

IN-VITRO RELEASE OF PARACETAMOL FROM SUPPOCIRE SUPPOSITORIES: ROLE OF ADDITIVES

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Paracetamol is commercially available in oral and rectal dosage forms for geriatric and pediatric patients. Limitation of oral drug delivery for pediatric patient is inconvenience to swallow the tablet, capsule and oral suspension; in such case suppositories are effective and often used. To achieve successful delivery of drug locally as well as systematically, rectal route has proved its potential. The main objective of this research was to evaluate the potential of Suppocire suppository bases and study the effect of incorporation of ionic and nonionic surfactants on in-vitro release characteristic of paracetamol. Suppocire bases evaluated were interesterified Suppocire bases (Std type) e.g. Suppocire D and C, esterified bases (N-type) e.g. Suppocire NCX and amphiphilic bases (P-type) e.g. Suppocire CP. Effect of various additives such as sodium lauryl sulfate (SLS), dioctyl sulfosuccinate (DOSS), Labrasol, lecithin, Miglyol 812, aerosil, Capryol PGMC (CPGMC) and span 80 were studied on drug release. Paracetamol Suppocire suppository using amphiphilic base in combination with Labrasol showed optimal drug release as compared to other Suppocire bases. The developed paracetamol Suppocire suppositories gave controlled as well as fast release depending upon the additives added to the formulation and proved to be a good suppository base. Newly incorporated additives such as Labrasol and Capryol PGMC have promise to be used as adjuvants in suppository formulation.

Keywords: Paracetamol suppository, Suppocire bases, Additives, In-vitro drug release

INTRODUCTION

Paracetamol is a well-established nonprescription antipyretic, analgesic drug. It has low toxicity and high therapeutic index, which is an important consideration in selection of drug for pediatric patients. It has strong antipyretic and mild analgesic antiinflammatory activity as compared to other non steroidal antiinflammatory drugs. Antipyretic effect and other antiinflammatory effects are related to inhibition of prostaglandin synthesis. Paracetamol is well absorbed through the rectum, though rectal absorption is slower than oral administration as shown by Shegokar and Singh (2005). The relative bioavailability is 80% to that of oral administration (Bertolini *et al.* 2006).

Rectal drug delivery is well known for its certain advantages over oral drug delivery (Van Hoogdalem, De Boer and Breimer 1991). The rectal mucosa (pH 7-8) has an abundant supply of blood vessels and lymphatic vessels (Zempsky 1998). Palatability and taste, which are the prime concern in oral dosage forms for children need not to be considered in case of rectal drug delivery (Degen, Maier-lenz and Windorfer 1982; Kolloffel, Driessen and Goldhoorn 1996; Nishimura *et al.* 2009). The most important aspect

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of this route is bypassing the first hepatic metabolism. In addition, specific membranes properties are responsible for the absorption of drug. Thus suppositories can prove to be a useful alternative dosage form in pediatric patients (Welch, Ek and Stromme 2006; Taki, Ogawa and Nikai 2008; Hirabayashi *et al.* 2009).

Suppositories are solid rectal dosage form (Higgins 2007; Kayhan *et al.* 2008; Wilasrusmee *et al.* 2008) and are prepared using either fatty bases or water soluble bases (Abd-el-Maeboud *et al.* 1991). Polyethylene glycol (PEG) bases being hydrophilic have the inherent risk of traumatising sensitive rectal mucosa. Natural fatty bases for e.g. cocoa butter have the drawback of polymorphism; semi synthetic bases are produced from vegetable oils and are chemically modified during their manufacture and usually used as suppository bases (Liversidge, Grant and Padfield 1979).

In a previous research by Berko *et al.* (2002), the effect of non ionic surfactant (Solutol HS 15, Cremophor RH 60 and Montanox 60 DF) on furosemide release from Suppocire AS2X suppository were studied. Surfactant concentration of 1% w/w with Suppocire AS2X showed maximum diffused drug percentage compared to other bases. Becirevic and Petricic (1986) studied the release of aminophenazone and propylphenazone from hydrophobic (Witepsol H15 and S55 & Suppocire BM and AS2) and hydrophilic bases (Macrogols). A higher proportion of mono and diglycerides in Witepsol S55 and Suppocire AS2 influences the solubility of drug which was thereby liberated more easily than from Witepsol H15 and Suppocire BM. 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 from PEG > SAP = WW45 > cocoa butter. Webster, Dowse and Walker (1998) carried out in-vitro drug release from different lipophilic suppositories and found that Suppocire A32 showed lowest drug release to that of Novata BD, 299 and Witepsol W35. Calis, Sumnu and Hincal (1994) proved Suppocire CM base showed suitability for delivery of vaginal microbicide C31G as compared to Witepsol H15.

Literature states successful use of Suppocire bases as suppository base (Lauroba *et al.* 1990; Omotunde and Oluwatoyin 2009); present study reports suitability of four semi synthetic Suppocire bases viz. Suppocire D, Suppocire C, Suppocire NCX and Suppocire CP with and without additives. Effect of various additives on physicochemical parameters like melting properties, disintegration time, hardness and in-vitro drug release was studied systematically.

METHODS

Paracetamol was obtained as a generous gift sample from IPCA Laboratories, Mumbai, India. Suppocire D, C (mixtures of triglycerides containing varying proportion of mono-diglycerides interesterified, 42°C to 45°C), Suppocire bases NCX (esterified suppository bases, 38°C to 40°C) and CP (amphiphilic suppository bases, 34°C to 38°C) were obtained from Gateffosse, France through Colorcon Asia Pvt. Ltd. India, Additives such as sodium lauryl sulfate (SLS), dioctyl sulfosuccinate (DOSS) and aerosil (Signet Ltd., India), Labrasol and Capryol PGMC (CPGMC) (Gatteffose, France through Colorcon Asia Pvt. Ltd., Goa), lecithin (Lipoid GmbH, Germany), Miglyol 812 (Sasol Ltd., Germany), and span 80 (Unichema Laboratories, India) were obtained.

Preparation of Paracetamol Suppositories

Paracetamol suppositories each containing 250 mg of the drug were prepared by the fusion method (Baba *et al.* 1983; Hanning *et al.* 1988; Nishioka *et al.* 1991; Yong *et al.* 2004; Miyake *et al.* 2006). Drug displacement value for each base was determined and the amount of drug required was calculated. Various suppository composition containing di and triglycerides (Suppocire D, C, NCX and CP) with and without additives were prepared using micronised paracetamol were shown in Table 1.

Table 1: Additives and their concentration evaluated.

Surfactants	Concentration (% w/w)
SLS	0.5 and 1
DOSS	0.5 and 1
Labrasol	2 and 5
Lecithin	1
Miglyol 812	10
Aerosil	1 and 2
CPGMC	2 and 5
Span 80	2

Evaluation of Suppositories

Prepared suppositories were evaluated for the following parameters.

Visual evaluation

Surface appearance was verified visually to access absence of fissuring, fat blooming, exudation and absence of migration of active ingredients. Longitudinal section of suppository was checked for homogeneity of active ingredient within the mass (Watanabe *et al.* 1986).

Uniformity weight

Twenty dosage forms were taken and weighed individually. The average weight and standard deviation was calculated.

Melting point (M.P.) range determination

A beaker containing 50 mL of purified water with immersed thermometers was kept on steam bath. The suppository was placed in water and its melting temperature was noted.

Mechanical strength or fracture index or hardness

Mechanical strength which is the determination of the mechanical force necessary to break a suppository indicates the brittle or elastic nature of the suppository. Erweka suppository hardness tester (Type SBT, Germany) was used to determine the hardness or breaking point of a suppository. The apparatus measures the weight under which suppository collapse. All suppository formulations with and without additive were tested for hardness.

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 2001) was followed to calculate the D.T. of test suppository.

Drug content or composite assay

Five suppositories were cut into small pieces and an appropriate mass was placed into a 250 mL volumetric flask. Phosphate buffer (pH 7.2) was added up to the mark and the volumetric flask was heated slightly to melt the suppository. The suppository was then allowed to cool. The solution was filtered through doubled layer Whatman filter paper followed by 0.45 μm disc filter. Absorbance of resultant solution was measured at 243 nm. Concentration was determined using standard calibration curve equation. A blank suppository (without containing the drug) was treated in a similar manner and used as reference control. The drug content percentage was calculated from calibration curve equation.

Content uniformity

Ten dosage forms were taken and their drug content was determined individually using the same procedure as discussed under drug content.

In-vitro drug release

In-vitro drug release ($n = 3$) was performed using the modified dissolution apparatus I (United States Pharmacopoeia 2005); 500 mL phosphate buffer (pH 7.2) maintained at $37\pm 0.5^\circ\text{C}$ was used as a dissolution medium. Basket was rotated at 50 rpm. 10 mL aliquots was taken at periodic intervals of 0.5, 1, 2, 3, 4, 5, 6, 7 and 8 h and replaced by equal volume of phosphate buffer. The solution was suitably diluted and the absorbance was taken using UV visible Jasco Spectrophotometer (Jasco, UK). Dissolution test was also performed simultaneously for blank formulation. The drug release (mean value of three suppository profiles) from various batches was plotted against time.

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 8 h drug release experiment. The type of drug

release kinetics applicable for the Suppocire suppository bases was determined by evaluation of zero-order kinetic model (Q vs. t , where Q is the amount of drug released at time ' t '). 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.

RESULTS

White coloured suppositories were formulated and evaluated for various parameters like appearance, melting range, uniformity of weight, disintegration time, % drug content and in-vitro drug release. The Suppocire bases selected were evaluated for displacement value with respect to drug and noted to be 1.4, 1.46, 1.4 and 1.43 for Suppocire D, C, NCX and CP, respectively. Values were further used to calculate the amount of base to be added in the formulation. The average weight of suppositories prepared using Suppocire D, C, NCX and CP was 1.042, 1.035, 1.038 and 1.035 g, respectively and further addition of adjuvants did not affect the weight.

Plain suppositories prepared showed a melting point range for Suppocire D (42°C–44°C), C (37°C–39°C), NCX (37°C–40°C) and CP (39°C–40°C) (Table 2). Addition of additives did not show any change in melting point of suppositories prepared using Suppocire D and NCX but in the case of Suppocire C it was marginally increased i.e. 41°C–42°C compared to that of plain Suppocire C suppositories whereas in the case of Suppocire CP the melting range was decreased by addition of Labrasol and CPGMC up to 37°C–38°C and for other additives it remained the same as seen from the Table 3.

Hardness was determined using Erweka suppository hardness tester; plain suppositories prepared using Suppocire D, C, NCX and CP showed hardness of 6.2, 2.1, 1.2 and 4.1 kg, respectively. Addition of additives showed a decreased in hardness of suppository up to 3.8 kg in case of Suppocire D whereas it remains unaffected for Suppocire C suppositories. Addition of SLS (0.5% and 1%), DOSS (0.5% and 1%), aerosil (1% and 2%), CPGMC (2% and 5%) showed increase in hardness maximum up to 3.8 kg and it remained unaffected by addition of other additives for Suppocire NCX suppositories. DOSS (0.5% and 1%), SLS (0.5% and 1%) and aerosil (1% and 2%) addition to Suppocire CP decreased the hardness. Increase in concentration of SLS i.e. up to 1% and aerosil i.e. up to 2% showed increase in hardness whereas DOSS (1%) showed reduction in hardness. Suppocire suppositories containing Labrasol (2% and 5%), CPGMC (2% and 5%), span 80 (2%) and Miglyol 812 (10%) showed hardness less than 0.6 kg (Tables 2 and 3).

Disintegration time noted for plain suppositories prepared using Suppocire D, C and CP was more than 30 min, whereas for NCX it was 29 min. Addition of additives did not affect the disintegration time of Suppocire suppositories prepared using D and C i.e. >30 min. Addition of DOSS (0.5% and 1%), SLS (0.5% and 1%), CPGMC (2% and 5%), Miglyol 812 (10%), aerosol (12%) and lecithin (1%) decreased the D.T. up to 20 min but the addition of Labrasol (2%) showed no change in D.T. i.e. 18 min; further increase in concentration of Labrasol increased the D.T. Span 80 at 2% concentration showed a D.T. of 18 min for suppositories prepared using Suppocire NCX. In the case of Suppocire CP

suppositories, addition of SLS (0.5% and 1%), CPGMC (2% and 5%), DOSS (2% and 5%) had a marginal effect on disintegration but the addition of lecithin (1%), span 80 (2%) and Miglyol 812 (10%) reduced the D.T. up to 20 min. Addition of aerosil at 1% concentration showed a 25 min. D.T., further increase in D.T. was observed by addition of higher concentration of aerosil. Labrasol at 1% and 2% concentration dramatically decreased the D.T. up to 18 min. All the suppositories formulated using Suppocire D, C, NCX and CP with and without additives showed drug content of 90%-110%.

Table 2: Evaluation of paracetamol suppositories prepared using plain Suppocire.

Properties/base	Suppocire			
	D	C	NCX	CP
Appearance	Good	Good	Good	Good
M.P. (°C)	42°C-	39°C-	39°C-	39°C-
	44°C	40°C	40°C	40°C
D.T. (min)	>30	>30	29	>30
Hardness (kg)	6.2	2.1	1.2	4.1
% assay	101.98	101.19	101.91	101.08

Suppositories were effectively prepared using Suppocire D with uniform appearance with no sign of fissuring, fat blooming, fracture and exudation observed. In-vitro drug release test was performed using pH 7.2 phosphate buffer as the dissolution media. Figure 1(a) shows the dissolution of drug from various compositions, prepared using Suppocire D. Dissolution of drug from plain (without additive) Suppocire D showed 7.88% at the end of 8 h. Addition of Labrasol increases the drug release by 7% to 8% at both the concentration, SLS (0.5% and 1%) enhanced the drug release by 10%-11% at the end of 8 h. Addition of DOSS (0.5%) markedly enhanced the dissolution rate by 20%-21%; further increase in concentration reduced the drug release. Aerosil at 1% concentration enhanced the drug release by 16% to 17% but further increase in concentration did not enhance the drug dissolution. CPGMC (2%) addition to suppositories increased drug release by 10%-11%; increase in the concentration up to 5% had a marginal enhancement on dissolution of drug. Drug dissolution was enhanced by addition of span 80 by 10%-11%. At 10% concentration of Miglyol 812 a 20%-21% enhancement of drug dissolution as compared with plain Suppocire D at end of 8 h was suddenly shown. In case of Suppocire D, the additives such as DOSS (0.5% and 1%), Miglyol 812 (10%), lecithin (1%) were found to give better results as compared with other additives.

Suppocire C with hydroxyl value of 20-30 mg KOH/gm gave good white suppositories. Dissolution profiles of various compositions of Suppocire C are as shown in Figure 1(b). Plain Suppocire C showed a much better drug release than Suppocire D i.e. 18% at end of 8 h. Lecithin had no effect on the drug release. Addition of 0.5% DOSS to Suppocire C showed enhancement in drug dissolution up to 29% whereas initially it was 18% at the end of 8 h. Further increase in concentration up to 1% had no effect; the drug release was noted to be up to 24%-25%. Addition of SLS (0.5% and 1%) had a marginal

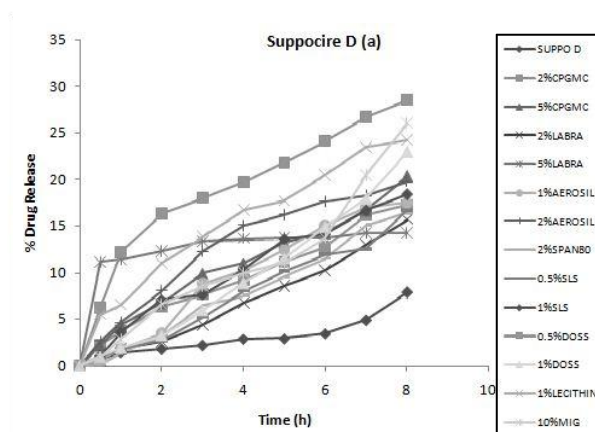
enhancement on drug dissolution i.e. up to 2% to 3%. Initially at 1% concentration aerosil showed 29%–30% drug release, further increase in concentration of aerosil (2%) did not show further enhancement in drug release i.e. was up to 26%–27%. Labrasol at lower concentration (2%) enhanced the drug release up to 23%–24% but at higher concentration (5%) increased the drug release from suppositories up to 15% to 16% compared with that of initial drug release. CPGMC at 2% concentration level showed 30%–32% drug release; further increase in concentration of CPGMC had no effect on drug dissolution, drug release was noted up to 20%–21%. Miglyol 812 at 10% concentration level increased the drug dissolution up to 24%–25% but addition of span 80 (2%) dramatically enhanced the percent drug release up to 38%–39% at the end of 8 h and was found to give better drug release as compared to other additives.

Suppocire NCX gave white coloured suppositories with no sign of fissuring, fat blooming and exudation. In-vitro drug release profiles of various compositions of Suppocire NCX were as shown in Figure 1(c). Plain Suppocire NCX showed good drug release of 98% at the end of 5 h and $t_{50\%}$ of 2.47 h and $t_{90\%}$ of 4.55 h respectively. This could probably be due to addition of hydrophilic excipients by the manufacturer. Addition of 1% SLS, 5% Labrasol and 2% span 80 had no further enhancement on drug dissolution with $t_{50\%}$ values of 2.95, 2.83 and 2.84 h, $t_{90\%}$ values of 5.31, 5.10 and 5.11 h, respectively. Addition of DOSS (0.5%) showed a 100.04% drug release at end of 4 h. Further increase in concentration up to 1% had marginal effect on drug release, the $t_{50\%}$ values noted were 2.99 and 3.88 h and $t_{90\%}$ of 5.39 and 6.84 h. Addition of aerosil decreased the drug release of 50.11% and 52.11% at 1% and 2% concentration with $t_{50\%}$ of 5 h, 4.79 h. As seen from Figure 1(c), Labrasol increased the drug release with increase in concentration, at 2%, and 5% level it showed $t_{50\%}$ of 3.71 and 2.83 h and $t_{90\%}$ of 6.68 and 5.10 h, respectively. CPGMC had marginal effect on drug release but increase in concentration to 5% level showed enhancement in drug release; 97.67% drug was being released at the end of 4 h with $t_{50\%}$ and $t_{90\%}$ of 2.04 and 3.68 h, respectively.

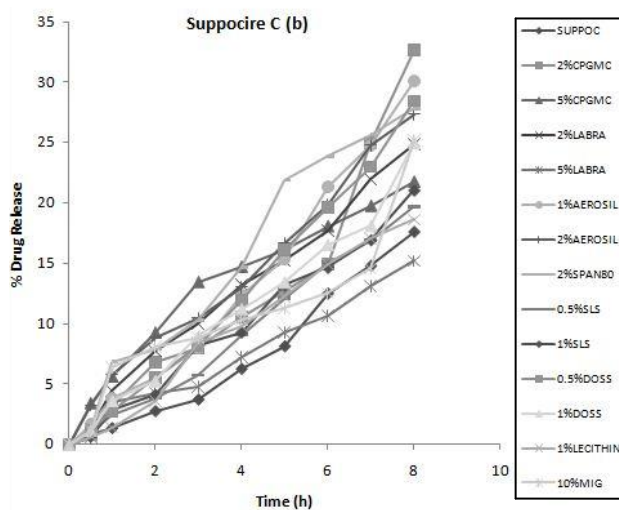
Suppocire CP also gave white coloured suppositories. The *in-vitro* drug release profiles are as shown in Figure 1(d), Plain Suppocire CP was found to give good drug release as compared to Suppocire D and C but was less than Suppocire NCX i.e. 37.60% at end of 8 h. DOSS at 0.5% level decreased the drug release by 10%; further increase in concentration had the drug release reduced further by 11%–12%. SLS at both concentrations reduced the drug release up to 30% to 31%. Same effect was observed for aerosil (1% and 2%) but the drug release was reduced was up to 33% to 35%. CPGMC at concentration 5% showed marginal enhancement in drug release but at lower concentration i.e. 2% it decreased the drug release by 2% to 3%. Addition of 2% span 80, 10% Miglyol 812 marginally decreased the drug release. Lecithin showed 32%–33% drug release at end of 8 h. Labrasol had dramatically affected the drug dissolution from Suppocire CP base. Addition of Labrasol (2%) enhanced the drug release with 101.5% of drug being released at 5 h. At 5% Labrasol concentration, up to 99.5% of drug was released at the end of 2 h. The $t_{50\%}$ and $t_{90\%}$ values for 2% and 5% Labrasol addition to Suppocire CP were 2.46 and 1.48 h, 4.43 and 2.67 h, respectively. This may be due to the hydrophilic nature of Labrasol i.e. HLB-14. However Labrasol had not much

Table 3: Compositions and evaluation of paracetamol suppository suppositories.

Properties /Additives (w/w)	0.5% DOSS	1% DOSS	0.5% SLS	1% SLS	1% Lecithin	1% Aerosil	1% Aerosil	2% Aerosil	2% Labrasol	5% Labrasol	2% CPGMC	5% CPGMC	2% Span80	10% Miglyol 812
Suppocire D														
Appearance	Good	Good	Good	Good	Good	Good	Good	Good	Good	Good	Good	Good	Good	Good
Hardness(Kg)	5.1	5.3	4.0	4.2	4.1	3.9	4.2	4.7	4.5	4.2	4.2	3.8	4.7	5.2
D.T (min)	>30	>30	>30	>30	>30	>30	>30	>30	>30	>30	>30	>30	>30	>30
% Assay	99.01	99.44	98.08	101.1	99.76	98.72	101.28	98.08	101.84	98.83	101.84	101.84	99.76	101.03
Suppocire C														
Appearance	Good	Good	Good	Good	Good	Good	Good	Good	Good	Good	Good	Good	Good	Good
Hardness(Kg)	2.5	2.2	2.3	1.8	2.8	3.0	2.7	2.3	1.7	2.1	2.2	2.2	1.8	2.3
D.T (min)	>30	>30	>30	>30	>30	>30	>30	>30	>30	>30	>30	>30	>30	>30
% Assay	97.84	100.21	98.88	99.92	100.32	98.32	100.88	99.98	99.89	97.92	101.92	101.92	102.55	98.16
Suppocire NCX														
Appearance	Good	Good	Good	Good	Good	Good	Good	Good	Good	Good	Good	Good	Good	Good
Hardness(Kg)	3.2	3.4	3.5	3.8	2.6	3.0	3.2	2.3	2.2	3.8	3.5	3.5	2.8	2.5
D.T (min)	20	20	20	20	22	21	25	18	20	20	20	20	18	20
% Assay	101.1	98.32	98.05	99.98	97.92	101.72	99.02	102.87	99.28	102.64	98.88	101.12	101.12	102.11
Suppocire CP														
Appearance	Good	Good	Good	Good	Good	Good	Good	Good	Good	Good	Good	Good	Good	Good
Hardness (Kg)	3.2	2.9	3.0	3.2	2.2	2.5	2.7	-	-	-	-	-	-	-
D.T(min)	>30	29	29	29	25	25	>30	18	18	>30	>30	>30	20	20
% Assay	101.3	100.2	98.88	100.31	101.42	102.13	101.2	97.68	99.68	100.32	99.04	99.04	98.49	101.92

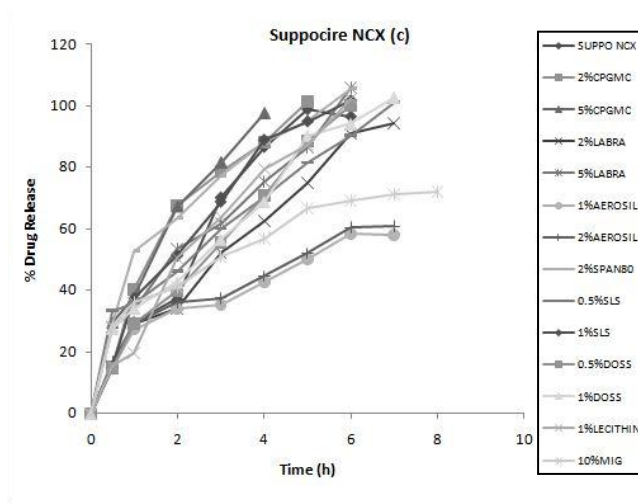


(a)

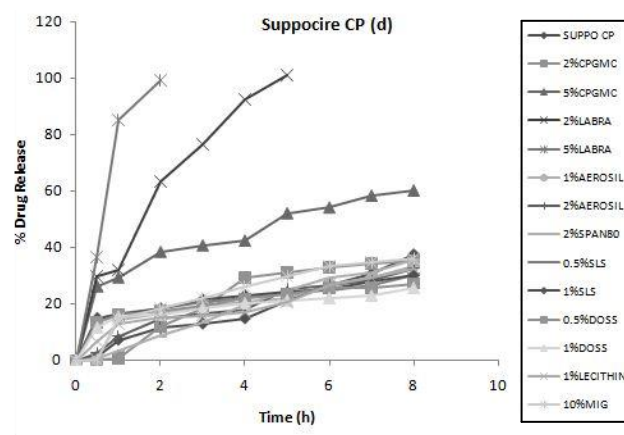


(b)

Fig. 1: In-vitro drug release studies from different Suppocire bases with various adjuvants (continued on next page).



(c)



(d)

Fig. 1: (continued).

effect on Suppocire D and C. Miglyol 812 (10%), DOSS (0.5%), SLS (0.5% and 1%), aerosil (1% and 2%) and CPGMC (2% and 5%) were found to have better drug release with Suppocire D and C as compared to other Suppocire bases. Labrasol surprisingly enhanced the drug dissolution in the case of Suppocire CP whereas with other bases it gave satisfactory enhancement. Plain Suppocire NCX was found to give good drug release when compared to Suppocire D, C and CP.

DISCUSSION

White coloured suppositories containing 250 mg unitary dose of paracetamol were effectively prepared using different grades of selected Suppocire bases i.e. Suppocire D, C, NCX and CP for pediatric use. The bases selected were of different categories such as interesterified, esterified and amphiphilic type having a stated acid and hydroxyl values in range of <0.5 to 1 and 20 to 50, respectively which may cause low irritation to mucous membrane (Shegokar and Singh 2006). Iodine value for Suppocire D, C is <2 whereas for Suppocire NCX and CP it is <3 and <1 respectively, which determines decomposition. Ideally the suppository base should have iodine value <7; bases possess a quite lower range of iodine value, which is a beneficial parameter. Suppocire bases with a variety of melting point ranges which were provided by Gatteffose, France affects the suppository manufacturing process as well as the dissolution of drug in rectum. All Suppocire suppositories were passed for uniformity of weight test as per British Pharmacopoeia (2001) and addition of adjuvants did not affect the weight.

Plain suppositories prepared showed a melting point range for Suppocire D, (42°C–44°C), C (37°C–39°C), NCX (37°C–40°C) and CP (39°C–40°C). Addition of additives did not show any change in melting point of suppositories prepared using Suppocire D and NCX but in case of Suppocire C it was marginally increased i.e. 41°C–42°C compared to that of plain Suppocire C suppositories. In the case of Suppocire CP the melting range was decreased by addition of Labrasol and CPGMC up to 37°C–38°C and for other additives it remained the same (Shegokar and Singh 2004). Young *et al.* (1987) explained that dissolution of fenbufen and ethanamine fenbufen from PEG 1500, Witepsol H12 and Suppocire AP suppository bases was significantly faster than the parent drug, with Witepsol H12 base giving the most rapid release. Addition of additives showed a decrease in hardness of suppository whereas it remains unaffected for some Suppocire suppositories. Suppocire suppositories containing Labrasol (2% and 5%), CPGMC (2% and 5%), span 80 (2%) and Miglyol 812 (10%) showed less hardness.

Disintegration is an important parameter to determine the dissolution of suppository. Fast dissolving suppository allow rapid spread of drug in local area. By addition of additive one can control the disintegration rate, thus by forming fast or slow disintegrating suppository formulation. Hosny, Abdel-hady and Eltahir (1996) showed that addition of Tween 80 to the formulation significantly increased the dissolution of the suppository by 52%–58% indicating the wetting effect of that additive. Suppocire bases appeared to give suppository no sign of fissuring, fat blooming, fracture and exudation. Dissolution of drug from plain (without additive) Suppocire base was slow but addition of additive markedly increased the drug release; the difference was observed especially for Labrasol, SLS, DOSS and aerosil. Realdon *et al.* (1997) also stated that the release rate of a drug from suppositories was affected by characteristics of the excipient used, melting temperature, rectal temperature and hydro-lipophilic characteristics of suppository.

Adequate characterisation of drug release rate from suppositories requires the determination of its appropriate release kinetics model. Poor release characteristics are not likely caused by degradation of the drug or its interaction with the bases. Another important factor that can influence the drug release is the water-absorbing property of the base which can facilitate penetration of the dissolution medium into the base with subsequent wetting and desorption of the embedded drug. It can therefore be asserted that the hydrophilic character of the Suppocire suppository base promotes the release of

paracetamol. All performed experiments indicated good reproducibility of production and in-vitro drug release (when tested on three suppository samples from same batch preparations) (Janicki *et al.* 2001; Welch, Ek and Stromme 2006).

The effects of the surfactants were shown to be concentration dependent (Hanaee *et al.* 2004). For example, increasing the concentration of Labrasol from 2% to 5% (w/w) was associated with a significant increase in the drug release. Also, there was a progressive increase in the release rate with increase in concentration of CPGMC. It was anticipated that the surfactants may decrease the interfacial tension between the drug and the dissolution medium with resultant improvement of drug solubility and subsequent release. An anionic surface-active agent, SLS has been shown to produce a very less enhancement of solubility and dissolution rate of paracetamol. The non-improvement of the drug release by surfactants as observed is not unusual as other studies have revealed that incorporation of surfactants may increase or decrease drug release from suppositories (Realdon *et al.* 1997; Shegokar 2003).

The pH of the dissolution medium used in this study (pH 7.2) reflects the rectal fluid (pH about 7.2 to 7.4). The decrease in drug release at higher surfactant concentration as obtained is most likely attributable to micellar entrapment of the drug, resulting in retardation of the drug release. Although the surfactants at optimum concentration did not improve drug release, their incorporation into the suppositories may still be useful since they have absorption-promoting effects as observed by Takatori *et al.* (2004). Zuber *et al.* (1998) discussed the importance of determining the physicochemical parameters of suppository samples stored at different temperatures. Furthermore, studies conducted by Berko *et al.* (2002) proved the suitability of Suppocire base for development of suppositories (Berko *et al.* 2002).

CONCLUSION

Addition of additives to Suppocire bases had a definite effect depending upon the type and concentration used. Addition of Doss and aerosil showed prolonged drug release where as newly used Labrasol and C PGMC gave much faster release. Thus, semi synthetic Suppocire bases proved their potential as promising suppository base.

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