



Rectal route in the 21st Century to treat children[☆]



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ABSTRACT

The rectal route can be considered a good alternative to the oral route for the paediatric population because these dosage forms are neither to be swallowed nor need to be taste-masked. Rectal forms can also be administered in an emergency to unconscious or vomiting children. Their manufacturing cost is low with excipients generally regarded as safe. Some new formulation strategies, including mucoadhesive gels and suppositories, were introduced to increase patient acceptability. Even if recent paediatric clinical studies have demonstrated the equivalence of the rectal route with others, in order to enable the use of this promising route for the treatment of children in the 21st Century, some effort should be focused on informing and educating parents and care givers. This review is the first ever to address all the aforementioned items, and to list all drugs used in paediatric rectal forms in literature and marketed products in developed countries.

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1. Introduction

Rectal forms are one of the oldest pharmaceutical dosage forms as their origin goes back to antiquity. The Old Testament refers to 'Magerarta' – suppository made of silver – and Hippocrates describes various compositions of acorns which were rectal dosage forms for local effects. The first usage of the word suppository goes back to 1763 in the Universal Pharmacopoeia of Lemery. The term *suppositorium* comes from the Latin word *supponere* which means 'substitute' because this dosage form was introduced as a substitute to enema [1].

At first rectal dosage forms were composed of solid supports impregnated with medicinal substances. These supports were made of baked honey, soap, tallow or even horn. These solid supports were substituted by cocoa butter in the late 18th Century. The first mention of the addition of an active substance in the suppository mass was made by Henry and Guibourt in 1841 by the introduction of opium pellets in the molten cocoa butter before moulding [2]. At that time the classical weight of a suppository for adults was 5 g. In the following century two alternative masses were proposed to cocoa butter: firstly a mixture of gelatine, glycerine and water in 1897, and secondly, hard fat which was introduced after the Second World War due to shortage of cocoa butter. In the 20th Century, most of the rectal drug products on the market were suppositories composed of fatty bases (hard fat), and are nowadays around 2 g for adults and 1 g for children. These rectal forms were particularly used in some European countries and in Japan where the use of suppositories is more accepted than in other territories like the United States of America or Laos for example. The first literature reference on the use of paediatric rectal dosage form (for premedication before anaesthesia) was reported in 1936 [3]. Even, if suppository was quite popular for adults during the 20th Century, the first market authorisation for a Paracetamol paediatric suppository in France was only granted in 1981 (Doliprane, Sanofi).

Administration of drug through the rectal route is amenable to both local and systemic drug delivery. It has been effectively used during the last centuries to treat local diseases of the anorectal area (for example haemorrhoids) as well as to deliver drugs systemically as an alternative to the oral route (including antipyretic and analgesic drugs such as Paracetamol or Diclofenac) [4]. The latter case can be useful for drugs which:

- possess limited absorption in the upper gastrointestinal tract,
- are unstable to proteolytic enzymes,
- exhibit a high hepatic first pass effect,
- cause irritation to the gastric mucosa,
- or need high doses and cannot easily be formulated in oral solid dosage forms.

The lower rectum is drained by the lower and middle haemorrhoidal veins and bypasses the liver, hence avoiding at least partially, the hepatic first pass effect and allowing drugs to exert systemic effect prior to metabolism in the liver. The rectal region is also extensively drained by the lymphatic circulation and could increase the systemic absorption of some highly lipophilic drugs. In adults, rectal dosage forms should be inserted in the lower part of the rectum to avoid the absorption of the drug by the upper haemorrhoidal vein which supplies blood to the portal vein. In addition, the empty rectum presents a constant and static environment as compared to the upper gastrointestinal tract, where the environment varies greatly depending on the section (e.g. pH, volume of stomach vs. duodenum) and in fasted or fed conditions. The volume

of liquid is reported as relatively low (1–3 mL) and the pH neutral (pH 7–8) with low buffer capacity [4]. Its surface area is reported to be of about 200–400 cm², without villi and microvilli, which is smaller than the upper gastrointestinal tract, but larger than nasal and buccal absorptive surfaces. However the epithelia in the rectum is made by a single layer of columnar or cuboidal cells and goblet cells, histologically similar to the upper gastrointestinal tract, giving them comparable abilities to absorb drugs [5].

Rectal dosage forms are also a good alternative to the peroral route for certain groups of patients who cannot easily swallow tablets or capsules: this can be in the case of children and the elderly, as well as in the cases where patients may be unconscious or vomiting.

Despite being one of the enteral routes, rectal drug delivery is not as popular as the oral route for various obvious and less obvious reasons. The aim of this review is to investigate these by looking at its applicability in children, its applicability to treat various conditions (whether already implemented in practice or under research) and also the applicability of various traditional or more novel dosage forms, to assess if and when it could have the desirable attributes for paediatric drug delivery.

2. The child and human dimensions

2.1. The child dimension

Designing any formulation implies that patient factors are taken into consideration. For paediatric subsets, extra challenges occur, the very central one being that children undergo physiological changes that could affect the pharmacokinetic/pharmacodynamic/pharmacogenomics. This is why the International Conference on Harmonisation [6] has proposed a subdivision for the purpose of paediatric medicines development to reflect biological ages.

- Preterm newborn infants
- Term newborn infants (0 to 27 days)
- Infants and toddlers (28 days to 23 months)
- Children (2 to 11 years)
- Adolescents (12 to 16/18 years, dependent on region).

The guideline on the investigation of medicinal products in the term and preterm neonate [7] states that rectal administration is not commonly used in these subsets and that it is associated with erratic absorption. If considered, it must be fully evaluated for safety and efficacy, in addition to appropriate bioavailability studies. Moreover rectal dosage forms should be used with extreme caution in premature infants, as the delicate rectal lining could be torn, introducing infection. For similar reasons it is not recommended to use this route in immunocompromised patients to avoid the risk of trauma leading to possible abscess formation [8].

However, more generally for the rectal route, similarities and differences between adults and children of various ages have not been systematically reported, despite this route being considered from preferred acceptability to best/preferred applicability in children under 6 years of age (preschool) [9].

Like most of the gut, the rectum is formed at birth but is only functional when the baby starts to feed orally, when development continues and when commensal bacteria and immunity kick in. The main anatomical difference is in size as described in Table 1 [10]. Therefore, if the PK

of rectally administered drugs is mainly determined by its anatomical properties, the possible changes of surface area for absorption add to the reported inconsistency of this route. If in turn the dominant factor is the first-pass metabolism, then as with adults, it depends on where the drug will be absorbed for children too. It is said that when inserting suppositories into children, the position beyond the rectal opening should be adapted to the size/age of the child. Some pragmatic approaches to determine the appropriate position have been proposed e.g. *using size of knuckles of fingers*, more than any evidenced approach.

Of the presystemic paediatric patient factors to consider, the contact time of the drug to be absorbed is paramount, as its retention will directly dictate its bioavailability and predictability of the clinical effect.

It is therefore important to explore rectal motility and rectal activity patterns, keeping in mind that unlike the small intestine, no cyclic motor activity takes place.

The rectum is the last, usually empty, portion of the large intestine located above the anal canal, where stools collect prior to evacuation from the body. The earliest stool of a new born is called meconium, which should be passed promptly and completely within about 2 days of birth. It is composed of materials ingested in utero such as intestinal epithelial cells, lanugo, mucus, amniotic fluid, bile, and water. It is odourless, almost sterile, viscous and sticky. From a dark green meconium, stools progress toward yellow (digested milk), until the introduction of weaning semi-solid foods at or around 6 months, when it changes to brown.

Faecal continence is maintained by the coordinated function of the pelvic floor, rectum and anal sphincters. When fullness (rectal distension) is felt, the abdominal muscles contract, increasing intra-abdominal pressure. The puborectal sling and the sphincters relax, and the rectal musculature contracts. The colon and rectum then descend, the rectum becomes elongated, faeces are discharged, and the anal canal is closed by its sphincters.

The normal frequency of evacuations has an inverse relationship with age. In breastfed infants, it was shown that the average daily defecation frequency halved during the first 3 months, whereas no significant changes were observed in infants fed standard formula or mixed feeding [11]. By 16 weeks, 2 was the mean frequency of bowel actions per day of infants of both feeding groups [12]. From the age of 3 years, normal stool frequency varies from three stools per week to three per day. Between 5 years and 8 years of age, the majority of children have a medium-sized bowel movement daily or every other day without straining or withholding [13]. In turn the passage of three or more loose or liquid stools per day is considered to be diarrhoea (WHO). Regardless of age, this high variability in what is perceived to be normal impacts on the applicability of the rectal route.

Moreover, applicability relies as well on the ability of the patient, who might need to hold the medicine to counteract the possible urge to push

it out. Voluntary control of the external anal sphincter is key in the voluntary deferring of evacuation until a socially opportune moment. Recent studies show most children to start bowel training between 24 and 36 months of age and fewer articles report it from 12 month onwards [14]. Ability to control sphincters requires coordination by the patient. It changes with development and depends not only on behaviour/training but also on integration of involuntary and voluntary neurological and muscular mechanisms, as well as cognitive control.

Constipation in children is a common health problem with a worldwide prevalence between 0.7% and 29.6% from newborns to young adults [13] and many children suffer from haemorrhoids too. Also, it has been estimated that children under 5 years have a global average of three bouts of diarrhoea per year compared to just under one in adults [15]. This higher incidence of gastrointestinal disorders is obviously not favourable for optimal rectal drug delivery.

Regardless of the extent of bacterial survival, there seem to be some residual bacterial enzymes in the rectum [16]. Nevertheless it is generally considered that presystemic loss by adsorption to faeces, intraluminal degradation by microorganisms, metabolism within the mucosal cell, and lymphatic drainage do not significantly affect the fate of rectally administered drugs [17]. However, there is a general lack of recent research work around rectal biopharmaceutical properties even in adults. In turn, the degree of ionization of a drug of a certain pKa depends on the rectal pH which is neutral (7.9) in adults [18].

The mean rectal contact pH was reported to be 9.6 with a wide range (7.2–12.1) for 100 healthy children aged less than 14 years (excluding neonates) [19]. This was not confirmed in a recent paper where pH measured in infants were just below neutrality [20]. Moreover there was no significant difference between well and unwell infants: 6.69 (95% CI 6.55–6.83) vs. 6.88 (95% CI 6.64–7.12) respectively, with rectal pH significantly lower in neonates 6.47 (6.29–6.65), yet still around the neutral region [20]. The only difference between the two papers being that the earlier measurements were only done if the rectal ampulla was free of faeces. Digital examination was not always done in the recent paper.

To conclude, there is very little specific information on paediatric rectal biopharmaceutical properties in the literature, let alone on permeability itself. It might be explained by the lack of popularity of this route as explained in the next sections, leading to a lack of research interests.

2.2. The human dimensions

2.2.1. General considerations

The breadth of potential for use of the rectal route in community and hospital settings will be clearly highlighted in the next section of this review. But does it make it appropriate for paediatrics?

Table 1

Age related changes in rectal dimensions adapted from [9] (A) and calculated volume of 1 g and 2 g suppositories (B).

A				
Age	Diameter (cm)	Length (cm)	Surface area ($2\pi r^2 + 2\pi rh$) (cm ²)	Volume ($2\pi r^2 h$) (cm ³)
1 month	1.5	3	18	11
3 months	3.0	6	71	85
1 year	3.5	7	96	135
2 year	4.0	8	126	201
6 year	4.5	9	159	286
10 year	5.0	12	228	471
B				
	Density (g/cm ³)	Volume of 1 g suppository (cm ³)	Volume of 2 g suppository (cm ³)	
Water	1.00	1.00	2.00	
Cocoa butter	0.86	1.16	2.33	
PEG 400	1.13	0.89	1.77	
Glycerinated gelatine	1.20	0.83	1.67	

Ideally rectal dose forms should deliver single paediatric doses. In the case of suppositories, dose adaptation can be a problem. However some new technologies such as dividable stick-shaped suppositories might allow some level of dose flexibility.

The rectal route might not be acceptable for very frequent dosing (more than once day and/or long term use). At the same time, prolonged release (if no early expulsion occurs) could be achieved through formulation, to minimize dosing frequency. It is commonly used when patients are nauseous or vomiting or in infants/children reluctant or unable to take oral medication if they are very poor, for example in fever. The rectal route seems to be valued for out-of-hospital emergency and life-saving situations. In the United States, Diazepam is the only FDA approved rectal formulation for the ambulatory treatment of early status epilepticus. It has even been suggested for its pre-referral emergency treatment applicability, for example, for malaria or neonatal sepsis in resource-poor settings. This might be due to the relative ease of administration in these situations and the quick onset of action.

Many articles showed that it can be appropriate for developing countries. Moreover there is a relatively good production vs. cost balance as technologies are relatively simple and costs of ingredients are cheap.

In general, excipients have a good safety profile in children. Some may be irritant, but as they are quite well established, the risk–benefit balance can be addressed early in development. In terms of risk of systemic toxicity, there is a general paucity of information, especially when it comes to rectal absorption. However if an excipient has a well known oral safety profile in the paediatric population, its profile, including potential allergies and sensitization, should be similar rectally, as the rectal epithelium has comparable abilities to absorb drugs. Some concerns are inherently taken out, such as with colouring or taste masking agents. Indeed, there are no issues with organoleptic characteristics, but in turn, different acceptability issues with children and parents/carers are reported in chronic use, and are not outweighed by practicalities such as being safely (self) administrable at home.

This administration route is not always reliable as it could suffer from variable absorption and patient acceptance (age, geo-socio-cultural background) can also be inconsistent as discussed later.

The reasons for and against developing/using the rectal route in children are multifactorial.

2.2.2. Drug factor

There is a multiple risk of presystemic loss mainly from non-emptiness of the rectum at the time of administration, or/and uncontrolled bowel movement upon administration. Combined with variable location for absorption at administration and considering the anatomy of haemorrhoidal veins in children is not different than in adults, bio-availability could be affected. Therefore it seems that the therapeutic index of the drug and the required speed of absorption will be important determinants to choose whether to formulate it for the rectal route, providing that solubility, stability and permeability are not limiting factors.

2.2.3. Dosage form factor

In the first half of the 20th Century the classical weight of suppositories was less than 4 g in Mexico, Italy, Sweden, Germany, and USA; but up to 8 g in the UK. This may help to explain the lack of development of this form in this territory. The smallest suppository weighted between 1 and 2 g and was most probably for paediatric dosing. Nowadays, most of suppositories weight 2 g for adults and 1 g for infants and children. Only few paediatric suppositories weight more than 1 g: laxative suppositories of glycerine weight up to 4 g and some drugs requiring high dosage (Metronidazole or Mesalazine for example) weight 2 g. Liquids, especially with larger volumes, would require the child to be able to hold in the medicine which is impossible in neonates and infants. Smaller volumes (1–5 mL) have more favourable acceptability [21]. By adjusting the viscosity it might be possible to keep the good spreading of liquids



Fig. 1. Example of dividable stick-shaped suppositories (scale in cm).

but facilitate patient retention. For example a Morphine gel was the preparation of choice compared to solution for 1–10 year old children in Sweden [22]. However any rectal dosage forms require a dedicated personal space and some time for administration which might not always be convenient, on top of being distressful if not painful for some.

The dosage form itself might be irritable to the rectal mucosa because of its composition (excipients), pH, and osmolarity. It is a well established way to treat constipation to use osmotic laxatives such as lactulose and macrogols. Avoiding cold administration (e.g. suppositories kept in the fridge) might increase administration comfort and decrease risk of expulsion and interruption of absorption.

2.2.4. Administration devices and ease of administration

It is more common for liquids and semi-solid to be package in or attached to the administration device itself. An applicator can also be dispensed separately. The applicator is usually like a syringe with a plunger, with or without the possibility to adapt the dose with a rectal tip of 4.4 to 6 cm. DIASTAT AcuDial is a non-sterile Diazepam gel provided in a prefilled unit-dose rectal delivery system for which the dose can be adjusted. For semi-solid formulations, a tip can be directly screwed on the tube and cleaned between administrations (Fig. 2).

For suppositories, although simple hygiene before and after administration should be sufficient, a finger cot can also be used. Interestingly, although it seems much more common for administration of pessaries or tablets via the vaginal route, very few suppository administration devices seem to be available (Fig. 3) and they are not paediatric specific whereas it is generally considered that using an appropriate device is generally correlated with more compliant administration of drugs [23]. In the case of rectal drug delivery, it might also help to overcome physical or psychological difficulties of administration and help to ensuring easier and more reproducible administration, which could in turn switch psychosocial factors such as beliefs, motivation, and attitude.

The suppository inserter shown in Fig. 3 has a 5.1 cm long, hollow plastic tip that holds a standard suppository, and spring-loaded design which pushes it out. With the handle, it measures 22 cm long, and can be sanitized easily. It is constructed from stainless steel with polyethylene collars and tips. The D-rings on the quad handles allow for easy adjustments [24]. The length of rectal tips aforementioned does not seem adapted to the rectal dimensions of neonates (Table 1) and the usability in infants and children remains to be established. Lubrication with water based lubricants, or even water itself, is often recommended to insert suppositories as well as tips and devices.

2.2.5. Patient barriers

Finally it is important to consider patients' real barriers versus cultural, perceived barriers or lack of understanding of the potential of



Fig. 2. Example of rectal devices: a) enema bottle (all in one); b) DIASTAT AcuDial rectal delivery system. c) Rectal Tube Tip for tubes (4.4 to 6 cm long).

the rectal route. Indeed the decision whether or not to use the rectal route might be beside positive pharmacological outcomes aforementioned, but superseded by ‘age, attitudes and tradition’ [25]. Some studies were conducted in order to evaluate the compliance and acceptability of rectal dosage forms. It is influenced by many factors: the state of health of the children, information – or the lack of – provided by the health authority, knowledge of federal advices by the care takers, care givers and parents, the influence of healers, the cost of goods, and cultural barriers [26–32].

It is common knowledge that there are very strong feelings about the rectal route of administration, especially in United Kingdom [9]. It is not the aim of this review to find out why but to provide some evidence of use and of acceptability, even if sparse and not systematic. A study in UK in the nineties examined the preference for routes of administration of post-operative analgesia. Adult patients were more tolerant of suppositories than hospital staff; however the majority preferred the intravenous route [33]. In another UK study parents rated the rectal route the most unpleasant compared to oral and parenteral routes [34]. However this is not necessarily always the case: in a study in Niger, the dropout rate after 3 days was higher in the intramuscular group as compared to patients treated with intrarectal quinine cream [35].

One can wonder whether in certain countries/regions the rectal route is not used because dosage forms available are not prescribed/accepted, because there are none available due to alternative choices, or if this is driven by social attitudes and market response. This is highlighted in emergency situations such as seizure management where the rectal route is used because outside of psychosocial negative factors, it has been shown to be effective, safe, and simple to use versus intravenous or even nasal administration [36,37]. It has also been praised to decrease the mortality of severe malaria due to treatment delays and to decrease the side-effects due to intramuscular administrations in Africa [30,35]. In their position paper on the pharmaceutical development of paediatric medicines [21], the WHO states that in severe disease conditions, for

example neonatal sepsis, some alternatives such as rectal preparations may be easier to apply by untrained caregivers. However in similar situations in other resource-poor settings in the world, e.g. Laos, use of the rectal route is mainly hindered by the lack of information and training, not only to the population but also to the health care teams [38]. On reflection, this might also be the case in developed countries, if rectal drug delivery for young children is favoured in some countries and not even thinkable in others. Interestingly even if paediatricians’ attitudes greatly influence parents’ behaviours and beliefs, a majority of Italian parents of children under 6 years reportedly preferred antipyretics suppositories to oral administration, versus only 27% of paediatricians. Parents surveyed thought that they are more practical, easier, more effective or faster acting than oral formulation [39]. The relatively good acceptability of the rectal route for preschool children versus the oral route was also reported in studies in Canada [40], and in German, French and Italian speaking regions of Switzerland [41], as well as in Iran [42]. However in another Iranian study paraffin oil received higher percentage of family satisfaction and compliance orally than rectally [43].

On top of therapeutic need and influence, age seems to be important and it is assumed that acceptability among children is generally poor. However no formal or systematic study or review is available from their perspective, although other some stakeholders (parents, carers, prescribers) have been surveyed. In Switzerland paediatricians would prescribe antipyretic drugs via the rectal routes for children aged 18 months–5 year old, whereas from 6 year old they tended to largely prescribe oral drugs [44]. It is anticipated that it would not be the route of choice in teenagers. In fact older children and adults often refuse treatment with Diazepam rectal gel due to social objections [37].

In general, in each society there are socio-cultural norms and recommendations regarding the knowledge, attitude, preference, and behaviour of people. It seems that there are many taboos, mainly acquired/transmitted rather than innate though, that surround proctology related topics that could play a role in the reticence of using this route. There is a

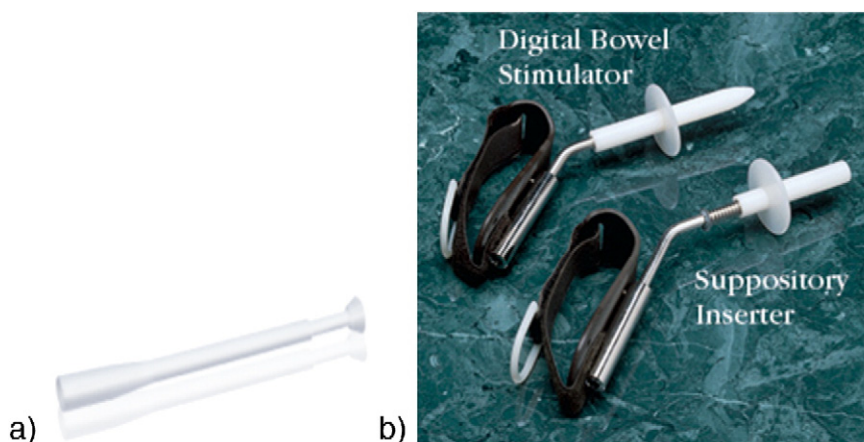


Fig. 3. Example of a) simple applicator sold for ovules pessaries and rectal suppositories (Medintin) b) suppository inserter (North Coast Medical, Inc.) Rectal tip 5.1 cm long, with the handle 22 cm long [176].

Table 2
Rectal forms and sub-categories described in the European Pharmacopoeia 7th edition.

Rectal form	Sub-category (if applicable)
Suppositories	Hard fat Macrogols Cocoa butter Gelatinous mixtures
Rectal capsules	Soft gelatine capsule with a lubricating coating
Rectal solutions, emulsions, suspensions	
Powders and tablets for rectal solutions and suspensions	
Semi-solid rectal preparations	Ointments Creams Gels
Rectal foams	
Rectal tampons	

need for prospective compliance studies to better understand and try to set up appropriate interventions to alleviate issues with the use of the rectal route.

3. Paediatric rectal dosage forms on the market and in the scientific literature

3.1. Rectal dosage forms in Pharmacopoeias

After consultation of the European, US and Japanese Pharmacopoeias (EP, USP, and JP, respectively), only the EP contains a special chapter on rectal dosage forms entitled “Rectal preparations/*Rectalia*” [45]. It defines rectal preparations as ‘systems intended for the rectal use in order to obtain a systemic or a local effect’. They can also be intended for diagnosis purposes. Seven different categories of rectal forms are distinguished as presented in Table 2.

The USP and JP do not include a specific chapter on rectal forms, but define the suppository dosage form. The USP defines suppositories as dosage forms adapted for application into the rectum. These suppositories can be composed of cocoa butter, glycerinated gelatine, hydrogenated vegetable oils and hard fats, mixtures of polyethylene glycols, and fatty acid esters of polyethylene glycols. In addition, some other forms intended for systemic action (called transmucosal route in the USP) are described, such as: gels, foams, creams, pastes and ointments. Furthermore, the USP glossary contains a definition of the rectal route as a ‘route of administration (mucosal) characterized by deposition into the rectum to provide local or systemic effect’. The JP gives a slightly different definition where suppositories are solid preparations intended

for insertion into the rectal or vaginal cavity. There is no mention of systemic effect in the JP.

3.2. Paediatric rectal dosage forms on the market

3.2.1. USA, Japan and 5 European countries

This overview of the market for paediatric rectal forms was limited to USA, Japan and Europe.

The Daily Med [46] and FDA [47] websites were consulted to build an exhaustive list of US paediatric rectal dosage forms presented in Table 3 in order of decreasing number of marketed drug products retrieved. The US market comprises a rather large list of rectal dosage forms for paediatric dosing compared to the limited amount of official monographs in the USP. The main rectal dosage form is the suppository (the only one with a specific monograph), but some alternatives exist in the form of enemas, aerosols, powders, gels or suspensions which can be used for transmucosal route.

Similarly, the Kusuri-no-shiori drug information website [48] was used to list Japanese paediatric rectal dosage forms presented in Table 4, where suppositories seem to be the only rectal dosage form available for the 4 drugs reported. However, there is no mention of the children's age in the label/marketing authorisation. Paediatric dosing is adapted by body weight of children, as indicated in the product label.

The analysis of the European market for paediatric rectal dosage forms was conducted for five countries which readily offer access to their drug product databases: France [49,50], Germany [51], Portugal [52], Spain [53], and the United Kingdom [54]. European countries such as France (18) or Germany (23) possess more drugs available as paediatric rectal dosage forms than the USA (10) or Japan (4). Among all marketed drug products available within these five countries, a series of six active ingredients were selected for their common use in at least two countries and reported in Table 5. Like in the USA and Japan, the main rectal dosage form is the suppository.

Suppositories are prevalent. The main drug available is Paracetamol, with a wide range of doses to accommodate for the age and body weight of infants and children. Diazepam marketed as an adhesive gel supplied with an applicator is an example of novel rectal dosage form.

The main indications of rectal dosage forms for children in these three regions are analgesic and antipyretic, anti-inflammatory, anti-emetic and laxative.

It should be noted that the US market is the only region without a Sodium Diclofenac suppository reference. In turn, in emerging and developing countries, other rectal paediatric forms are marketed because of their efficacy, ease of administration and low cost. Hence, suppositories of Artemether and Artemisinin were marketed recently to treat

Table 3
Paediatric rectal forms marketed in the USA.

Form	Drug	Dose	Indications ^a ; age	Number of marketed drug products
Suppository	Bisacodyl	10 mg	Laxative (OTC); children under 6 years of age: consult a doctor	13
Suppository	Prochlorperazine	12.5, 25, 50 mg	Anti-emetic, antipsychotic, tranquilizer; from 2 years	10
Suppository	Promethazine HCl	12.5, 25, 50 mg	Antihistaminic; From 2 years	9
Suppository	Paracetamol	80, 120, 325 mg	Pain/antipyretic (OTC); children under 3 years of age: consult a doctor	9
Solution	Lactulose	10 g/15 mL	Laxative; children/portal-systemic encephalopathy; from infant	7
Powder	Sodium polystyrene sulfonate	454 mg/BOT	Hyperkalemia; from newborn	5
Enema	Mesalamine	4 g/60 mL	Distal ulcerative colitis, proctosigmoiditis or proctitis; paediatric: not still established/prescription	4
Suspension	Sodium polystyrene sulfonate	15 g/60 mL	Hyperkalemia; from newborn	4
Enema	Hydrocortisone	100 mg/60 mL	Ulcerative colitis; paediatric: not still established/prescription	3
Aerosol	Hydrocortisone acetate	10%	Ulcerative colitis; paediatric: not still established/prescription	1
Gel	Diazepam	2.5 mg/0.5 mL	Anticonvulsant; from 2 years	1
Suppository	Mesalamine	1 g	Ulcerative colitis; paediatric: not still established/prescription	1
Suppository	Prochlorperazine	25 mg	Antiemetic/antipsychotic/tranquilizer; From 2 years	1
Suppository	Caffeine, Ergotamine tartrate	100, 2 mg	Headaches; safety and effectiveness have not been confirmed/prescription	1

^a All listed drug products are human prescription drug label except those containing ‘OTC’ over-the-counter drug products (14 references selected after a FDA and Daily Med search, March, 8th 2013).

Table 4
Paediatric rectal forms marketed in Japan.

Form	Drug	Dose	Indications, age	Number of marketed drug products
Suppository	Paracetamol	50, 100, 200 mg	Pain/antipyretic, 10–15 mg/kg (no indication of age, dosing by weight)	2
Suppository	Sodium Diclofenac	12.5, 25, 50 mg	NSAID, from 1 year (dosing by weight)	1
Suppository	Domperidone	10, 30, 60 mg	Anti-emetic, under 3 years (dosing by weight)	1
Suppository	Sodium bicarbonate, Anhydrous monobasic sodium phosphate	NA	Laxative, no indication of age or weight	1

5 references selected after a Kusuri-no-shiori search, March, 8th 2013.

malaria in Africa. These dosage forms can be administered to children in rural areas where oral or parenteral dosing is impossible, and hence substantially reduce the risk of death or permanent disability [55].

Surprisingly, Japan, which was known in the 20th Century for its common usage of rectal forms, only possesses a suppository monograph in its Japanese Pharmacopoeia and only four drug products on the paediatric market. It was not possible in the remit of this review to access sales/market share and prescription trends to link it with the number of rectal dosage forms aforementioned, except in France.

3.2.2. Case study in France: evolution of the market over the last 20 years

France is one of the main countries for suppository manufacturing and usage for children. In 1970, 7.5% of all prescriptions in France were formulations intended for rectal administration (for both adults and children) [4]. In 2012, rectal forms still represented 1.2% of the total amount of drug products sold in France (ANSM data, <http://ansm.sante.fr/>). This market was studied in depth as paediatric usage of rectal dosage forms is well documented [56,57]. The evolution of rectal dosage forms in France between 1990 and 2012 is shown in Table 6, in order to check if the implementation of the European Paediatric Regulation in January 2007 (Regulation (EC) No 1901/2006 and No 1902/2006) may have impacted on the availability of rectal dosage forms. Most of the marketed drug product stayed the same ($n = 15$), there were very few introductions of new references ($n = 3$) but some withdrawals ($n = 10$). However, among the fifteen drug products remaining

on the market, a restriction of use was applied on nine of them (i.e. for children over 30 months only). The evolution of the French market can be explained by three main reasons: economic withdrawal, legal withdrawal, and restriction of use due to active ingredients being deemed inappropriate for young children. These restrictions of use were implemented in France in 2011. It was also noticed during this investigation that some withdrawals also took place from the Spanish and Portuguese market, at approximately the same time around 2010.

These changes highlight the fact that national health agencies have taken into account some specific paediatric needs.

3.3. Paediatric rectal forms cited in the scientific literature: a scoping exercise

The keywords used for this Scopus search were [suppository OR rectal] AND [children OR paediatric]. Out of the 8942 references proposed by Scopus, were included only articles written in English (6664 references) where a rectal dosage form was mentioned (either for formulation work on rectal dosage forms or for clinical studies – 128 references). More than half of the literature references (69 out of 128) on rectal dosage forms for paediatrics were published since 2000 showing the interest of this route of administration to treat children.

The scientific literature also shows a clear preference for suppositories, as 84% of publications on paediatric rectal dosing refer to this

Table 5
Paediatric rectal forms marketed in five European countries: France (F), Germany (D), Portugal (P), Spain (S), and United Kingdom (UK).

Form	Drug	Country	Dose	Indications ^a , age
Suppository	Paracetamol	F	80, 100, 150, 200, 300 mg (OTC)	Analgesic, antipyretic
		D	75, 125, 250, 500 mg	
		P	75, 125, 250, 500 mg	
		S	125, 250 mg (OTC)	
		UK	60, 125, 250 mg	
Suppository	Bisacodyl	D	10 mg	Laxative
		P	10 mg	
		S	10 mg (OTC)	
		UK	5 mg	
		F	5, 10 mg	
Gel	Diazepam	D	5, 10 mg	Epilepsy
		P	5, 10 mg	
		S	10 mg	
		UK	5, 10 mg	
		D	10 mg	
Suppository	Diazepam	P	5, 10 mg	Epilepsy
		F	25 mg	
		D	12.5, 25, 50 mg	
Suppository	Sodium Diclofenac	UK	12.5, 25, 50 mg	NSAID
		F	1.25 g (OTC)	
		D	0.85, 1.5, 2 g (OTC)	
		P	0.686, 1, 1.1 g (OTC)	
		S	Up to 2 g (OTC)	
Suppository	Glycerine	UK	1 g (OTC)	Laxative
		P	NA (OTC)	
		S	NA (OTC)	
		D	75, 150 mg	
		P	75, 125, 150 mg	

^a All listed drug products are human prescription drug label except those containing 'OTC' over-the-counter drug products (57 references selected after an ANSM, Thériaque, eMC, AEMPS, Pharmanet-Bund, and Infarmed search, March, 8th 2013).

Table 6

Evolution of the French market for paediatric rectal forms between 1990 and 2012.

Therapeutic class	Drug	Marketed drug products ^a listed in 1990	Marketed drug products ^a listed in 2012	Modification
Analgesic	Paracetamol	2	3	1 new reference
	Aspirin + Phenobarbital	2	0	Withdrawn in 1997
	Glafenine	1	0	Withdrawn in 1992
	Paracetamol + Promethazine	1	1	From 2 to 5 years
Anti-emetic	Metoclopramide	1	0	Withdrawn in 2012
Anti-infectious	Clofoctol	1	0	Withdrawn in 2005
Laxative	Gelatine + Glycerine	1	1	None
	Mannitol	2	0	Withdrawn in 1992
	Sodium bicarbonate + Potassium bitartrate	1	1	None
	Sorbitol	1	1	None
	Glycerine	1	2	1 new reference
	Ox bile	1	0	Withdrawn in 1992
	Diclofenac	1	1	None
	Niflumic acid	1	1	None
NSAIDs	Naproxen	1	0	Withdrawn in 1997
	Bamifylline	1	0	Withdrawn in 2003
	Theophylline	1	0	Withdrawn in 2010
Respiratory	Citral + Guaiacol + Terpeneol + Pine + Thyme	1	1	Withdrawal of infant dosage in Feb. 2012. Restriction of use: only for children over 30 months.
	Eucalyptol + Guaiacol + Pine + Amylene HCl	1	1	
	Sodium teonate + Eucalyptus	1	1	
	Sodium teonate + Eucalyptus + Paracetamol	1	1	
	Guaifenesine + Eucalyptol + Bismuth	1	1	
	Niaouli + Grindelia + Gelsenium	1	1	
	Guaifenesine + Eucalyptol + Camphor	1	1	
	Bismuth + Eucalyptol + Guaiacol + Camphor	0	1	
	Turpentine	1	1	
	Turpentine + Diprophylline	1	1	
	Terpine + Pine + Niaouli + Eucalyptus	1	0	Withdrawn in 2012

^a Multiple doses may exist for each drug product listed in this table.

dosage form. The other forms described in these papers are solutions (7%), enemas (6%), and gels (3%).

Suppositories are a versatile rectal dosage form as they can be used for all the main therapeutic indications listed in Table 7. On the other hand, alternative rectal dosage forms are mainly used in hospitals for premedication, anaesthesia or postoperative pain management in the case of rectal solutions [58–67] and gels [68], and for preparation of the colon before colonoscopy with enemas [69]. Exceptions are the use of Valproate retention enema to treat epilepsy [70], and gels or systems that form gel in situ [71–73]. This latter type of novel dosage form will be discussed later.

Table 8 shows the top 6 pharmaceutical active ingredients formulated in rectal dosage forms.

Most of the time paediatric suppositories are used for systemic effect. Paracetamol [74–96] and Sodium Diclofenac [97–113] are the two main active ingredients studied in the literature and are as well the two main drugs available on the market. Apart from Sodium Diclofenac, other non-steroidal anti-inflammatory drugs are also formulated in suppository form as for example: Ibuprofen [76,114], Niflumic acid [93,115], Aspirin [116,117], Ketoprofen [118–121], Mephenamic acid [122], Indomethacin [71,72,123], Suprofen [96], Nimesulide [73], and Tinoridine [124]. These suppositories are intended to treat (post-operative) pain, migraine, and fever.

Table 7

Therapeutic indications of paediatric rectal dosage forms.

Therapeutic indication	% of citations
Analgesic	37
Anti-infectives	18
Laxatives	10
Premedication	10
Antipyretic	9
Anti-emetic	6
Anaesthetic	4

As found in the scientific literature from 1975 to 2013 (128 publications selected after a Scopus search, February, 26th 2013.)

Another main indication of paediatric suppositories for systemic effect is anti-infectives (Ampicillin [125–136], Ceftizoxime [137–139], and Azithromycin [140,141]) and in some antimalarial drugs (Artesunate [29,30,38,142], Artemether in association with Azithromycin [143], and Artemisinin [30]). *It should be noted that all twelve references on the in vivo effect of Ampicillin suppositories were published in 1983 by Japanese researchers in the same volume of the Japanese Journal of Antibiotics.* Suppositories are a dosage form of choice to administer the high doses required for antibiotics, minimising the need for multiple oral dosing to reach the desired drug level [4]. In addition, suppository formulations avoid the problem of poorly palatable antibiotics that are difficult to administer to children [144].

Suppositories are also used to treat febrile seizures and epilepsy with Diazepam [145–147] or Valproate [70], nephropathic cystinosis with Cysteamine [148], asthma with Aminophylline [149], cough with terpenic derivatives [150] or *Ephedra* decoction (a Traditional Chinese Medicine) [151], and pain with Pentazocine [152] or migraine with Ergotamine tartrate [117].

Suppositories can also be the form of choice for indications where the oral route is not usable. This is the case of anti-emetic drugs such as: Dimenhydrinate [153–156], Promethazine [157], Domperidone [158,159], and Metoclopramide [159].

Like rectal solutions, suppositories are used in hospital for premedication (Midazolam in association with Famotidine [160], Bromazepam [161,162], Diazepam [163–165], Pentobarbital [166], Chloral hydrate [162]), postoperative pain management (Codeine [167] alone or in association with Paracetamol [168]).

Suppositories can also be used for local effects such as laxative in substitution to enema, with the use of active ingredients like glycerine, bisacodyl or a combination thereof [169–180], or Mesalamine for the treatment of ulcerative proctitis [181,182].

3.4. Suppositories: considerations for paediatric dosing

Rectal dosage forms, as described by the European Pharmacopoeia, can be suppositories, capsules, solutions, suspensions, ointments, creams,

Table 8

Active ingredients formulated in paediatric rectal dosage forms.

Active Pharmaceutical Ingredient	% of citations
Paracetamol	20
Sodium Diclofenac	15
Ampicillin	10
Diazepam	6
Artesunate	3
Dimenhydrinate	3

As found in the scientific literature from 1975 to 2013 (128 publications selected after a Scopus search, February, 26th 2013).

gels, foams, and tampons (Table 2). The most commonly used rectal form is by far suppositories as demonstrated by the commercial drug products and literature review aforementioned.

Suppositories for paediatric dosing are generally torpedo-shaped dosage forms weighting 1 g. There are also novel stick-shaped suppositories with a line of breakability to divide the dosage form in two halves which allow reducing the dose for smaller children. The weight of 1 g for paediatric dosing [4] facilitates the insertion of the smaller suppository in the child's rectum while allowing having an object easily manipulated by the parent or care-giver. Paediatric suppository doses are generally adjusted from adult doses based on body weight. Taking into account the difference of available surface for absorption in the rectum (Table 1) would certainly be a better option.

3.4.1. Choice of the excipient

Paediatric suppositories are generally composed of the same excipients as the adult dosage forms, that is to say, either composed of:

- fatty bases (hard fat or cocoa butter that melts at the temperature of the rectum) or
- water-soluble bases (polyethylene glycol (PEG) or glycerinated gelatine that dissolves in the rectum).

The choice between these two types of suppository masses depends on the physicochemical properties of the active ingredient and the desired release profile [4]. Formulators generally choose to disperse drugs in suppository masses where it is not soluble, to facilitate the release of the drug from the dosage form. Hence, water-soluble drugs are formulated with fatty bases and lipophilic drugs in water-soluble bases. Since most of the active pharmaceutical drugs used by the rectal route are water-soluble (Biopharmaceutics Classification System – BCS class I) such as Paracetamol, Diazepam, Ketoprofen, Midazolam, and Aspirin, or are weak acids showing limiting dissolution by the oral route (BCS class II) but which are soluble in the rectum for example Sodium Diclofenac, Ibuprofen and Indomethacin [183], the choice of fatty bases is most of the time the best way to formulate suppositories.

Suppositories composed of fatty bases should melt at a temperature near to body temperature (37 °C) and the resulting melt should cover the rectum with a thin film of fat where the drug can diffuse out and reach the rectum mucosa. Among fatty bases, hard fat is the most common suppository mass used in Europe (mainly Southern and Eastern Europe including Russia), North Africa, Middle East, People's Republic of China, and Japan.

Various types of hard fats are available on the market with two main characteristics: their drop point ranging from 32 to 45 °C [4], and their hydroxyl value ranging from less than 3 to 50 mg KOH per gram of fat. The main commercial names for hard fats are Suppocire® (Gattefossé) and Witepsol® (Sasol). The drop point (alternative method to evaluate the melting properties of fat) of suppository masses varies around 37 °C in order to allow the incorporation of all types of drugs. As a matter of fact, drugs which are soluble in the suppository mass will induce a decrease of the melting temperature of the excipient. Hence a hard fat with a drop point higher than 37 °C should be chosen to obtain, after inclusion of the drug, a formulation which softens/melts between 36 and 37 °C. On the contrary, for drugs which are not soluble in the excipient

mass and possess a high dose, the viscosity of the melt can be too high to allow an adequate softening at the rectum temperature. In order to reduce the viscosity at this temperature, a hard fat with a drop point lower than 37 °C is classically chosen. Hard fats also possess a large range of hydroxyl values depending on the number of free hydroxyl groups in the excipient mass. These free hydroxyl groups come from partial glycerides i.e. monoglycerides and diglycerides, and also from free glycerol. Hard fats with high hydroxyl value generally crystallise faster than other types of hard fats because their content of monoglycerides is higher and these molecules present a solidification temperature higher than the main components of hard fat: triglycerides. These free hydroxyl groups also impact the ability of the suppository mass to interact with water and hence can increase the dissolution rate of active ingredient.

These lipophilic excipients are derived from natural vegetable oils and are well tolerated by the rectal mucosa [184]. However, one publication has suggested that hard fat bases with high hydroxyl value could be irritant to the rectal mucosa [185]. Hard fats also conform to the recommendations for paediatric excipients because they allow minimisation of the number of excipients (most of the time only one suppository mass is used); risk additives can be avoided (e.g. colouring agent, antimicrobial preservatives, sweetening agents, taste-masking agents or solubility enhancers), and also they do not cause religious concerns (in opposition to rectal capsules composed of gelatine) [186]. However, some fatty bases may contain some additives such as phospholipids (to accommodate for high dose of powdered drug), monoglycerides (to accelerate drug release), and non-ionic surfactant (polysorbates to facilitate the emulsification of hydrophilic liquid drug into the fatty base) preferred to ionic surfactants which are often irritant to the rectal mucosa.

The cost of goods for fatty bases is relatively low for excipients, in comparison to other excipients classically used in oral dosage forms. Hard fats are considered as global commodities because the raw materials are easily available at low price and the processes needed to transform them into fatty bases are simple and non-proprietary. The price of such materials is about 10-fold lower than functional excipients for oral dosage forms.

Due to climate constraints, PEGs can be used as a substitute to hard fats in tropical regions such as Africa. This mass can be irritating to mucosa by causing stinging [187] or even cause hypersensitivity (particularly for PEGs with lower molecular weights) [188]. For this reason PEGs are less adapted to paediatric dosing than natural hard fats.

For these regions other solid alternatives recommended include rectal soft gelatine capsules with a lubricating coating. This is the case in the South American market for example. These rectal forms composed of water-soluble bases should dissolve freely in the rectum liquid at 37 °C.

Regarding rectal solutions, water-soluble drugs – as powders or formulated in rectal tablets – are often extemporaneously dissolved in aqueous media such as distilled water, sterile water, or sodium chloride solution as reported for anaesthetic drugs in the literature. However, we found on the market a Diazepam rectal solution containing excipients less adapted to children like ethanol or benzyl alcohol [189]. The rectal solution is administered with an appropriate prefilled-syringe equipped with a lubricated catheter to facilitate introduction in the children's rectum.

3.4.2. Manufacturability

The manufacture of suppositories is a four-step process including the preparation of raw materials, mixing of the drug with the melted mass, moulding of suppositories in blisters, and subsequent crystallisation of the formulation. Some alternative methods to moulding are described in the literature and will be presented in the following section dedicated to the future of rectal dosage forms. Even if the moulding process seems straightforward, some steps and parameters should be looked at closely to avoid major drawbacks for paediatric dosing, such as non-homogeneity or crystallisation of the drug on the surface of the dosage form.

The suppository mass should be melted at a temperature 10 to 20 °C above its stated melting point to allow a complete melting of all crystals. If the drug is soluble in the suppository mass, it should be dissolved in the appropriate excipients. If not, the particle size of the drug should be controlled [45] because it can affect the viscosity of the mixture (small particles in suspension tend to increase the viscosity of the medium) and the homogeneity of the dosage form. The mixing of the drug with the melted excipient should provide for a homogeneous system. The moulding step of the mixture should be conducted at the appropriate temperature to allow for a rapid crystallisation of the mass and hence limit the ability of the drug to precipitate at the bottom of the blister. This temperature is determined by thermorheology and corresponds to the temperature where the viscosity of the melt starts to sharply increase. Moulding at the lowest temperature possible will also facilitate the crystallisation of the suppository and avoid drawbacks caused by a too high difference between pouring and crystallisation temperatures: polymorphism (fat blooming on the surface of suppositories), cracks (contraction of lipid during rapid solidification), or sedimentation of the drug. This latter step is particularly important for paediatric suppositories because it can affect the weight (formation of chimney at the base of the suppository), and the homogeneity of mass, which can be problematic for scored suppositories.

In some developing countries, suppositories can still be moulded manually within metal moulds. The same manufacturing process can be implemented as for industrial process with the addition of a scraping step after solidification of the suppository mass to remove the extra-mass of mixture. This manual process is also used in some hospitals for extemporaneous compounding of drugs not commercially available as paediatric rectal forms on the market. Metallic moulds available on the market do not allow producing suppository of less than 1 g. In addition, producing smaller dosage forms will compromise the ability of these suppositories to conform to pharmacotechnical tests.

3.4.3. Pharmacotechnical testing of suppositories

The European Pharmacopoeia (EP) is the only Pharmacopoeia describing some specific pharmacotechnical tests for rectal dosage forms such as suppositories and vaginal pessaries [45]. These tests aim to verify the ability of the dosage form to quickly disintegrate in contact with water (for water-soluble bases [190]) or to soften at a temperature close to the rectum temperature (for fatty bases [191]) in order to release the active ingredient [192]. The uniformity of mass [193] and content [194] is needed for these single-dose preparations. The uniformity of drug repartition within the suppository is also particularly important for adult doses which are sometimes cut in halves to accommodate for paediatric dosing. This is an unlicensed use that can take place in some hospitals. In most cases the suppository is cut in its length in order to have a homogeneous content of drug even if the drug has sedimented in the tip of the dosage form [195]. However, recasting adult suppositories into moulds of smaller size (generally 1 g) is a better option to ascertain a homogeneous repartition of the drug within the dosage form. Interestingly, some forms on the market already exist as scored stick-shaped suppositories, in order to accommodate for two doses (Fig. 1): Paracetamol scored suppositories at 100 mg, and Morniflumate scored suppositories at 400 mg (dividable in 200 mg halves), for example [88].

Additional tests, actually not described in any Pharmacopoeia, are classically used to assay suppositories such as resistance to crushing, slip melting temperature or appearance evaluation.

4. Paediatric clinical studies: a 10-year overview

This section focuses on clinical trials conducted in children within the last ten years with several well-known drugs. In brief, it collates paediatric clinical studies focusing on the comparison of the rectal route with other routes of administration, the determination of paediatric rectal doses and the evaluation of drug associations. These clinical studies

are listed by indication: analgesics/antipyretics, antiepileptics, and antimalarial drugs.

4.1. Analgesics, antipyretics and NSAIDs

Paracetamol was used in several clinical trials as an analgesic in pre- and post-operative pain management for minor surgery, sometimes associated with Codeine, or in chronic diseases [79–81,168,196,197], with good results. Paracetamol administered by the rectal route is less efficient than the intravenous route in the case of pain management after major surgery, [91], and it must not be used in the specific case of new born after assisted vaginal delivery [198]. However, it is recommended as an antipyretic in emergency cases [199] and the rectal route is as efficient as the oral route [40]. A meta-analysis compares the oral and rectal routes for reducing fever. It concluded by the equivalence of these two routes and may change the point of view of The American Academy of Pediatrics, whose recommendation was, so far, to refrain rectal administration of Paracetamol to children [82].

Diclofenac is used as an analgesic in pre- and post-operative pain management after surgery and shows good efficacy by rectal administration alone, or in association with other drugs [97,112,200].

Ketoprofen administered by the rectal route is a good alternative to the intravenous or oral routes [118,201].

Midazolam can reduce, or even avoid, the use of general anaesthesia for dental treatments [202].

Mesalamine suppository is a safe and efficient treatment of ulcerative proctitis for children [181].

4.2. Antiepileptics

Diazepam administration by the rectal route is sure, efficient and better than the nasal route [37,145,146].

The use of Paraldehyde by the rectal route is efficient in the case of prolonged tonic-clonic convulsions [203].

4.3. Antimalarial drugs

Malaria is referenced as a tropical disease with prevalence in children under 5 years of age [204]. Numerous clinical trials on children were conducted lately with old active pharmaceutical ingredients. This high number of studies can be explained by the need to have dosage forms that can be easily administered in case of emergency, the prevalence of this pathology, and the involvement of many non-governmental organizations. Three main conclusions can be drawn from these clinical trials.

- Rectal administration can either be used with only one drug in emergency [55,205–207], or as a long-term treatment [208–210]. The rectal form of Artesunate was also tested in association with Mefloquine and this allowed improving the efficiency, and/or shortening the treatment [211–213]. Rectal diazepam was tested as an anti-convulsing drug in the cases of children with severe *Falciparum malaria* and convulsions, but its efficiency seems lower than parenteral administration [214].
- The use of rectal dosage forms allowed the treatment of children in rural areas where the parenteral administration of drug is not possible. Some clinical studies were performed to compare the rectal and parenteral routes, either using the same drug [35,215–217] or two different active substances. In every case the rectal route has either given comparable or greater efficiency [218–220].
- Two studies concluded to the importance of Artesunate as pre-referral treatment of severe childhood malaria and on the cost effectiveness of the rectal form [221,222]. Another study demonstrated the urgent need to develop an association of two drugs: antimalarial and antibacterial in the same rectal dosage form to decrease the cost of the treatment and avoid many deaths (up to 400,000) [223].

As a conclusion, it appears that the administration of antimalarial drugs by the rectal route is very effective (especially in the case of emergencies), well adapted to endemic areas, able to be used at home by any care giver, and cost effective. The association of antimalarials and antibacterials seems to be possible; nevertheless there are no recent studies on antibiotic rectal forms, despite some studies initiated in the 1990s [224]. This association was at the same time the most efficacious, the most cost effective, and also well adapted to emergency situations in cases with a lack of diagnostics.

5. The future

Research on paediatric rectal forms consists presently in the improvement of actual forms (especially suppositories and gels), and in the development of dosage forms classically used in other routes such as tablets for example. Obviously these so-called classical forms must be adapted to the specificities of the rectal route (e.g. small amount of liquid).

5.1. *In vitro* and preclinical studies

5.1.1. *Thermosensitive and/or mucoadhesive gels*

In order to solve some drawbacks of conventional solid suppositories, various formulation strategies have been developed such as thermosensitive and mucoadhesive *in situ* gel systems. The combination of thermosensitive and mucoadhesive properties in a single formulation presents many advantages. First, the thermosensitive preparation is liquid at ambient temperature which facilitates its preparation and handling, but also eases its spreading in the rectal cavity where it gels at the body temperature. Secondly, in the rectal cavity, the development of mucoadhesive properties helps to maintain the hydrogel for a prolonged period of time and allows complete drug release, thus favouring systemic absorption.

Over the last two decades, thermosensitive polymers and hydrogels have focused a growing interest in the pharmaceutical field. Depending on their composition, the sol–gel transition temperature can be adjusted around 37 °C for pharmaceutical applications [73,225–231].

5.1.2. *Suppositories*

Some new suppository developments are on-going on three main topics: muco-adhesiveness, controlling drug release, and improving stability/storage at high-temperature.

5.1.2.1. *Muco-adhesiveness.* The addition of mucoadhesive excipients in suppository formulations permits the adhesion of the dosage form in the lower rectum and hence avoids the drainage of the drug by the upper haemorrhoidal veins (leading to hepatic first pass effect). Carbomer (Carbopol®) is described in several studies for the development of such mucoadhesive properties. For example, the association of this polymer (2% of the 934-P grade) to hard fat allows obtaining Ramosetron suppositories with efficiency comparable to the intravenous administration of the drug [230]. Furthermore, this percentage of carbomer did not induce irritation of the rectal mucosa of rabbits.

Double-phased mucoadhesive suppositories were also described in two other formulations containing either Lidocaine or Diclofenac as active ingredients. These studies were performed on rats and rabbits [232, 233]. Double-phased suppositories consist of a mucoadhesive front layer containing wax and a mucoadhesive terminal layer containing the drug. The anchoring phase (adhesion and spatial configuration of the suppository within the rectum) strictly limits the absorption of the drug in the lower rectum and the formulation of the terminal layer modulates drug release properties. This double-phased suppository may be useful for improving bioavailability of drugs with significant first-pass effect.

5.1.2.2. *Controlling drug release.* The addition of surfactants in suppository formulations can also help increase drug release provided that they

are not irritant to rectal mucosa [234]. Surfactants such as polysorbate 80 (2%) and sodium lauryl sulphate (0.75%) increase the dissolution rate of Salbutamol from suppositories. However, sodium lauryl sulphate could cause greater damage on mucosa than polysorbate 80 because it is an anionic surfactant [235]. The addition of rectal absorption enhancer, like snail mucin, was also tested with Insulin in rats [236].

Sustained-release hollow-type (SR-HT) suppositories are a new platform developed with sodium alginate (Alg-Na), sodium polyacrylate (PANa) or polyacrylate-PANa co-polymer (PA-PANa) as gelling agents. The gelling agent is either combined with the drug inside the hollow part of the suppository or mixed with the shell. A study of SR-HT containing Aminophylline conducted on rabbits showed that these suppositories could be used for rectal administration of various drugs needing a prolonged plasma concentration [237].

Hollow-type suppositories containing 10 mg of Morphine in sodium hyaluronate solutions of various viscosities were prepared. It appears that the selection of the relevant viscosity of sodium hyaluronate solution contributes to the improvement of Morphine bioavailability after rectal administration to rabbits [238]. This model has been studied with other active pharmaceutical ingredients and/or excipients and gave similar improvement of drugs bioavailability [239–241].

Self-emulsifying suppositories were developed for β -Artemether and Indomethacin [242,243]. These forms induce sustained release for β -Artemether in comparison to PEG suppository, and a similar increase of bioavailability of Indomethacin after oral and rectal administration.

5.1.2.3. *Improved stability at high-temperature.* Suppositories able to withstand tropical climates can be developed with excipients possessing melting points above 50 °C. Such suppositories can be formulated with high-molecular PEG such as PEG 4000 and PEG 1500. The use of these water-soluble bases with Azithromycin produced suppositories with good bioavailability in rabbits when compared to other rectal forms (hard gelatin capsules, gels and oily suspension) [140].

5.1.3. *Other forms*

Other systems are being developed or adapted to the rectal route:

- New disintegrating excipients used for oro-dispersible tablets such as croscopovidone or sodium croscarmellose are able to disintegrate the dosage form with minimal amounts of liquid (2 to 3 mL). These new excipients could also be used for recto-dispersible tablets [244]. It was used to formulate two drugs (Artesunate and Azithromycin) for emergency treatment of Malaria (Larroure, D. et al. Development of antimalaric-antibiotic association in a fast dispersible tablet using rectal route. 3rd Conference of the European Paediatric Formulation Initiative (EuPFI), Strasbourg, France, 2011).
- Mucoadhesive polymers allow production of bio-adhesive microspheres, whose properties can improve the *in situ* stabilisation, enhance the spreading of the formulation on mucosa, and/or modify the drug release [245–247].
- Emulsions could be an alternative to rectal form in order to modify drug release as demonstrated by some studies with Diazepam [248–250].

The tolerability of these oral excipients may be extrapolated to the rectal route as this mucosa is more resistant than the upper gastrointestinal one because of its limited surface and the presence of mucus. However safety of excipients, especially if novel, in children is paramount and should be checked with appropriate studies first, prior to promoting their use widely.

5.2. *Vaccination by the rectal route*

Recent publications have shown the interest of the rectal route for mucosal or systemic vaccination. The mucosal route is mainly used for vaccination because most infections affect or start from a mucosal surface. In these infections, topical application of the vaccine is often

required to induce the protective immune response [251,252]. The use of appropriate adjuvants such as toxins or cytokine [253,254] can increase the efficiency of the rectal vaccination. Furthermore, the rectal route offers additional advantages, especially in developing countries, such as a reduced risk of viral transmission (no need of injections), less side effects, and the possibility to administer the drug product without medical training [255].

Vaccination by the rectal route was tested for tuberculosis and it was as efficient as the parenteral route in mice, guinea pigs and macaques [255]. This route was also experimented for Herpes vaccination with good results [253,256,257]. The main area of research for mucosal vaccination is HIV, an infection transferred by mucosal contamination (vaginal or rectal). The combination of local and systemic protection seems to be appropriate [254,258] and the FDA presents prophylaxis strategies using the rectal route against HIV infection [259]. These investigations give very encouraging and positive results in animals, but have not yet been tested in humans. Even if this type of vaccination will face the same socio-ethical barriers as classical rectal dosage forms, children should be included in future positive development or rectal vaccination research programmes where relevant.

6. Conclusions

The rectal route is usually better known for its disadvantages than for its advantages. The main disadvantages are the introduction of a solid unit in the rectum (leading to poor acceptability and compliance), the low absorption capacity of the lower rectum to some drugs, and the high inter-individual variability of the drug bioavailability mainly depending on how the dosage form is inserted.

Rectal dosage forms present many advantages, especially in developing countries, because of their low cost, the possible administration of the form without any medically trained person (in contrast to intravenous route for example) and the possibility to dose drug product in emergencies even to unconscious or vomiting children. In the case of emergency administration there may be lower psychological and social barriers because of the seriousness of the situation.

Finally mindsets may be changing regarding the dosing of drugs rectally to children, as some of the main disadvantages of suppositories are being solved: the variable absorption of drugs due to variable insertion/retention of the dosage forms can be controlled by adapted formulation (muco-adhesive dosage forms) or appropriate devices. Also some paediatric clinical studies through meta-analysis have recently demonstrated the equivalence of rectal dosage forms versus oral dosage forms like in the case of Paracetamol. In order to enable the use of this promising route for the treatment of children in the 21st Century, some effort should be focused on marketing, informing and educating parents and care givers on the benefits of these novel rectal dosage forms. Their comprehension should ensure the acceptability, compliance, and correct usage of the rectal forms.

References

- [1] J.M. Aiache, R. Renoux, D. Fistre, History of the suppository form [Historique de la forme suppositoire], in: B. Glas, C.J. de Blaeys (Eds.), *Rectal Therapy: Proceedings of the Symposium on the Advantages and Problems Encountered in Rectal Therapy*, J.R. Prous Publishers, Barcelona, 1984, pp. 5–8.
- [2] N.J.B.G. Guibourg, N.E. Henry, *Pharmacopée Raisonnée ou Traité de Pharmacie Pratique et Théorique*, Mequignon-Marvis, Père et Fils, Paris, 1841.
- [3] J.T. Gwathmey, Rectal administration of evipal soluble. A safe, reversible and controllable preanesthetic medication a preliminary report, *Am. J. Surg.* 32 (1936) 411–416.
- [4] J.H. Rytting, J.A. Fix, Drug delivery – rectal route, in: J. Swarbrick, J.C. Boylan (Eds.), *Encyclopedia of Pharmaceutical Technology*, Marcel Dekker, Inc., New York, 2002, pp. 932–944.
- [5] H.E. van, A.G. de Boer, D.D. Breimer, Pharmacokinetics of rectal drug administration, part I. General considerations and clinical applications of centrally acting drugs, *Clin. Pharmacokinet.* 21 (1991) 11–26.
- [6] ICH harmonised tripartite guideline, clinical investigation of medicinal products in the pediatric population – E11 [on line], Available on: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E11/Step4/E11_Guideline.pdf (consulted 3–4–2013).
- [7] Guideline on the investigation of medicinal products in the term and preterm neonate (CHMP/PCDO) – EMEA/536810/2008 [on line], Available on: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003750.pdf (consulted 22–3–2013).
- [8] Alternative routes of drug administration—advantages and disadvantages (subject review), *American Academy of Pediatrics Comm. Drugs Pediatr.* 100 (1997) 143–152.
- [9] Committee for Medicinal Products for Human Use (CHMP), reflection paper: formulations of choice for the paediatric population (EMA/CHMP/PEG/196810/2005) [on line], Available on: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003782.pdf (consulted 22–3–2013).
- [10] R.C. Woody, E.S. Golladay, S.C. Fiedorek, Rectal anticonvulsants in seizure patients undergoing gastrointestinal surgery, *J. Pediatr. Surg.* 24 (1989) 474–477.
- [11] J. den Hertog, E. van Leengoed, F. Kolk, L. van den Broek, E. Kramer, E.J. Bakker, E. Bakker-van Gijssel, A. Bulk, F. Kneepkens, M.A. Benninga, The defecation pattern of healthy term infants up to the age of 3 months, *Arch. Dis. Child Fetal Neonatal Ed.* 97 (2012) F465–F470.
- [12] L.T. Weaver, G. Ewing, L.C. Taylor, The bowel habit of milk-fed infants, *J. Pediatr. Gastroenterol. Nutr.* 7 (1988) 568–571.
- [13] S.M. Mugie, C. Di Lorenzo, M.A. Benninga, Constipation in childhood, *Nat. Rev. Gastroenterol. Hepatol.* 8 (2011) 502–511.
- [14] D.M. Mota, A.J. Barros, A. Matijasevich, I.S. Santos, Longitudinal study of sphincter control in a cohort of Brazilian children, *J. Pediatr. (Rio. J.)* 86 (2010) 429–434.
- [15] Population and human development, in: World Resource Institute (Ed.), *World Resources 1992–1993: A Guide to the Global Environment—Toward Sustainable Development*, University Press, Oxford, 1992.
- [16] O.M. Wrong, Definitions and history, in: J.H. Cummings, J.L. Rombeau, T. Sakata (Eds.), *Physiological and Clinical Aspects of Short-Chain Fatty Acids*, Cambridge University Press, Cambridge, 2004, pp. 5–8.
- [17] J.P. Jantzen, P. Diehl, Rectal administration of drugs. Fundamentals and applications in anesthesia, *Anaesthesist* 40 (1991) 251–261.
- [18] W. Bitterman, R.J. Spencer, K.A. Huizenga, R.G. Shorter, Contact pH of rectal mucosa in humans and dogs, *Dis. Colon Rectum* 12 (1969) 96–98.
- [19] J.P. Jantzen, I. Tzanova, P.K. Witton, A.M. Klein, Rectal pH in children, *Can. J. Anaesth.* 36 (1989) 665–667.
- [20] C. Turner, T.N. Aye Mya, P. Turner, F. Nosten, N.J. White, Rectal pH in well and unwell infants, *J. Trop. Pediatr.* 58 (2012) 311–313.
- [21] Development of paediatric medicines: points to consider in formulation, WHO Expert Committee on Specifications for Pharmaceutical Preparations, WHO Press – World Health Organization, Geneva, 2012. 179–226.
- [22] S. Lundberg, P. Hatava, M. Lagerkranser, G.L. Olsson, Perception of pain following rectal administration of morphine in children: a comparison of a gel and a solution, *Paediatr. Anaesth.* 16 (2006) 164–169.
- [23] S. Winnick, D.O. Lucas, A.L. Hartman, D. Toll, How do you improve compliance? *Pediatrics* 115 (2005) e718–e724.
- [24] Digital bowel stimulator and suppository inserter [on line], Available on: https://www.ncmedical.com/item_389.html?item_num=NC28704 (consulted 15–3–2013).
- [25] B. Jensen, L. Matsson, Oral versus rectal midazolam as a pre-anaesthetic sedative in children receiving dental treatment under general anaesthesia, *Acta Paediatr.* 91 (2002) 920–925.
- [26] R.L. Hinton, A. Auwun, G. Pongua, O. Oa, T.M. Davis, H.A. Karunajeewa, J.C. Reeder, Caregivers' acceptance of using artesunate suppositories for treating childhood malaria in Papua New Guinea, *Am. J. Trop. Med. Hyg.* 76 (2007) 634–640.
- [27] F.A. Kaona, M. Tuba, A qualitative study to identify community structures for management of severe malaria: a basis for introducing rectal artesunate in the under five years children in Nakonde District of Zambia, *BMC Public Health* 5 (2005) 28.
- [28] E.A. Makundi, H.M. Malebo, P. Mhame, A.Y. Kitua, M. Warsame, Role of traditional healers in the management of severe malaria among children below five years of age: the case of Kilosa and Handeni Districts, Tanzania, *Malar. J.* 5 (2006) 58.
- [29] S.O. Sam-Wobo, O.A. Agbeyangi, U.F. Ekpo, O.A. Akinloye, C.F. Mafiana, M.A. Adeleke, Rectal artesunate, their utilization, and parental perception in the management of malaria in children from Abeokuta, southwestern Nigeria, *Vector Borne Zoonotic Dis.* 12 (2012) 151–155.
- [30] D.O. Simba, M. Warsame, O. Kimbute, D. Kakoko, M. Petzold, G. Tomson, Z. Premji, M. Gomes, Factors influencing adherence to referral advice following pre-referral treatment with artesunate suppositories in children in rural Tanzania, *Trop. Med. Int. Health* 14 (2009) 775–783.
- [31] D.O. Simba, D.C. Kakoko, M. Warsame, Z. Premji, M.F. Gomes, G. Tomson, E. Johansson, Understanding caretakers' dilemma in deciding whether or not to adhere with referral advice after pre-referral treatment with rectal artesunate, *Malar. J.* 9 (2010) 123.
- [32] M.A. Thera, F. Keita, M.S. Sissoko, O.B. Traore, D. Coulibaly, M. Sacko, V. Lameyre, J.P. Ducret, O. Doumbo, Acceptability and efficacy of intra-rectal quinine alkaloids as a pre-transfer treatment of non-per or malaria in peripheral health care facilities in Mopti, Mali, *Malar. J.* 6 (2007) 68.
- [33] S.A. Colbert, D. O'Hanlon, O. McAnena, N. Flynn, The attitudes of patients and health care personnel to rectal drug administration following day case surgery, *Eur. J. Anaesthesiol.* 15 (1998) 422–426.
- [34] N. Seth, N.E. Llewellyn, R.F. Howard, Parental opinions regarding the route of administration of analgesic medication in children, *Paediatr. Anaesth.* 10 (2000) 537–544.
- [35] H. Barennes, D. Kailou, E. Pussard, J.M. Munjakazi, M. Fernan, H. Sherouat, A. Sada, F. Clavier, F. Verdier, Intrarectal administration of quinine: an early treatment for severe malaria in children? *Sante* 11 (2001) 145–153.

- [36] S. Smith, I. Sharkey, D. Campbell, Guidelines for rectal administration of anticonvulsant medication in children, *Paediatr. Perinat. Drug Ther.* 4 (2001) 140–147.
- [37] V. Ivaturi, R. Kriel, R. Brundage, G. Loewen, H. Mansbach, J. Cloyd, Bioavailability of intranasal vs. rectal diazepam, *Epilepsy Res.* 103 (2013) 254–261.
- [38] S. Inthavilay, T. Franchard, Y. Meime, E.A. Ashley, H. Barennes, Knowledge and acceptability of the rectal treatment route in Laos and its application for pre-referral emergency malaria treatment, *Malar. J.* 9 (2010) 342.
- [39] E. Chiappini, A. Parretti, P. Becherucci, M. Pierattelli, F. Bonsignori, L. Galli, M.M. de, Parental and medical knowledge and management of fever in Italian pre-school children, *BMC Pediatr.* 12 (2012) 97.
- [40] D. Scolnik, E. Kozar, S. Jacobson, S. Diamond, N.L. Young, Comparison of oral versus normal and high-dose rectal acetaminophen in the treatment of febrile children, *Pediatrics* 110 (2002) 553–556.
- [41] S.A. Lava, G.D. Simonetti, A. Ferrarini, G.P. Ramelli, M.G. Bianchetti, Regional differences in symptomatic fever management among paediatricians in Switzerland: the results of a cross-sectional web-based survey, *Br. J. Clin. Pharmacol.* 75 (2013) 236–243.
- [42] S.A. Karbasi, M. Modares-Mosadegh, M. Golestan, Comparison of antipyretic effectiveness of equal doses of rectal and oral acetaminophen in children, *J. Pediatr. (Rio J.)* 86 (2010) 228–232.
- [43] F. Farahmand, K. Eftekhari, V. Modarresi, M. Najafi-Sani, A. Khodadad, F. Motamed, Comparing oral route paraffin oil versus rectal route for disimpaction in children with chronic constipation; a randomized control trial, *Iran. J. Pediatr.* 20 (2010) 291–296.
- [44] S.A. Lava, G.D. Simonetti, G.P. Ramelli, S. Tschumi, M.G. Bianchetti, Symptomatic management of fever by Swiss board-certified pediatricians: results from a cross-sectional, web-based survey, *Clin. Ther.* 34 (2012) 250–256.
- [45] Rectal Preparations EP 01/2008:1145, European Pharmacopoeia, European Directorate for the Quality of Medicines & HealthCare, Strasbourg, 2011. 732–733.
- [46] DailyMed Current Medication Information [on line], Available on: <http://dailymed.nlm.nih.gov/dailymed> (consulted 8-3-2013).
- [47] U.S. Food and Drug Administration [on line], Available on: www.fda.gov/default.htm (consulted 8-3-2013).
- [48] Kusuri-no-shiori Drug Information Sheet [on line], Available on: <http://www.rad-ar.or.jp/siori/english/kensaku.cgi> (consulted 8-3-2013).
- [49] ANSM – Agence Nationale de sécurité du Médicament [on line], Available on: <http://ansm.sante.fr/> (consulted 8-3-2013).
- [50] Thériaque [on line], Available on: <http://www.theriaque.org> (consulted 8-3-2013).
- [51] PharmNet.bund – the drug information portal of the Bund (Federal Government) and the Länder (States) [on line], Available on: <http://www.pharmnet-bund.de/dynamic/de/index.html> (consulted 8-3-2013).
- [52] INFARMED – National Authority of Medicines and Health Products [on line], Available on: <http://www.infarmed.pt/portal/page/portal/INFARMED> (consulted 8-3-2013).
- [53] Agencia Española de Medicamentos y Productos Sanitarios [on line], Available on: <http://www.aemps.gob.es/> (consulted 8-3-2013).
- [54] Home electronic Medicines Compendium [on line], Available on: <http://www.medicines.org.uk/emc/> (consulted 8-3-2013).
- [55] M.F. Gomes, M.A. Faiz, J.O. Gyaopong, M. Warsame, T. Agbenyega, A. Babiker, F. Baiden, E.B. Yunus, F. Binka, C. Clerk, P. Folb, R. Hassan, M.A. Hossain, O. Kimbute, A. Kitua, S. Krishna, C. Makasi, N. Mensah, Z. Mrango, P. Olliaro, R. Peto, T.J. Peto, M.R. Rahman, I. Ribeiro, R. Samad, N.J. White, Pre-referral rectal artesunate to prevent death and disability in severe malaria: a placebo-controlled trial, *Lancet* 373 (2009) 557–566.
- [56] P. Dorosz, Guide pratique des médicaments, elevened ed. Maloine, Paris, 1990.
- [57] P. Dorosz, D. Vital Durand, C. Le Jeune, Guide pratique des médicaments, thirty-second ed. Maloine, Paris, 2012.
- [58] N.C. Ahn, G.W. Andersen, A. Thomsen, N. Valentin, Preanaesthetic medication with rectal diazepam in children, *Acta Anaesthesiol. Scand.* 25 (1981) 158–160.
- [59] A. Bejersten, G.L. Olsson, L. Palmer, The influence of body weight on plasma concentration of atropine after rectal administration in children, *Acta Anaesthesiol. Scand.* 29 (1985) 782–784.
- [60] R.S. Hannallah, M.D. Abramowitz, W.A. McGill, B.S. Epstein, Rectal methohexitone induction in pediatric outpatients: physostigmine does not enhance recovery, *Can. Anaesth. Soc. J.* 32 (1985) 231–234.
- [61] J.M. Julia, A. Rochette, C. Ricard, Y. Jullien, J. du Cailar, Comparative study of rectal premedication with midazolam and flunitrazepam in infants, *Ann. Fr. Anesth. Reanim.* 3 (1984) 185–188.
- [62] I.G. Kestin, W.B. McIlvaine, C.H. Lockhart, K.J. Kestin, M.A. Jones, Rectal methohexital for induction of anesthesia in children with and without rectal aspiration after sleep: a pharmacokinetic and pharmacodynamic study, *Anesth. Analg.* 67 (1988) 1102–1104.
- [63] L.M.P. Liu, N.G. Goudsouzian, P.L. Liu, Rectal methohexital premedication in children, a dose-comparison study, *Anesthesiology* 53 (1980) 343–345.
- [64] L.M.P. Liu, P. Gaudreault, P.A. Friedman, N.G. Goudsouzian, Methohexital plasma concentrations in children following rectal administration, *Anesthesiology* 62 (1985) 567–570.
- [65] M.A.K. Mattila, M.K. Ruoppi, E. Ahlstrom-Bengs, H.M. Larni, P.O. Pekkola, Diazepam in rectal solution as premedication in children, with special reference to serum concentrations, *Br. J. Anaesth.* 53 (1981) 1269–1272.
- [66] C. Saint-Maurice, C. Esteve, J. Holzer, Premedication with rectal midazolam. Effective dose in paediatric anaesthesia, *Ann. Fr. Anesth. Reanim.* 3 (1984) 181–184.
- [67] T.J. White III, R.L. Siegle, G.J. Burckart, D.R. Ramey, Rectal thiopental for sedation of children for computed tomography, *J. Comput. Assist. Tomogr.* 3 (1979) 286–288.
- [68] D. Westerling, Rectally administered morphine: plasma concentrations in children premedicated with morphine in hydrogel and in solution, *Acta Anaesthesiol. Scand.* 29 (1985) 653–656.
- [69] J.O. Barrish, M.A. Gilger, Colon cleanout preparations in children and adolescents, *Gastroenterol. Nurs.* 16 (1993) 106–109.
- [70] L.M. Holle, B.E. Gidal, D.M. Collins, Valproate in status epilepticus, *Ann. Pharmacother.* 29 (1995) 1042–1044.
- [71] S. Miyazaki, C. Yokouchi, T. Nakamura, N. Hashiguchi, W.M. Hou, M. Takada, Pluronic F-127 gels as a novel vehicle for rectal administration of indomethacin, *Chem. Pharm. Bull. (Tokyo)* 34 (1986) 1801–1808.
- [72] S. Miyazaki, F. Suisha, N. Kawasaki, M. Shirakawa, K. Yamatoya, D. Attwood, Thermally reversible xyloglucan gels as vehicles for rectal drug delivery, *J. Control. Release* 56 (1998) 75–83.
- [73] Y. Yuan, Y. Cui, L. Zhang, H.P. Zhu, Y.S. Guo, B. Zhong, X. Hu, L. Zhang, X.H. Wang, L. Chen, Thermosensitive and mucoadhesive in situ gel based on poloxamer as new carrier for rectal administration of nimesulide, *Int. J. Pharm.* 430 (2012) 114–119.
- [74] P.D. Walson, M. Halvorsen, J. Edge, M.J. Casavant, M.T. Kelley, Pharmacokinetic comparison of acetaminophen elixir versus suppositories in vaccinated infants (aged 3 to 36 months): a single-dose, open-label, randomized, parallel-group design, *Clin. Ther.* 35 (2013) 135–140.
- [75] S. Ali, K. Maryam, Comparison of midazolam with lidocaine and fentanyl for caudal analgesia in children, *J. Med. Sci.* 7 (2007) 660–664.
- [76] N. Bilenko, H. Tessler, R. Okbe, J. Press, R. Gorodischer, Determinants of antipyretic misuse in children up to 5 years of age: a cross-sectional study, *Clin. Ther.* 28 (2006) 783–793.
- [77] P.K. Birmingham, M.J. Tobin, T.K. Henthorn, D.M. Fisher, M.C. Berkelhamer, F.A. Smith, K.B. Fanta, C.J. Coté, Twenty-four-hour pharmacokinetics of rectal acetaminophen in children: an old drug with new recommendations, *Anesthesiology* 87 (1997) 244–252.
- [78] M.C. Chang, Y.C. Chen, S.C. Chang, G.D. Smith, Knowledge of using acetaminophen syrup and comprehension of written medication instruction among caregivers with febrile children, *J. Clin. Nurs.* 21 (2012) 42–51.
- [79] C.R.H. Cormack, S. Sudan, R. Addison, J. Keating, R.A. Sherwood, E.M.C. Ashley, The pharmacokinetics of a single rectal dose of paracetamol (40 mg·kg⁻¹) in children with liver disease, *Paediatr. Anaesth.* 16 (2006) 417–423.
- [80] M. Dahi-Taleghani, S. Mousavifard, S. Tahmoureszade, A. Dabbagh, Rectal acetaminophen versus peritonsillar infiltration of bupivacaine for postoperative analgesia after adenotonsillectomy in children, *Eur. Arch. Otorhinolaryngol.* 268 (2011) 581–584.
- [81] G.A. Dashti, S. Amini, E. Zanguee, The prophylactic effect of rectal acetaminophen on postoperative pain and opioid requirements after adenotonsillectomy in children, *Middle East J. Anesthesiol.* 20 (2009) 245–250.
- [82] L.H. Goldstein, M. Berlin, M. Berkovitch, E. Kozar, Effectiveness of oral vs rectal acetaminophen: a meta-analysis, *Arch. Pediatr. Adolesc. Med.* 162 (2008) 1042–1046.
- [83] E.S. Golladay, S. Hutter, E. Koehn, T. Hunt, R. Gutta, F. Gerbasi, C. Corpron, A. Hagan, T. Dell, K. Selley, A comparison of caudal block and acetaminophen preemptive analgesia in pediatric peritoneoscopy, *Pediatr. Endosurg. Innov. Tech.* 7 (2003) 153–159.
- [84] T.W. Hahn, S.W. Henneberg, R.J. Holm-Knudsen, K. Eriksen, S.N. Rasmussen, M. Rasmussen, Pharmacokinetics of rectal paracetamol after repeated dosing in children, *Br. J. Anaesth.* 85 (2000) 512–519.
- [85] H.L. Helgadottir, M.E. Wilson, Parents' knowledge and choice of paracetamol dosing forms in 3- to 6-year-old children, *Scand. J. Caring Sci.* 22 (2008) 93–97.
- [86] V.M. Jones, Acetaminophen injection: a review of clinical information, *J. Pain Palliat. Care Pharmacother.* 25 (2011) 340–349.
- [87] A. Khalid, S.Z. Siddiqui, S. Haider, S. Aftab, Single dose caudal tramadol with bupivacaine and bupivacaine alone in pediatric inguinoscrotal surgeries, *J. Coll. Phys. Surg. Pak* 17 (2007) 519–522.
- [88] T.W. Kim, C.L. Rognerud, C.N. Ou, Accuracy in the alteration of acetaminophen suppositories, *Anesth. Analg.* 100 (2005) 1303–1305.
- [89] H. Li, Y. Li, Y. Wang, J. Wang, C. Hou, Y. Lin, L. Wang, X. Yang, Evidence-based evaluation and selection of essential medicine for township health centre in China: 3. common cold, *Chin. J. Evid.-Based Med.* 12 (2012) 868–877.
- [90] C.J. Montgomery, J.P. McCormack, C.C. Reichert, C.P. Marsland, Plasma concentrations after high-dose (45 mg·kg⁻¹) rectal acetaminophen in children, *Can. J. Anaesth.* 42 (1995) 982–986.
- [91] S.A. Prins, M. Van Dijk, P. Van Leeuwen, S. Searle, B.J. Anderson, D. Tibboel, R.A.A. Mathot, Pharmacokinetics and analgesic effects of intravenous propacetamol vs rectal paracetamol in children after major craniofacial surgery, *Paediatr. Anaesth.* 18 (2008) 582–592.
- [92] P. Sajedi, M. Nazem, K. Kaznavi, Effect of pre vs. post incision inguinal field block on postoperative pain after pediatric herniorrhaphy, a different approach, *J. Res. Med. Sci.* 12 (2007) 1–6.
- [93] B. Samaké, Y. Coulibaly, A. Diallo, M. Keita, M.A. Doumbia, Medical care of post-operative pain in pediatric surgery: comparison of three protocols, *Le Mali Méd.* 24 (2009) 7–9.
- [94] R. Singh, M. Kharbanda, N. Sood, V. Mahajan, C. Chatterji, Comparative evaluation of incidence of emergence agitation and post-operative recovery profile in paediatric patients after isoflurane, sevoflurane and desflurane anaesthesia, *Indian J. Anaesth.* 56 (2012) 156–161.
- [95] J.D. Tobias, Weak analgesics and nonsteroidal anti-inflammatory agents in the management of children with acute pain, *Pediatr. Clin. N. Am.* 47 (2000) 527–543.
- [96] G. Weippl, N. Michos, E.J. Sundal, H. Stocker, Clinical experience and results of treatment with suprofen in pediatrics. 2nd communication: use of suprofen suppositories as an antipyretic in children with fever due to acute infections/a

- single-blind controlled study of suprofen versus paracetamol, *Drug Res. (Arzneim. Forsch.)*, 35 (1985) 1724–1727.
- [97] E.S. Adarsh, R. Mane, C.S. Sanikop, S.M. Sagar, Effect of pre-operative rectal diclofenac suppository on post-operative analgesic requirement in cleft palate repair: a randomised clinical trial, *Indian J. Anaesth.* 56 (2012) 265–269.
 - [98] F. Bano, S. Haider, S.T. Sultan, Comparison of caudal bupivacaine and bupivacaine-midazolam for peri and postoperative analgesia in children, *J. Coll. Phys. Surg. Pak.* 14 (2004) 65–68.
 - [99] D.K. Bhowmick, K.M. Akhtaruzzaman, N. Ahmed, M.S. Islam, M.M. Hossain, M.M. Islam, Postoperative pain relief in children after subumbilical surgeries—a comparison between caudal bupivacaine and bupivacaine-clonidine, *Mymensingh Med. J.* 20 (2011) 93–97.
 - [100] J. Borkar, N. Dave, Analgesic efficacy of caudal block versus diclofenac suppository and local anesthetic infiltration following pediatric laparoscopy, *J. Laparoendosc. Adv. Surg. Tech. A* 15 (2005) 415–418.
 - [101] D. Findlow, L.M. Aldridge, E. Doyle, Comparison of caudal block using bupivacaine and ketamine with ilioinguinal nerve block for orchidopexy in children, *Anaesthesia* 52 (1997) 1110–1113.
 - [102] N. Gupta, R. Wakhloo, A. Mehta, D. Wali, S.D. Gupta, Post-operative analgesia in children: caudal block with bupivacaine, rectal diclofenac and combination of both, *J. Anaesthesiol. Clin. Pharmacol.* 24 (2008) 321–324.
 - [103] S. Gupta, R. Maheshwari, S.C. Dulara, Wound instillation with 0.25% bupivacaine as continuous infusion following hysterectomy, *Middle East J. Anesthesiol.* 18 (2005) 595–610.
 - [104] I.H. Littlejohn, M.M. Tarling, P.J. Flynn, A.J. Ordman, A. Aiken, Post-operative pain relief in children following extraction of carious deciduous teeth under general anaesthesia: a comparison of nalbuphine and diclofenac, *Eur. J. Anaesthesiol.* 13 (1996) 359–363.
 - [105] P.R. McGowan, H. May, Z. Molnar, M. Cunliffe, A comparison of three methods of analgesia in children having day case circumcision, *Paediatr. Anaesth.* 8 (1998) 403–407.
 - [106] K. Mikawa, K. Nishina, N. Maekawa, M. Asano, H. Obara, Oral clonidine premedication reduces vomiting in children after strabismus surgery, *Can. J. Anaesth.* 42 (1995) 977–981.
 - [107] S. Oztekin, H. Hepagüslar, A.A. Kar, D. Ozzeybek, O. Artıkaslan, Z. Elar, Preemptive diclofenac reduces morphine use after remifentanyl-based anaesthesia for tonsillectomy, *Paediatr. Anaesth.* 12 (2002) 694–699.
 - [108] A. Saeed, A.R. Khan, V. Lee, A. Aslam, J. Brain, M.P.L. Williams, L. Brennan, R. Campbell, M. Samuel, Pain management for unilateral orchidopexy in children: an effective regimen, *World J. Surg.* 33 (2009) 603–606.
 - [109] J.F. Standing, D. Tibboel, R. Korpela, K.T. Olkkola, Diclofenac pharmacokinetic meta-analysis and dose recommendations for surgical pain in children aged 1–12 years, *Paediatr. Anaesth.* 21 (2011) 316–324.
 - [110] T. Strengell, M. Uhari, R. Tarkka, J. Uusimaa, R. Alen, P. Lautala, H. Rantala, Antipyretic agents for preventing recurrences of febrile seizures: randomized controlled trial, *Arch. Pediatr. Adolesc. Med.* 163 (2009) 799–804.
 - [111] P. Sylaidis, T.J. O'Neill, Diclofenac analgesia following cleft palate surgery, *Cleft Palate Craniofac. J.* 35 (1998) 544–545.
 - [112] C.D. Van Der Marel, B.J. Anderson, J. Romsing, E. Jacqz-Aigrain, D. Tibboel, Diclofenac and metabolite pharmacokinetics in children, *Paediatr. Anaesth.* 14 (2004) 443–451.
 - [113] I. Yamamoto, H. Yukioka, M. Fujimori, Clinical study of postoperative sedation in pediatric patients. Effects of inhalation anesthetics and postoperative analgesics, *Jpn. J. Anesthesiol.* 43 (1994) 1191–1195.
 - [114] D. Hadas, I. Youngster, A. Cohen, E. Leibovitch, I. Shavit, I. Erez, Y. Uziel, M. Berkovitch, Premarketing surveillance of ibuprofen suppositories in febrile children, *Clin. Pediatr.* 50 (2011) 196–199.
 - [115] A. Boucher, P. Vilette, N. Crassard, N. Bernard, J. Descotes, Urinary toxicological screening: analytical interference between niflumic acid and cannabis, *Arch. Pediatr.* 16 (2009) 1457–1460.
 - [116] J.M. Cholette, L. Mamikonian, G.M. Alfieri, N. Blumberg, N.B. Lerner, Aspirin resistance following pediatric cardiac surgery, *Thromb. Res.* 126 (2010) 200–206.
 - [117] J. Saugier, Migraine in children, *Rev. Med. Tours* 12 (1978) 41–45.
 - [118] H. Kokki, H. Tuomilehto, K. Tuovinen, Pain management after adenoidectomy with ketoprofen: comparison of rectal and intravenous routes, *Br. J. Anaesth.* 85 (2000) 836–840.
 - [119] A. Messeri, P. Busoni, B. Noccioli, S. Murolo, G. Ivani, R. Grossetti, C. Gallini, L. Maestri, G. Fedele, R. Novellini, Analgesic efficacy and tolerability of ketoprofen lysine salt vs paracetamol in common paediatric surgery. A randomized, single-blind, parallel, multicentre trial, *Paediatr. Anaesth.* 13 (2003) 574–578.
 - [120] M. Shaban, S.M. Asida, Oral midazolam with low dose ketamine, fentanyl, or ketoprofen for the prevention of emergence agitation after pediatric ambulatory surgery, *Egypt. J. Anaesth.* 24 (2008) 27–33.
 - [121] H. Tuomilehto, H. Kokki, R. Ahonen, J. Nuutinen, Postoperative behavioral changes in children after adenoidectomy, *Arch. Otolaryngol. Head Neck Surg.* 128 (2002) 1159–1164.
 - [122] R. Leaver, H. Wegner, S. Furman, A comparison of the antipyretic efficacy of mefenamic acid 126-mg suppository and 60-mg suspension in pediatric patients and an evaluation of the local tolerability of the suppositories, *Curr. Ther. Res. Clin. Exp.* 55 (1994) 645–652.
 - [123] C. Sims, C.M. Johnson, R. Bergesio, S.J. Delfos, E.A. Avraamides, Rectal indomethacin for analgesia after appendicectomy in children, *Anaesth. Intensive Care* 22 (1994) 272–275.
 - [124] F. Cataldo, M.A. Trippiedi, G. Gucci, Clinical use of tinoridine in pediatrics, *Curr. Ther. Res. Clin. Exp.* 33 (1983) 123–131.
 - [125] S. Furukawa, T. Okada, Clinical effects of ampicillin suppository (KS-R1) on infections in pediatric field, *Jpn. J. Antibiot.* 36 (1983) 1877–1881.
 - [126] K. Kida, N. Watanabe, H. Matsuda, M. Murase, Clinical effects of ampicillin suppository (KS-R1) in pediatric field, *Jpn. J. Antibiot.* 36 (1983) 1882–1887.
 - [127] Y. Kobayashi, T. Haruta, S. Kuroki, K. Okura, Clinical evaluation of ampicillin suppository (KS-R1), *Jpn. J. Antibiot.* 36 (1983) 1871–1876.
 - [128] T. Motohiro, T. Fujimoto, T. Nishiyama, Comparative well-controlled study of ampicillin rectal suppository versus intravenous administration of ampicillin against acute pneumonia in pediatric field, *Jpn. J. Antibiot.* 36 (1983) 1785–1805.
 - [129] T. Motohiro, K. Tanaka, T. Koga, Fundamental study on ampicillin suppository (KS-R1) in adults and children, *Jpn. J. Antibiot.* 36 (1983) 1713–1768.
 - [130] S. Nakazawa, H. Sato, K. Niino, Fundamental and clinical studies of ampicillin suppository (KS-R1) in pediatric field, *Jpn. J. Antibiot.* 36 (1983) 1814–1820.
 - [131] T. Nishimura, T. Takashima, K. Tabuki, Comparative well-controlled study of ampicillin rectal suppository versus oral form of ampicillin against acute respiratory tract infections in pediatric field, *Jpn. J. Antibiot.* 36 (1983) 1769–1784.
 - [132] T. Nishimura, K. Tabuki, T. Takashima, Basic and clinical studies of ampicillin suppository (KS-R1) in pediatric field, *Jpn. J. Antibiot.* 36 (1983) 1863–1870.
 - [133] Z. Sakaguchi, E. Asano, Y. Miyauchi, K. Ohara, T. Okamoto, Clinical experience with ampicillin suppository (KS-R1) in the pediatric field, *Jpn. J. Antibiot.* 36 (1983) 1888–1894.
 - [134] T. Sekiguchi, T. Ichioka, T. Hosoda, M. Masuda, M. Miyao, Clinical experience with ampicillin suppository (KS-R1) in bacterial infection of children, *Jpn. J. Antibiot.* 36 (1983) 1895–1899.
 - [135] T. Shinozaki, B. Kim, O. Arimasu, S. Hashira, R. Fujii, Clinical studies of ampicillin suppository (KS-R1) in pediatric field, *Jpn. J. Antibiot.* 36 (1983) 1821–1826.
 - [136] M. Yafuso, T. Nakashima, K. Aso, Clinical studies on ampicillin suppository (KS-R1) in the field of pediatric infection, *Jpn. J. Antibiot.* 36 (1983) 1846–1850.
 - [137] S. Furukawa, T. Okada, Clinical effects of ceftizoxime suppository on pediatric infection, *Jpn. J. Antibiot.* 38 (1985) 2943–2951.
 - [138] K. Kida, H. Matsuda, Clinical use of ceftizoxime suppositories in pediatric infection, *Jpn. J. Antibiot.* 38 (1985) 2970–2976.
 - [139] K. Sunakawa, A. Hirota, N. Saito, Y. Ishizuka, Clinical studies of ceftizoxime suppository in pediatric field, *Jpn. J. Antibiot.* 38 (1985) 2889–2895.
 - [140] T. Kaus, K. Gaudin, A. Gaubert, B. Ba, S. Tagliaferri, F. Fawaz, J.L. Fabre, J.M. Boiron, X. Lafarge, N.J. White, P.L. Oliaro, P. Millet, Screening paediatric rectal forms of azithromycin as an alternative to oral or injectable treatment, *Int. J. Pharm.* 436 (2012) 624–630.
 - [141] T. Kaus, A. Gaubert, C. Boyer, B.B. Ba, M. Manse, S. Massip, J.M. Léger, F. Fawaz, M. Lembege, J.M. Boiron, X. Lafarge, N. Lindegardh, N.J. White, P. Oliaro, P. Millet, K. Gaudin, Pharmaceutical development and optimization of azithromycin suppository for paediatric use, *Int. J. Pharm.* 441 (2013) 218–226.
 - [142] S. Campos, P. de la Cerda, A. Rivera, Fatal artesunate toxicity in a child, *J. Pediatr. Infect. Dis.* 3 (2008) 69–75.
 - [143] K. Gaudin, T. Kaus, A. Gaubert, V. Viaud, J.P. Dubost, P. Oliaro, N.J. White, P. Millet, Simultaneous determination of artemether and azithromycin in suppositories by reversed phase HPLC, *Anal. Lett.* 44 (2011) 2732–2743.
 - [144] D.A. Van Riet-Nales, S. Wang, A. Saint-Raymond, J.L. Robert, The EMA quality guideline on the pharmaceutical development of medicines for paediatric use, *Int. J. Pharm.* 435 (2012) 132–134.
 - [145] L.M. Chiang, H.S. Wang, H.H. Shen, S.T. Deng, C.H. Tseng, Y.I. Chen, M.L. Chou, P.C. Hung, K.L. Lin, Rectal diazepam solution is as good as rectal administration of intravenous diazepam in the first-aid cessation of seizures in children with intractable epilepsy, *Pediatr. Neonatol.* 52 (2011) 30–33.
 - [146] Y. Hirabayashi, A. Okumura, T. Kondo, M. Magota, S. Kawabe, N. Kando, H. Yamaguchi, J. Natsume, T. Negoro, K. Watanabe, Efficacy of a diazepam suppository at preventing febrile seizure recurrence during a single febrile illness, *Brain and Development* 31 (2009) 414–418.
 - [147] T. Tanabe, Y. Awaya, T. Matsui, K. Iyoda, T. Nagai, M. Kurihara, K. Yamamoto, K. Minagawa, K. Maekawa, Management of and prophylaxis against status epilepticus in children with severe myoclonic epilepsy in infancy (SMEI; Dravet syndrome) — a nationwide questionnaire survey in Japan, *Brain and Development* 30 (2008) 629–635.
 - [148] B. Buchan, G. Kay, K.H. Matthews, D. Cairns, Suppository formulations as a potential treatment for nephropathic cystinosis, *J. Pharm. Sci.* 101 (2012) 3729–3738.
 - [149] Z. Kato, A. Yamagishi, M. Nakamura, N. Kondo, Theophylline-associated status epilepticus in an infant: pharmacokinetics and the risk of suppository use, *World J. Pediatr.* 5 (2009) 316–318.
 - [150] N. Kolassa, Menthol differs from other terpenic essential oil constituents, *Regul. Toxicol. Pharmacol.* 65 (2013) 115–118.
 - [151] N. Nishimura, N. Doi, T. Uemura, T. Taketani, G. Hayashi, T. Kasai, R. Kanai, S. Yamaguchi, K. Iwamoto, K. Naora, Pharmaceutical analysis and clinical efficacy of Kampo medicine, maoto, extract suppository against pediatric febrile symptoms, *Yakugaku Zasshi* 129 (2009) 759–766.
 - [152] H. Kasai, K. Sasaki, H. Tsujinaga, T. Hoshino, Pain management in advanced pediatric cancer patients — a proposal of the two-step analgesic ladder, *Japan. J. Anesthesiol.* 44 (1995) 885–889.
 - [153] W.E. Cayley, Antiemetics for acute gastroenteritis-related vomiting in children and adolescents, *Am. Fam. Physician* 85 (2012) 1054–1056.
 - [154] Z. Fedorowicz, V.A. Jagannath, B. Carter, Antiemetics for reducing vomiting related to acute gastroenteritis in children and adolescents, *Sao Paulo Med. J.* 130 (2012) 270.
 - [155] U. Uhlig, N. Pfeil, G. Gelbrich, C. Spranger, S. Syrbe, B. Huegle, B. Teichmann, T. Kapellen, P. Houben, W. Kiess, H.H. Uhlig, Dimenhydrinate in children with infectious gastroenteritis: a prospective, RCT, *Pediatrics* 124 (2009) e622–e632.

- [156] I.D. Welters, M. Graef, T. Menges, C. Beikirch, H. Kaufmann, G. Hempelmann, Post-operative nausea and vomiting after Faden operation, *Graefes Arch. Clin. Exp. Ophthalmol.* 238 (2000) 59–63.
- [157] D.A. Christakis, J.A. Wright, F. Rivara, P. Saur, Promethazine therapy for gastroenteritis: towards a better understanding of use, risks and benefits, *Ambul. Child Health* 4 (1998) 181–187.
- [158] F. Dhondt, S. Traen, M. van Eygen, Domperidone (R 33 812) suppositories: an effective antiemetic agent in diverse pediatric conditions. A multicenter trial, *Curr. Ther. Res. Clin. Exp.* 24 (1978) 912–923.
- [159] M. van Eygen, E. Heck, F. Dhondt, L. Ameryckx, H. Van Ravensteyn, A double-blind comparison of domperidone and metoclopramide suppositories in the treatment of nausea and vomiting in children, *Postgrad. Med. J.* 55 (1979) 36–39.
- [160] A. Iwamoto, R. Uchiyumi, T. Hidaka, K. Taniguchi, N. Honda, Y. Okuno, The efficacy of midazolam-famotidine suppository for premedication in children, *Japan. J. Anesthesiol.* 44 (1995) 263–267.
- [161] N. Kambara, S. Kitamura, A. Taniguchi, W. Hamao, M. Matsuyama, Premedication in children: a comparison of oral midazolam and rectal bromazepam, *Japan. J. Anesthesiol.* 44 (1995) 1707–1711.
- [162] M. Shimoyama, T. Mizuguchi, S. Yozoru, Premedication in children. A clinical trial of bromazepam and chloral hydrate suppositories, *Japan. J. Anesthesiol.* 39 (1990) 64–69.
- [163] C. Koizumi, Y. Yamamoto, K. Tohyama, Y. Mizukoshi, Diazepam suppository for premedication of anesthesia in children, *Hokuriku J. Anesthesiol.* 31 (1997) 19–22.
- [164] Y. Sakurai, T. Obata, A. Odaka, K. Terui, M. Tamura, H. Miyao, Buccal administration of dexmedetomidine as a preanesthetic in children, *J. Anesth.* 24 (2010) 49–53.
- [165] R. Uchiyumi, T. Hidaka, A. Miyagawa, K. Sugino, K. Taniguchi, N. Honda, Clinical evaluation of diazepam suppository for premedication in children, *Japan. J. Anesthesiol.* 43 (1994) 102–105.
- [166] F. Marchat, B. Moulinier, R. De Prado, R. Lambert, L'oesophago-gastro-duodénoscopie en pédiatrie, *Acta Endos.* 5 (1975) 15–19.
- [167] A. McEwan, P.E. Sigston, K.A. Andrews, H.A. Hack, A.M.C. Jenkins, L. May, N. Llewellyn, A. Mackersie, A comparison of rectal and intramuscular codeine phosphate in children following neurosurgery, *Paediatr. Anaesth.* 10 (2000) 189–193.
- [168] V. Owczarzak, J. Haddad, Comparison of oral versus rectal administration of acetaminophen with codeine in postoperative pediatric adenotonsillectomy patients, *Laryngoscope* 116 (2006) 1485–1488.
- [169] G.K. Blair, J.J. Murphy, G.C. Fraser, Internal sphincterotomy in post-pull-through Hirschsprung's disease, *J. Pediatr. Surg.* 31 (1996) 843–845.
- [170] S.M. Borowitz, D.J. Cox, B. Kovatchev, L.M. Ritterband, J. Sheen, J. Sutphen, Treatment of childhood constipation by primary care physicians: efficacy and predictors of outcome, *Pediatrics* 115 (2005) 873–877.
- [171] M. Bulut, G. Tekant, Encopretic children: experience with fifty cases, *Turk. J. Pediatr.* 33 (1991) 167–172.
- [172] R. Burgers, E. Bonanno, E. Madarena, F. Graziano, L. Pensabene, W. Gardner, H. Mousa, M.A. Benninga, C. Di Lorenzo, The care of constipated children in primary care in different countries, *Acta Paediatr.* 101 (2012) 677–680.
- [173] S.J. Griffin, E.J. Parkinson, P.S.J. Malone, Bowel management for paediatric patients with faecal incontinence, *J. Pediatr. Urol.* 4 (2008) 387–392.
- [174] S.N. Khadr, S.E. Ibhanebeh, C. Rennix, H.E. Fisher, C.M. Manjunatha, D. Young, R. C. Abara, Randomized controlled trial: impact of glycerin suppositories on time to full feeds in preterm infants, *Neonatology* 100 (2011) 169–176.
- [175] A. Lachaux, P. Roy, Constipation in children, *Arch. Pediatr.* 15 (2008) 95–101.
- [176] S.R. Leibold, Achieving continence with a neurogenic bowel, *Pediatr. Clin. N. Am.* 57 (2010) 1013–1025.
- [177] M.C. Luxem, E.R. Christophersen, P.C. Purvis, D.M. Baer, Behavioral-medical treatment of pediatric toileting refusal, *J. Dev. Behav. Pediatr.* 18 (1997) 34–41.
- [178] P. Masi, E. Miele, A. Staiano, Pediatric anorectal disorders, *Gastroenterol. Clin. N. Am.* 37 (2008) 709–730.
- [179] R. Seth, M.B. Heyman, Management of constipation and encopresis in infants and children, *Gastroenterol. Clin. N. Am.* 23 (1994) 621–636.
- [180] E.R. Wald, T.D. Jagodzinski, S.C.L. Moyer, A. Wald, J.C. Eickhoff, M.B. Edmonson, Validation and clinical utility of a bowel habit questionnaire in school-age children, *J. Pediatr. Gastroenterol. Nutr.* 53 (2011) 520–523.
- [181] M.B. Heyman, J. Kierkus, J. Spénard, H. Shbaklo, M. Giguere, Efficacy and safety of mesalamine suppositories for treatment of ulcerative proctitis in children and adolescents, *Inflamm. Bowel Dis.* 16 (2010) 1931–1939.
- [182] E.R. Perito, E. Mileti, D.H. Dalal, S.J. Cho, L.D. Ferrell, M. McCracken, M.B. Heyman, Solitary rectal ulcer syndrome in children and adolescents, *J. Pediatr. Gastroenterol. Nutr.* 54 (2012) 266–270.
- [183] C.Y. Wu, L.Z. Benet, Predicting drug disposition via application of BCS: transport/absorption/elimination interplay and development of a biopharmaceutics drug disposition classification system, *Pharm. Res.* 22 (2005) 11–23.
- [184] R.C. Moreton, Suppository bases, hard fat, in: R.C. Rowe, P.J. Sheskey, W.G. Cook, M.E. Fenton (Eds.), *Handbook of Pharmaceutical Excipients*, Pharmaceutical Press, London — Philadelphia, 2012, pp. 831–835.
- [185] C. De Muynck, C. Cuvelier, D. Van Steenkiste, L. Bonnarens, J.P. Remon, Rectal mucosa damage in rabbits after subchronical application of suppository bases, *Pharm. Res.* 8 (1991) 945–950.
- [186] H.G. Kristensen, WHO guideline development of paediatric medicines: points to consider in pharmaceutical development, *Int. J. Pharm.* 435 (2012) 134–135.
- [187] B. Barner, D. Wallick, Polyethylene glycol, in: R.C. Rowe, P.J. Sheskey, W.G. Cook, M.E. Fenton (Eds.), *Handbook of Pharmaceutical Excipients*, Pharmaceutical Press, London — Philadelphia, 2012, pp. 585–591.
- [188] A.A. Fisher, Immediate and delayed allergic contact reactions to polyethylene glycol, *Contact Dermatitis* 4 (1978) 135–138.
- [189] V. Fabiano, C. Mameli, G.V. Zuccotti, Paediatric pharmacology: remember the excipients, *Pharmacol. Res.* 63 (2011) 362–365.
- [190] Disintegration of Suppositories and Pessaries EP 01/2008:20902, European Pharmacopoeia, European Directorate for the Quality of Medicines & HealthCare, Strasbourg, 2008. 265–266.
- [191] Softening Time Determination of Lipophilic Suppositories EP 01/2008:20922, European Pharmacopoeia, European Directorate for the Quality of Medicines & HealthCare, Strasbourg, 2011. 288.
- [192] Dissolution Test for Lipophilic Solid Dosage Forms EP 01/2008:20942, European Pharmacopoeia, European Directorate for the Quality of Medicines & HealthCare, Strasbourg, 2011. 319–320.
- [193] Uniformity of Mass of Single-Dose Preparations EP 01/2008:20905, European Pharmacopoeia, European Directorate for the Quality of Medicines & HealthCare, Strasbourg, 2011. 265–266.
- [194] Uniformity of Content of Single-Dose Preparations EP 01/2008:20906, European Pharmacopoeia, European Pharmacopoeia, European Directorate for the Quality of Medicines & HealthCare, Strasbourg, 2011. 266.
- [195] R. Sagraves, Pediatric dosing and dosage forms, in: J. Swarbrick, J.C. Boylan (Eds.), *Encyclopedia of Pharmaceutical Technology*, Marcel Dekker, Inc., New York, 2002, pp. 2045–2066.
- [196] R. Gandhi, R. Sunder, Postoperative analgesic efficacy of single high dose and low dose rectal acetaminophen in pediatric ophthalmic surgery, *J. Anaesthesiol. Clin. Pharmacol.* 28 (2012) 460–464.
- [197] S.M. Heidari, S.Z. Mirlohi, S.J. Hashemi, Comparison of the preventive analgesic effect of rectal ketamine and rectal acetaminophen after pediatric tonsillectomy, *Int. J. Prev. Med.* 3 (2012) S150–S155.
- [198] E.M. Tinner, I. Hoelsli, K. Jost, N. Schobi, M.Y. Ulrich, T. Burkhardt, A. Krafft, H.U. Bucher, D. Surbek, M. Nelle, C. Buhner, Rectal paracetamol in newborn infants after assisted vaginal delivery may increase pain response, *J. Pediatr.* 162 (2013) 62–66.
- [199] J.D. Losek, Acetaminophen dose accuracy and pediatric emergency care, *Pediatr. Emerg. Care* 20 (2004) 285–288.
- [200] S.M. Mireskandari, J. Makarem, Effect of rectal diclofenac and acetaminophen alone and in combination on postoperative pain after cleft palate repair in children, *J. Craniofac. Surg.* 22 (2011) 1955–1959.
- [201] H. Kokki, M. Karvinen, P. Suhonen, Pharmacokinetics of intravenous and rectal ketoprofen in young children, *Clin. Pharmacokinet.* 42 (2003) 373–379.
- [202] B. Uldum, A.L. Hallonsten, S. Poulsen, Midazolam conscious sedation in a large Danish municipal dental service for children and adolescents, *Int. J. Paediatr. Dent.* 18 (2008) 256–261.
- [203] A.G. Rowland, A.M. Gill, A.B. Stewart, R.E. Appleton, K.A. Al, C. Cramp, L.K. Yeung, Review of the efficacy of rectal paraldehyde in the management of acute and prolonged tonic-clonic convulsions, *Arch. Dis. Child.* 94 (2009) 720–723.
- [204] World Malaria Report, WHO press, Geneva, 2013.
- [205] E. Landais, C. Poisson, J.L. Condamine, Analysis of 1697 cases of childhood malaria treated using intra-rectal Quinimax (QR) in the Tilaberi health district in Niger, *Med. Trop. (Mars.)* 67 (2007) 471–476.
- [206] J.L. Ndiaye, R.C. Tine, B. Faye, H.L. Dieye el, P.A. Diack, V. Lameyre, O. Gaye, H.D. Sow, Pilot feasibility study of an emergency paediatric kit for intra-rectal quinine administration used by the personnel of community-based health care units in Senegal, *Malar. J.* 6 (2007) 152.
- [207] K. Pengsaa, C. Sirivichayakul, K. Na-Bangchang, I. Thairaporn, A. Chaivisuth, A. Wongsuwan, P. Attanath, C. Pojaroen-Anant, P. Wisetsing, P. Chanthavanich, A. Sabchareon, Life-saving rectal artesunate for complicated malaria in children, Southeast Asian, *J. Trop. Med. Public Health* 36 (2005) 597–601.
- [208] H.A. Karunajeewa, K.F. Ilett, K. Dufall, A. Kemiki, M. Bockarie, M.P. Alpers, P.H. Barrett, P. Vicini, T.M. Davis, Disposition of artesunate and dihydroartemisinin after administration of artesunate suppositories in children from Papua New Guinea with uncomplicated malaria, *Antimicrob. Agents Chemother.* 48 (2004) 2966–2972.
- [209] S. Krishna, T. Planche, T. Agbenyega, C. Woodrow, D. Agranoff, G. Bedu-Addo, A. K. Owusu-Ofori, J.A. Appiah, S. Ramanathan, S.M. Mansor, V. Navaratnam, Bioavailability and preliminary clinical efficacy of intrarectal artesunate in Ghanaian children with moderate malaria, *Antimicrob. Agents Chemother.* 45 (2001) 509–516.
- [210] R.C. Tine, B. Faye, C.T. Ndour, J.L. Ndiaye, M. Ndiaye, C. Bassene, P. Magnussen, I.C. Bygbjerg, K. Sylla, J.D. Ndour, O. Gaye, Impact of combining intermittent preventive treatment with home management of malaria in children less than 10 years in a rural area of Senegal: a cluster randomized trial, *Malar. J.* 10 (2011) 358.
- [211] E.A. Gomez, M.H. Jurado, N. Cambon, Randomised efficacy and safety study of two 3-day artesunate rectal capsule/mefloquine regimens versus artesunate alone for uncomplicated malaria in Ecuadorian children, *Acta Trop.* 89 (2003) 47–53.
- [212] C. Sirivichayakul, A. Sabchareon, K. Pengsaa, I. Thairaporn, A. Chaivisuth, K. Na-Bangchang, P. Wisetsing, P. Chanthavanich, C. Pojaroen-Anant, Comparative study of the effectiveness and pharmacokinetics of two rectal artesunate/oral mefloquine combination regimens for the treatment of uncomplicated childhood falciparum malaria, *Ann. Trop. Paediatr.* 27 (2007) 17–24.
- [213] P. Wilairatna, S. Krudsood, U. Silachamroon, P. Singhasivanon, S. Vannaphan, S. Faithong, M. Klabprasit, S.N. Bangchang, P. Olliaro, S. Loareesuwan, Clinical trial of sequential treatments of moderately severe and severe malaria with dihydroartemisinin suppository followed by mefloquine in Thailand, *Am. J. Trop. Med. Hyg.* 63 (2000) 290–294.
- [214] B.R. Ogutu, K.R. Newton, J. Crawley, S.N. Muchohi, G.O. Otieno, G. Edwards, K. Marsh, G.O. Kokwaro, Pharmacokinetics and anticonvulsant effects of diazepam in children with severe falciparum malaria and convulsions, *Br. J. Clin. Pharmacol.* 53 (2002) 49–57.

- [215] J. Achan, J. Byarugaba, H. Barennes, J.K. Tumwine, Rectal versus intravenous quinine for the treatment of childhood cerebral malaria in Kampala, Uganda: a randomized, double-blind clinical trial, *Clin. Infect. Dis.* 45 (2007) 1446–1452.
- [216] H. Barennes, T. Balima-Koussoubé, N. Nagot, J.C. Charpentier, E. Pussard, Safety and efficacy of rectal compared with intramuscular quinine for the early treatment of moderately severe malaria in children: randomised clinical trial, *BMJ* 332 (2006) 1055–1059.
- [217] E. Pussard, C. Straczek, I. Kabore, A. Bicaba, T. Balima-Koussoubé, P. Bouree, H. Barennes, Dose-dependent resorption of quinine after intrarectal administration to children with moderate *Plasmodium falciparum* malaria, *Antimicrob. Agents Chemother.* 48 (2004) 4422–4426.
- [218] J.R. Aceng, J.S. Byarugaba, J.K. Tumwine, Rectal artemether versus intravenous quinine for the treatment of cerebral malaria in children in Uganda: randomised clinical trial, *BMJ* 330 (2005) 334.
- [219] K.I. Barnes, J. Mwenchanya, M. Tembo, H. McIlleron, P.I. Folb, I. Ribeiro, F. Little, M. Gomes, M.E. Molyneux, Efficacy of rectal artesunate compared with parenteral quinine in initial treatment of moderately severe malaria in African children and adults: a randomised study, *Lancet* 363 (2004) 1598–1605.
- [220] F. Esamai, P. Ayuo, W. Owino-Ongor, J. Rotich, A. Ngindu, A. Obala, F. Ogaro, L. Quoqiao, G. Xingbo, L. Guangqian, Rectal dihydroartemisinin versus intravenous quinine in the treatment of severe malaria: a randomised clinical trial, *East Afr. Med. J.* 77 (2000) 273–278.
- [221] L. Conteh, S. Yeung, Assessing the cost-effectiveness of prereferral rectal artesunate for treatment of severe childhood malaria, *Expert Rev. Pharmacoecon. Outcome Res.* 11 (2011) 141–145.
- [222] Y. Tozan, E.Y. Klein, S. Darley, R. Panicker, R. Laxminarayan, J.G. Breman, Prereferral rectal artesunate for treatment of severe childhood malaria: a cost-effectiveness analysis, *Lancet* 376 (2010) 1910–1915.
- [223] J. Buchanan, B. Mihaylova, A. Gray, N. White, Cost-effectiveness of pre-referral antimalarial, antibacterial, and combined rectal formulations for severe febrile illness, *PLoS ONE* 5 (2010) e14446.
- [224] E. Bergogne-Berezin, A. Bryskier, The suppository form of antibiotic administration: pharmacokinetics and clinical application, *J. Antimicrob. Chemother.* 43 (1999) 177–185.
- [225] N.S. Barakat, In vitro and in vivo characteristics of a thermogelling rectal delivery system of etodolac, *AAPS Pharm. Sci. Tech.* 10 (2009) 724–731.
- [226] K. Gaudin, A. Barbaud, C. Boyer, M.H. Langlois, A.M. Lagueny, J.P. Dubost, P. Millet, F. Fawaz, In vitro release and stability of an artesunate rectal gel suitable for pediatric use, *Int. J. Pharm.* 353 (2008) 1–7.
- [227] A.A. Koffi, F. Agnely, G. Ponchel, J.L. Grossiord, Modulation of the rheological and mucoadhesive properties of thermosensitive poloxamer-based hydrogels intended for the rectal administration of quinine, *Eur. J. Pharm. Sci.* 27 (2006) 328–335.
- [228] A.A. Koffi, F. Agnely, M. Besnard, B.J. Kablan, J.L. Grossiord, G. Ponchel, In vitro and in vivo characteristics of a thermogelling and bioadhesive delivery system intended for rectal administration of quinine in children, *Eur. J. Pharm. Biopharm.* 69 (2008) 167–175.
- [229] C.S. Yong, H. Sah, Y. Jahng, H.W. Chang, J.K. Son, S.H. Lee, T.C. Jeong, J.D. Rhee, S.H. Baek, C.K. Kim, H.G. Choi, Physicochemical characterization of diclofenac sodium-loaded poloxamer gel as a rectal delivery system with fast absorption, *Drug Dev. Ind. Pharm.* 29 (2003) 545–553.
- [230] R. Yahagi, Y. Machida, H. Onishi, Mucoadhesive suppositories of ramosetron hydrochloride utilizing Carbopol, *Int. J. Pharm.* 193 (2000) 205–212.
- [231] A. El-Kamel, M. El-Khatib, Thermally reversible in situ gelling carbamazepine liquid suppository, *Drug Deliv.* 13 (2006) 143–148.
- [232] A.A. Ramadan, Preparation, characterization and in-vivo evaluation of double-phased mucoadhesive suppositories containing diclofenac in rats, *J. Appl. Sci. Res.* 8 (2012) 746–752.
- [233] R. Yahagi, H. Onishi, Y. Machida, Preparation and evaluation of double-phased mucoadhesive suppositories of lidocaine utilizing Carbopol and white beeswax, *J. Control. Release* 61 (1999) 1–8.
- [234] J. Hanaee, Y. Javadzadeh, S. Taftchi, D. Farid, A. Nokhodchi, The role of various surfactants on the release of salbutamol from suppositories, *Farmaco* 59 (2004) 903–906.
- [235] E.R. Cooper, Increased skin permeability for lipophilic molecules, *J. Pharm. Sci.* 73 (1984) 1153–1156.
- [236] M.U. Adikwu, Evaluation of snail mucin motifs as rectal absorption enhancer for insulin in non-diabetic rat models, *Biol. Pharm. Bull.* 28 (2005) 1801–1804.
- [237] H. Shiohira, M. Fujii, N. Koizumi, M. Kondoh, Y. Watanabe, Novel chronotherapeutic rectal aminophylline delivery system for therapy of asthma, *Int. J. Pharm.* 379 (2009) 119–124.
- [238] Y. Matsumoto, I. Yamamoto, Y. Watanabe, M. Matsumoto, Enhancing effect of viscous sodium hyaluronate solution on the rectal absorption of morphine, *Biol. Pharm. Bull.* 18 (1995) 1744–1749.
- [239] T. Kondo, T. Irie, K. Uekama, Combination effects of alpha-cyclodextrin and xanthan gum on rectal absorption and metabolism of morphine from hollow-type suppositories in rabbits, *Biol. Pharm. Bull.* 19 (1996) 280–286.
- [240] Y. Matsumoto, Y. Watanabe, T. Tojima, R. Murakoshi, C. Murakami, M. Matsumoto, Rectal absorption enhancement of gentamicin in rabbits from hollow type suppositories by sodium salicylate or sodium caprylate, *Drug Des. Deliv.* 4 (1989) 247–256.
- [241] Y. Matsumoto, Y. Watanabe, I. Yamamoto, M. Matsumoto, Difference in rectal absorption of morphine from hollow-type and conventional suppositories in rabbits, *Biol. Pharm. Bull.* 16 (1993) 150–153.
- [242] D. Gugulothu, S. Pathak, S. Suryavanshi, S. Sharma, V. Patravale, Self-microemulsifying suppository formulation of beta-artemether, *AAPS Pharm. Sci. Tech.* 11 (2010) 1179–1184.
- [243] J.Y. Kim, Y.S. Ku, Enhanced absorption of indomethacin after oral or rectal administration of a self-emulsifying system containing indomethacin to rats, *Int. J. Pharm.* 194 (2000) 81–89.
- [244] K. Welch, R. Ek, M. Stromme, Comparative drug release measurements in limited amounts of liquid: a suppository formulation study, *Curr. Drug Deliv.* 3 (2006) 299–306.
- [245] E.S. El-Leithy, D.S. Shaker, M.K. Ghorab, R.S. Abdel-Rashid, Evaluation of mucoadhesive hydrogels loaded with diclofenac sodium-chitosan microspheres for rectal administration, *AAPS Pharm. Sci. Tech.* 11 (2010) 1695–1702.
- [246] K.C. Ofokansi, M.U. Adikwu, V.C. Okore, Preparation and evaluation of mucin-gelatin mucoadhesive microspheres for rectal delivery of ceftriaxone sodium, *Drug Dev. Ind. Pharm.* 33 (2007) 691–700.
- [247] S.B. Patil, K.K. Sawant, Mucoadhesive microspheres: a promising tool in drug delivery, *Curr. Drug Deliv.* 5 (2008) 312–318.
- [248] M. Gajewska, M. Sznitowska, S. Janicki, Diazepam submicron emulsions containing soya-bean oil and intended for oral or rectal delivery, *Pharmazie* 56 (2001) 220–222.
- [249] M. Sznitowska, S. Janicki, M. Gajewska, M. Kulik, Investigation of diazepam lipospheres based on Witepsol and lecithin intended for oral or rectal delivery, *Acta Pol. Pharm.* 57 (2000) 61–64.
- [250] M. Sznitowska, M. Gajewska, S. Janicki, A. Radwanska, G. Lukowski, Bioavailability of diazepam from aqueous-organic solution, submicron emulsion and solid lipid nanoparticles after rectal administration in rabbits, *Eur. J. Pharm. Biopharm.* 52 (2001) 159–163.
- [251] M.R. Neutra, P.A. Kozlowski, Mucosal vaccines: the promise and the challenge, *Nat. Rev. Immunol.* 6 (2006) 148–158.
- [252] J. Holmgren, C. Czerkinsky, Mucosal immunity and vaccines, *Nat. Med.* 11 (2005) S45–S53.
- [253] N. Pareze, C. Fourgeux, A. Mohamed, C. Dubuquoy, M. Pillot, A. Dehee, A. Charpilienne, D. Poncet, I. Schwartz-Cornil, A. Garbarg-Chenon, Rectal immunization with rotavirus virus-like particles induces systemic and mucosal humoral immune responses and protects mice against rotavirus infection, *J. Virol.* 80 (2006) 1752–1761.
- [254] M. Yu, M. Vajdy, Mucosal HIV transmission and vaccination strategies through oral compared with vaginal and rectal routes, *Expert. Opin. Biol. Ther.* 10 (2010) 1181–1195.
- [255] M. Abolhassani, M. Lagranderie, P. Chavarot, A.M. Balazuc, G. Marchal, *Mycobacterium bovis* BCG induces similar immune responses and protection by rectal and parenteral immunization routes, *Infect. Immun.* 68 (2000) 5657–5662.
- [256] S. Tengvall, D. O'Hagan, A.M. Harandi, Rectal immunization generates protective immunity in the female genital tract against herpes simplex virus type 2 infection: relative importance of myeloid differentiation factor 88, *Antivir. Res.* 78 (2008) 202–214.
- [257] I.F. Barinskii, F.R. Makhmudov, Inactivated herpes simplex virus types 1 and 2 divaccine as an agent for effective immunoprophylaxis of recurrent genital herpes, *Vopr. Virusol.* 55 (2010) 35–40.
- [258] K. Hamajima, Y. Hoshino, K.Q. Xin, F. Hayashi, K. Tadokoro, K. Okuda, Systemic and mucosal immune responses in mice after rectal and vaginal immunization with HIV-DNA vaccine, *Clin. Immunol.* 102 (2002) 12–18.
- [259] N. Deredre-Bosquet, L. Morelato-Castillo, J. Brouwers, P. Augustijns, K. Bouchemal, G. Ponchel, O.H. Ramos, C. Herrera, M. Stefanidou, R. Shattock, L. Heyndrickx, G. Vanham, P. Kessler, G.R. Le, L. Martin, MiniCD4 microbicide prevents HIV infection of human mucosal explants and vaginal transmission of SHIV(H2P3) in cynomolgus macaques, *PLoS Pathog.* 8 (2012) e1003071.