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Formulation Screening for pH Modification in Solid Dosage Forms

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Abstract

Oral solid dosage forms are often preferred during drug product development as offering a flexible and cost-effective solution for patients, hence improving patient adherence. The efficacy of an orally administered drug is nonetheless limited by its bioavailability. pH modification is an effective solution to improve solubility of weak acidic or basic drugs via the formation of a microenvironmental pH. The objective of this study was to evaluate different formulation approaches to develop an immediate-release tablet or capsule containing fumaric acid as pH-modifier for enhancing the bioavailability of a weakly basic API. The goal was to maximize the bioavailability of the drug with acceptable amounts of pH-modifier to ensure manufacturability and reduced capsule / tablet size for improved patient experience. In vitro data suggested that the over-encapsulated tablet prototype led to improved bioavailability even in highly buffered achlorhydric conditions and was therefore the most robust formulation toward elevated gastric pH. However, in low buffered achlorhydric conditions the monolayer tablet with acid exhibited similar dissolution rate and prototypes with less close contact between the API and the organic acid also demonstrated improved dissolution rates. These results suggested that the acidic microenvironment may not require such a high degree of contact between the API and the pH-modifier. The outcomes of this study, and consequently the bio-relevance of tested media, will have to be further evaluated in vivo.

Keywords: formulation; solubility; dissolution; bioavailability; pH-modification; achlorhydria; patient-centricity

1. Introduction

Oral solid dosage forms are often preferred during drug product development as offering a flexible and cost-effective solution for patients, hence improving patient adherence. The efficacy of an orally administered drug is nonetheless limited by its bioavailability. Bioavailability is "the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of drug action"[1]. Despite the convenience and high patient adherence of oral solid dosage forms, various physicochemical and biological barriers can interfere with the biopharmaceutical performance of an active pharmaceutical ingredients (API), such as limited dissolution rates or precipitation and membrane permeability [2]. The Biopharmaceutical Classification System (BCS) was developed to categorize APIs based on these two factors, leading to the definition of four classes: BCS class I – high solubility and permeability, class II – low solubility and high permeability, class III – high solubility and low permeability, class IV – low solubility and permeability [3]. While BCS class I APIs represent about 40% of marketed products, it is estimated that new pharmaceutical pipelines are mainly composed of BCS class II APIs, which represents a challenge for formulators due to their solubility-limited absorption [4]. To address this challenge, a

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wide array of solubility enhancing approaches are available, such as chemical approaches (e.g. co-solvents, solubilizing agents), crystal engineering (e.g. salt or cocrystal formation) or physical approaches (e.g. amorphous solid dispersion, cyclodextrins complexation, lipid-based formulation, particle size reduction) [5]. Selected approach should consider not only bioavailability, but also product stability and manufacturing complexity.

pH modification is an effective strategy to improve solubility by creating a microenvironmental pH around the drug [6]. This is particularly relevant for weakly basic drugs, whose solubility decreases at elevated gastric pH, potentially leading to under-exposure. Gastric pH variability is indeed well described in literature as being influenced by several physiological factors such as food effect [7–9]. Gastric pH variability can also increase in some patient populations due to reduced acid secretion [10], disease [11,12], ethnicity [13] or age [14]. These populations may experience elevated gastric pH, also referred to as hypo- or achlorhydria (i.e. too low or no gastric acid secretion). Strategies to mitigate the effect of high gastric pH on bio-performance include: co-administration with acidic beverages, pre-treatment with organic acid, development of solid dosage formulations containing organic acid and the development of enabling formulations [15]. The two first strategies are considered less patient-centric as they require an additional action from the patient [16,17]. The development of an enabling formulation can greatly increase the development timelines. The use of a pH-modifier in the formulation is an easy-to-implement and patient-centric solution to create a favorable microenvironment [18].

A few studies reported the use of organic acids added to a formulation to overcome elevated gastric pH. Onoue et al. described the use of fumaric acid inside granule formulation to improve the bioavailability of dipyridamole under hypochlorhydria [19]. Badawy et al. evaluated 11 formulations containing tartaric acid (intra- and extra-granular), citric acid, succinic acid or cyclodextrins [20]. Based on their study, the bioavailability of BMS-56389 could be improved by using tartaric acid in the extra-granular phase. Pu et al. also performed the screening of organic acids and surfactants to reduce the pharmacokinetics variability of a weakly basic drug compound, showing reduced variability with citric acid and sodium lauryl sulfate [21]. Similarly, Mitra et al. compared the bioavailability of capsules formulations with and without citric acid added either in the extra-granular phase or co-melt with compound A [22]. In their study, the highest performance was obtained by the citric acid co-melted with the API. The authors attributed this result to the intimate contact between the API and pH-modifier. Finally, Taniguchi et al. evaluated ten organic acids in granule formulations containing dipyridamole considering manufacturability, product stability and bio-performance [23]. This study concluded that p-toluene sulfonic acid monohydrate met the three criteria. This last study nonetheless highlighted that organic acid, and the weak base are likely to interact, thus limiting product stability. These studies exemplify the difficulty of developing a manufacturable, stable and yet performant formulation using organic acids. Tanigushi et al. especially highlighted that the level of microenvironmental pH and its duration in vivo can be key factors for improving drug dissolution [24]. As a result, the way to incorporate a pH-modifier in a formulation is expected to affect the drug product performance.

This study reports the formulation development of an immediate release oral solid dosage form (tablet or capsule) to enhance the bioavailability of a weakly basic API to treat patients with potentially elevated gastric pH. A granules-in-capsule (GiC) formulation containing fumaric acid in the extra-granular phase was evaluated in a previous pharmacokinetic study in pre-treated dogs as proof of concept. A 2.4-fold increase in the Cmax was achieved compared to the GiC formulation without fumaric acid [25]. Based on this proof of concept, bio-relevant dissolution tests were developed and different formulation strategies for incorporating a pH-modifier in the formulation were evaluated. The goal was to maximize the bioavailability of the drug with acceptable amounts of pH-modifier to ensure manufacturability, product stability and reduced capsule / tablet size for improved patient experience.

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2. Materials and Methods

2.1. Materials

The API was characterized as a weakly basic BCS class II molecule with a pH dependent solubility profile. Lactose monohydrate (Pharmatose 200, DFE pharma, Netherlands) and microcrystalline cellulose (MCC, Avicel PH102, Dupont, Ireland) were used as fillers. Sodium croscarmellose (Ac-Di-Sol, Dupont, Ireland) was used as disintegrant. Colloidal silicon dioxide (Aerosil 200, Evonik, Germany) was used as glidant. Hydroxy-propyl cellulose (HPC, Klucel EF, Ashland, USA) was used as binder. Magnesium stearate (Ligamed MF 2V, Peter Greven, Netherlands) was used as lubricant. Following tests with several organic acids, fumaric acid (Merck, Germany) was selected as pH-modifier as showing a good manufacturability and maximizing the bio-performance. Hypromellose capsules (VCaps, Capsugel, France) of various sizes were used for encapsulated prototypes.

2.2. Prototypes Design

Ten prototypes were developed to evaluate the impact of the degree of contact between fumaric acid and the API on the bio-performance. Indeed, a high degree of contact is expected to improve bio-performance, but also to negatively affect the stability of the drug product. All prototypes were individually optimized to ensure manufacturability while limiting formulation variations that could interfere with comparability. Therefore, all formulations containing fumaric acid targeted an acid/API ratio of 0.22, which was considered as the optimal ratio regarding bio-performance during pre-tests. As all prototypes were based on granules, the same batch of granules was used for all. Whenever possible critical physical attributes (such as tablet porosity for instance) were kept identical between prototypes. Table 1 provides a summary of the developed formulations.

Table 1. Summary of developed formulations.

#	Prototype name	Description	Picture
1	GiC without acid	Granules-in-Capsule (GiC) without acid	
2	GiC with acid	GiC with acid in the extra-granular phase	
3	CiC	Capsule-in-Capsule (CiC) with acid in the inner capsule and API in the outer capsule	
4	Tablet without acid	Monolayer tablet without acid	
5	Tablet with acid	Monolayer tablet with acid in the extra-granular phase	
6	Over-encapsulated tablet	Over-encapsulated tablet with acid in the extra-granular phase	
7	Bilayer tablet	Bilayer tablet with an active layer and a layer with acid	
8	TiT	Tablet-in-Tablet (TiT) with an acid core tablet and an active shell	
9	Mini-tablets in capsule	Mini-tablets in capsule with acid and active mini-tablets	
10	TiC with acid as powder	Tablet (without acid) and acid as powder in capsule	

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2.2.1. Granules Manufacturing

The drug product process was based on wet granulation, followed by final blending and either capsule filling or tableting. Based on pre-tests, it was decided to add the fumaric acid in the extra-granular phase. The granule composition was therefore the same for all tested formulations and was composed of 40.00% API, 44.92% of lactose monohydrate, 6.36% of MCC, 2.22% of sodium croscarmellose, 0.50% of colloidal silicon dioxide and 6.00% of HPC. The same batch of granules was used in all formulations.

Raw materials were first manually sieved on a 2 mm screen and poured to a 30 L bin (Servolift GmbH, Offenburg, Germany). Materials were then blended for 15 min at 15 rpm. Obtained pre-blend was then granulated using twin-screw granulation (Consigma-1, GEA, Wommelgem, Belgium). Granulation parameters were optimized to ensure that suitable granules attributes were achieved. The granulator was mounted with a 2x6-SCE screw (i.e. two kneading zones of six kneading elements with a stagger angle of 60° and an additional zone with size control elements to reduce fines). The feeder was set to 16 kg/h, the screw speed to 650 rpm, the liquid-to-solid ratio to 40% and the barrel temperature to 25 °C. Wet granules were then dried using GPCG2 fluid-bed dryer (Glatt, Binzen, Germany). The inlet air temperature was set to 70 °C. The air flow rate was initially set to 100 m^3/h and adapted based on fluidization during the drying. The drying was stopped when the residual moisture content of the granules was below 1.5%. Dried granules were finally milled using SLS U5 conical mill (Quadro, Waterloo, Canada) mounted with a square 0.813 mm screen and mill speed set at 1750 rpm.

2.2.2. Granules-in-Capsule Manufacturing (Prototypes 1 and 2)

Prototypes 1 and 2 were granules-in-capsule prototypes without and with fumaric acid, respectively. Both prototypes were used as a references regarding bio-performance, as it had previously been tested during a pharmacokinetic study in pre-treated dogs [25]. Prototype 1 (i.e. GiC without acid) was used as baseline for bio-relevant dissolution tests as known to underexpose subjects with achlorhydria. Prototype 2 (i.e. GiC with acid) was used as a target for bio-relevant dissolution tests as known to improve exposure of subjects with achlorhydria.

Prototypes contained 225.0 mg of granules and 1.1 mg of magnesium stearate. Prototype 2 also contained 20 mg of fumaric acid. For both prototypes, excipient(s) were first manually sieved on a 1 mm screen. Granules and sieved excipient(s) were then poured into a T2G Turbula blender (WAB group, Nidderau, Germany). Blending was performed for 3 min at 22 rpm. Blends were manually filled into size 1 capsules. It has to be noted that only half of the daily dose (i.e. 90 mg) could be fitted in a single size 1 capsule. These prototypes would therefore require two capsules to be administered to reach the target dose and/or larger capsule sizes which may not be well accepted by patients.

2.2.3. Capsule-in-Capsule Manufacturing (Prototype 3)

Prototype 3 was a capsule-in-capsule (CiC) formulation. It was assessed to physically separate the fumaric acid from the API, still considering a capsule formulation. For this prototype, 20 mg of fumaric acid were inserted into a size 4 capsule. This capsule was inserted into a size 00 capsule, also containing the active blend. The active blend was composed of 225.0 mg of granules, 25.3 mg of MCC and 2.5 mg of magnesium stearate was prepared. The manufacturing process was similar to prototypes 1 and 2 (i.e. Turbula blending and manual encapsulation). As for prototypes 1 and 2, only half of the daily dose (i.e. 90 mg) could be fitted in a single size 1 capsule, hence the size 00 capsule was selected for testing though it is not realistic in terms of patients' acceptability.

2.2.4. Tablet Manufacturing (Prototypes 4 and 5)

Prototypes 4 and 5 were monolayer tablet prototypes without and with fumaric acid, respectively. They were developed to compare with corresponding GiC prototypes (i.e. prototypes 1 and 2). Prototype 4 was composed of 450.0 mg of granules, 64.3 mg of MCC, 10.7 mg of sodium

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croscarmellose, 2.7 mg of silicon dioxide and 5.3 mg of magnesium stearate. The composition of prototype 5 was similar as 40 mg of the MCC was replaced by 40 mg of fumaric acid.

For both prototypes, extra-granular phase excipients were manually sieved on a 1 mm screen. Granules and all excipients except magnesium stearate were blended using a T2G Turbula blender for 5 min at 22 rpm. Magnesium stearate was then added to the blend and blending was extended for 3 min at 22 rpm. Tablets were produced using Styl'one Evolution compaction simulator (Medelpharm, Beynost, France). 16x7.37 mm punches were used, allowing to fit the intended dose of 180 mg of API in a single tablet of acceptable dimensions for swallowability. A pre-compression height of 6.5 mm and a compression height of 3.8 mm were applied, resulting in a tablet hardness of about 120 N and a tablet thickness of about 6.8 mm for both prototypes. It has to be noticed that tablets were also produced at 250 N to ensure that dissolution results in biorelevant media were not sensitive to tablet hardness, hence ensuring comparability of the different prototypes.

2.2.5. Over-Encapsulated Tablet Manufacturing (Prototype 6)

Prototype 6 was an over-encapsulated tablet. For this prototype, it was hypothesized that dissolution or gastric liquid would enter the capsule shell before its disintegration and pre-dissolve the components of the tablet, hence creating a microenvironment saturated in acidifier inside the capsule shell.

For this prototype, the monolayer tablet with acid (prototype 5) was manually inserted into a size 0 capsule. Though the target dose could not fit into a single size 1 capsule, formulation optimization and punch design was expected to be sufficient to achieve this goal. As this study aimed at screening different approaches to include the acidifier in the formulation, such optimization was not performed to ease prototypes comparison.

2.2.6. Bilayer Tablet Manufacturing (Prototype 7)

Prototype 7 was a bilayer tablet containing the API in one layer and the acid in the other layer. It was designed to physically separate the API from the acid while keeping a relatively close contact to enable the acidic microenvironment. This bilayer tablet was composed of an active layer containing 450.0 mg of granules blended with 122.5 mg of MCC, 2.4 mg of colloidal silicon dioxide and 5.1 mg magnesium stearate; and an acidic layer composed of 40 mg of fumaric acid, 42.8 mg of MCC, 0.8 mg of sodium croscarmellose and 1.4 mg of magnesium stearate.

Excipients were manually sieved on a 1 mm screen. Both the active blend and the acidic blend were produced by blending all ingredients except the magnesium stearate for 5 min at 22 rpm using T2G Turbula blender. Magnesium stearate was then added, and the blending was extended for 3 min at 22 rpm. Bi-layer tablets were produced using Styl'one Evolution compaction simulator mounted with 14.48x8.13 mm punches. The compression started with the active layer, which was pre-compressed at 80 daN to achieve a layer hardness of 60 N. The acidic layer was fed on top of the active layer and compressed to reach a tablet hardness of 230 N, hardness required to maintain tablet integrity during friability test. As for previous tablets prototypes, the target dose of 180 mg of API could be achieved in a single tablet of acceptable dimensions for swallowability.

2.2.7. Tablet-in-Tablet Manufacturing (Prototype 8)

Prototype 8 was a tablet-in-tablet (TiT) formulation containing the acid in the inner tablet (acid core) and the API in the external tablet (active shell). It was developed as alternative to the bilayer tablet to keep the separation between the acid and the API while changing the kinetics of the microenvironment creation during the dissolution.

The acid core was composed of 40 mg of fumaric acid, 41.0 mg of MCC, 0.8 mg of sodium croscarmellose and 0.4 mg of magnesium stearate. This acid core tablet was compressed into an active tablet shell composed of 450.0 mg of granules, 40.6 mg of MCC and 5.1 mg of magnesium stearate.

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The active and acidic blends were manufactured similarly to prototype 7 (i.e. bilayer tablet). The TiT prototypes were manufactured using Styl'one Evolution compaction simulator. Acid cores were first produced with 5.5 mm round punches targeting a hardness of 80 N. To insert the acid core inside the active shell, a first layer of active blend was pre-compressed at 80 daN using 16x7.37 mm punches. One acid core was then centred on top of this first layer, and the matrix was filled with more active blend to reach the target weight. The powder was then compressed to reach a hardness of 165 N, hardness required to maintain tablet integrity during friability test. As for previous tablets prototypes, the target dose of 180 mg of API could be achieved in a single tablet of acceptable dimensions for swallowability.

2.2.8. Mini-Tablets in Capsule Manufacturing (Prototype 9)

Prototype 9 was a mini-tablets in capsule formulation. It consisted in active mini-tablets containing the API, and acid mini-tablets containing the fumaric acid inserted into a capsule. This prototype was developed to obtain a physical barrier between the API and the acid, while enabling the acidic microenvironment inside the capsule shell.

The active mini-tablets were composed of 450.0 of granules, 78.0 mg of MCC and 4.7 mg of magnesium stearate. The acid mini-tablets were composed of 40.0 mg fumaric acid, 13.6 mg MCC, 0.8 mg sodium croscarmellose and 0.8 mg magnesium stearate. 505.62 mg of active mini-tablets and 88.35 mg of acid mini-tablets were encapsulated in a size 00 capsule.

The active and acidic blends were manufactured similarly to prototypes 7 and 8 (i.e. bilayer tablet and TiT). The mini-tablets were manufactured using Styl'one Evolution compaction simulator mounted with 2.5 mm multi-tips punches targeting a 2.5 mm thickness. Acid and active mini-tablets were then manually filled into capsules. As for previous prototypes in capsule, the target dose could not fit into a single size 1 capsule, hence the size 00 capsule was selected for testing though it is not realistic in terms of patients' acceptability.

2.2.9. Tablet-in-Capsule Manufacturing (Prototype 10)

Prototype 10 was a tablet-in-capsule (TiC) formulation with fumaric acid as powder. It was developed to obtain a physical separation between the API and the acid, while trying to enable the acidic microenvironment inside the capsule shell. For this prototype, various acid/API ratios were evaluated during pre-tests, concluding that a higher acid/API ratio of 0.94 was needed to obtain an effect of the fumaric acid on dissolution. This was likely due to the reduced level of contact between the fumaric acid and the API. The monolayer tablet without acid (prototype 4) was manually inserted into a size 00 capsule with 169 mg of fumaric acid added as a powder. As for previous prototypes in capsule, the target dose could not fit into a single size 1 capsule, hence the size 00 capsule was selected for testing though it is not realistic in terms of patients' acceptability.

2.3. Prototypes Evaluation

All prototypes were assessed in terms of bio-performance, stability and patient-centricity.

2.3.1. Prototypes Bio-Performance – Biorelevant Dissolution Tests

Prototypes bio-performance was estimated via biorelevant dissolution tests in various media. The different prototypes were analysed in biorelevant dissolution tests for 2 h in USP II at 37 °C with the paddle speed set at 50 rpm using peak vessel. A two-stage dissolution test was used, where the drug is first exposed to gastric medium, then the transfer to the small intestine is simulated by adding a hybrid intestinal concentrate (buffer of FaSSIF-V1 and bile slat composition of FaSSIF-V2) at equal volume. As the target dose of 180 mg of API could not be achieved in a single unit for prototypes 1, 2 and 3, two capsules containing 90 mg of API were put in the dissolution bath to ensure comparability.

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Biorelevant dissolution conditions were selected based on the in vitro study in dogs to evaluate the GiC with and without acid. Three gastric media were used in this study: a standard healthy gastric medium (FaSSGF), a low buffered capacity achlorhydric medium and a highly buffered achlorhydric medium (10 times buffer capacity). The compositions of the gastric media was inspired by previous studies [26,27]. The standard healthy gastric medium (FaSSGF) was composed of 300 mL pH 1.6 NaCl solution, with biorelevant surfactants. The low buffered capacity achlorhydric medium was composed of 300 mL of acetate/phosphate buffer 1 mM pH 7.0 with biorelevant surfactants, which was expected to be physiologically relevant for the target patient population. The highly buffered achlorhydric medium was composed of 300 ml of acetate/phosphate buffer 10 mM pH 7.0 with biorelevant surfactants and was selected for its high discriminative power. The starting intestinal medium was composed of 300 mL of FaSSIF double concentrate pH 6.36 for achlorhydric conditions and pH 7.5 for the healthy condition.

Samples were taken at 0 – 5 – 10 – 20 – 29 min (gastric medium) and 35 – 40 – 50 – 60 – 90 – 120 – 150 – 180 min (intestinal medium). Samples were analysed using in-house UPLC method. Results were expressed as percentage of the dissolved dose of label claim. The pH of the dissolution media was measured at the end of the gastric phase and at the end of the intestinal phase. The dissolution profiles were performed on six replicates, with the results displayed as mean and standard deviation.

2.3.2. Prototypes Stability – Stress Studies

Prototypes stability was evaluated by stress studies. The prototypes were stored for 6 months in open containers at 40 °C/10%RH, 40 °C/75%RH and for 12 months in closed containers at 25 °C/60%RH with and without desiccant. Samples were analysed after 3 weeks, 6 weeks, 3 months, 6 months and 12 months. Visual appearance, assay, impurity profiles, dissolution rate and solid state via X-ray powder diffraction were evaluated at each time point using in-house methods.

2.3.3. Prototypes Patient-Centricity

Regarding patient-centricity, the goal was to fit the expected dose of 180 mg of API into a single capsule or tablet of a maximum length of 18 mm to ensure swallowability.

3. Results

The GiC prototypes with and without fumaric acid had been tested during a previous pharmacokinetic study in beagle dogs, demonstrating that the GiC containing fumaric acid allowed a 2.4-fold increase in the Cmax compared to the GiC formulation without fumaric acid [25]. Based on this proof of concept, different formulation strategies for incorporating a pH-modifier in the formulation were evaluated in three bio-relevant dissolution conditions to estimate their bioavailability.

3.1. Dissolution Behaviour in Highly Buffered Achlorhydric Media

The first screening was performed in highly buffered achlorhydric media (10 mM) to maximize the discrimination between prototypes. Dissolution results are shown in Figure 1.

The performance of the GiC (◊) and tablet (○) without acid was limited in this media, while the GiC with acid (♦) presented a higher dissolution in the intestinal compartment (> 30 min) as observed during the pharmacokinetic dog study. The bilayer tablet (▲) and mini-tablets in capsule (■) presented similar dissolution rates as the prototypes without acid, suggesting that the degree of contact between the API and acid was not sufficient to create the acidic microenvironment in such highly buffered condition. The CiC and TiT prototypes (dissolution results not shown) showed even worst performances as the inner capsule with acid did not disintegrate before the granule with API was completely dissolved and the core tablet with acid did not disintegrate before the active shell was fully dispersed. These formulations could have been optimized to improve disintegration, which was not considered following positive results of other prototypes (see below). The monolayer tablet

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with acid (◍) allowed a higher initial dissolution of the API in the gastric compartment (> 30 min). This was due to the faster disintegration of the tablet compared to the capsule. The rapid dissolution of the API in the gastric compartment was followed by precipitation, resulting in a dissolved dose similar to prototypes without acid in the intestinal compartment. The TiC prototype with acid as powder (−) led to slightly higher drug dissolution in the intestinal compartment. However, the amount of fumaric acid had to be drastically increased (acid/API ratio 0.94) to achieve such a limited improvement. Finally, the over-encapsulated tablet (●) allowed achieving a much higher dissolution in the intestinal compartment. Interestingly, a parachute effect was also observed. As the API and fumaric acid are in close contact inside the tablet, it was hypothesized that this close contact synergized with the capsule shell to create the acidic microenvironment inside the capsule for the API to dissolve. The over-encapsulated tablet therefore seemed to be the best candidate to maximize *in vivo* exposure, potentially achieving an even better performance than the GiC with acid formulation.

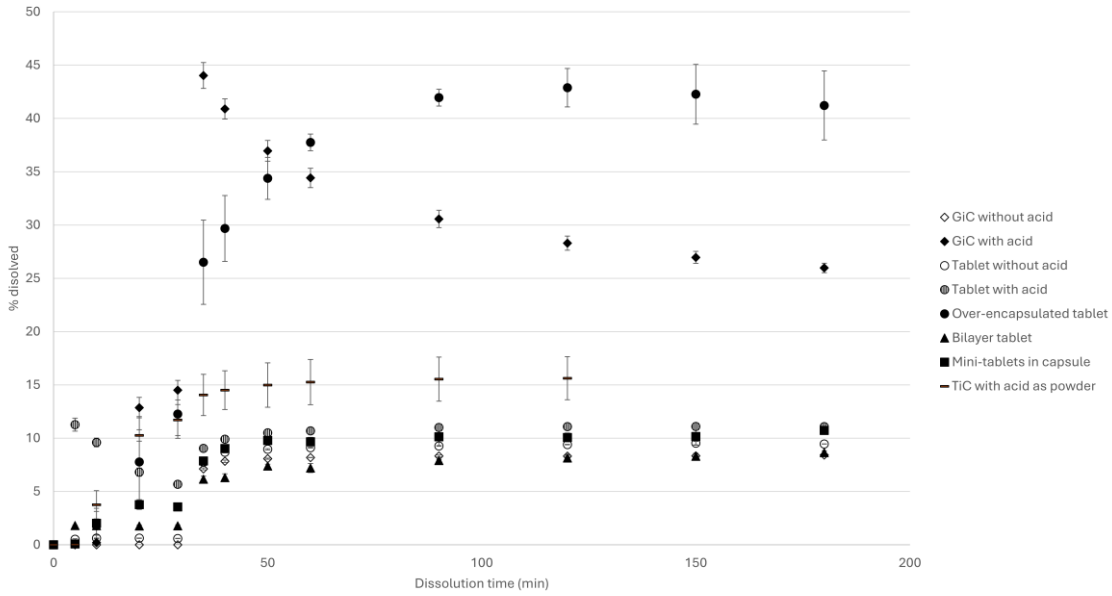

Figure 1. Two-stage dissolution results in highly buffered achlorhydria media.

The pH of the dissolution media was measured at the end of the gastric phase and at the end of the intestinal phase (Figure 2) to evaluate the ability of the prototypes to acidify the dissolution media. Only minor variations were observed, suggesting that the enhanced dissolution rate of the GiC with acid and of the over-encapsulated tablet was due to the creation of an acidic microenvironment inside the capsule shell and not to the acidification of the whole dissolution medium, especially as any bulk pH shift is counteracted by the well stirred, high buffer capacity medium.

3.2. Dissolution Behaviour in Low Buffered Capacity Achlorhydric Media

Following the tests performed in highly buffered achlorhydric media, a second screening was performed in low buffered capacity achlorhydric media (1 mM). This media has been reported to be more representative to simulate intragastric environment under hypochlorhydric conditions [26,27]. Dissolution results are shown in Figure 3.

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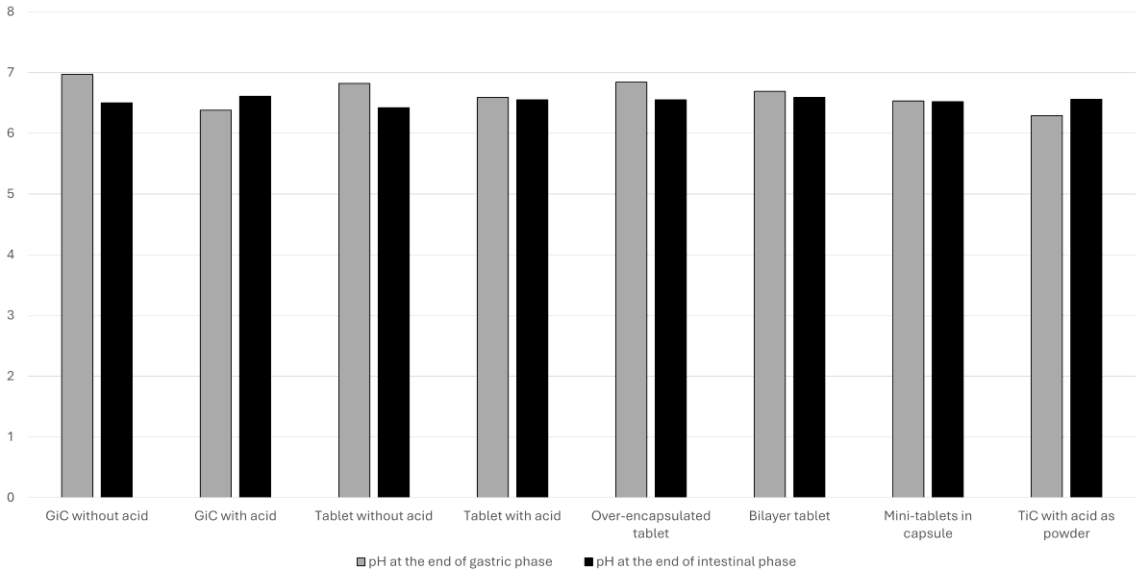

Figure 2. pH measurements at the end of the gastric and intestinal phase in highly buffered achlorhydria media.

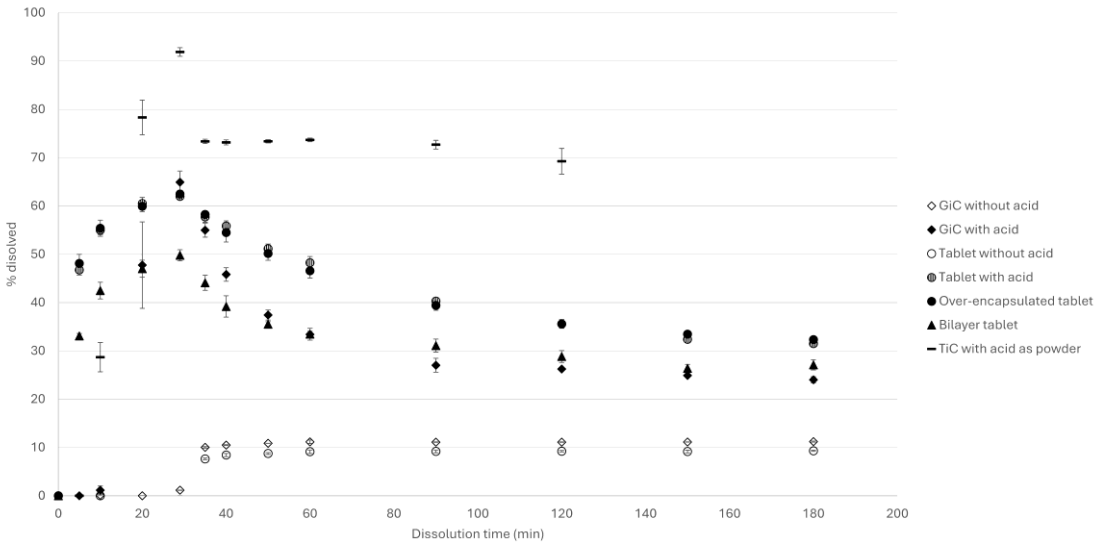

Figure 3. Two-stage dissolution results in low buffered capacity achlorhydria media.

In low buffered conditions, the GiC without acid (◊) and tablet without acid (○) still present reduced dissolution rates. However, the bilayer tablet (▲) showed similar performance to the GiC with acid (♦). The monolayer tablet with acid (◍) and over-encapsulated tablet with acid (●) performed similarly and slightly better than the GiC with acid. The TiC with acid as powder (−) showed the highest dissolution rate in these dissolution conditions.

When comparing the dissolution results with pH measurements taken at the end of the gastric and intestinal phases (Figure 4), a clear link was observed between the dissolution rate, the extent of pH reduction in the gastric phase and the acid/API ratio. Specifically, the TiC with acid as powder prototype, which contained a higher amount of acid, resulted in a more pronounced decrease in gastric pH. This result emphasized that, in low buffered capacity achlorhydric medium, the dissolution rate is driven by the acidification of the dissolution media, which was not possible in

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highly buffered dissolution media. As a result, in low buffered capacity media, increased dissolution rates are observed for all prototypes containing fumaric acid, regardless of the degree of contact between the API and the fumaric acid.

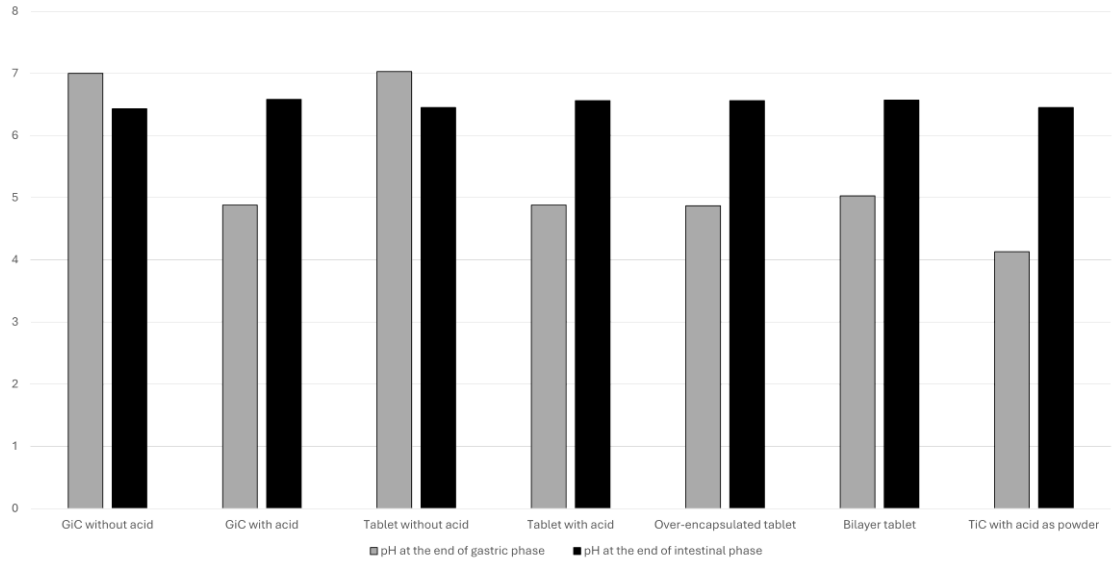

Figure 4. pH measurements at the end of the gastric and intestinal phase in low buffered capacity achlorhydria media.

It has to be noted that, in both achlorhydria media (i.e. low buffered and highly buffered), the dissolution media is maintained under agitation. Hence, the hydrodynamics in the dissolution vessel is not representative of the gastro-intestinal tract. In patients' stomach, small amounts of fumaric acid may shift the pH around disintegrating tablet or capsule without changing the bulk gastric pH, whereas *in vitro* stirring ensures that fumaric acid is distributed throughout the medium, thus influencing the bulk pH. It can be assumed that the low buffered capacity media reflects the microenvironmental pH around the tablet or capsule in the stomach. The bio-performance of the different prototypes is therefore likely to be between the two tested achlorhydric media.

3.3. Dissolution Behaviour in Healthy Conditions

Based on dissolution tests in achlorhydric media, the GiC with and without acid, the tablet with and without acid and the over-encapsulated tablet prototypes were evaluated in bio-relevant two-stage dissolution media mimicking healthy volunteers (Figure 5).

The tablet with (◍) and without acid (○) presented a higher dissolution in gastric media compared to the encapsulated prototypes, which was due to the relatively slow disintegration of the capsule shell. The over-encapsulated tablet (●) showed an even slower dissolution in the gastric phase as the tablet could not fully disintegrate inside the capsule shell. Despite the observed differences in the gastric phase, all prototypes reached a similar asymptote in the intestinal media.

As expected, the pH measurements at the end of the gastric and intestinal phase did not present any significant variation between prototypes (Figure 6). Selected prototypes therefore seemed suitable for patients without achlorhydria.

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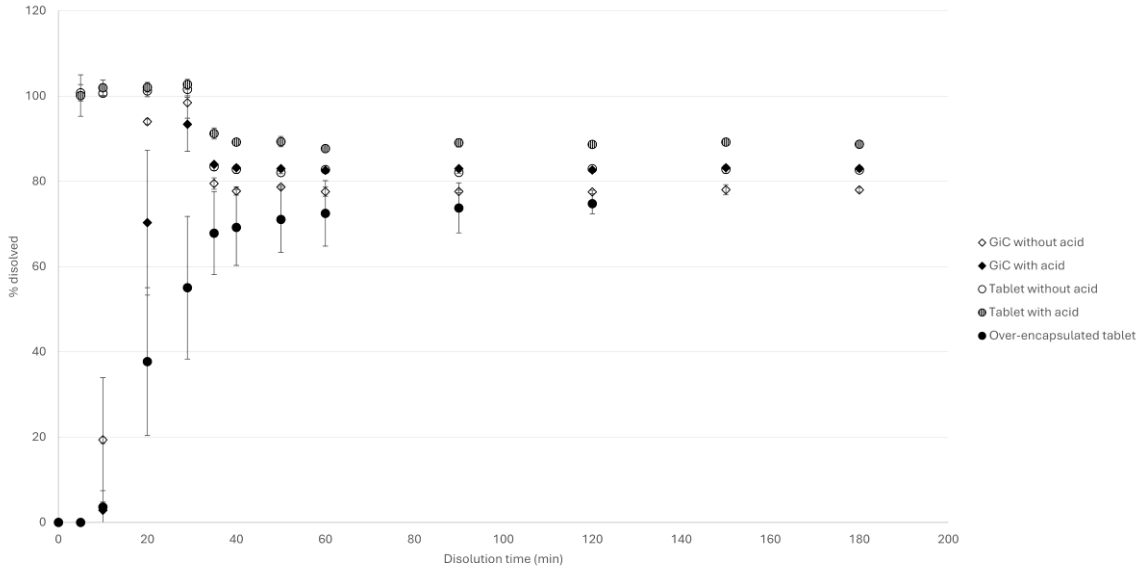

Figure 5. Two-stage dissolution results in healthy conditions.

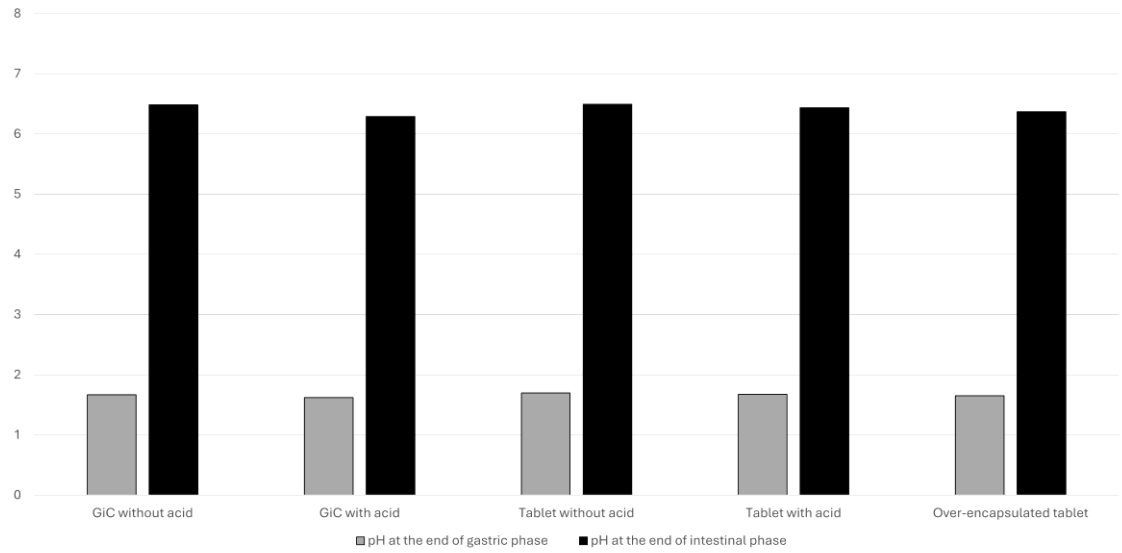

Figure 6. pH measurements at the end of the gastric and intestinal phase in healthy conditions.

3.4. Stability Evaluation

Based on dissolution tests in the different media, the GiC with and without acid, the tablet with and without acid, the bilayer tablet and the over-encapsulated tablet prototypes were evaluated for stability under accelerated conditions. As expected, the GiC and tablet without acid showed no degradation in all tested conditions. All prototypes containing fumaric acid, even the bilayer tablets presented a change of colour from white to yellow after only three weeks in open containers at 40 °C/75%RH. This change of colour was associated to a decrease in assay and dissolution rate and an increase in impurities and fumarate salt. Interestingly, this degradation was not observed in open containers at 40 °C/10%RH nor in closed containers at 25 °C/60%RH with and without desiccant.

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These observations confirmed the risk associated with acidifiers in close contact with weak basis in formulations. However, they also suggested that this risk could be efficiently mitigated by appropriate packaging design. Therefore, the stability criteria were no longer considered as critical for selecting prototypes.

3.5. Prototypes Comparison

Prototypes were compared based on their bio-performance as reported in sections 3.1 to 3.3, stability as reported in section 3.4 and patient centricity as mentioned in section 2.2. As all prototypes could be manufactured, manufacturability was not taken into account at this stage. Regarding bio-performance, dissolution data clearly identified the over-encapsulated tablet and GiC with acid as the most robust prototypes. The monolayer and bilayer tablets with acid also led to good dissolution rates, but only in low buffer conditions. The TiC with acid as powder could also lead to improved dissolution rates, but it required an increase amount of fumaric acid. From a patient point of view, tablets prototypes were preferred as allowing to fit the daily dose in a single tablet, while capsules would require the ingestion of two capsules to reach the intended dose. In this study, the over-encapsulated tablet could not directly fit into a size 1 capsule, but its shape and formulation could be optimized to reach this goal. As the same trend was observed for all prototypes containing fumaric acid in stress studies, it was therefore concluded that the over-encapsulated tablet met all development criteria with a high expected robustness, while the monolayer and bilayer tablets seemed more at risk of underperforming in vivo.

4. Discussion

Ten formulation prototypes have been evaluated in biorelevant dissolution conditions to identify the best strategy for incorporating a pH-modifier inside the formulation. As for all *in vitro* tests, assumptions were made on the representativity of the tests. In particular, and as previously highlighted, hydrodynamics in dissolution vessels and in patients' stomach differ dramatically. Though *in vivo* tests would avoid making such hypothesis, *in vitro* testing allowed to reduce animal use for such a large screening of formulation prototypes. By basing the prototypes selection on three dissolution conditions, it was possible to estimate prototypes *in vivo* performance with a reduced uncertainty.

To explain the improved performance predicted in highly buffered media for the over-encapsulated tablet, it was assumed that the dissolution media first entered the capsule shell, hence creating an acidic microenvironment inside the capsule for the API to dissolve, which effect is maintained after capsule disintegration. This is only a hypothesis and understanding the role of the capsule shell, and especially differences in behaviour *in vivo* compared to *in vitro* would help strengthening the prototypes selection.

Similarly, the differences observed between highly and low buffered conditions were explained by the acidification of the dissolution media. While fumaric acid would disperse rapidly in the dissolution bath due to media agitation, it is expected to stay around the tablet or capsule in the stomach. As the stomach presents a low buffered capacity, the creation of the acidic microenvironment is expected to take place *in vivo* even without the capsule to maintain the API and fumaric acid together for dissolution enhancement. In this study, the bulk pH of the dissolution media was hypothesized to be representative of the microenvironmental pH occurring in the stomach. Being able to monitor microenvironmental pH during *in vivo* studies and designing representative bio-relevant tests specifically to support formulations strategies based on pH-modification would help to assess prototypes.

Finally, formulation selection should not only consider bio-performance, but also drug product stability, manufacturability and patient-centricity. Regarding drug product stability, preventing the direct contact between the API and the pH-modifier would solve potential physico-chemical incompatibility. However, as instability induced by organic acid is based on moisture adsorption, protective packaging may also be considered to improve product stability without impairing

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manufacturability and bio-performance. In terms of manufacturability, all prototypes could be produced successfully at laboratory scale. It has nonetheless to be noted that a successful prototype would then have to be industrialized. While the GiC and monolayer tablets would be easily scalable, the bilayer tablet, TiT and minitablets in capsule require specific tooling and potentially reduced manufacturing speed. The over-encapsulated tablet and TiC with acid as powder require an additional process step with specific equipment as well. In terms of patient-centricity, the target dose could not fit into a single size 1 capsule for prototypes in capsule (i.e. GiC, CiC, over-encapsulated tablet, minitablets in capsule and TiC with acid as powder). This may negatively impact patient adherence by increasing pill burden. Prototypes developed in this study were however not optimized in terms of shape and dimensions. While the GiC, CiC and minitablets in capsule prototypes required either two size 1 capsules or one size 00 capsule to fit the target dose, the over-encapsulated tablet and the TiC with acid as powder could however be optimized to fit into a size 1 capsule.

5. Conclusions

In this study, ten formulation strategies were evaluated in biorelevant dissolution media to select the right approach for incorporating a pH-modifier into an oral solid dosage form. The goal was to maximize the bioavailability of the drug with acceptable amounts of pH-modifier to ensure manufacturability and reduced capsule / tablet size for improved patient experience.

In vitro data suggested that the over-encapsulated tablet prototype led to improved bioavailability even in highly buffered achlorhydric conditions and was therefore the most robust formulation toward elevated gastric pH. However, in low buffered achlorhydric conditions the monolayer tablet with acid exhibited similar dissolution rate and prototypes with less close contact between the API and the organic acid also demonstrated improved dissolution rates. These results suggested that the acidic microenvironment may not require such a high degree of contact between the API and the pH-modifier. The outcomes of this study, and consequently the bio-relevance of tested media, will have to be further evaluated *in vivo*.

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Abbreviations

The following abbreviations are used in this manuscript:

API	Active Pharmaceutical Ingredient
BCS	Biopharmaceutical Classification System
CiC	Capsule-in-Capsule
GiC	Granules-in-Capsule
HPC	Hydroxy-Propyl Cellulose
MCC	Microcrystalline Cellulose
TiC	Tablet-in-Capsule

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TiT Tablet-in-Tablet

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