and sodium salicylate were observed for the suppository formulations. Using Kitazawa plots, all formulations showed two dissolution rate constants, k1 and k2 intersecting at time t1, with formulations containing 5 to 20 % w/w of methylcellulose exhibiting a third dissolution rate constant, k3 intersecting with k2 at time t2.Conclusion: The physical and release properties of metronidazole suppositories are influenced considerably by the bases and adjuvants employed. Tween 80 and sodium salicylate can probably be used to formulate only immediate-release suppositories while methylcellulose can be useful for sustained-release metronidazole suppositories. Some insight into these inferences can be obtained from parameters derived from Kitazawa plots.

Keywords: metronidazole, suppository bases, adjuvants, physical and release properties, Kitazawa plots.

INTRODUCTION

Suppositories have been recognized as an alternative to the oral route in situations such as when the patient is comatose, unable to swallow or when the drug produces nausea or vomiting. In the light of this, efforts have been made in recent times to present a good number of drugs in suppository form1,2,3,4. However, investigators have shown that the physical and release properties of many suppositories depend considerably on the physicochemical properties of the drug, suppository base and formulation adjuvants1,5,6 and a lot of formulation work is therefore normally required to optimise the properties of suppository preparations. In the case of metronidazole, which has also been presented in suppository form2,7,8,9 due to various factors, especially gastrointestinal disturbances and nausea when given orally6,7, there have been reports of a lot of variability in drug release from different suppository formulations2,7. Consequently, the goal of this study was to learn more about how to improve the physical and release features of metronidazole suppositories by investigating the impacts of various formulation parameters. Researching how various formulation adjuvants affect the physicochemical and release characteristics of metronidazole in witepsol and polyethylene glycol (PEG) suppository formulations was deemed an interesting endeavor.

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MATERIALS AND METHODS

Materials

Rhone Poulenc of France supplied the metronidazole BP, Huls AG of France supplied Witepsol H15 and E75, Merck of Germany supplied PEG 1500 and PEG 6000, Tween 80 and sodium salicylate also came from Merck, and Bufa B.V. of the Netherlands supplied the methylcellulose.

Methods for making suppositories

The fusion procedure was followed by a previously known method2 to make suppositories (1g) containing 200 mg of metronidazole each. Witepsol H15 and Witepsol E75 were used, along with blends of polyethylene glycol 1500 and 6000, respectively, with proportions of 70%:30% and 4650 and 2850 and 2850 of PEG. Melted on a water bath were the correct amounts of each suppository base.

The powder of metronidazole was first put through a 100 µm mesh filter before it was incorporated.

The same sieve was also used to micronize sodium salicylate. Using displacement value calculations, 200 milligrams of metronidazole powder, with and without an adjuvant, were mixed with trituration. Three different amounts of adjuvants (Tween 80, sodium salicylate, or methylcellulose) were added: 1, 3, 5, or 10% w/w for Tween 80 and sodium salicylate, and 1, 5, 10, or 20% w/w for methylcellulose. The process of mixing was maintained until the mixture became uniform. After pouring the mixture into stainless steel molds, the suppositories were taken out after cooling. In order to ensure that the suppositories solidified uniformly and transformed into crystals, they were left at room temperature for 24 hours after being removed from the mold and then weighed. Before they were put away in a dessicator to be used, the prepared suppositories were wrapped in aluminum foil and kept in the fridge.

Assessment of the physical characteristics of suppositories

There were a number of physical tests done on the produced suppositories. In order to determine how easy it was to shape the suppositories, we timed how long it took for the molten mixture to harden in the mould.

The point of solidification was further established. In a test tube, the test suppository was heated to 450C until it melted. Thermometer was mechanically spun while submerged in the cooling mass. A solidification point10 was noted as the temperature at which the bulk first started to stick to the thermometer.

Using the increasing melting point approach, the melting range was calculated.

The test suppositories were dissolved in water. A straight capillary tube had one end immersed in the liquid. After the molten mass had risen to a height of 5 cm in the capillary tube, it was chilled for 24 hours. Finally, the capillary tube was dropped into a water bath that was heated at a rate of 10C per minute and connected to a thermometer that was graded in 0.20 increments. A melting point range was determined by recording the temperature at which the suppository started to melt and the temperature at which clarity was seen.

We used twenty (20) suppositories of each formulation to test the produced suppositories for weight uniformity (BP technique 11). The spectrophotometric approach was used to determine the content homogeneity. Each suppository was dissolved in 100 milliliters of phosphate buffer after being melted separately. We used a 275 nm-wavelength spectrophotometer (Pye Unicam, SP 6-550, Cambridge, England) to measure the absorbance after dilution. Preliminary trials demonstrated that metronidazole absorption was unaffected by the suppository bases and other substances.

The suppositories' crushing resistance was measured using the Erweka breaking strength tester, which is made by Erweka Apparatebau GmbH in Germany. We used a quadruplicate design for all of our calculations.

The suppositories' disintegration and release characteristics were evaluated.

The time it took for the suppositories to dissolve was calculated. The suppository that was going to be tested was put in a separate glass container that had perforated ends and then submerged in a water bath that was kept at a temperature of 37 ± 10C. Within

the glass container, a magnetic stirrer was positioned with its speed set at 100rpm.

Once the suppository has dissolved (PEG) or melted (Witepsol), the disintegration time was recorded.

In vitro release studies were conducted utilizing the Hanson Easi-Lift dissolving apparatus in accordance with the USP XX basket technique. A flask containing 500 ml of a phosphate buffer solution (pH 7.2) kept at a constant temperature (37 ± 0.50C) was used for each suppository after it was put in the basket 12. A steady pace of 50 revolutions per minute was used to spin the basket. Five milliliters of sample fluid was removed at predetermined times. To replace the same volume of withdrew samples, a new buffer solution was employed, which was kept at experimental temperature.The concentration of metronidazole in every sample was determined using a 275 nm spectrophotometer (Pye Unicam, SP 6-550, Cambridge, England). For each formulation, the drug release was calculated as the mean of four measurements. Below is the integrated version of the equation proposed by Yes and Whitney13. This form has been extensively used to describe the kinetics of drug release from tablet dosage forms14, 15, 16:

$$\ln[C_s/(C_s-C)] = kt$$

The solute's saturation concentration (Cs), its concentration at time t (C), and the dissolving rate constant (k) are all variables in this equation. The kinetics of suppository formulation release may be described by this equation, according to Adegboye and Itiola2. Each formulation was analyzed by creating a Kitazawa plot of ln[Cs/(Cs-C)] vs t.

Evaluation using statistical methods

The mean plus or minus the standard deviation of four individual assessments is used to represent the results. The statistical significance of differences across groups was tested using analysis of variance (ANOVA).

RESULTS

Table 1 displays the outcomes of all physical examinations. None of the prepared suppositories had weights that were more than 5% off from the average, proving that they all met the BP requirement11 for weight homogeneity. It was also discovered that the majority of suppository formulations met the BP requirement11 for content consistency in terms of the mean drug content.

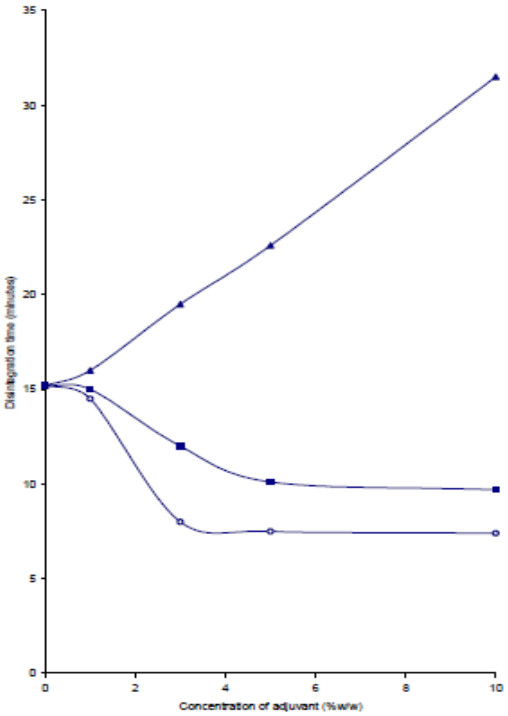

Figure 1: Plots of disintegration time against concentration of adjuvant for witepsol H15 formulations containing different adjuvants. ○– Tween 80; ■ – sodium salicylate; ▲ – methylcellulose

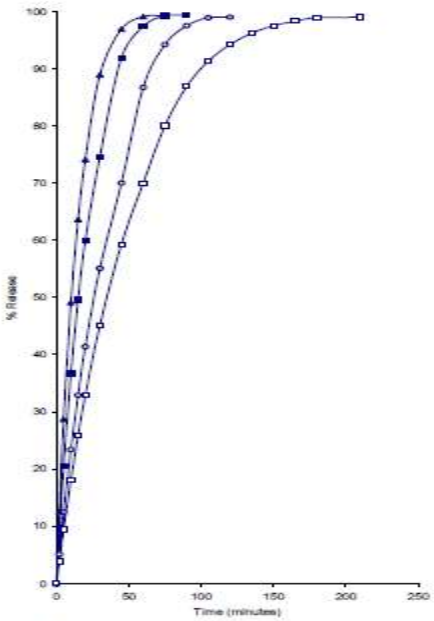

Figure 2: Plots of release profiles of metronidazole from witepsol E75 containing 5%$^{w}/_{w}$ of the different adjuvants. ○ – blank; ▲ – Tween 80; ■ – sodium salicylate; □– methylcellulose.

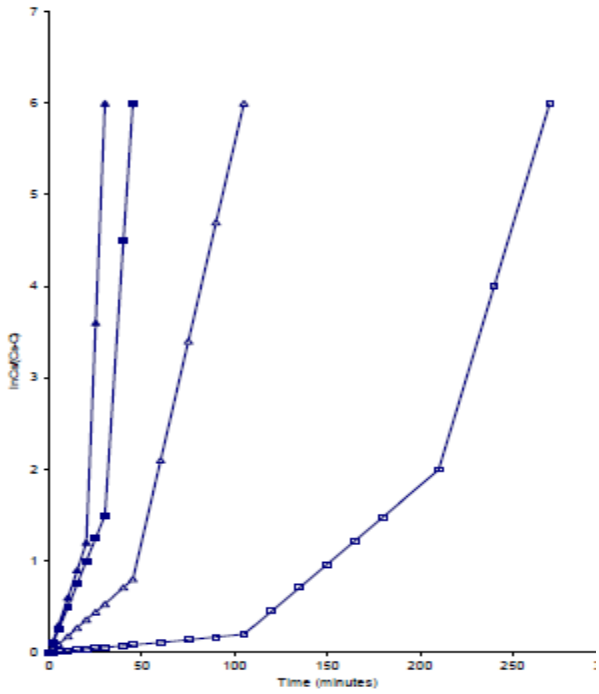

Figure 3: Kitazawa plots of release of metronidazole from PEG 4650 formulations containing 5%w/w of the different adjuvants. Δ- blank; ■- Tween 80;▲- sodium salicylate; □- methylcellulose.

None of the suppository formulations had less than 90% and none had more than 110% of expected metronidazole content.

Table 1: Physicochemical properties of metronidazole suppositories

Base	Adjuvant	Conc. of adjuvant	Setting time (min) S(SD)	Weight(g) X(SD)	Drug content %(SD)	Solidification point ^{0}C(SD)	Melting range^{0}C	Crushing strength N (SD)
Witepsol H15	-	0.0	17.50(0.12)	1.010(0.020)	98.4(2.4)	30.0(0.4)	33.5-35.0	14.7(1.0)
	Tween 80	1.0	17.15(0.24)	1.014(0.040)	96.2(1.8)	30.0(1.9)	33.5-	15.1(1.6)
		3.0	14.80(1.44)	1.018(0.080)	96.9(1.5)	29.5(2.2)	35.0	15.7(2.7)
		5.0	14.00(1.12)	1.025(0.024)	98.4(0.8)	29.0(1.9)	32.5-	16.7(2.1)
		10.0	13.55(1.32)	1.040(0.050)	98.2(2.3)	28.5(0.5)	34.0	16.9(1.4)
							31.5-32.5	
							30.0-31.5	
	Sodium salicylate	1.0	15.00(0.24)	1.011(0.034)	96.2(1.8)	32.0(1.9)	33.5-	16.7(1.3)
		3.0	13.86(1.44)	1.014(0.018)	96.9(1.5)	32.5(2.2)	35.5	19.6(2.4)
		5.0	9.60(1.12)	1.019(0.024)	98.4(0.8)	33.5(0.9)	33.5-	21.5(0.1)
		10.0	8.50(1.32)	1.028(0.015)	98.2(2.3)	34.5(1.5)	36.0	22.2(1.2)
							33.5-36.5	
							33.5-37.0	
	Methylcellulose	1.0	13.50(0.24)	1.019(0.017)	96.2(1.8)	32.5(1.9)	33.5-	18.6(1.0)
		5.0	10.10(1.44)	1.024(0.080)	96.9(1.5)	33.0(1.3)	36.0	24.9(2.7)
		10.0	6.40(1.12)	1.033(0.024)	98.4(0.8)	34.5(1.8)	34.0-	28.4(2.1)
		20.0	5.80(1.32)	1.056(0.005)	98.2(2.3)	35.5(1.6)	36.0	32.0(0.8)
							34.5-37.0	
							35.0-38.0	

Witepsol E75	-	0.0	10.55(0.12)	1.060(0.020)	97.6(1.3)	34.0(1.1)	36.5-38.0	21.6(2.0)
	Tween 80	1.0	10.00(0.24)	1.066(0.045)	96.2(1.8)	34.0(2.7)	36.5-38.0	22.7(2.2)
		3.0	8.50(1.44)	1.070(0.037)	96.9(1.5)	33.5(1.1)	36.0-37.0	25.5(2.3)
		5.0	7.75(1.12)	1.077(0.024)	98.4(0.8)	33.0(1.4)	35.0-36.0	26.3(0.9)
		10.0	7.20(1.32)	1.080(0.019)	98.2(2.3)	32.5(1.2)	34.5-35.0	27.4(1.0)
	Sodium salicylate	1.0	9.00(0.24)	1.062(0.012)	96.2(1.8)	35.5(1.8)	36.5-38.5	28.0(1.4)
		3.0	8.10(1.44)	1.065(0.016)	96.9(1.5)	36.5(0.9)	36.5-39.0	30.8(2.3)
		5.0	6.00(1.12)	1.069(0.028)	98.4(0.8)	37.0(1.1)	36.5-39.5	31.6(1.7)
		10.0	5.40(1.32)	1.075(0.031)	98.2(2.3)	38.0(1.1)	36.5-40.0	32.5(0.4)
	Methylcellulose	1.0	7.00(0.24)	1.071(0.019)	96.2(1.8)	36.0(1.3)	37.0-38.5	29.4(0.1)
		5.0	5.80(1.44)	1.078(0.027)	96.9(1.5)	37.0(1.2)	37.5-39.0	34.5(0.6)
		10.0	4.40(1.12)	1.085(0.025)	98.4(0.8)	37.5(1.7)	37.5-39.5	37.2(1.6)
		20.0	3.00(1.32)	1.096(0.005)	98.2(2.3)	38.5(0.5)	38.0-40.0	41.1(0.9)
0PEG 2850	-	0.0	14.70(0.12)	1.040(0.020)	98.4(2.4)	31.0(0.4)	35.0-37.0	17.6(0.5)
	Tween 80	1.0	14.00(0.24)	1.045(0.240)	96.2(1.8)	31.5(1.9)	35.0-37.0	18.6(0.7)
		3.0	12.90(1.44)	1.048(0.180)	96.9(1.5)	31.5(1.2)	34.5-36.0	20.5(1.6)
		5.0	11.00(1.12)	1.054(0.024)	98.4(0.8)	32.0(1.6)	34.0-35.5	22.5(1.4)
		10.0	10.50(1.32)	1.060(0.005)	98.2(2.3)	32.5(1.5)	33.5-35.0	25.4(1.2)
	Sodium salicylate	1.0	12.00(0.24)	1.041(0.240)	96.2(1.8)	31.5(1.9)	33.5-36.5	19.0(2.0)
		3.0	6.42(1.44)	1.043(0.180)	96.9(1.5)	32.0(1.1)	36.0-37.5	21.5(1.9)
		5.0	6.00(1.12)	1.046(0.024)	98.4(0.8)	33.0(0.3)	36.5-38.0	25.5(0.2)
		10.0	5.20(1.32)	1.050(0.005	98.2(2.3)	34.0(1.4)	36.0-38.5	30.4(0.8)
	methylcellulose	1.0	10.00(0.24)	1.048(0.240)	96.2(1.8)	32.0(1.3)	35.5-37.0	21.6(0.6)
		5.0	8.50(1.44)	1.055(0.180)	96.9(1.5)	33.5(1.2)	36.5-38.0	25.5(2.2)
		10.0	6.25(1.12)	1.065(0.024)	98.4(0.8)	34.0(1.5)	37.0-39.0	29.4(1.1)
		20.0	5.00(1.32)	1.080(0.005	98.2(2.3)	35.0(1.5)	37.5-39.0	37.2(1.0)

PEG 4650	-	0.0	7.40(0.12	1.090(0.020	97.6(1.3)	34.5(2.0)	38.0-40.0	24.5(0.1)
	Tween 80	1.0	7.20(0.24)	1.093(0.240)	96.2(1.8)	34.5(1.3)	38.0-	25.4(1.2)
		3.0	6.00(1.44)	1.097(0.180)	96.9(1.5)	35.0(1.0)	39.5	26.5(0.2)
		5.0	4.80(1.12)	1.099(0.024)	98.4(0.8)	35.5(1.6)	37.5-	28.4(0.5)
		10.0	4.10(1.32)	1.103(0.005	98.2(2.3)	36.0(1.5)	39.0	30.3(0.8)
							37.0-38.5	
							36.5-38.0	
	Sodium salicylate	1.0	6.50(0.24)	1.091(0.240)	96.2(1.8)	35.0(1.0)	38.0-	26.5(2.5)
		3.0	4.40(1.44)	1.093(0.180)	96.9(1.5)	35.5(1.2)	40.0	27.5(0.7)
		5.0	4.00(1.12)	1.095(0.024)	98.4(0.8)	36.0(0.1)	38.0-	29.4(1.3)
		10.0	3.50(1.32)	1.099(0.005	98.2(2.3)	37.0(2.5)	41.0	33.3(0.9)
							38.0-41.5	
							38.0-42.0	
	methylcellulose	1.0	5.00(0.24)	1.095(0.240)	96.2(1.8)	35.5(2.2)	38.0-	27.4(1.0)
		5.0	4.00(1.44)	1.099(0.180)	96.9(1.5)	36.5(1.2)	40.5	32.3(2.0)
		10.0	2.80(1.12)	1.103(0.024)	98.4(0.8)	37.5(1.8)	39.0-	38.2(1.5)
		20.0	2.00(1.32)	1.110(0.005)	98.2(2.3)	39.0(0.5)	41.0	44.1(1.8)
							39.5-41.5	
							40.0-42.0	

Moreover, as can be shown from Table 1, the various bases were ranked according to the setting time, which represents the ease of molding: witepsol H15 > PEG 2850 > witepsol E75 > PEG 4650. It is worth mentioning that the order of the bases was reversed when it came to solidification point, melting range, and crushing strength: PEG 4650 > witepsol E75 > PEG 2850 > witepsol H15. As can be seen from Table 1, the adjuvants had a significant impact on the various metrics. Incorporating all of the adjuvants shortened the setting time and boosted the crushing strength. In contrast, methylcellulose and sodium salicylate raised the melting range and solidification point values, whereas Tween 80 lowered them.

Time to disintegration (DT) vs. adjuvant concentration is shown in Figure 1 visually. Witepsol E75, which contains 5%w/w of the various adjuvants, exhibits characteristic metronidazole release patterns in Figure 2. For each formulation, the time required for the release of 80% of the metronidazole (t80) was determined. Table 2 displays the values of DT and t80. Both parameters also display the ranking for the various bases, which is the inverse of what was seen for setup time: The following are the rankings of witepsol: 4650 > E75 > 2850 > H15. As the concentration of Tween 80 and sodium salicylate rose, DT and t80 values fell. In contrast, methylcellulose caused the values to rise.

Here are some typical Kitazawa plots of metronidazole release from PEG 4650 formulations with various adjuvants at a concentration of 5% w/w (Figure 3). Formulations with 5, 10, or 20% w/w methylcellulose produced a third regression line with a slope of k3, intersecting at time t2, in addition to the two linear regression lines with slopes k1 and k2 that met at time t1 for all substances. In Table 2, you can see the values of all the parameters that were obtained from the Kitazawa plots. It can be seen that when the concentration of Tween 80 or sodium salicylate grew, the values of k1 and k2 dropped. In contrast, the opposite was true for methylcellulose. As the methylcellulose content in the relevant suppository formulations increased, the k3 values likewise reduced.

DISCUSSION

In order to better understand how to optimize the rectal formulation of metronidazole, researchers examined the physicochemical and release characteristics of the antibiotic in suppositories. The findings show that the produced suppositories were consistent in weight and content according to the approved specifications (Table 1). The findings demonstrate that the formulation factors had a significant impact on the suppositories' physical and release qualities (Tables 1 and 2). Metaronidazole suppository formulations with a range of physical and release qualities for varied applications may likely be made using the bases, since they rank well for most physical and release criteria. Additionally, the rankings imply that most parameters' values improved when the setting time, a measure of how easily the suppositories were molded in the various bases, increased.

According to Table 2, the release rate of metronidazole increases with time, as shown by the

dissolution rate constants k1 < k2 < k3. While the t1 values for Tween 80 and sodium salicylate decreased as concentrations rose, the methylcellulose values increased. As the methylcellulose concentration grew, so were the t2 values (for formulations with5,10, and 20% w/w methylcellulose). Time t1 was typically longer than disintegration time, DT, for all formulations, as shown in Table 2. For this reason, DT happened before t1, and the formulations' disintegration time did not coincide with the time for the transition from k1 to k2 at t1. The increased anxiety that comes with the disintegration test15 might be to blame, but it could also

Table 2: Release properties of metronidazole suppositories

Base	Adjuvant	Conc. of adjuvant	D_T (min)	t_{80} (min)	k_1	k_2	k_3	t_1 (min)	t_2 (min)
Witepsol H15	-	0.0	15.20(1.11)	23.60(0.56)	0.067	0.081	-	20	-
	Tween 80	1.0	14.42(1.56)	16.58(1.21)	0.090	0.210	-	15	-
		3.0	7.85(1.48)	11.15(0.04)	0.135	0.315	-	10	-
		5.0	7.53(2.36)	10.90(1.71)	0.137	0.333	-	10	-
		10.0	7.41(2.56)	10.82(0.84)	0.140	0.350	-	10	-
	Sodium salicylate	1.0	15.00(1.56)	22.80(0.22)	0.069	0.104	-	20	-
		3.0	14.80(1.48)	22.00(0.90)	0.072	0.122	-	20	-
		5.0	10.15(2.36)	16.45(1.06)	0.093	0.206	-	15	-
		10.0	9.56(2.56)	16.24(0.34)	0.096	0.216	-	15	-
	Methylcellulose	1.0	16.00(1.56)	36.56(0.65)	0.045	0.060	-	30	-
		5.0	19.50(1.48)	53.30(1.11)	0.030	0.042	0.066	45	75
		10.0	22.64(2.36)	70.00(0.70)	0.015	0.032	0.043	60	90
		20.0	31.50(2.56)	88.68(0.04)	0.007	0.021	0.035	75	150
Witepsol E75	-	0.0	28.60(1.11)	53.65(0.54)	0.026	0.055	-	45	-
	Tween 80	1.0	27.00(1.56)	37.90(0.78)	0.040	0.060	-	30	-
		3.0	20.65(1.48)	24.40(1.12)	0.065	0.082	-	20	-
		5.0	19.44(2.36)	24.00(0.92)	0.067	0.085	-	20	-
		10.0	19.25(2.56)	23.70(1.40)	0.070	0.087	-	20	-
	Sodium salicylate	1.0	28.00(1.56)	50.55(1.36)	0.030	0.057	-	45	-
		3.0	27.48(1.48)	48.68(1.78)	0.032	0.061	-	45	-
		5.0	20.72(2.36)	34.00(0.06)	0.045	0.076	-	30	-
		10.0	19.58(2.56)	33.80(0.50)	0.046	0.078	-	30	-
	Methylcellulose	1.0	29.00(1.56)	67.55(0.99)	0.022	0.042	-	60	-
		5.0	32.40(1.48)	75.00(0.22)	0.020	0.027	0.053	60	75
		10.0	36.16(2.36)	93.00(1.00)	0.016	0.019	0.041	75	105
		20.0	41.00(2.56)	136.00(0.21)	0.013	0.008	0.028	90	180
PEG 2850	-	0.0	20.88(1.11)	38.55(0.88)	0.042	0.055	-	30	-
	Tween 80	1.0	19.25(1.56)	34.68(0.58)	0.046	0.062	-	30	-
		3.0	15.82(1.48)	24.00(0.96)	0.066	0.079	-	20	-
		5.0	12.56(2.36)	23.35(1.24)	0.069	0.082	-	20	-
		10.0	13.98(2.56)	25.36(0.95)	0.064	0.068	-	20	-
	Sodium salicylate	1.0	20.00(1.56)	30.20(0.61)	0.053	0.064	-	30	-
		3.0	14.95(1.48)	17.20(0.72)	0.086	0.113	-	15	-
		5.0	14.40(2.36)	16.95(0.30)	0.093	0.115	-	15	-
		10.0	13.85(2.56)	16.65(0.48)	0.093	0.117	-	15	-
	methylcellulose	1.0	22.00(1.56)	50.00(0.55)	0.032	0.061	-	30	-
		5.0	25.45(1.48)	57.20(0.81)	0.027	0.040	0.053	45	75
		10.0	29.24(2.36)	71.56(0.76)	0.013	0.028	0.042	60	105
		20.0	34.65(2.56)	96.80(0.88)	0.006	0.019	0.028	75	165
PEG 4650	-	0.0	29.54(2.11)	69.45(1.14)	0.019	0.055	-	60	-
	Tween 80	1.0	27.00(1.56)	64.40(1.32)	0.023	0.068	-	60	-
		3.0	23.45(1.48)	35.25(0.16)	0.043	0.071	-	30	-
		5.0	19.58(2.36)	33.68(0.96)	0.046	0.075	-	30	-
		10.0	20.64(2.56)	36.00(0.48)	0.041	0.074	-	30	-
	Sodium salicylate	1.0	28.00(1.56)	53.20(0.64)	0.026	0.062	-	45	-
		3.0	23.10(1.48)	35.52(1.14)	0.045	0.072	-	30	-
		5.0	22.56(2.36)	33.65(0.80)	0.046	0.075	-	30	-
		10.0	21.25(2.56)	32.56(0.16)	0.049	0.078	-	30	-
	methylcellulose	1.0	31.00(1.56)	87.90(0.18)	0.016	0.036	-	60	-
		5.0	34.68(1.48)	104.10(0.46)	0.015	0.020	0.028	60	90
		10.0	40.40(2.36)	123.45(0.44)	0.007	0.010	0.016	75	135
		20.0	46.60(2.56)	168.00(0.36)	0.003	0.007	0.012	90	240

it is not always the case that the moment at which the suppository melts or dissolves corresponds precisely to the time at which the dissolution rate changes.

Some pill formulations' release kinetics have been well explained using the Kitazawa plot. The release kinetics of these formulations were shown to be either biphasic (using both k1 and k2) or monophasic (involving just k1)14, 15, 16. It is worth mentioning that a considerable percentage of metronidazole suppositories in this study have shown triphasic release kinetics, namely k1, k2, and k3. That means there were more steps and complexity required in the release from these suppositories compared to the tablet versions. This discovery might provide light on why suppository release rates are so unpredictable2, 7. Different kinds of suppositories for various reasons may be created by manipulating the formulation using these discoveries. This is because sustained-release suppositories aren't always the best option for treatment, even when compared to immediate-release ones. For long-term management of conditions including hypertension, AIDS, anemia, diabetes, and postoperative or cancer pain, particularly in patients who are bedridden, sustained-release formulations are helpful.numbers 17, 18, and 19

Some suppositories may have a biphasic release rate because the surface area of the suppository limits the release of metronidazole at first, and then the drug is released more quickly from a melting or dissolving suppository mass during the second phase. The triphasic release profile of methylcellulose suppositories may be explained by the fact that, at certain doses, methylcellulose has the potential to expand and form a matrix gel structure. Since metronidazole is best released gradually from a slowly melting or dissolving material, it is likely that these suppositories were able to retain their integrity for a longer duration to allow for this release. Sodium salicylate and Tween 80 both accelerated the rate of metronidazole release from the suppositories. Tween 80's capacity to increase the base matrix's wettability and, by extension, the diffusion of the inserted drug molecules20, may explain this. Sodium salicylate's high solubility may explain why it boosted the release rate, but the exact mechanism is still unclear21, 22. To enhance drug release, the suppository should become more porous and have increased water sorption due to the rapid leaching of the sodium salicylate, which is a water-soluble compound.

An significant takeaway from this study is that the values of the physical and release parameters examined (t80, setting time, crushing strength, disintegration time, k1, and k2) may be used to determine the best adjuvant doses (Tables 1 and 2). When it came to PEG formulations with Tween 80 or sodium salicylate (≥ 3% w/w), as well as witepsol formulations comprising Tween 80 (>3% w/w) or sodium salicylate (>5% w/w), the values of these parameters were often not substantially different ($\rho>0.05$). It follows that these specific amounts of Tween 80 and sodium salicylate seem to be ideal for the various formulations. Conversely, all the parameters that were tested were significantly affected by methylcellulose at all doses ($p<0.05$).

Suppositories with sodium salicylate and Tween 80 released metronidazole at a much faster pace than those using methylcellulose. Table 2 shows that formulations using methylcellulose had lower terminal dissolving rate constant (k2) values compared to those containing Tween 80 and sodium salicylate in suppositories. In comparison to formulations including Tween 80 and sodium salicylate, the t1 values for relevant methylcellulose formulations were much greater. Table 2 shows that methylcellulose formulations have t80 values of up to 168 minutes (2.8 hours) and t2 values of up to 240 minutes (4.0 hours). These values imply that methylcellulose could be useful for formulating metronidazole suppository formulations with a sustained release, whereas Tween 80 and sodium salicylate are likely only useful for formulations with an immediate release.

CONCLUSION

The results of the research demonstrate that different formulation adjuvants and bases may produce metronidazole suppositories with varying physical features and release rates. An immediate-release suppository may be made using the optimal amounts of sodium salicylate and Tween 80.

Additionally, the findings indicate that methylcellulose might be used to create metronidazole suppositories with a prolonged release. Kitazawa plot characteristics may provide light on these conclusions about the suppositories' release kinetics, and the results of this study might be used to develop a metronidazole rectal administration system.

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