International Journal of Pharmaceutics 395 (2010) 37–43

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Review

Specific aspects of gastro-intestinal transit in children for drug delivery design

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ARTICLE INFO

Article history:
Received 29 April 2010
Accepted 30 April 2010
Available online 15 May 2010

Keywords:
Oral drug delivery
Paediatric
Multiple unit dosage form

ABSTRACT

This mini-review discusses relevant aspects of gastro-intestinal transit in different ages of paediatric patients with an attempt to highlight factors which should be considered in oral dosage form design, in particular multi-particulate dosage forms. This emphasis is due to multi-particulates possessing many of the benefits of liquid oral formulations (such as ease of swallowing and dose adaptability) without many of their drawbacks (such as stability issues and lack of enteric or modified release functionalities). It is commonly stated that children are not merely small adults with regards to medicines. However, there has been very little research regarding how different dosage forms transit through the gastro-intestinal tract in children compared to adults, due to both ethical and practical hurdles. Due to this lack of studies on dosage form transit in children, information which was available on the transit of food, milk and liquids (often dependent upon the age of the patient) has been used to look at how various aspects of transit vary with age and, where possible, when they reach adult values and how these may affect the fate of dosage forms in vivo: swallowability, oesophageal transit, gastric emptying and pH, intestinal and colonic transit are discussed.

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1. Introduction

In January 2007, the enforcement of the Paediatric Regulation dramatically changed the regulatory environment for paediatric medicines in Europe (Regulation (EC) No 1901/2006). For medicinal products that have not yet been authorised, marketing-authorisation applications have to include the results of studies conducted in the paediatric population, in compliance with an agreed paediatric investigation plan (PIP), unless the EMEA has granted a deferral or waiver for their provision. Waivers may be granted for medicines intended to treat conditions that occur only

Abbreviations: API, active pharmaceutical ingredient; BW, body weight; CTT, colonic transit time; EMEA, European Medicines Agency; EU, European Union; $GET_{1/2}$, gastric half emptying time; GORD, gastro-oesophageal reflux disease; IR, immediate release; MMC, migrating motor complex; MR, modified release; PIP, paediatric investigation plan; PUMA, paediatric use marketing authorisation.

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doi:10.1016/j.ijpharm.2010.04.048

Table 1
Features of an ideal paediatric formulation (adapted from EMEA, 2005 EMEA/CHMP/PEG/194810/2005. Committee for Medicinal Products for Human Use, 2005).

Minimal dosage frequency
One dosage form fits all or a full range
Minimal impact on life style
Minimum, non-toxic excipients
Convenient, easy, reliable administration
Easily produced, elegant, stable
Cost and commercial viability

in adults and for medicines that may be unsafe or ineffective, or do not offer significant therapeutic benefit and/or fulfil a therapeutic need in children. Once authorisation is obtained in all EU Member States and study results are included in the product information, the medicine is eligible for six months' patent extension. Orphan-designated medicinal products are subject to the same requirements as above, and benefit from 2 years of market exclusivity, in addition to the 10-year exclusivity awarded under the EU Orphan Regulation. Some medicines, such as generics, are exempt from these requirements.

For authorised, patented medicinal products, the requirements described above also apply to applications to vary a marketing authorisation to add a new indication (including paediatric), a new pharmaceutical form, or a new route of administration. In these cases, the PIP and/or waiver must cover all existing and new indications, formulations and routes of administration.

Off-patent medicines developed specifically for paediatric use and with an appropriate formulation can benefit from a new marketing authorisation: paediatric use marketing authorisation (PUMA). Provided the product development follows an agreed PIP, the company will benefit from 10 years of data protection.

As a result industry faces an extra challenge: meeting the needs of the heterogeneous paediatric population. The following subsets are conventionally referred to for clinical investigation: EMEA/CHMP/ICH/2711/99 (1999) (Online).

- pre-term newborn infants (<37 weeks of gestational age);
- term newborn infants (0–27 days);
- infants and toddlers (1 month to 23 months);
- children (2–11 years);
- adolescents (12–18 years).

This division in subpopulations is based on the biological changes, such as metabolic capacity, organ maturation and drug clearance hence adult data cannot easily be applied to children. Additionally the behavioural and cognitive age as well as the psychosocial age has to be taken in account when it comes to design an age appropriate dosage form. From age 2 to age 12, children change drastically and for formulation purposes, including them in the same group might not be realistic. Often preschoolers and toddlers (e.g. below 6 years of age) are considered separately due to significant differences to older children.

Finally other important parameters such as the disease itself and its related symptoms, the dose, dosing scheme and duration of treatment along with the physicochemical properties of the API have to be critically assessed to choose the best route of administration and dosage form in order to fulfil the characteristics of an ideal paediatric formulation (Table 1).

Many drugs may benefit from the use of MR formulations, either to protect from the gastric environment or to provide prolonged release especially as it can be difficult for children to receive medicines at school. As children cannot easily swallow tablets, multi-particulates could provide an excellent way of achieving such functionalities in child-friendly formulations, providing they can swallow the multi-particulates without chewing. Multi-particulate systems may also be approached when taste masking or better stability of a formulation is required which can be difficult to achieve with liquid dosage forms and would often require the use of numerous excipients such as sugars, preservatives and solvents or co-solvents in children with elevated toxicological risks (Breitkreutz and Boos, 2007). It is generally considered that the size of individual multi-particulates may influence the palatability, ability to swallow, gastric emptying, gastric transit times, intestinal transit and all the various developmental aspects of the gastrointestinal physiology relevant to the bioavailability of drugs. Such information is currently sparse or lacking completely.

However, based on the limited literature available, the aim of this mini-review is to consider specific aspects of gut physiology, from swallowing to gastro-intestinal pH and transit in children that need to be taken into account when formulating different oral dosage forms (liquid versus monolithic or multi-particulate solids) and delivery systems (IR versus MR) for various paediatric population subsets.

2. Preamble

Little is known about how any formulation, let alone multiparticulates would transit through the paediatric gastric-intestinal tract. There are a number of reasons for this gap in knowledge. Due to the radiation burden or invasive nature of diagnostic methods involved, the few available studies which occur generally were carried out on paediatric patients already suffering from gastro-intestinal symptoms. Hence most of the gastric emptying data available was from infants suffering from Gastro-Oesophageal Reflux Disease (GORD) and much of the intestinal transit information is from paediatric patients under investigation for constipation. Much less data is available from healthy or control patients. Often trials have a large age range classification in order to recruit enough patients and many reported the results only as a mean and standard deviation without age stratification. The significance of these averaged values seems debatable especially when details on how physiological parameters change from year to year or even week to week in pre-term infants are not known. The conditions of testing also affect the results achieved. Much of the data for gastric emptying was in pre-term and term infants using liquids (milk), due to the obvious restrictions in administering solids in this age group. Infants will often have small diameter feeding tubes which are not compatible with the size of commercially available multi-particulates. In older children, food was used for transit studies but different types of meals were used which gave different results making trial comparison difficult. This is further complicated by the different methods used for assessing gastro-intestinal transit (commonly ultrasound measurements, scintigraphy, coloured/radiopaque makers and breath tests) and the variety of experimental protocols used covering parameters such as the patient's posture on measurement, the time period of pre-fasting and the method of reporting results.

3. Swallowing

Swallowing or deglutition occurs in three phases, controlled by three separate neurological mechanisms. The oral phase is voluntary. This is the phase that involves chewing and mixing with saliva (when required but that should be avoided with solid dosage forms to be swallowed whole) which produces a bolus and when inhalation is automatically prevented. When it reaches the posterior wall of the pharynx, the involuntary pharyngeal phase begins as the bolus is forced into the pharynx by the tongue. The airway is closed to prevent the bolus entering the respiratory system and

Table 2
Oesophageal transit time in seconds as a function of age, of few ml of water containing Tc-99m sulphur colloid (adapted from Guillet et al., 1983).

Age	6–120 days	4–12 months	1–4 years	4–8 years	8–16 years
n	18	16	16	16	10
Mean (s)	3.4	4.4	4.2	4.6	4.6
SD (s)	1	1.5	1.6	1.0	1.9
Range (s)	1.5–4.5	2.5–8	2–6	3.5–6	2–6

Neonates and young infants were in their mothers' arm whereas older children drank in the standing position.

the tongue is retracted to prevent food re-entering the oral cavity. The oesophageal phase is also involuntary and the bolus is moved down the oesophagus by peristalsis and gravity until it reaches the stomach (Rogers and Arvedson, 2005).

There are a number of anatomical differences which contribute to young children's difficulty of swallowing solids but the development of feeding and swallowing in infants is the result of complex interactions between the developing nervous system, physiological systems and the environment that begin in embryologic and foetal periods and continue to take place from birth, through infancy and into early childhood.

Before 4 or 5 months of age, infants possess an extrusion reflex that enables them to swallow only liquids. This is a protective mechanism where the tongue is thrust forward to prevent any non-liquid food or objects from entering the oral cavity. It coincides to the weaning period which is dependant not only on physiological factors (milk is easily digestible and intestines/kidneys have to be mature enough to cope with a more diverse diet), anatomical factors (the neuromuscular coordination development is not sufficient to allow infants to eat solid foods) but also nutritional factors (there can be an increased risk of infections and allergies with early introduction of solids but it has to be balanced with infant's developmental nutrient and energy requirements). Nature has done well as the first tooth usually appears at around six months of age. The complete set of 20 primary teeth (baby teeth) is usually present by the age of two-and-a-half years.

Moreover a gag reflex of varying degrees is apparent up until about seven to nine months of age. This normal reflex is independent of swallowing as the two are independently innervated; it is caused by touch over the posterior tongue or pharynx and results in tongue protrusion, head and jaw protrusion and pharyngeal muscles contraction (Delaney and Arvedson, 2008).

Hence from birth, liquid medicines seem to be the dosage form of choice whereas by 6 months of age, children can physiologically and anatomically swallow thick/liquid semi-solid formulations which may include e.g. multi-particulates in soft food or beverages. The size, shape and hardness of particles in suspension can influence the oral sensory perception and palatability (Tyle, 1993). However grittiness and risk of chewing has never been formally investigated. This could be especially detrimental if the particles are functionalised (taste masked or modified release formulation). Finally there is no clear evidence based answer for the age at which children can swallow a monolithic dosage form. Five to six years of age is often mentioned although younger children can do it with some training (Czyzewski et al., 2000; Yeung and Wong, 2005) or if the tablet is small e.g. with a diameter of 3 mm (Thomson et al., 2009).

4. Oesophageal transit

No study on oesophageal transit of solid dosage forms in children was found however some non-invasive methods were used to characterise oesophageal transit of amounts of liquids similar to a paediatric medicine dose. It is comparable to adults' normal values for mean oesophageal transit (less than 5 s) as illustrated in Table 2.

The oesophageal time was also less than 5 s when 10 ml of Kr-81m in 5% glucose solution in a single swallow was given in the sitting position to a 4 and a 14-year-old children and 2 ml given in supine position to 3 infants (3, 4 and 6 months old) (Ham et al., 1985). In another study, the mean oesophageal transit time of 5 ml of milk containing Tc Sn colloid in sitting/erect position was less than 3 s in infants ($n = 25$, 1 year old and $n = 8$, <2 years old) (Cronin et al., 1995).

5. Gastric-emptying time

The structure of the stomach is largely developed by 14 weeks of gestation and motility and secretion by around 20 weeks (Lu and Lebenthal, 1994). Gastric motility and emptying develop further when the infant swallows amniotic fluid from around 28 weeks of gestation (Carlos et al., 1997). The proximal stomach or fundus is responsible for the regulation of fluid emptying through a pressure gradient between the fundus and the duodenum. In contrast, the distal stomach is responsible for the grinding and propulsive motion required to empty solids (Grill et al., 1985). There are no contractions of the stomach to propel solids during the first few days of life (Heyman, 1998) and hence gastric emptying can be delayed immediately after birth in both term and pre-term infants (McLeod et al., 1992). In adults, one of reasons for the use of multi-particulates is to circumvent the need for the MMC stage III (housekeeping wave) for emptying into the intestine. Information related to the limiting size of particles for pyloric passage in various ages of children would be of great interest.

Scintigraphy showed that gastric emptying of milk was slower in premature infants born at a gestational age of less than 32 weeks but in older pre-term and term infants, the emptying time was the same. A similar pattern of reduced gastric-emptying time was also seen using ultrasound in patients born at 26 weeks gestational age and followed through until 32 weeks. Gastric-emptying time of milk further decreases until it reached adult values by around 6–8 months of age as commonly reported in textbooks since the 1960s (Heimann, 1980).

Little data was found on gastric emptying of solid dosage forms. Two trials were found which looked at the gastric emptying of pancreatin pellets alongside food (pancake) within paediatric patients. However both of these trials used a wide age range of cystic fibrosis patients (from 5 to 38 years old) who often had gastrointestinal symptoms. The pellets (size before coating = 0.8–2 mm) were labelled with a 99 Technetium tin colloid before being enteric-coated with Eudragit® (no data was given on the grade of Eudragit® or size of the coated pellets). The half emptying time ($GET_{1/2}$) was found to be 103 ± 41 min for the pancake and $<93 \pm 62$ min for the pellets showing considerable variation in emptying rate and little mixing of the pellets and food (Hillel et al., 1998). These results were reproducible (Taylor et al., 1999).

Alternatively, the emptying of other materials must be considered. The most common solid test meals appear to be boiled eggs or bread and ham. A key consideration when paediatric patients are involved, be it medicine or food, is the acceptability to the patient. With this is mind, a team of British researchers selected seven, child-friendly, easy-to-prepare, standard foods which were suitable for labelling for gastric emptying studies and asked patients to vote for their favourite three foods (Singh et al., 2006). The list

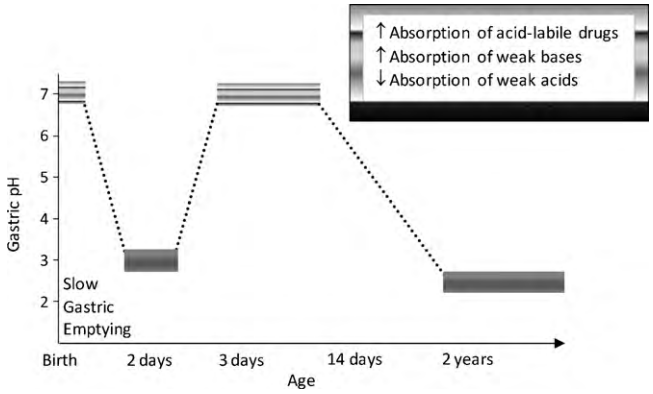

Fig. 1. Fasted gastric pH changes with age and its effect on drug absorption (provided by S.D. Krämer, ETH Zurich, CH, adapted from Maffei and Nóbrega (1975), Fackler et al. (2001) and Bartelink et al. (2006).

by decreasing order of preference included chocolate crispy cakes, Angel Delight®, jelly, scrambled egg on toast, yoghurt and fromage frais. Lack of compliance, either intentional or unintentional is very important; with many trials excluding patients who cannot tolerate or even finish the test meal within the designated time; it may involve patients being exposed to invasive or radioactive procedures for no benefit. To standardise quantity and completion of intake, 30 g was chosen since it was large enough to stimulate a fed response but below the range eaten (30.05–42.87 g) so that every patient were able to finish the test meal (Singh et al., 2006). All 5–10 years old (mean 8.1 ± 1.76, $n = 25$) showed a mean $GET_{1/2}$ of 107.2 min (range 54.6–159.8 min). A further study showed excellent reproducibility using the labelled crispy cake both by scintigraphy and carbon breath test (Eradi et al., 2006).

Liquids seem to show even greater variation in gastric emptying times than solids. This is probably due to the range of viscosities, osmolarities, calorific contents and other feed characteristics which have been shown to affect gastric-emptying times. Impedance measurements showed rapid gastric emptying of water (5 ml/kg) with no variation between premature infants and full-term infants within an average of 6.9 min which was within the adult range (Lange et al., 1997). Scintigraphic imaging has also shown that water cleared very rapidly with only 0–10% antral retention index after an hour, as did neonatal formula and breast milk whilst infant formula, cow's milk, orange juice and milk with additives (such as cereal, chocolate or flour) cleared much more slowly at 30–75% retention index after 1 h (Gomes et al., 2003). Hence with so many different variables, milk can have vastly different emptying times ranging from anywhere from 30 to 120 min, depending on its type and fortification (which can make it semi-solid rather than liquid), patient and investigation characteristics.

6. Gastrointestinal pH and transit

6.1. Gastric pH

Gastric pH and volume measurements are commonly made by one-off aspiration of the stomach contents but continuous pH probes are occasionally used. Their determinations are predominantly carried out on patients undergoing surgery. As the patient has been fasting, aspiration of the stomach contents is achievable as there should not be any solid lumps and that the patient is already sedated/anesthetised which allows the insertion of tubes into the stomach and minimises the trauma to the patient. However these results do not mirror the fed patient. Fig. 1 gives an overview of the gastric pH variation during childhood.

Generally, the gastric pH is rather neutral in neonates and then drops to acidic values over the first 2 years of life. There are very limited data concerning maturational changes of the neonatal gastrointestinal tract that may influence bioavailability. Gastrointestinal absorption is influenced by factors such as gastric and intestinal pH and motility, blood flow and tissue perfusion, surface area, pancreatic function, intestinal microbial flora, transit time as well as maturation of transporters and receptors. In principle, all these factors are reduced or immature in the neonate (Committee for medicinal products for human use and paediatric committee, 2009; Doc. Ref. EMEA/536810/2008) For example gastric pH measured three to 4 min post-birth ranged from 1.4 to 7.8 (with a pH above seven being observed in all patients born before 34 weeks) (Miclat et al., 1978). This alkaline pH is due to the presence of amniotic fluid (pH 6.9–7.9). It became acidic after removal of the gastric contents and drops to 2.2 (on average) 5–6 h later (Ebers et al., 1956). There was a general trend of increasing pH from 1 to 3 h, followed by an increase at 4 h which is no longer seen by 24 h of age (Avery et al., 1966). Even pre-term infants from 24 weeks of gestation were able to maintain pH below 4 when measured during their first 6–12 h of life although the proportion of time the gastric pH is below 4, 3 or 2 were all less than in adults and correlate with the post-delivery age (Sandheimer et al., 1985.) Lower gestational age premature infants were seen to have higher gastric acid values (especially within the first 3 days of life) (Kelly et al., 1993). These pH values were seen to slightly rise but then have decreased again by day 17, with all infants having a median pH between 1.3 and 2.3 by their third week of life.

The early post-natal developmental pattern may additionally be highly variable due to environmental factors (i.e., diet, drug administration), genetic factors and underlying pathophysiology and it is likely that many changes in bioavailability during the early post-natal period will occur. However the oral route in premature neonates and young neonates is not very common and will not be the main emphasis of this paper. The physiological factors affecting oral absorption in full-term newborn up to infant can be summarised as in Table 3. The pharmacokinetic outcome is that the rate and the extent of absorption are variable and that the first pass effect will be significantly reduced but is reaching adult's values in infants. Hence even when a compound is absorbed, its metabolic fate may be different in different ages of paediatric due to the differential maturation of liver processes.

In adults, average values are available for many of these variables including fasted free stomach volume (45 ± 18 ml), acid output (6–40 mEq/h), gastric pH (1.0–2.5) and small intestinal transit time (3–4 h) as discussed elsewhere (McConnell et al., 2008). The maximal acid output is similar to that of adults at 0.2 mEq/h/kg of body weight by 6 months of age hence is always quoted as the time at which gastric acid secretion reaches adult values (Boyle, 2003). This does not however mean that gastric pH-profiles are the same. On continuous pH monitoring, adults maintain their gastric pH below two for around 65% of time whereas for a group of children, a similar percentage of time below pH 2 was not achieved until around 14 years (Nagita et al., 1996). The gastric acidity profile hence changes rapidly through infancy to 3 years old and then even more slowly until it reaches adult values around 13–14 years old. Variations in pH amongst children under 2 or 3 are especially relevant when developing pH-sensitive multi-particulate formulations. The effects of gastric pH are further pronounced when gastric residence time is prolonged and depending upon the characteristics of the drug e.g. the pK_a, solubility profile, etc.

Fasted gastric volume increases with age and is frequently reported in the units of ml/kg (Cook-Sather et al., 2003). Difficulties in determining the age at which it meets adult values stem from the different fasting and sampling conditions. From one of the trials, an interesting effect was seen with temazepam elixir

Table 3
Age differences in gastrointestinal factors relative to adult values modified from Alcorn and McNamara (2003) and de Zwart et al. (2004).

Physiological factors	New born (full-term)	Neonate	Infant
Volume stomach (fasted)		2.5 ml	2.5 ml
Acid/pepsin output		Relatively low	~Adult (/BW)
Gastric pH	Neutral at birth then 1–3	>5	~Adult
Gastric-emptying time	Reduced (variable)	Reduced (variable)	Increased
Gastric motility	Low in first days of life		~Adult (6–8 months)
Intestinal surface area	Reduced	Reduced	~Adult
Intestinal transit time	Reduced	Reduced	Increased
Pancreatic/biliary function	Very immature	Immature	~Adult
Bacterial flora	Very immature	Immature	Immature
Enzymes/transporter activities	Very immature	Immature	Approaching adult

BW: body weight.

as a premedication (Meakin et al., 1987) The elixir was seen to significantly increase both gastric volume and pH which was not seen with temazepam capsules although the age of the capsule group was higher with a mean age of 9.1 years versus 6.6 years in the elixir group due to swallowing issues in younger children. This increase in gastric volume and pH are thought to be due to the composition of the elixir vehicle (ethanol 9%, sorbitol 45% and glycerol 50%). Glycerol is an irritant which stimulates mucus secretion and both glycerol and sorbitol have osmotic properties which can cause the influx of waster into the stomach. Both mechanisms dilute and increase the volume of the stomach contents. Due to the mechanism of action, these effects will also occur in adults or older children and it is simply the ratio of dose volume to stomach content volume that renders them more significant in young children. Hence it is not the excipients per se that are the issue, just their use level: the elixir is an adult formulation containing ethanol and this example serves as a reminder of the problems of using adult formulations in paediatrics without due thought.

6.2. Small intestinal pH

A radio-transmitting pH capsule (24 mm × 7 mm) was used to determine the time taken to pass through the gut and pH at various points in fasting patients (Fallingborg et al., 1990). This technique gave useful information about the conditions throughout the gastrointestinal tract but due to the large size of capsule could only be used in older children. Twelve healthy 8–14 years old (median age 12 years) were found to have a mean gastric pH of 1.5. The pH became more alkaline (6.4) in the duodenum up to 7.4 in the distal region of the small intestine before reaching 5.9 in the caecum. These pH values were similar to those found in adults. Similar values of small intestinal pH determined by aspiration have also been seen in children ranging from neonates to adolescents (mean pH 6–7.8) (Ellett, 2004).

6.3. Intestinal transit

There is a great lack of information on the developmental aspects of intestinal transit that would be needed in the development of age appropriate formulations. The rhythmic activity of the intestine increased with gestational age with disorganised activity from 25 to 33 weeks giving way to a propagating MMC and eventually mature interdigestive motility at full-term (Commare and Tappenden, 2007). A general overview of how the intestinal characteristics of younger children differ from adults can be seen in Table 3. The choice of test to determine intestinal transit can be dependent upon age: there is a risk of harm by younger infants or neonates attempting to swallow pellets and lactose ^{13}C Ureide test is unsuitable in infants less than 8 months as they lack the enzyme required to metabolise it (Van Den Driessche et al., 2000). Hence most of the time carmine dye is used as it is easy to administer and appears to be well tolerated in all age groups but it only gives the time taken for the dye to transit from the mouth to excretion in the faeces.

Lactulose-Hydrogen breath tests which measure oral-to-caecal transit time and hence remove the long colonic transit phase were found to have a transit time of 80–90 min on average in patients aged from 1 to 5 years old (Myo-Khin et al., 1999). However, lactulose increased the intestinal motility through its osmotic effects as was seen by the greater time of 255 min using the lactose ^{13}C Ureide test in children aged from 3 to 17 years (Van Den Driessche et al., 2000).

Pre-term infants generally have longer intestinal transit times than infants born at term. The intestinal transit time of a pre-term infant decreases with enteral feeding (milk) and on increasing gestational age (Berseth, 1990). Despite the fact the intestine grows, the issue of when intestinal transit time reaches adult values is less clear. No difference in intestinal transit time were found in children aged from 2 months to 3 years versus 3 to 12 years (with large pellets of 5 mm which were swallowed with milk having an average whole-gut-transit-time of 23.7 ± 3.08 and 25.4 ± 3.7 h, respectively) nor when children grouped by year from age 1–5 years were investigated using a breath test (Corazziari et al., 1985; Myo-Khin et al., 1999). A standard time of normal transit is often used in constipation studies. It is defined as when a radioactive tracer reaches the caecum within 6 h and is largely excreted within 24 h (Clarke et al., 2009). Other data seemed to also support a whole-gut-transit-time of carmine somewhere between 12 and 48 h as normal in children aged 3–13 years (Dimson, 1970).

Pellets have the advantage that they can be detected throughout the child's stool so that they can be reported as a range unlike carmine which can only be reported as the first appearance of red stool. When children less than 3 years old were tested with cuboids pellets (2.7–3 mm) and carmine dye, the time to first red stool and first appearance of pellets were similar (17.5 h versus 19.7 h, respectively) and in the majority of children occurred in the same stool. However this was not the case for patients suffering from diarrhoea where there appeared to be sequestering of pellets in the bowel and the carmine streaming into the liquid phase (Higgs et al., 1975). Similar mean transit times of pellets (diameter 5 mm) were seen in older children (up to 12 years old) (Corazziari et al., 1985). Transit of non-disintegrating solids seems to be affected by size and smaller particles (3–5 mm) seemed to behave more like liquids and semi-solids than larger objects (2 cm). This pattern is similar in adults.

For total colonic transit time (CTT), a comparison of previously reported normal values in children is detailed in Table 4. The findings were based on single ingestion of markers with serial micrographs or repeated ingestion of markers (single shaped or differently shaped, mixed or separated with details not always fully described) with single abdominal radiograph. These methods were comparable, well tolerated, non-invasive and had low radiation exposure. The mean CTT was slightly slower although comparable to adult values (35 ± 2.1 h) when measured using radioactive

Table 4
Total and segmental colonic transit time in hours of healthy children (adapted from Wagener et al., 2004).

n	Age (year)	Total CTT (SD) (h)	Right colon (h)	Left colon (h)	Rectosigmoid colon (h)	Country
78	2 months to 12 years	25 (3.7)	–	–	–	Italy
30	2–14	29.08 (8.3)	7.25 (5.75)	6.6 (6.2)	15 (8.7)	Spain
15	3–14	22.3 (4.8)	5.4 (3)	7.1 (3.4)	9.8 (3.2)	Italy
22	4–15	39.6 (21.4)	–	–	18.2 (13.3)	UK
10	6–14	37.8 (6.2)	10.8 (3.5)	12.2 (2.7)	14.7 (2.1)	Spain
23	15	29 (4.0[a])	7.7	8.7	12.4	France
13	12–18	30.2 (13.2)	6.7 (3.9)	7.9 (7.8)	15.6 (10.7)	Brazil

[a] Standard error.

markers (Metcalf et al., 1987). Gender differences were not studied.

The geometry and density of the object transiting is important to consider especially for larger, non-disintegrating objects. The residence time of the a pH-sensitive, radio-transmitting capsule (24 mm by 7 mm) in the fasted stomach of 8–14 years old ($n = 12$) ranged from 0.2 to 2.3 h whereas the small intestinal transit time ranged from 5.1 to 9.2 h and the colonic transit time from 6.2 to 54.7 h. The capsule spent 75% of the small intestinal transit time in the distal region and 43% of the colonic transit time in the caecum (Fallingborg et al., 1990). These values are comparable to adult transit times (Fallingborg et al., 1989) In younger children, a study of radiopaque swallowed foreign bodies, predominantly British one and five pence coins (1.8–2 cm diameter), found that transit time ranged from 1 to 46 days (with a median of 6 days). Here the median transit time increased with age but very few of the patients studied were older than three (Macgregor and Ferguson, 1998).

7. Conclusion

Due to practical and ethical concerns, there has been a lack of research into the transit of formulations in children. The limited physiological data available using food, milk or liquids were considered in an attempt to highlight specific aspects of gastro-intestinal transit in children.

In summary, oesophageal transit time of liquids was not seen to differ between children and adults. Patients older than 6 months of age may be able to swallow multi-particulates in soft food, although the occurrence of chewing and the significance of grittiness of the formulation must be considered for taste masked, enteric-coated or modified release particles. Gastric emptying has been seen to be delayed in children aged 6–8 months compared with adults. The gastric pH can reach adult values around 2 years of age. This might be of consideration when developing enteric-coated multi-particulates. In general, the intestinal transit time is reduced amongst younger infants but the total colonic transit time is slightly slower amongst children, which could potentially decrease or increase absorption from multi-particulates in these respective parts of the gut. From the few studies retrieved, pellets seemed to behave more similarly to liquids in children as well.

Multi-particulate formulations offer an alternative and compromise between solid and liquid dosage forms to meet the needs of the heterogeneous paediatric population. Due to the large number of variables (e.g. investigative method, types of meal, age ranges and co-morbidities), direct comparisons between studies were difficult. Moreover there were very few studies looking at dosage form transit in children. Less invasive/hazardous investigations such as ultrasound may allow data to be ethically obtained from children, in order to fill in the gaps in this field of research.

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