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Comparative dissolution studies of rectal formulations using the basket, the paddle and the flow-through methods: II. Ibuprofen in suppositories of both hydrophilic and lipophilic types

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Abstract

The applicabilities of the paddle, basket and flow-through methods have been investigated for four different rectal compositions of both hydrophilic and lipophilic types containing ibuprofen. The formulations were studied with respect to in vitro dissolution rate and behaviour in the different apparatus. The reproducibility of the three techniques was also tested by using a hydrophilic and a lipophilic composition. None of the techniques appeared to be more applicable than the others for the compositions tested, though the dissolving suppositories are less sensitive to the technique used than the melting ones. It has been found necessary to consider the behaviour of the product, with regard to its composition and the in vitro method used, when judging the applicability of a dissolution test for a rectal dosage system. Comparison to our previous data on paracetamol also shows that the physical-chemical properties of the drug substance are of great importance, and must be considered, when the judgement of applicability is made.

Keywords: Dissolution testing; Ibuprofen; Suppository; Paddle dissolution method; Basket dissolution method; Flow-through dissolution method

1. Introduction

In addition to the basket and paddle techniques, the flow-through technique has now been adopted as an in vitro dissolution technique for solid oral dosage forms in the European Pharmacopoeia (Ph. Eur) and the Pharmacopoeia of the United States (USP). A number of in vitro dissolution techniques for determination of the dissolution rate of drug substances from suppositories are described in the literature. The techniques can be divided roughly into two groups; those not using membranes and those that do use membranes (Bornschein et al., 1985). However, there are still no official dissolution methods available

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to test for drug release and dissolution rate from rectal dosage systems.

The aim of this study was to investigate whether the in vitro dissolution methods established for oral dosage forms are applicable to rectal dosage systems. Different rectal compositions of a model drug, ibuprofen, were studied regarding their behaviour during dissolution tests and the dissolution rate using the USP basket, paddle and flow-through techniques. The reproducibility of the three techniques was assessed by studying the in vitro dissolution profiles and variability of dissolution results from hydrophilic and lipophilic suppositories.

2. Materials and methods

2.1. Chemicals

The following chemicals were used in the different formulations: ibuprofen, batch no. 883413 (Boots Pharmaceuticals, U.K.); Adeps Solidus, Ph. Eur (Witepsol, Hüls Werk Witten, Germany); Adeps solidus, Ph. Eur (Novata, Henkel KGaA, Germany); Paraffinum Liquidum, Ph. Eur. (Witco BV, The Netherlands); polyethylene glycol 3350, DAB 8 (BP Chem. Ltd, U.K.) and polyethylene glycol ointment 1550, DAB 8 (BP Chem. Ltd, U.K.).

The physical-chemical properties of ibuprofen are as follows – log D: 1.14, octanol-water (HPLC) (Dunn et al., 1986); solubility (pH 7.4, 37°C): 4.7 mg/ml; pK_a: 5.2 (Albert and Serjeant, 1984).

2.2. Solid rectal systems

The compositions investigated are listed in Table 1. One suppository product was taken from regular production (Lot 1T, kindly supplied by Boots) and the other suppository formulations were produced manually on a small scale by homogenising ibuprofen (500 mg/suppository) into the melted suppository base by a jet-stream mixer (Ystral). The melt was poured into moulds of stainless steel, and allowed to cool at room temperature. Excess base was scraped off after solidification. 120 suppositories were moulded on each occasion. The weight of 20 separate suppositories was checked and found to be within ±5% of the theoretical weight. Before moulding suppositories of the dissolving type, e.g., based on polyethylene glycol, it was necessary to lubricate the moulds with liquid paraffin.

Table 1
Compositions of the suppository formulations tested. Each suppository contains 500 mg of ibuprofen

Suppository base	Type	Total suppository weight
Adeps solidus (Witepsol H12)	Lipophilic melting [a]	2.3 g
Adeps solidus (Novata 299)	Lipophilic melting [a]	2.3 g
Adeps solidus [b]	Lipophilic melting [c]	2.1 g
Polyethylene glycol (PEG 3350 [e] + 1500 [f])	Hydrophilic dissolving	2.7 g [d]

[a] Melting point 34.0–35.3°C.
[b] Brufen™ suppositories (Boots Co. PLC, Nottingham, U.K.).
[c] Melting point 37.9°C.
[d] The same volume as the Witepsol and Novata suppositories.
[e] 95% of the total suppository weight.
[f] 5% of the total suppository weight.

Comparisons were made with paracetamol suppositories described by Gjellan and Graffner (1989). These suppositories contained 500 mg of paracetamol dispersed in the same amount of Witepsol H12, Novata 299 and polyethylene glycol according to the same process as the ibuprofen suppositories.

2.3. In vitro dissolution techniques

The in vitro dissolution rate of ibuprofen from the suppositories was examined using the basket (Apparatus I, USP XXII), paddle (Apparatus II, USP XXII) and flow-through method (Apparatus IV, USP XXII).

Phosphate buffer (pH 7.4; 37 ± 0.5°C), deaerated by heat, was used as a dissolution medium. The beaker methods (Sotax AT 6, Sotax AG, Switzerland) required 900 ml and samples of 5 ml test solution were collected manually after 5, 10, 20, 30, 50, 75 and 120 min for hydrophilic suppositories and after 5, 10, 30, 60, 90, 150, 210, 300

and 370 min for lipophilic suppositories. In Apparatus II a net of stainless steel (mesh width = 1 mm) was placed between the paddle and the suppository and a metal helix was mounted around the suppository to prevent it from floating up to the surface of the medium after insertion into the beaker. The speed of rotation of the paddle was 50 rpm. Apparatus I was used unmodified at a speed of rotation of 100 rpm, and the size of the basket was 40 mesh.

The flow-through cells used (Disotest/Dissotest CY, Sotax AG, Switzerland) had a diameter of 12 mm and a flow rate of 16 ml/min was employed.

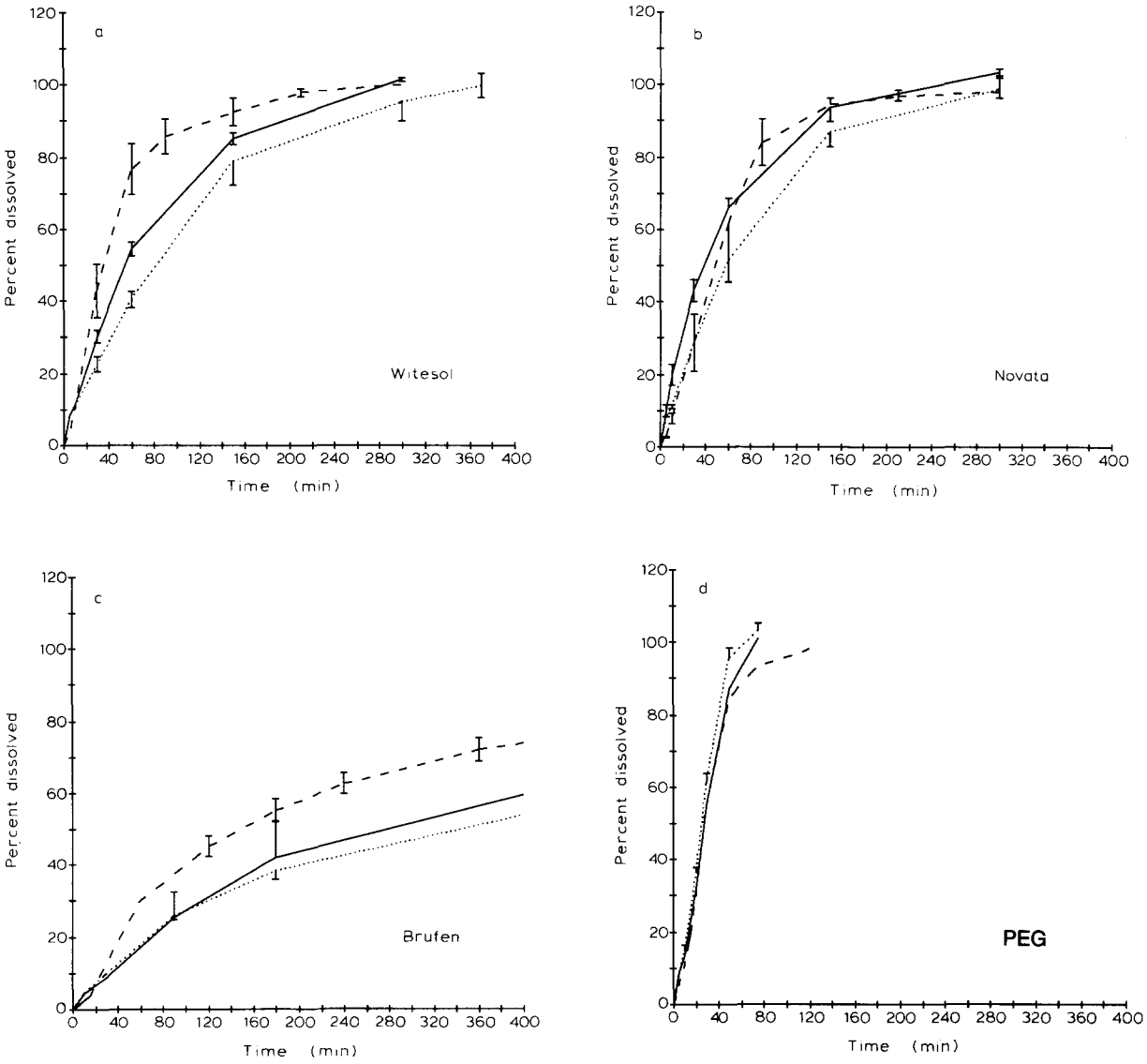

Fig. 1. In vitro dissolution rate of ibuprofen from lipophilic and hydrophilic suppositories. Error bars given as standard deviation: (a) Witepsol, (b) Novata, (c) Brufen^{TM}, (d) PEG. In vitro dissolution techniques given by the lines: paddle, 50 rpm (continuous line); basket, 100 rpm (dotted line); flow-through, 16 ml/min (broken line).

The dissolution tests were performed with six separate dosage units for each technique. The reproducibility tests were carried out with 12 lipophilic and 12 hydrophilic suppositories based on Witepsol and PEG, respectively.

The amount of dissolved ibuprofen was detected spectrophotometrically at 264 nm.

2.4. Calculations

Mean dissolution time (MDT) (Gibaldi, 1984) in vitro was estimated from the ratio between the area above the curve obtained when the cumulative percentage dissolved was plotted vs time up to infinity and the percentage finally dissolved (Brockmeier and Hattingberg, 1982). If 100% of the drug was not dissolved during the dissolution experiment, the tail of the curve was estimated using an exponential model.

2.5. Statistical methods

Descriptive statistics were applied to the in vitro dissolution profiles of the different compositions. Student's t-test was used to make a paired comparison of the MDTs calculated for each composition tested using the three techniques. Statistical significance was declared for an outcome of p values less than or equal to 0.05.

3. Results

3.1. Behaviour of the suppositories during dissolution testing

The suppositories with a melting point of 37.9°C did not melt, deform or spread as easily as those with a lower melting point.

The lipophilic melting suppositories based on Witepsol and Novata and the dissolving PEG suppositories behaved in the same way as similar compositions containing paracetamol described by Gjellan and Graffner (1989). This was observed with all three techniques. For the suppositories based on PEG it was observed that the wax dissolved faster than the ibuprofen.

It should be emphasised that the basket method is not entirely suitable for the testing of melting suppositories, since it was observed that in some of the beakers the melted fat managed to leave the basket through the gap between the basket and the holder. This phenomenon was also observed for similar suppositories containing paracetamol (Gjellan and Graffner, 1989).

It has been stated that it is important to maintain the hydrodynamic conditions constant during dissolution testing (F.I.P., 1981). In the flow-through cell two different agitation phenomena were observed. In some cells the dissolution medium passed the melted mass in a continuous stream. In other cells the dissolution medium started bubbling through the melt, at different times, in particular during the reproducibility tests. The bubbling resulted in a different agitation of the melt compared to the continuous stream of medium, and the dissolution results show that it promoted the release of ibuprofen.

3.2. Dissolution rate of ibuprofen

The dissolution profiles of ibuprofen from melting and dissolving suppositories are shown in Fig. 1a–d, and the MDTs are given in Table 2.

For suppositories based on Witepsol, ibuprofen is released faster using the flow-through cell than the paddle and the basket. The MDT obtained is significantly separated from the those determined using the beaker techniques.

Table 2
Mean dissolution time (MDT) in vitro for the four suppository compositions studied in the basket, paddle and flow-through technique

Suppository base	MDT (h)		
	Basket	Paddle	Flow-through
Witepsol H12	1.76	1.33	0.88
	(0.30)	(0.05)	(0.15)
Novata 299	1.38	0.94	1.08
	(0.17)	(0.12)	(0.13)
Brufen™	10.41	8.48	5.23
	(1.75)	(2.92)	(1.12)
PEG	0.45	0.50	0.58
3350+1500	(0.02)	(0.04)	(0.02)

Mean values ($n = 6$) with standard deviations in parentheses.

When ibuprofen is dispersed in Novata the MDT from the flow-through cell and the paddle is not significantly separated but the basket still results in slower release, compared to the other two techniques resulting in a larger MDT ($p < 0.03$ and $p < 0.002$).

The suppositories with a high melting point released the ibuprofen respectively in the same rank order as the Witepsol suppositories, however, the dissolution rate was lower. The MDT from the flow-through cell was significantly lower than from the other two MDTs which were statistically equal. The flow-through cell resulted in 72% being dissolved after 6 h compared to 77 and 62% after only 1 h for the Witepsol and Novata suppositories, respectively.

For the dissolving suppositories the basket results in a faster dissolution rate than the flow-through cell or paddle. For all three techniques 100% is released after 75 min, and the MDTs from the three techniques are significantly separated.

On comparing the standard deviations given as error bars in Fig. 1, it can be seen that the dissolving suppositories give more consistent data than the melting suppositories. Error bars are only given for one of the dissolution profiles from PEG in Fig. 1d, since they are of the same size for all three profiles.

3.3. Reproducibility of the in vitro dissolution tests performed on melting and dissolving suppositories containing ibuprofen

The variation coefficients of the percentage of ibuprofen dissolved at different times using the three techniques are given for one lipophilic type (Witepsol) and the hydrophilic suppository (PEG) in Table 3. For the lipophilic suppositories a marked difference in the coefficients of variation were obtained between different apparatuses; the coefficients of variation were approx. 3–15 times larger, depending on the time, when using the flow-through cell. A similar difference is not seen for the dissolving suppositories except during the initial 10 min when the flow-through cell seemed to show at most twice the coefficient of variation of the beaker techniques.

3.4. Comparison of reproducibility data performed on Witepsol based suppositories containing ibuprofen and paracetamol

Table 4 lists the coefficients of variation for suppositories investigated in the present study

Table 3
Reproducibility of the in vitro dissolution techniques performed on lipophilic melting suppositories (LIP) (Witepsol) and hydrophilic dissolving suppositories (HYD) (PEG) containing ibuprofen

Time (min)	Basket (100 rpm)		Paddle (50 rpm)		Flow-through (16 ml/min)	
	LIP	HYD	LIP	HYD	LIP	HYD
5	4 (15.9)	4 (6.7)	5 (18.9)	4 (7.5)	3 (45.4)	5 (14.3)
10	6 (10.0)	10 (5.6)	9 (11.2)	8 (6.0)	7 (52.0)	10 (10.3)
20		30 (11.2)		21 (12.6)		26 (10.5)
30	17 (3.8)	52 (8.8)	30 (6.3)	39 (16.7)	23 (62.5)	48 (12.1)
45		81 (4.9)		65 (14.0)		76 (9.6)
60	36 (5.4)	94 (3.6)	56 (2.8)	83 (8.7)	46 (56.5)	88 (4.1)
90		97 (1.0)		96 (1.3)	63 (47.7)	95 (1.9)
120	66 (8.6)		82 (1.9)		72 (39.1)	96 (1.1)
180	77 (8.1)		93 (1.7)		85 (21.5)	
240	83 (6.3)		97 (1.5)		91 (16.1)	
300					93 (12.2)	

Mean values ($n = 12$) of percentage dissolved of labelled amount and coefficient of variation (in parentheses) from parallel runs on 12 separate units.

based on Witepsol containing ibuprofen and the corresponding values from our previous study with paracetamol (Gjellan and Graffner, 1989). It is seen that for the basket technique the coefficients are comparable during the first hour of release of the two substances. Using the paddle a 3-fold variation is obtained during the first 10 min when ibuprofen is compared to paracetamol. In the flow-through cell the coefficient of variation increases successively during the first 30 min for ibuprofen while the variation decreases for paracetamol. The variation in ibuprofen dissolution data is, thus, 2–10 times as great as for paracetamol.

4. Discussion

4.1. Applicability of dissolution technique in relation to behaviour and dissolution rate

The basket and paddle techniques result in the same rank order of the mean dissolution profiles of ibuprofen from the three melting suppositories, while the results from the flow-through are different. The flow-through cell lead to more rapid dissolution which is explained by the different spreading conditions of the melting mass. Also, there is a continuous flow of fresh dissolution medium which is passing the melt compared to the the beaker techniques where the volume of medium is constant during the test. This phenomenon might support the dissolution process of ibuprofen.

A comparison of the dissolution profiles for paracetamol (Gjellan and Graffner, 1989) and ibuprofen from Witepsol suppositories shows that the three techniques give almost superimposable profiles of paracetamol. This is not seen for ibuprofen. The most likely explanation is that the dissolution process for paracetamol is not influenced by the different spreading patterns in the different techniques to the same extent as ibuprofen because of the greater solubility of paracetamol in the medium used (21.4 mg/ml at 37°C in water). Consequently, the ibuprofen release is more dependent on the spreading pattern and thereby the available contact area with the dissolution medium.

For PEG based suppositories containing ibuprofen there is a tendency toward a faster dissolution rate when using the basket. This was not observed for paracetamol (Gjellan and Graffner, 1989). Despite the fact that the PEG unit tends to not spread or disintegrate, a successive loosening in the structure is seen due to more rapid dissolution of PEG than of ibuprofen. This might result in different dependencies on the surrounding hydrodynamics and a differentiation of the dissolution profiles due to different techniques.

Table 4
Comparison of coefficients of variation for the in vitro dissolution techniques performed on lipophilic melting suppositories (Witepsol H12) containing paracetamol (PARA) and ibuprofen (IBU)

Time (min)	Basket 100 rpm		Paddle 50 rpm		Flow-through 16 ml/min	
	IBU	PARA	IBU	PARA	IBU	PARA
5	15.9	15.8	18.9	5.5	45.4	17.1
10	10.0	5.7	11.2	4.8	52.0	12.1
20		6.3		6.3		9.2
30	3.8	5.7	6.3	5.9	62.5	7.1
60	5.4	4.2	2.8	4.2	56.5	5.6
90		2.7		2.8	47.7	3.3
120	8.6		1.9		39.1	
150		1.2		0.7		1.3
180	8.1		1.5		21.5	
240	6.3				16.1	
300					12.2	

Data are from parallel runs of 12 separate units. Paracetamol data are taken from Gjellan and Graffner (1989).

The more gradually decreasing size of the dissolving suppositories in contrast with the deformation and spreading of the melting suppositories explains the differences in the magnitude of the error bars seen in Fig. 1. Melting suppositories produce a greater variation in dissolution data.

4.2. Reproducibility

The differences in coefficients of variation for lipophilic suppositories between the beaker techniques and the flow-through cell indicate that the two different kinds of dissolution apparatus concerning hydrodynamics, agitation, amount of dissolution media and spreading conditions have a large effect on the variation of data. The results from each single cell show that the variation in data for ibuprofen is related to how the dissolution medium passes the melted mass. Those cells for which bubbling behaviour is seen produce more similar profiles than those where the medium passes as a continuous stream. The bubbling results in more intensive agitation of the melt which results in faster dissolution. This supports the principle that hydrodynamics should be controlled during dissolution testing generally. In this case the bubbling phenomenon could be observed visually at different time intervals.

For the basket there is a tendency toward a faster dissolution rate for those replicates where some of the melt has left the basket and is floating freely in the beaker. This was also seen for paracetamol (Gjellan and Graffner, 1989).

Table 4 shows that there is a general tendency toward greater variance in the ibuprofen data compared to paracetamol for all techniques, possibly due to the lower solubility of ibuprofen which is thus more sensitive to different spreading patterns and available dissolution medium during the dissolution process.

4.3. Preference of dissolution technique

The study of the behaviour of different ibuprofen suppositoriy formulations in the three dissolution apparatus has not indicated any one technique to be preferable.

Studies of every composition by each technique show a similar rank order of the dissolution profiles at least for the different lipophilic melting compositions.

The flow-through technique deviates from the other techniques concerning the variation in data. Although the same tendency was seen for paracetamol, the difference is greater for ibuprofen. Focusing on the data variance would probably result in exclusion of the flow-through cell as a technique for testing dissolution rate from lipophilic suppositories containing ibuprofen. However, as these results illustrate, the variation in data can be explained by a combination of the spreading pattern, hydrodynamics and agitation conditions in the flow-through cell and the physical-chemical properties of the drug.

5. Conclusion

It is necessary to consider the behavioural changes which occur to a rectal dosage form in an in vitro method when judging the applicability of a dissolution test. The physical-chemical properties of the drug substance are also of great importance.

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