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Physical and Release Properties of Metronidazole Suppositories TA Adegboye and OA Itiola

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Abstract

In order to better understand how to optimize the rectal formulation of metronidazole, this research examined the physical and release features of metronidazole suppositories and how various bases and adjuvants affected these qualities.

The following steps were used to make suppositories: (1) witepsol (H15 and E75) and (2) polyethylene glycol (PEG 2850 and 4650) bases containing 200 mg of metronidazole each; as adjuvants, various amounts of Tween 80, sodium salicylate, and methylcellulose were used. In addition to the crushing strength, disintegration time, and time for 80% metronidazole release (t80), the suppositories' setting time, solidification point, and melting range were also determined.

The results showed that witepsol H15 had the shortest setting time of the suppositories, followed by PEG 2850, witepsol E75, and PEG 4650. In contrast, the order of solidification point, melting range, crushing strength, disintegration time, and the time it took for 80% of metronidazole to be released from the suppositories (t80) was the exact opposite of the ranking for setting time. For the suppository formulations, the ideal amounts of Tween 80 and sodium salicylate were noted. The Kitazawa plots revealed that at time t1, all of the formulations had two dissolving rate constants, k1 and k2, which intersected. Formulations with 5 to 20% w/w methylcellulose displayed a third dissolution rate constant, k3, which intersected with k2 at time t2.

In conclusion, the bases and adjuvants used have a significant impact on the physical and release characteristics of metronidazole suppositories. While methylcellulose is effective for sustained-release metronidazole suppositories, tween 80 and sodium salicylate are likely only suitable for use in formulating immediate-release suppositories. Parameters determined from Kitazawa plots may provide some light on these findings.

Suppository bases, metronidazole, adjuvants, physical and release qualities, Kitazawa plots, and keywords are all part of this study.

INTRODUCTION

It has been acknowledged that suppositories may be used instead of the oral route in cases when the patient is unconscious, has trouble swallowing, or has nausea or vomiting due to the medicine. This is why several medications have recently been developed for suppository administration1,2,3,4.

Researchers have shown that the physicochemical properties of the drug, suppository base, and formulation adjuvants significantly impact the physical and release properties of many suppositories1,5,6. As a result, optimizing the properties of suppository preparations typically requires a lot of formulation work. Several variables, including gastrointestinal issues and nausea when administered orally6,7, have led to metronidazole's presentation in suppository form2,7,8,9. One of these reasons is the high degree of variability in drug release reported from different suppository formulations2,7.

In order to better understand how to optimize the physical and release features of metronidazole suppositories, the current study set out to evaluate the impact of various formulation parameters on these qualities. The physicochemical and release properties of metronidazole in witepsol and polyethylene glycol (PEG) suppository formulations were thought to be interesting enough to warrant investigating the effects of several formulation adjuvants with varying characteristics.

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MATERIALS AND METHODS

Materials

Ingredients included metronidazole BP (Rhone Poulenc, France), Witepsol H15 and E75 (Huls AG, France), polyethylene glycol (PEG), sodium salicylate (Merck, Germany), tween 80 (Merck, Germany), and methylcellulose (Bufa B.V., Netherlands).

Suppositories preparation

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. On a water bath, the correct amount of each suppository base was melted.

A 100 μm screen filter was used to sift the metronidazole powder through before it was included.

Additionally, sodium salicylate was micronized and filtered using the same sieve. The amounts of metronidazole powder with and without the adjuvant were mixed using trituration in accordance with the displacement value estimates, which were 200 milligrams. There were a variety of amounts of adjuvants (Tween 80, sodium salicylate, or methylcellulose) 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 being put in the fridge, the ready-made suppositories were covered in aluminum foil and kept in a dessicator.

Evaluation of physical properties of suppositories

Several physical tests were performed on the manufactured suppositories. The suppositories' ease of molding was determined by timing the molten mass's setting time, which was also the time it took for the suppository to set in the mould10. We also found the solidification point to be 10. In a test tube, the test suppository was heated to 450C until it melted. A mechanically-rotated thermometer was lowered into the cooling mass. The solidification point10 was the reported temperature at which the mass first started to stick to the thermometer. Trop. J. Pharm. Res., Itiola & Adegboye, 889, March 2008, 7, 1.The range of melting points was found by using the rising melting point approach 10. 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. Twenty (20) suppositories of each formulation were produced and tested for weight uniformity using the BP method11. Spectrophotometric analysis was used to ascertain the degree of content homogeneity. Each suppository was dissolved in 100 milliliters of phosphate buffer after being melted separately. A spectrophotometer (Pye Unicam, SP 6-550, Cambridge, England) was used to measure the absorbance at 275 nm 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. The results were presented in a quadruplicate format.

Evaluation of disintegration and release properties of the suppositories

The time it took for the suppositories to dissolve was calculated. I submerged the suppository that was going to be tested in a water bath that was kept at 37 ± 10C. The glass container had perforated ends. The glass container was then filled with a magnetic stirrer that was set at 100rpm.

We measured the disintegration time after the suppository dissolved (PEG) or melted (Witepsol) in the specified medium. The Hanson Easi-Lift dissolve apparatus was used to conduct in vitro release studies in accordance with the USP XX basket technique. The procedure included placing each suppository in the designated basket and then placing it into a flask that contained 500 ml of a phosphate buffer solution with a pH of 7.2. The flask was kept at a constant temperature of 37 ± 0.50C. At all times, the basket

was spun at 50 revolutions per minute. 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.Spectrophotometric analysis was performed at 275 nm (Pye Unicam, SP 6-550, Cambridge, England) to determine the concentration of metronidazole in every sample. The drug release from each formulation was calculated using 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, 6. This is the formula: ln[Cs/(Cs-C)] = kt (1). The solute's saturation concentration (Cs), its concentration at time t (C), and the dissolving rate constant (k) are all variables in this equation. This equation may be used to describe the release kinetics of suppository formulations, according to Adegboye and Itiola2. We plotted the logarithm of Cs/(Cs-C) over time for every single formulation using the Kitazawa method.

Statistical analysis

The mean plus or minus the standard deviation of four separate assessments is used to represent the results. To determine if there were statistically significant differences between the groups, analysis of variance (ANOVA) was used. Table 1 displays the outcomes of all physical examinations. With no more than a 5% variation from the mean, the findings demonstrate that all manufactured suppositories met the BP requirement11 for weight homogeneity. Most suppository formulations also met the BP requirement11 for content homogeneity, meaning their mean drug content was satisfactory.

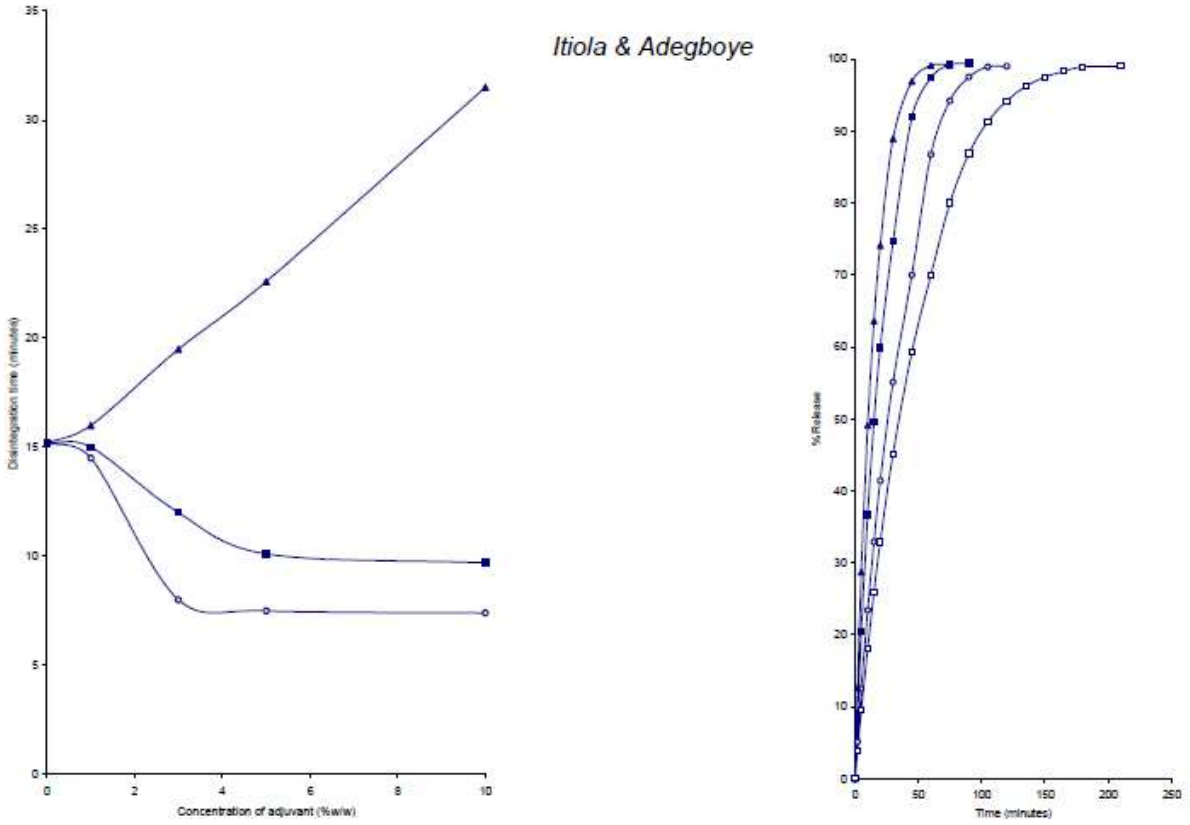

Figure 1: Disintegration time vs. concentration plots Various witepsol E75 adjuvant formulations containing metronidazole are shown in Figure 2 as plots of their respective release patterns. Includes methylcellulose adjuvants at a concentration of 5%w/w, Tween 80, sodium salicylate, and other ingredients. **blank**, **Tween 80**, **sodium salicylate**, and **methylcellulose** are the ingredients.

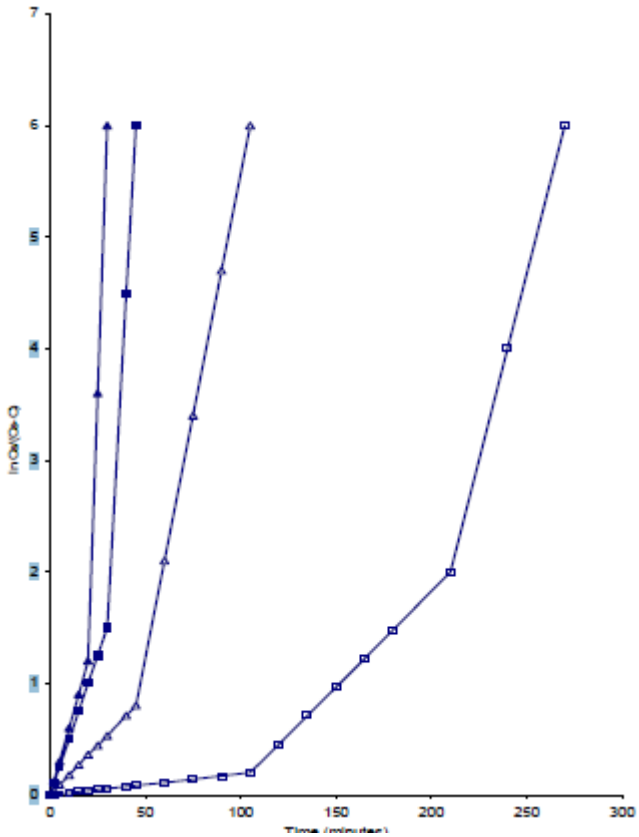

Figure 3: Release of metronidazole from PEG 4650 formulations including various adjuvants at a concentration of 5%w/w according to the Kitazawa plot. The ingredients listed are Δ-blank, ■-Tween 80, ▌-sodium salicylate, and □-methylcellulose.

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)	33.5-35.0	15.1(1.6)
		3.0	14.80(1.44)	1.018(0.080)	96.9(1.5)	29.5(2.2)	32.5-34.0	15.7(2.7)
		5.0	14.00(1.12)	1.025(0.024)	98.4(0.8)	29.0(1.9)	31.5-32.5	16.7(2.1)
		10.0	13.55(1.32)	1.040(0.050)	98.2(2.3)	28.5(0.5)	30.0-31.5	16.9(1.4)
	Sodium salicylate	1.0	15.00(0.24)	1.011(0.034)	96.2(1.8)	32.0(1.9)	33.5-35.5	16.7(1.3)
		3.0	13.86(1.44)	1.014(0.018)	96.9(1.5)	32.5(2.2)	33.5-36.0	19.6(2.4)
		5.0	9.60(1.12)	1.019(0.024)	98.4(0.8)	33.5(0.9)	33.5-36.5	21.5(0.1)
		10.0	8.50(1.32)	1.028(0.015)	98.2(2.3)	34.5(1.5)	33.5-37.0	22.2(1.2)
	Methylcellulose	1.0	13.50(0.24)	1.019(0.017)	96.2(1.8)	32.5(1.9)	33.5-36.0	18.6(1.0)
		5.0	10.10(1.44)	1.024(0.080)	96.9(1.5)	33.0(1.3)	34.0-36.0	24.9(2.7)
		10.0	6.40(1.12)	1.033(0.024)	98.4(0.8)	34.5(1.8)	34.5-37.0	28.4(2.1)
		20.0	5.80(1.32)	1.056(0.005)	98.2(2.3)	35.5(1.6)	35.0-38.0	32.0(0.8)
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)	38.0-39.5	25.4(1.2)
		3.0	6.00(1.44)	1.097(0.180)	96.9(1.5)	35.0(1.0)	37.5-39.0	26.5(0.2)
		5.0	4.80(1.12)	1.099(0.024)	98.4(0.8)	35.5(1.6)	37.0-38.5	28.4(0.5)
		10.0	4.10(1.32)	1.103(0.005	98.2(2.3)	36.0(1.5)	36.5-38.0	30.3(0.8)
	Sodium salicylate	1.0	6.50(0.24)	1.091(0.240)	96.2(1.8)	35.0(1.0)	38.0-40.0	26.5(2.5)
		3.0	4.40(1.44)	1.093(0.180)	96.9(1.5)	35.5(1.2)	38.0-41.0	27.5(0.7)
		5.0	4.00(1.12)	1.095(0.024)	98.4(0.8)	36.0(0.1)	38.0-41.5	29.4(1.3)
		10.0	3.50(1.32)	1.099(0.005	98.2(2.3)	37.0(2.5)	38.0-42.0	33.3(0.9)
	methylcellulose	1.0	5.00(0.24)	1.095(0.240)	96.2(1.8)	35.5(2.2)	38.0-40.5	27.4(1.0)
		5.0	4.00(1.44)	1.099(0.180)	96.9(1.5)	36.5(1.2)	39.0-41.0	32.3(2.0)
		10.0	2.80(1.12)	1.103(0.024)	98.4(0.8)	37.5(1.8)	39.5-41.5	38.2(1.5)
		20.0	2.00(1.32)	1.110(0.005)	98.2(2.3)	39.0(0.5)	40.0-42.0	44.1(1.8)

The ordering of setting time, which represents the ease of molding, for the various bases was witepsol H15 > PEG 2850 > witepsol E75 > PEG 4650, as can be seen from Table 1. In contrast to the order in which the bases were ranked for setting time, the following bases were ranked for 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. Tween 80 reduced melting range and solidification point values, while methylcellulose and sodium salicylate enhanced these

values.Disintegration time (DT) vs. adjuvant concentration is shown in Figure 1 as typical maps. 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. In Table 2, you can see the DT and t80 values. Interestingly, both parameters rank for the various bases, which is the inverse of what happened when setting the time: The following are the rankings of witepsol: 4650 > E75 > 2850 > H15. While methylcellulose caused DT and t80 to rise, Tween 80 and sodium salicylate had the opposite effect. 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. Table 2 contains the values of all parameters obtained from Kitazawa plots. As the concentrations of Tween 80 and sodium salicylate rose, the values of k1 and k2 fell, whereas the concentrations of methylcellulose rose. For the relevant suppository formulations, the values of k3 likewise declined as the content of methylcellulose increased.

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). Tables 1 and 2 further demonstrate that the formulation factors used had a significant impact on the suppositories' physical and release characteristics. The suppository bases may be used to create metronidazole suppository formulations with varying physical and release qualities for diverse uses, according to the rankings of 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 dissolution rate constants for the relevant formulations were ranked as k1 < k2 < k3, indicating that the rate of metronidazole release increased with time. Tween 80 and sodium salicylate exhibited decreasing t1 values as concentrations rose, but methylcellulose exhibited increasing t1 values. For formulations with 5, 10, and 20% w/w methylcellulose, the t2 values likewise rose as the methylcellulose concentration rose. Additionally, as can be seen from Table 2, the disintegration time, DT, was often less than the period t1 for all formulations. Accordingly, DT happened before t1, and the formulations' disintegration time did not coincide with the time for the transition from k1 to k2 at t1. This might be because the disintegration test15 causes more anxiety, 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	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
	Sodium salicylate	1.0	28.00(1.56)	53.20(0.6					
		3.0	23.10(1.48)	35.52(1.1					
		5.0	22.56(2.36)	33.65(0.8					
		10.0	21.25(2.56)	32.56(0.1					
	methylcellulose	1.0	31.00(1.56)	87.90(0.1					
		5.0	34.68(1.48)	104.10(0.					
		10.0	40.40(2.36)	123.45(0.					
		20.0	46.60(2.56)	168.00(0.					

Some pill formulations' release kinetics have been well explained using the Kitazawa plot. One or two phases of release kinetics were observed for these formulations14,15, 16. A number of metronidazole suppositories in this study showed triphasic (k1, k2, and k3) release kinetics, which is an intriguing finding. Therefore, it seems that the release mechanism from these suppositories was more extensive and intricate compared to the release procedure from those tablet formulations. Some of the observed diversity in suppository release rates may be explicable by this discovery2, 7. Different kinds of suppositories for various reasons may be created by manipulating the formulation using these discoveries. This is due to the fact that sustained-release suppositories are not always the best option

for therapeutic purposes. When a patient is bedridden, sustained-release formulations are particularly helpful for the long-term management of conditions including hypertension, anemia, diabetes, AIDS, and postoperative or cancer pain.2017, 18, 19.Because metronidazole is initially bound to the suppository's surface area, some suppositories may have a biphasic release rate. In the second phase, known as rapid release, the drug is released at an increasing rate from the mass of the suppository as it melts or dissolves. At certain quantities, methylcellulose may expand and form a matrix gel structure, which may explain the triphasic release characteristic of suppositories containing this ingredient. The metronidazole in these suppositories likely remained intact for a longer length of time, allowing for a gradual rise in the drug's concentration as it was released from a slowly disintegrating bulk. The rates of metronidazole release from the suppositories were both boosted by Tween 80 and sodium salicylate. This could be because Tween 80 increases the incorporated drug molecules' diffusion by making the base matrix more wettable. Sodium salicylate's high solubility may explain why it boosted the release rate, but the exact mechanism is still unclear21, 22. Because sodium salicylate is a water-soluble medication, its rapid leaching into the suppository should increase drug release by creating pores and increasing water sorption. Note that the values of most of the physical and release parameters evaluated (Tables 1 and 2) – setting time, crushing strength, disintegration time, t80, k1 and k2 – may be used to get the optimal doses of adjuvants. In regards to PEG formulations comprising Tween 80 or sodium salicylate (≥ 3% w/w), as well as witepsol formulations containing 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, methylcellulose had a significant impact on every parameter tested at all concentrations ($p<0.05$). Metronidazole was released at a much slower rate from methylcellulose suppositories compared to those containing Tween 80 and sodium salicylate. 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. Tween 80 and sodium salicylate formulations had much lower t1 values compared to equivalent methylcellulose formulations, which had significantly higher t2 values. The results showed that methylcellulose could be used to make metronidazole suppository formulations with a sustained release of up to 168 minutes (2.8 hours) and 240 minutes (4.0 hours) of t2 (Table 2), whereas Tween 80 and sodium salicylate are likely only useful for making suppositories with an immediate release of up to an hour.

CONCLUSION

The research demonstrated that different formulation adjuvants and bases may produce metronidazole suppositories with variable physical features and release rates. An immediate-release suppository may be made using the optimal amounts of sodium salicylate and Tween 80. The findings also indicate that methylcellulose might be used to create metronidazole suppositories with a prolonged release. The results of this study may be used to develop a metronidazole rectal delivery system, and characteristics acquired from Kitazawa plots can shed light on these conclusions about the suppository release kinetics.

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