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Assessment of the effect of base type and surfactant on the release properties and kinetics of paracetamol suppositories

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ABSTRACT

In the formulation of different drugs as suppositories, there is the need to determine the optimum formulation factors which depend on the drug candidate itself, suppository base and the presence of an adjuvant or absorption enhancers. 1g paracetamol suppositories each containing 250mg of paracetamol were prepared by the fusion method (BP, 2012) utilizing cocoa butter, PEG 1500, PEG 4000, PEG 1500/4000(3:1) and Suppocire® as suppository bases. A proper combination of the polyethylene glycol bases (PEG) i.e. PEG 1500/4000 in ratio of 75%:25% gave more suitable release profile than the singular use of either water soluble base examined. The base Suppocire S2 blend incorporating 0.5% tween 40 was the best base in terms of release profiles with over 95% of paracetamol being released within 10minutes. The major mechanism of drug release fit the Higuchi release kinetic model. The presence of 2% span 80 and 0.5% tween 40 not only affected drug release but also the physicochemical characteristics of the suppository bases.

INTRODUCTION

The mechanism of drug absorption from the rectum is probably not different from that in the upper part of the gastrointestinal tract despite the presence of substantial differences in the physiological condition i.e. pH, surface area and fluid content between the two regions. Absorption of drugs from suppositories is dependent on the nature of the suppository base, the use of surfactants or other additives and the solubility of the drug in the suppository base [1].

In the formulation of different drugs as suppositories, there is the need to determine the optimum formulation factors which depend on the drug candidate itself, suppository base and the presence of an adjuvant or absorption enhancers.

Cocoa butter (theobroma oil) as a suppository base is well known [2], however, its use poses several challenges during formulation of dosage forms of suitable quality and stability. It is for this reason that research and development initiatives have focused on the search for more appropriate and suitable synthetic or semi-synthetic alternatives that retain the desirable characteristics yet eliminate the inappropriate ones of cocoa butter, as a suppository base.

Semi-synthetic fats are usually white, brittle, solid, odorless and unctuous to touch and produce suppositories that are white and have an attractive, clean, polished appearance. Hard fats are available in a variety of grades with

different melting ranges, hydroxyl values and other physicochemical characteristics. Examples of semi-synthetic fatty suppository bases that are available commercially include fractionated palm kernel oil B.P and hard fats such as Massa Estarium®, Massupol®, Suppocire® and Witepsol®.

Macrogol or polyethylene glycols (PEGs) are amongst the most widely used hydrophilic polymer suppository bases. PEGs are polymers of ethylene oxide and water, prepared in a variety of chain lengths, molecular weights and physical states [2]. PEGs with a molecular weight ranging between 200 and 600 exist as liquids and, as the molecular weights increase to above 1000- they exist as wax-like solids [3,4]. In addition, as the molecular weights increase, their water solubility and hygroscopicity decrease [4]. The wide range of melting points and solubilities make possible the formulation of suppositories with various degrees of heat stability and with different dissolution rates [4]. PEGs of different molecular weights can be combined to achieve a suppository base of the desired consistency and that can achieve a specific drug release rate profile. The use of high melting point solids as suppository bases permits convenient storage of the suppositories without the need for refrigeration and without the danger of excessive softening in warm climates.

Surfactants have been used as adjuvants in formulation of suppositories and they have been seen to modulate and increase the release of drugs from various bases. The effect of non ionic surfactant (Solutol HS 15, Cremophor RH 60 and Montanox 60 DF) on furosemide release from Suppocire AS2X suppository have been previously studied[5]. Surfactant concentration of 1% w/w with Suppocire AS2X showed maximum diffused drug percentage compared to other bases. Nair and Bhargava (1999) discussed comparative in-vitro release studies of fluconazole from PEG, Suppocire AP (a polyglycolised glyceride), cocoa butter and Witepsol (W45 and WW 45). They observed that the order of drug release is fast with PEG > SAP > WW45 > cocoa butter. Literature states successful use of Suppocire bases as suppository base [6,7]

Paracetamol also known as Acetaminophen sodium is a synthetic non-opiate derivative of p-aminophenol which produces analgesia and antipyresis. Acetaminophen sodium a major metabolite of phenacetin occurs as a white crystalline powder with a slightly bitter taste.

The aim of the study is to assess the effect of the various bases and adjuvants utilized and their effect on the pharmacokinetic release parameters of the suppository.

EXPERIMENTAL SECTION

Paracetamol BP was purchased from Sigma chemical company St Louis USA, Theobroma oil from Raymond lamb chemicals United Kingdom; Tween 40 (Polyoxyethylene sorbitan monopalmitate), Brij 30 (Polyoxyethylene 4lauryl ether), Sodium lauryl sulphate, from Sigma chemical company St Louis USA. PEG 1500 and PEG 4000 from Penn Pharmaceuticals Ltd United Kingdom. Suppocire® S2 from colorcon Asia pvt ltd Gattefosse, France.

All the reagents used were of pharmaceutical and analytical grade.

FORMULATION OF PARACETAMOL SUPPOSITORIES.

1g paracetamol suppositories each containing 250mg of paracetamol were prepared by the fusion method (BP, 2012) utilizing cocoa butter, PEG 1500, PEG 4000, PEG 1500/4000 and Suppocire® as suppository bases. A 100µm mesh sieve was utilized to sieve the paracetamol powder prior to addition of the base. Suppositories were prepared with and without surfactants. The displacements values were obtained prior to formulation incorporating paracetamol [8,9]. To ensure uniform solidification and crystal transformation the suppositories were kept at room temperature for 24 h after removal from the mould after which they were stored at 4°C.

Dissolution test (In vitro release study)

The apparatus used was designed to provide reasonable control over the interfacial area for drug dissolution. The method employed was based on the apparatus used by Martin Stewart *et al* 2003[10,11]. Dissolution test for the various paracetamol suppositories was carried out dissolution test apparatus. Each suppository was placed in a beaker with a stirrer at a height of 2mm from the bottom of the beaker. The stirrer rotated at 100rpm and the system was maintained at constant temperature of 37±1°C. The beaker contained 500ml of 0.2 M phosphate buffer, pH 7.0 (USP 2002). 5 ml samples were taken at different time intervals and replaced with 5 ml of fresh dissolution medium

maintained at the same temperature. Filtered samples were suitably diluted and assayed spectrophotometrically at 243nm. Results obtained were expressed as mean \pm SD of three determinations.

Content uniformity

Randomly selected Paracetamol suppositories from each of the batches of the samples were melted in 100 ml with the dissolution medium containing phosphate buffer pH 7.2 and shaken on a shaker for 19minutes to allow for the drug to dissolve. The solution was diluted, filtered and assayed using a UV/Visible Spectrophotometer at a wavelength of 243nm and compared against blank prepared without drug. The mean concentrations of drug \pm SD was calculated.

The crushing strength of the suppositories was determined using a Monsanto hardness tester.

Disintegration time (D.T.)

Disintegration time (D.T.) for suppositories was determined in water maintained at $37\pm 0.5^\circ\text{C}$. Disintegration criteria (British Pharmacopoeia 2012) was followed to calculate the D.T. of test suppository.

Weight variation of these varying suppositories was also assessed.

Solidification point was also determined. The test suppository was melted in a test tube at 45°C . A thermometer was dipped inside the cooling mass and rotated mechanically. The temperature at which the mass first began to adhere to the thermometer was recorded as the solidification point.

Data analysis

The extent of drug release was assessed from the total amount of drug present in the dissolution medium at the end of the drug release experiment. The type of drug release kinetics applicable for the Suppocire suppository bases was determined by evaluation of different kinetic models. The model that consistently produced the highest correlation among the suppository preparations was used for the assessment of drug release rates, and a slope obtained from linear regression analysis of the plot was determined as the drug release rate constant. The results expressed as mean \pm SD were generated from replicate determinations for each suppository preparation.

TABLE 1. PHYSICOCHEMICAL PARAMETERS OF FORMULATED PARACETAMOL SUPPOSITORIES

Base	Adjuvant	Weight (+SD)	Drug composite Assay % (+SD)	Appearance	DT (minutes)	Solidification point (OC)	Melting Point (OC)	Crushing strength (N)
Cocoa Butter		1.005(0.014)	89.9 (3.2)	Good	28	27.9 (0.50)	36.7	16.5 (0.9)
PEG 1500		1.103(0.323)	85.7(1.6)	Good (but quite soft to touch)	27	28.8(0.10)	34.5	20.3 (0.6)
PEG 1500	2% Span 80	1.055(0.124)	98.5(1.6)	Good	29	29.8(0.41)	36.9	28.8 (1.2)
PEG 1500	0.5% Tween 40	1.084(0.045)	99.6(0.9)	Good	28	32.1(0.86)	36.7	30.0(0.9)
PEG 4000		1.089(0.74)	80.0(0.1)	Good	35	35.5(0.91)	43.5	35.5 (1.1)
PEG1500/4000 (3:1)		1.099(0.13)	90.9(0.7)	Good	30	30.0(0.33)	36.0	31.2 (0.7)
PEG 1500/4000 (3:1)	2% Span 80	1.035(0.24)	99.8(1.2)	Good	30	29.8(0.83)	35.8	29.1(0.5)
PEG 1500/4000 (3:1)	0.5% Tween 40	1.103(0.74)	101.4(0.9)	Good	30	30.1(0.72)	35.5	29.8(0.83)
Suppocire S2		1.09(0.24)	97.2(1.0)	Good	30	30.2(0.10)	35.1	29.0(0.01)
Suppocire S2	2% Span 80	1.002(0.54)	100.0(0.5)	Good	27	28.3 (0.10)	36.4	28.3 (0.1)
Suppocire S2	0.5% Tween 40	1.025(0.099)	99.99(1.2)	Good	30	29.5(0.20)	36.5	28.2 (0.2)

RESULTS AND DISCUSSION

Table 1 shows that all the suppository formulations satisfied the BP requirement for drug content, uniformity of weight and appearance. Weight variations recorded were less than 5%. The Suppocire and cocoa butter bases were evaluated for displacement value with respect to the drug paracetamol. Values of 1.40 and 1.33 were obtained for Suppocire and cocoa butter respectively. Values were further used to calculate the amount of base to be added in the formulation. The average weight of suppositories prepared using cocoa butter, PEG 1500, PEG 4000, PEG 1500

/4000(3:1) and Suppocire S2 were 1.005, 1.0103, 1.084 and 1.004 g, respectively. Further addition of adjuvants did not grossly affect the average weight of the suppositories.

Melting point range for Suppocire S2 was 35°C–36.5°C, Cocoa butter 36°C PEG (39°C–40°C) (Table 1). Incorporation of adjuvant Span 80 and tween 40 caused changes in melting point of suppositories prepared utilizing Suppocire S2, and PEG 1500/4000 bases. A slight decrease in the melting point compared to that of plain Suppocire S2 suppositories was observed and an increase in the PEG 1500/4000 suppositories incorporated with adjuvants. Hardness was determined using Monsanto hardness tester; crushing strength in newtons (N) was measured (table 1). The PEG 1500 base experienced an increase in hardness when either span 80 or tween 40 was incorporated, while a reduction in the hardness was observed for the Suppocire bases where a reduction of almost 2N was recorded. These results are in accordance with that of other workers [5].

Disintegration (DT) for plain suppositories prepared was averagely all less than 30 minutes. The presence of 2% span was attributed with a slight reduction in the DT of Suppocire S2 suppository, however this was not the same observed with the PEG 1500 suppository where an increase was observed as reflected in table 1. The presence of 2% span 80 and 0.5% tween 40 however had no effect on the DT of the PEG blend of 1500/4000 which gave DT of about 30 minutes. PEG 4000 reflected the highest DT due to the high molecular weight ethylene glycol polymer which it contains. Cocoa butter gave a DT of 28 minutes a slightly higher time than 27 minutes recorded for PEG 1500.

All the suppositories formulated with and without additives showed drug content of 80%–110%.

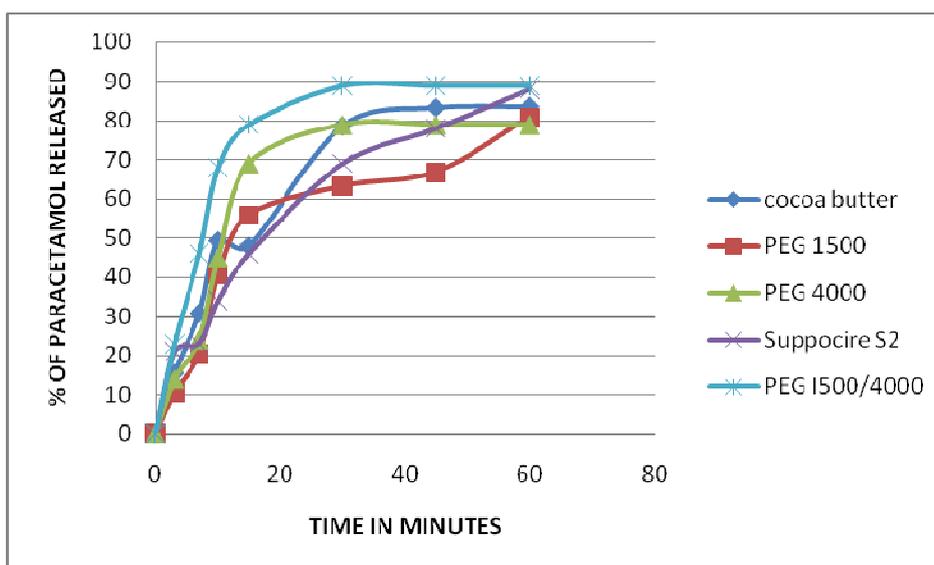


Figure 1 Dissolution profiles of Paracetamol suppositories

The dissolution profiles of paracetamol from suppositories from varying formulations shown in Fig 1. These results indicate that in the absence of surfactants the polyethylene glycol blend of 1500/4000 evidently exhibited the best release characteristics, with 90% of the drug released in less than 30 minutes. Polyethylene glycols are water soluble polymers that often melt at temperatures higher than the rectal or physiological temperature of 37°C. Consequently, when used in rectal formulations, the drug is released gradually, as a result of the progressive dissolution of the PEG excipients in an aqueous dissolution medium. High molecular weight PEGs have high melting points, as seen in Table 1, and consequently have slower dissolution rates, compared to PEGs of intermediate molecular weight and this was the basis of formulating the PEG 1500/4000 blend. PEG 4000 released paracetamol at a slower rate than PEG 1500. The PEG 1500/4000 released paracetamol to a greater extent than from fatty base suppositories; however a need to improving the rate and extent of release of paracetamol from fatty bases is required, since PEG bases have been reported to be irritant to mucosal tissues. The interaction of a base and a base/drug complex with the rectal mucosa can significantly alter the physiological barrier in drug absorption [12,13]. The interaction of a number of

fatty bases, like Suppocire and cocoa butter with the rectal mucosa, was reversible within 24 hours, whereas that of the PEG bases appeared to aggravate the mucosal membrane tissue irritation for a longer period. Hydroxyl value appears to be of some significance for suppositories manufactured using various grades of Suppocire®. The S2 grade was utilized due to the fact that the drug being delivered is therapeutically an antipyretic thus requiring fast release. The melting of a base is a prerequisite for drug liberation, in addition to contributing to a dissolution lag time (time in which less than 5% of the drug has been dissolved) [14]. Melting of a fatty base is followed by several successive mechanistic steps, such as spreading of the molten mass, particle sedimentation, passage across the interface and finally dissolution of the drug in the hydrophilic rectal fluids or dissolution test media [15]. It is therefore clearly evident that the complete melting of a suppository in a dissolution vessel is required for paracetamol to have the potential to be released completely during *in vitro* testing. The melting point observed were favourable except where PEG4000 was utilized. (Table1)

The effect of surfactant Paracetamol release

To evaluate the effects of incorporating surfactants into the paracetamol suppository bases, dissolution rates, the dissolution behavior of formulations containing either 2%Span 80 (HLB 4.3)or 0.5%Tween 40 (HLB 15.6)were compared to that of drug release from formulations that contained paracetamol alone using only PEG1500/4000 and Suppocire as the base Fig2.

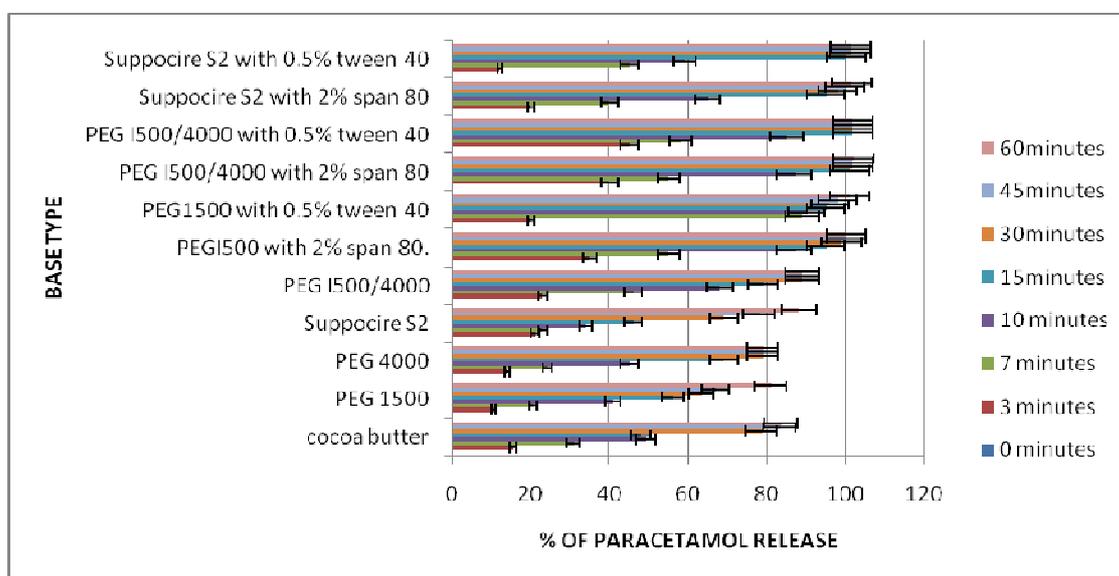


Figure 2 Effect of Base type and surfactants (adjuncts) on the dissolution profile release of paracetamol at varying time intervals

It is evident from these studies that the addition of a surfactant to a fatty suppository base appears to have a significant effect on the release of paracetamol from bases with high hydroxyl values. The mechanism by which added surfactant may influence release rates is complex and is not fully understood, due to the large variety of effects surfactants may produce. It has been reported that, in the presence of a surfactant, drug release from suppositories is favored by various mechanisms, *viz.* increasing the surface area of the suppository mass, as a result of their moistening effects, shortening disintegration times of lipophilic suppositories as a result of changing their lipophilic characteristics to a lipo-hydrophilic nature [16.17]. The HLB value of a surfactant provides an indication of the hydrophilic-lipophilic balance of the compound and the higher the HLB value, the more hydrophilic the compound [18]. The action of Tween 40 a non –ionic surfactant, is due to the increased water incursion into the base thereby decreasing interfacial tension, although a higher concentration of this surfactant has been observed to decrease drug release due to the formation of entrapped drug molecules in an emulsion like matrix.

In addition, an increase in the hydrophilic character of a fatty base may reduce the affinity of a base for lipophilic substances, thereby promoting drug release. The effects are pronounced on the Suppocire base as the release of 100% of the drug was obtained within 15mins with the use of tween 40. There was no profound difference in the use

of either tween or span as a surfactant as they both increased incursion of fluid into the bases facilitating increase drug release in to the dissolution medium for both the PEG blend utilized and the Suppocire S2 base.

Table 2 Kinetic Release Parameters obtained from fitting Paracetamol dissolution data to Zero order, First order and Higuchi mathematical models

	Zero Order model		First order model		Higuchi model	
	R ²	K ₀	R ²	K ₁	R ²	K _H
Cocoa butter	0.531	0.010	0.501	0.0057	0.951	1.8273
PEG 1500	0.9315	0.0812	0.633	0.006	0.814	1.7614
PEG1500 with 2% Span 80	0.964	0.0769	0.481	0.0048	0.973	1.5671
PEG1500 with 0.5% tween 40	0.961	0.0777	0.487	0.0051	0.951	1.6991
PEG4000	0.320	0.0234	0.444	0.005	0.732	1.748
PEG1500/4000	0.9214	0.0872	0.575	0.0048	0.973	2.001
PEG1500/4000 with 2% Span 80	0.9472	0.0693	0.542	0.0057	0.950	1.886
PEG1500/4000 with 0.5% tween 40	0.9111	0.0889	0.482	0.0037	0.9182	1.879
SuppocireS2	0.6982	0.0811	0.471	0.0033	0.9401	1.998
SuppocireS2 with 2% Span 80	0.7301	0.0341	0.462	0.0034	0.9731	2.001
SuppocireS2 with 0.5% tween 40	0.7915	0.0239	0.442	0.0035	0.995	1.997

The release kinetics of paracetamol suppositories was fitted to the Higuchi, Zero and First order models and the model with the highest R² adjusted value was selected as the best fit. The data were best fitted to the Higuchi model, which complements so we can say that the release mechanism from suppositories involves more than one process, such as diffusion, and should consider the combined effects of melting and drug partitioning in addition to diffusion. The PEG 1500 however was best fit to the zero order model Table 2 where the drug is released in a controlled manner irrespective of concentration. This has been reported by other workers as well [19, 20, 21,]. However it is worthy of note that in the PEG 1500 paracetamol suppositories incorporated with either span 80 or tween 40 the release rate followed the Higuchi release, as the values obtained were just slightly higher than those obtained for the zero order rate [22,23,24,25]. Based on these results it was inferred that in the development of an appropriate mathematical model is necessary for the evaluation of drug release and characterization of dissolution profiles from suppository dosage forms.

CONCLUSION

A proper combination of the polyethylene glycol bases (PEG) i.e. PEG 1500/4000 in a ratio of 75%:25% gave more suitable release profiles than the singular use of either water soluble base. The base Suppocire S2 blend incorporating 0.5% tween 40 was the best base in terms of release profiles and physicochemical characteristics. The addition of surfactant facilitated and increased release of Paracetamol on from the base into the dissolution medium generally following the Higuchi model in both the Suppocire S2 and the PEG 1500/4000 bases.

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