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Modeling of the luminal butyrate concentration to design an oral formulation capable of achieving a pharmaceutical response

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ABSTRACT

Butyrate concentrations required for a direct effect on intestinal epithelial cells lie between 2–5 mM. In order for butyrate to affect the small intestine the local pharmacokinetics need to be understood.

We used a mathematical approach to model the luminal butyrate concentration after oral administration of an immediate release formulation or a sustained release formulation to humans. This model was used to design an oral formulation capable of achieving a local pharmaceutical response in the small intestine.

The model showed that an immediate release formulation is only capable of maintaining pharmacologically active concentrations during the first half hour after the formulation has entered the small intestine. A sustained release formulation is capable of maintaining pharmacologically active concentrations for hours and thus throughout the whole small intestine. To reach these concentrations the sustained release formulation requires a zero order release rate of 0.08-0.2 mmol/h. The anticipated release rates are expected to result in luminal butyrate concentrations that are high enough at the surface of the epithelial cells to improve the intestinal barrier and to have anti-inflammatory properties. However, it is uncertain if the duration of exposure, and quantity of exposed epithelial cells is adequate to have a clinical effect.

1. Introduction

Butyrate is a promising therapeutic agent which is thought to be of benefit in the treatment of several noncommunicable diseases (NCDs) when administered to the small intestine. NCDs are diseases in which chronic low-grade inflammation plays an important role. This low-grade inflammation could be caused by damage of the gastrointestinal barrier which is pivotal for efficient host defense [1]. Butyrate might influence gut integrity via different mechanisms of action. Direct interaction with the intestinal epithelial cells (IECs) but also direct interaction with immune cells present within and just below the mucosal membrane. Several studies indicated earlier that butyrate can improve the intestinal barrier and modulate local immune responses in the small intestine [2–4].

Butyrate can be produced by the bacteria in the gastrointestinal tract as a result of fiber fermentation [5–7]. Butyrate-producing bacteria are abundantly present in the colon, so butyrate levels are high there. Butyrate-producing bacteria are less abundantly present in the small intestine, so butyrate levels are relatively lower there. The upper part of the small intestine in particular lacks butyrate [8,9]. Therefore, the small intestine would be a highly interesting target for novel butyrate containing drug formulations.

The small intestine is part of the gastrointestinal tract and extends from the stomach to the beginning of the colon. From the inside to the outside, the intestinal wall consists of a mucus layer, epithelial cells and the lamina propria with immune cells [10].

Since we focus on how butyrate affects IECs, which are present along the whole small intestine, it could be speculated that butyrate needs to be available throughout all the IECs along the small intestinal wall. Additionally, butyrate should be present in a concentration that results in a pharmacological response. The pharmacologically active concentration of butyrate to affect IECs lies between 2–5 mM [11–14]. At these concentrations, the intestinal barrier is improved and the local mucosal immune response seemed to be affected. Therefore our goal is to develop a butyrate formulation that reaches these concentrations at

Abbreviations: IECs, intestinal epithelial cells; IM, immediate release; NCDs, noncommunicable diseases; SR, sustained release

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the surface of the IECs, preferably along the entire length of the small intestine.

Butyrate is a drug with a high solubility, causing it to dissolve very fast in the luminal fluid. The luminal fluid is not distributed homogeneously over the small intestine, but is present in separated pockets with variable volumes [15,16]. Therefore butyrate will only dissolve in the volume available in one pocket, the pocket where the oral formulation is present, and not in the total volume available in the whole small intestine.

Once butyrate is dissolved, it starts to diffuse across the mucus and is subsequently absorbed by the IECs. The remaining butyrate concentration in the lumen at a certain moment is determined by both the amount that is released and the amount that is diffused and absorbed. In other words, the concentration is determined by the balance between influx and outflux. The overall absorption rate of butyrate in the small intestine has been studied by Schmitt et al [17]. They investigated the disappearance rate of butyrate out of the lumen making it possible to model the butyrate concentration in the lumen after intake of an oral immediate release or sustained release butyrate formulation with specified release characteristics.

This study aims to model the butyrate concentration in the small intestine after oral administration of a butyrate formulation to humans. With the help of this mathematical model we anticipate developing a formulation suitable to maintain pharmacologically active butyrate concentrations in the small intestine to treat NCDs. We consider knowledge of a dosing regimen as a biopharmaceutical prerequisite to perform clinical studies.

2. Methods

2.1. Schematic representation of the small intestine

A mathematical approach was used to model the luminal butyrate concentration after intake of an oral formulation by humans. To build this model we made several assumptions, which will be described below.

As described before, small intestinal fluid is present in several fluid pockets. The total volume of these pockets and the volume distribution across these pockets has been studied before [16,18]. Although the volume of one pocket is variable, in this model the volume of luminal fluid present for butyrate to dissolve in was set constant. This volume was used to calculate the available butyrate concentration in one pocket. The mean volume in one pocket is reported to be 6 +/- 2 ml after intake of 240 ml of water [16]. Therefore a constant volume of 6 ml was used in our model.

To the best of our knowledge the origin and the exact kinetics of a pocket containing an oral formulation are unknown. Therefore the assumption was made that the butyrate formulation when entering the small intestine gets captured in a fluid pocket and the luminal fluid surrounding the formulation and the formulation itself move forward in the small intestine simultaneously (Fig. 1). The butyrate formulation will thus be present in one fluid pocket during the intestinal transit from stomach to the colon and for this specific pocket the butyrate concentration will be calculated. As the pocket transits through the small intestine, the location of the formulation changes in time, as illustrated by the red rectangle in Fig. 1.

The butyrate concentration was modelled in the luminal fluid of one pocket. The butyrate that is present in the luminal fluid diffuses across the mucus to the surface of the intestinal epithelial cells (IECs) where it can exert its effect. We assume that the butyrate concentration in the luminal fluid will be equal to the butyrate concentration at the surface of the IECs, because butyrate is a small and hydrophilic molecule and because the mucus layer in the small intestine is very thin [18].

Additionally, the dimensions of one pocket in the model were set, namely the diameter and the length available for absorption. A pocket can be described as a cylinder with a diameter of 2.5 cm (10). The length of one pocket was calculated to be 1.2 cm based on the volume of 6 ml, see Fig. 2.

2.2. The absorption of butyrate

The absorption of butyrate was studied by Schmitt et al and was used to model the absorption rate of butyrate [17]. It was shown that the absorption rate of butyrate is concentration dependent and can be described by Michaelis-Menten kinetics, see Fig. 3 [17]. The Michaelis-Menten equation, Eq. (1), was used to reproduce the data of Schmitt et al. with regard to the absorption rate corresponding to the concentration range of interest, the linear part of the curve in Fig. 3:

$$V = V_{max}\frac{C}{C + K_M} \tag{1}$$

where V is the absorption rate of butyrate in mmol/h/cm, V_{max} is the maximum absorption rate of butyrate (0.820 mmol/h/cm), K_M is the Michaelis constant of butyrate in the small intestine (25.6 mM) and C is the butyrate concentration available in the small intestine in mM (18). Michaelis-Menten kinetics indicate that the absorption of butyrate is driven by active transport, especially at the concentration range of our interest. At higher concentrations active transport is saturated and diffusion of butyrate will further increase the absorption rate of butyrate.

As already indicated, the anticipated pharmacologically active concentration is 2–5 mM. The absorption rate corresponding to this concentration range, can be found in the linear part of the curve. The values on the y-axis of Fig. 3 were converted from mmol/h/cm to mmol/h/the length of one pocket and the values on the x-axis of Fig. 3 were converted from mM to mmol in the volume of one pocket, as shown in Fig. 4. By this conversion the data were adapted to the situation in one pocket and first order kinetics could be used to describe the absorption. The absorption of butyrate in one pocket of the small intestine can be described by the following equation:

$$Rate\ of\ absorption\ of\ butyrate = -k_{abs} \times A(t) \tag{2}$$

where A(t) is the amount of butyrate in one pocket of the small intestine in mmol, t is time in h and k_{abs} is the first order absorption rate constant of butyrate in h^{-1}. The data was fitted linearly from 0 to 0.09 mmol butyrate in one pocket with a R^2 of 1. k_{abs} equals 4, as can be seen in Fig. 4.

2.3. Model of sustained release formulation

The butyrate concentration in the lumen was first calculated for a sustained release (SR) formulation. This was done by subtracting the amount of butyrate absorbed out of the lumen from the amount of butyrate released into the lumen, as shown in Eq. (3).

$$\underbrace{Rate\ of\ change\ of\ butyrate\ in\ the\ small\ intestine}_{} = \underbrace{Rate\ of\ release\ of\ butyrate\ from\ formulation}_{\text{Part 1}} - \underbrace{Rate\ of\ absorption\ of\ butyrate}_{\text{Part 2}} \tag{3}$$

Part 1 of Eq. (3) shows the rate of butyrate released from a SR formulation. The release of butyrate can be adequately described by zero order kinetics. The equation of a zero order release formulation is shown in Eq. (4):

$$Rate\ of\ release\ of\ butyrate\ from\ formulation = R_{rel} \tag{4}$$

where R_{rel} is the zero order release rate from the formulation in mmol/h.

Part 2 of Eq. (3) is described previously in Eq. (2). Eq. (3) can be translated to Eq. (5) by combining Eq. (2), the absorption of butyrate, and Eq. (4), the release of butyrate from a formulation.

$$\frac{dA(t)}{dt} = R_{rel} - k_{abs} \times A(t) \tag{5}$$

Because we were interested in the butyrate concentration in the lumen, we substituted A(t) by C(t) times V, yielding Eq. (6):

$$\frac{d[C(t) \times V]}{dt} = R_{rel} - k_{abs} \times C(t) \times V \tag{6}$$

where V is the mean constant volume of one pocket in the small

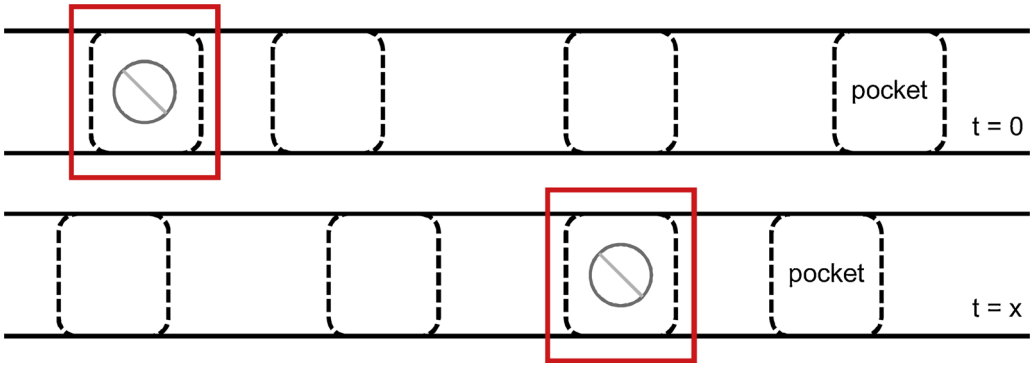
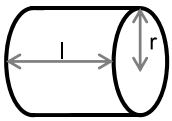


Fig. 1. Representation of the movement of the formulation containing pocket through the small intestine. Concentrations will be calculated for the area within the red rectangle. Different time points therefore also reflect different positions in the small intestine.



Volume of one pocket= π r² l

Fig. 2. Schematic representation of a pocket in the small intestine. r = radius of the small intestine: 1.25 cm (10); l = length of the pocket: 1.2 cm. The volume of one pocket in our model is 6 cm^3.

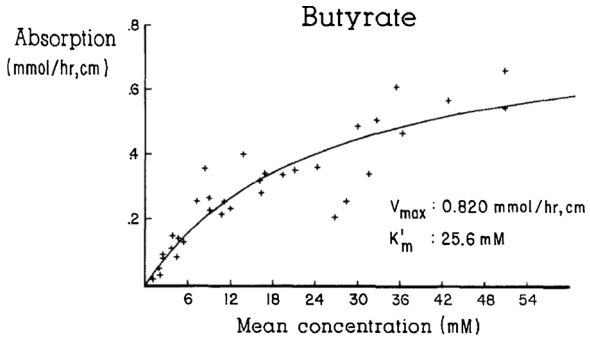


Fig. 3. Absorption data obtained from Schmitt et al with permission [17].

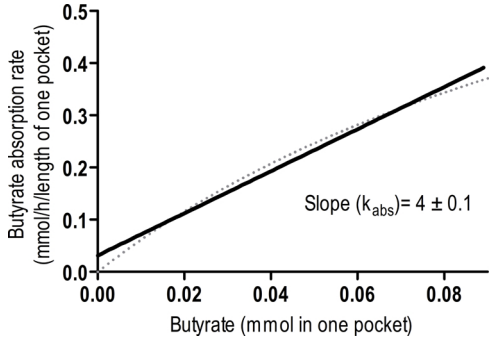


Fig. 4. The dotted grey line shows the converted data of Schmitt et al to the situation in one pocket (volume = 6 ml, length = 1.2 cm). Data were lineary fitted to obtain the slope (k_{abs}) [17].

intestine, 6 ml. This resulted in the following equation for the change of butyrate concentration in the lumen with time (Eq. (7)).

$$\frac{dC\,(t)}{dt} = \frac{1}{V} \times R_{rel} - k_{abs} \times C(t) \tag{7}$$

Eq. (7) is solved over time, yielding the following equation for C(t):

$$C(t) = \frac{1}{V} \times \frac{R_{rel}}{k_{abs}} + cst_{SR} \times e^{-k_{abs} \times t} \tag{8}$$

where cst_{SR} is the constant of integration, which was calculated by solving Eq. (8) for a known concentration at a known timepoint, namely a concentration of 0 mM at t = 0 h. At t = 0 h, the formulation will enter the upper small intestine of which it is known that it lacks butyrate [9].

Butyrate concentrations in the pocket containing the formulation were modelled using Eq. (8). We aim to reach a concentration of 2–5 mM, 15 min after the formulation enters the small intestine to ensure that a pharmacologically active concentration of butyrate gets available to the IECs from the beginning of the small intestine until the end of the small intestine. Therefore, we calculated the R_{rel} to find the release rate needed to reach pharmacologically active concentrations.

2.4. Model of immediate release formulation

Contrary to a SR formulation, an immediate release (IR) formulation has no constant supply of butyrate into the lumen. We assumed that the butyrate present in an IR formulation will instantly dissolve in the volume of a pocket. The dissolved butyrate will subsequently be absorbed out of the lumen. This means that only absorption will play a role in the rate at which the butyrate concentration changes in the small intestine, see Eq. (9).

Rate of change of butyrate in the small intestine

$$= -Rate\ of\ absorption\ of\ butyrate \tag{9}$$

Eq. (9) can be translated to Eq. (10):

$$\frac{dA\,(t)}{dt} = -k_{abs} \times A(t) \tag{10}$$

where A(t) is the amount of butyrate in one pocket of the small intestine in mmol, t is time in h and k_{abs} is the first order absorption rate constant of butyrate in h^{-1}. Because we were interested in the concentration we substituted A(t) by C(t) times V, yielding Eq. (11):

$$\frac{d[C(t) \times V]}{dt} = -k_{abs} \times C(t) \times V \tag{11}$$

where C(t) is the butyrate concentration in one pocket of the small intestine and V is the mean constant volume of one pocket in the small intestine, 6 ml. This resulted in the following equation for the change of butyrate concentration in the lumen with time (Eq. (12)).

$$\frac{dC(t)}{dt} = -k_{abs} \times C(t) \tag{12}$$

Eq. (7) is solved over time, yielding the following equation for C(t):

$$C(t) = cst_{IR} \times e^{-k_{abs} \times t} \tag{13}$$

where cst_{IR} is the constant of integration, which was calculated by solving Eq. (13) for a known concentration at a known time point,

namely the butyrate concentration available directly after dissolving the total amount of butyrate present in the IR formulation in the volume of one pocket at t = 0 h, (C(0)). Meaning that cst_{IR} equals the dosage of butyrate in the formulation divided by the volume of the pocket.

Butyrate concentrations in the lumen were modelled using Eq. (13). We aim to reach a concentration of 2–5 mM, 15 min after the formulation entered the small intestine. Therefore, we varied C(0) in the equation to find the dosage needed to reach pharmacologically active concentrations. Additionally, Eq. (13) gives information about the contact time of butyrate with the IECs after a SR formulation left the pocket and a butyrate concentration will stay present at the surface of the mucus layer. In this case C(0) is the butyrate concentration available at the surface of the mucus layer after the SR formulation left the pocket.

2.5. Data analysis

Graphpad Prism 5.0 was used to fit and plot the data.

3. Results

3.1. Sustained release formulation

A butyrate concentration of 2–5 mM is needed to achieve a pharmacological response [11–14]. Our aim was to obtain these concentrations within 15 min after the formulation reaches the small intestine. The butyrate concentration after oral administration of a sustained release (SR) formulations was modelled using Eq. (8) where $k_{abs} = 4\,h^{-1}$, V = 0.006 l and C(0.25) = 2 mM or 5 mM. The R_{rel} corresponding to C(0.25) = 2 mM is 0.08 mmol/h and the R_{rel} corresponding to C(0.25) = 5 mM is 0.2 mmol/h. Fig. 5 shows the concentration-time curves for SR formulations with these release rates. As can be seen, the steady state concentrations in the pocket will be reached within one hour, reaching levels of approximately 3 mM when C(0.25) = 2 mM and of approximately 8 mM when C(0.25) = 5 mM.

3.2. Immediate release formulation and local concentration after passage of a pocket

As stated, an immediate release (IR) formulation will immediately deplete its butyrate content. The IR results in high concentrations in the pocket containing the formulation. For example, a dose of 10 mg butyrate would yield a concentration of 19.14 mM in a pocket of 6 ml.

The concentration-time profile of such a pocket was calculated using Eq. (13) where $k_{abs} = 4\,h^{-1}$, V = 0.006 liters and C(0.25) = 2 mM or 5 mM, see Fig. 6. The C(0) corresponding to C(0.25) = 2 mM is 5.4 mM and the C(0) corresponding to C(0.25) = 5 mM is 13.6 mM. In addition, these concentrations can be converted to the amount of butyrate in the volume of one pocket, consequently being the amount of butyrate in the IR formulation. This resulted in IR formulations with a

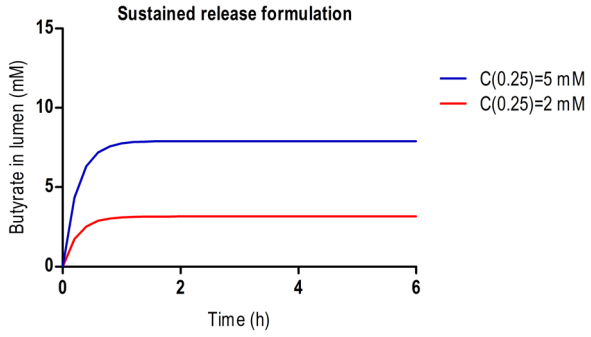


Fig. 5. Concentration-time curve of butyrate in a pocket passing the lumen of the small intestine after intake of two different sustained release formulations with a zero order release rate of 0.08 mmol/h (red) and 0.2 mmol/h (blue).

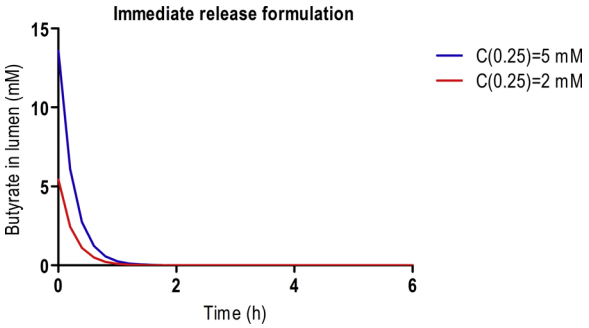


Fig. 6. Concentration–time curve of butyrate in a pocket passing the lumen of the small intestine after intake of two different immediate release formulations with a dosage of either 33 μmol (red) or 82 μmol (blue).

dosage of 33 μmol butyrate to reach a concentration of 2 mM after 15 min and of 82 μmol butyrate to reach a concentration of 5 mM after 15 min.

The butyrate concentration rapidly drops and within one hour hardly any butyrate is left in the pocket because of the relatively high absorption rate. This means a high exposure of butyrate to the upper part of the small intestine while the lower part of the intestine will have no exposure to butyrate at all. Fig. 6 represents the concentration profile in a pocket that is transiting the small intestine while containing an IR formulation or its content. However, principally the same profile reveals at any spot at the surface of the mucus when a SR formulation containing pocket transits through the small intestine. The butyrate containing pocket is in contact with the apical side of the mucus layer causing butyrate to diffuse for the lumen to the surface of the mucus. After the SR formulation containing pocket transits further along the small intestine, butyrate will still be present in the mucus and the butyrate diffuses from the surface of the mucus to the IEC's. The butyrate concentration in a pocket where the SR was present will rapidly fall when considering Fig. 6. In this situation a pharmacologically active concentration can be reached along the whole small intestine in the pocket where the formulation was present, although this is only valid for a period of one hour at maximum.

4. Discussion

4.1. Sustained release versus immediate release

In this study we determined the required release rate of an oral butyrate sustained release (SR) formulation to achieve pharmacologically active concentrations in the small intestine. The model provided by this study helps to develop the first butyrate containing oral drug product to treat noncommunicable diseases (NCDs) in which mucosal barrier disturbance are involved.

A SR formulation is capable of maintaining pharmacologically active concentrations in the pocket where the formulation is present for multiple hours throughout the whole small intestine. SR formulations reach a steady state concentration after approximately 2 h and the level of this steady state concentration depends on the release rate of the formulation in relation to the absorption rate. Immediate release (IR) formulations are only capable of maintaining pharmacologically active concentrations within the first half hour after the formulation has reached the small intestine and thus will not target the whole small intestine. A higher immediate butyrate dose would be capable of maintaining concentrations above the minimal required concentration of 2 mM throughout larger parts of small intestine, but this would at the same time result in a very high concentration in the beginning of the small intestine of which toxicity is unknown. In short, a SR formulation is most promising to treat NCDs via the small intestine without toxicity. In order to maintain pharmacologically active concentrations throughout the small intestine, it requires a release rate of 0.08 to 0.2 mmol/h and sufficient butyrate to

be able to release butyrate for approximately 3 h [19].

In our model the formulation and the luminal fluid surrounding it simultaneously move forward in the small intestine. As a consequence, the butyrate concentration in the lumen is calculated for the pocket in the small intestine in which the formulation is present. The duration a formulation stays in one pocket in the small intestine is unknown. The length of time that butyrate will be exposed to the intestinal epithelial cells stays thus also unknown, but will be limited. The length of time butyrate stays present in the mucus at the surface of the epithelial cells after the formulation moves forward in the intestine can be estimated by considering Figure 7. The butyrate in the mucus will be only taken up by the cells, which makes the process comparable to an IR formulation in other words; only absorption (k_{abs}) plays a role. Figure 7 shows that the butyrate concentration decreased to almost 0 mM approximately half an hour after a pharmacologically active butyrate concentration was present in a pocket. This indicates that butyrate has to act on the intestinal epithelial cells in a short period of time. At this moment it is unclear if pharmacological response is to be expected under these conditions. Pharmacological experiments are normally carried out at constant concentrations.

A formulation passes through the stomach before it enters the small intestine, meaning that some butyrate is released in the stomach before it reaches the small intestine. There are two strategies to ensure that enough butyrate reaches the small intestine: the formulation can either be coated with a gastric resistant coating to prevent butyrate release in the stomach or the formulation can be left uncoated and consist of sufficient butyrate for release in the stomach and the small intestine. Because the upper part of the small intestine lacks butyrate, we prefer an uncoated formulation which will immediately start to release butyrate in the small intestine, while a coated formulation will release a limited amount of butyrate in the upper part of the small intestine because the coating first needs to dissolve [20,21]. The gastric emptying time of an oral formulation is highly variable and depends on the fasted or fed state. The median gastric emptying time of a non-disintegrating capsule or tablet of at least 5 mm in the fasted state is less than 30 min and in the fed state around 5 h [22]. To make sure that the SR formulation consists of sufficient butyrate to have butyrate release along the whole small intestine, the SR formulation should consist of sufficient butyrate for an 8 h release in total, more specific a 5 h release in the stomach and a 3 h release in the small intestine [19,22]. The SR formulation requires a butyrate release rate of 0.08-0.2 mmol/h and a butyrate release of 8 h. This results in a total dosage of 0.64–1.6 mmol butyrate, which equals 55.7–139.4 mg butyrate.

4.2. Limitations

Our model is designed based on several assumptions and thus has some limitations. During the calculation of the available butyrate concentration in the small intestine, the volume and length of one pocket were estimated. We used the mean volume after intake of a glass of water, 6 ml. Nevertheless, this volume is susceptible to inter-individual and intraindividual variability. In 60% of the pockets the volume ranges from 0.5 to 2.5 ml, and in 10% of the pockets the volume is larger than 20 ml [16]. The volume of one pocket will influence the performance of the oral formulation, because a different volume results in a different luminal butyrate concentration. A smaller pocket with a lower fluid volume results in a higher butyrate concentration and a larger pocket with a higher fluid volume results in a lower butyrate concentration than calculated by our model.

Another factor that influences the performance of the oral formulation is the diameter of the small intestine, because it influences the area available for absorption. In the model we assigned the small intestine a diameter of 2.5 cm. The diameter of the small intestine differs per segment and ranges from 2 to 4 cm [23]. This diameter influences the absorption rate constant, because it changes the length of one pocket in our model (see Fig. 3). A thinner small intestine increases the k_{abs} and a thicker small intestine decreases the k_{abs}. A change in k_{abs} results for the oral formulation in a different luminal butyrate concentration. Namely, a thinner small intestine results in a lower butyrate concentration and a thicker small intestine result in a higher butyrate concentration.

The fluid in the small intestine does not move with a constant flow from beginning to end, but moves forward with a wave like motion, called peristaltic movement. Peristalsis can have different propagation velocities and distances of spread depending on the segment of the small intestine. The luminal fluid spreads with a high velocity over a long distance in the duodenum, which makes it unclear to what extent mass transfer between the fluid pocket and the mucus takes place. Furthermore, it may be questionable whether butyrate comes into contact with the intestinal wall throughout the whole duodenum. The luminal fluid spreads with a moderate velocity over a shorter distance in the jejunum, which makes it more likely that butyrate comes into contact with a large area of the jejunum wall. The luminal fluid spreads with a slow velocity and a short distance in the ileum, which makes it likely that butyrate comes into contact with a large area of the ileum wall [22,24].

The incidence of an oral formulation passing intestinal segments without fluid pockets is unknown, while in our model we assume that the formulation is always present in a pocket with 6 ml fluid [15]. To build a more accurate model information is needed on the interaction between oral formulations and the intestine which accurately reveals how an oral formulation moves through the small intestine and how the fluid in the small intestine moves through the small intestine in relation to the oral formulation.

5. Conclusion

Butyrate is thought to offer promising properties to treat non-communicable diseases in which mucosal barrier disturbances are involved. Pharmacological data indicate that intestinal epithelial cells should be exposed to concentration in the range of 2–5 mM. This paper applies a mathematical model which enables estimation of the concentrations in the small intestine when administering either an immediate release or a sustained release (SR) oral formulation. The model shows that only SR formulations will be able to yield pharmacologically active concentrations along the whole small intestine, although these concentrations will get in contact with the intestinal epithelial cells relatively short.

The results can be used to develop an oral butyrate formulation with the right release characteristics to reach pharmacologically active concentrations. The SR formulation should have a release rate of 0.08 to 0.2 mmol/h and does not need a gastric resistant coating. This information is necessary to develop an oral formulation that has a chance to succeed in a clinical study. The anticipated release rates are expected to result in luminal butyrate concentrations that are high enough at the surface of the epithelial cells to improve the intestinal barrier and to have anti-inflammatory properties. However, it is uncertain if the duration of exposure, and quantity of exposed epithelial cells is adequate to have the desired clinical effect

Declaration of Competing Interest

The authors report no conflicts of interests. JG is employed by Danone Nutricia Research.

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