Study of a delayed-release system for hard and soft capsules coated with eudragit® s100 acrylic polymers

Luciana Arantes Soares1 and Eduardo Crema2*

1Programa de Pós-graduação em Ciências da Saúde, Universidade Federal do Triângulo Mineiro, Uberaba, Minas Gerais, Brazil. 2Departamento de Cirurgia, Universidade Federal do Triângulo Mineiro, 38025-440, Uberaba, Minas Gerais, Brazil. *Author for correspondence. E-mail: cremaufm@mednet.com.br

ABSTRACT. The objective of this study was to evaluate a pH-dependent system of ileocolonic release of active ingredients using the polymer Eudragit® S100. A spouted bed was used in the coating process of soft capsules containing palm oil and of hard capsules containing glutamine under standardised experimental conditions. The height and diameter of the palm oil and glutamine capsules were measured using a calliper. The following variables were analysed: Eudragit® S100 dispersion amount used in the capsule coating process, nozzle air pressure, nozzle air flow rate, spray rate and temperature of the spouted bed coating process. The Eudragit® S100 dispersion formulation, trademarked as Quickstart® by Evonik Industries, was used with modifications to prepare the enteric coating. The results showed that the adequate temperature for the spouted bed coating process was 50°C and that 0.2 mL of 6.5% Eudragit® S100 coating per cm² capsule was resistant for 60 minutes at pH 6.8. The findings demonstrate the pharmaceutical application of Eudragit® S100 in the modification of the coating and the preparation of a delayed-release system of hard and soft capsules, thus enabling ileal release of active ingredients.

Keywords: polymers; delayed-action preparations; capsules.

Received on June 20, 2019. Accepted on January 30, 2020.

Introduction

Coating is defined as the process of applying a layer of material on a pharmaceutical form (solid surface) with a pharmaceutical composition (Martins & Oliveira, 2003). Coating is an adaptation of food preservation methods Pharmaceutical forms are primarily coated for active ingredient protection (Hampel, Buck, Peglow, & Tsotsas, 2013), and coating was first used by the pharmaceutical industry in 1953, when the Abbot Laboratory developed the first film coating (Lachman, Lieberman, & Kanig, 2001).

Biodegradable pharmaceutical capsule coating is an emerging technology exploited by medicine and the pharmaceutical industry (Villanova, Oréfice, & Cunha, 2010). The field of biotechnology sciences has grown to a large scale in the last decade. Numerous molecules are used as models for various pharmaceutical and food industry applications. Products based on methacrylic acid, acrylic acid and their derivatives are notable in the pharmaceutical industry (Shen et al., 2011).

Eudragit® polymers are acrylate and methacrylate polymers that are commercially available in different ionic forms including polycations with dimethylamino/amino quaternary groups (Eudragit® E, RL, RS and NE) and polyanions with carboxylate groups (Eudragit® L100 and S100). Depending on the pH, these polymers can be used for different therapeutic purposes (Moustafine, Kabanova, Kemenova, & Van den Mooter, 2005). The anionic copolymer Eudragit® S100 consists of a solid substance in the form of a white powder with a faint odour (Singh, Neelam, Arora, & Singla, 2015). A delayed-release system is a method of delivering specific active ingredients to the small intestine while protecting them from acidic conditions, such as those found in the stomach (Freire, Podczeck, Sousa, & Veiga, 2006). This system releases the active ingredient in a manner that is dependent on the pH of the biological medium. Among the various types of polymers, Eudragits (S and L) are the most commonly used because they dissolve at pH values above 6 and 7 (Thakral, Thakral, & Majumdar, 2013).

Ideally, enteric release systems meet the following criteria: I) controlled release rate of the active ingredient; II) masking of unpleasant flavours and odours; III) improve the aesthetics of the product; IV) protection from humid environments; and V) provide the product with mechanical resistance (Ansel, Popovich, & Allen Junior, 2000).
Since palm oil and glutamine release capsules are only composed of edible ingredients commonly present in the diet of the population (lipids and proteins), this study is of great relevance for the use of palm oil and glutamine release capsules at pH 6.8 to stimulate the hypoglycaemic hormones PYY and GLP-1 and improve clinical outcomes for disorders such as type 2 diabetes. A possible therapeutic target for weight loss and the control of type 2 diabetes is the production of hormones in the body, particularly the intestines (Soares et al., 2018). According to several studies related to the satiety mechanism (Lieverse, Jansen, Masclée, Revati, & Lamers, 1994; Van Citters, & Lin, 1999; Diepvens, Soenen, Steijns, Arnold, & Westerterp-Plantenga, 2007; Olsson, Sundberg, Viberg, & Haenni, 2011; Heer, 2012), the release of intestinal peptides due to food content in the intestine depends on the nutritional status of the individual and may contribute to the control of obesity and type 2 diabetes. The obese population has increased worldwide over the last several decades, and combatting obesity is a difficult problem (Bernardo, Maria Junior, Salomão, & Baracat, 2014). The increase in the obese population has been associated with increased incidence of diseases such as type 2 diabetes (Pontes, Sousa, & Navarro, 2009). Intervention strategies using intestinal peptide stimulation may hold promise for the control of type 2 diabetes and obesity (Rebello, Martin, Johnson, O’Neil, & Greenway, 2012). Several intestinal peptides have been implicated in gastrointestinal signalling, and the most prominent among these peptides are glucagon-like peptide (GLP-1) and YY peptide (PYY), which are associated with satiety (Soares et al., 2018), prolongation of gastric emptying, and increased insulin secretion and sensitivity (Samocha-Bonet et al., 2011; Chang et al., 2013; Meek et al., 2016). Research suggests that ingestion of functional foods, such as palm oil (Bester, Esterhuyse, Truter, & van Rooyen, 2010) and glutamine (Galera et al., 2010), may act as a line of defence in controlling metabolic events (Agostoni et al., 2015). Palm oil is a medium-chain lipid extracted from the oil palm Elaeis guineensis and exhibits proven therapeutic properties, such as cardioprotective and antioxidant effects (Edem, 2002; Bester et al., 2010; Ortuño Sahagún, Márquez-Aguirre, Quintero-Fabián, López-Roa, & Rojas-Mayorquín, 2012; Takeuti et al., 2014). Glutamine is an amino acid with several nutrition-related beneficial effects, including reducing the risk of infections, maintaining intestinal integrity and controlling diabetes (Galera et al., 2010). Although the functional foods examined in this study have been proven to exhibit properties related to diabetes control and weight reduction, coating these foods with Eudragit® S100 may have important implications for future therapeutic applications. Enteric coatings provide pharmatechnical improvement related to the protection of the active agent against reactive environments (e.g., acidic environments) and pH-dependent release at pH 6.8. Such coatings allow the release of the active agent directly in the terminal ileum, thus stimulating intestinal peptides.

More precisely, the formulation we propose herein aims to release the active ingredients at a pH of 6.8, thus allowing their gastro-resistant release. Nutrients released in the small intestine, specifically in the colon and ileum, could stimulate L cells to secrete intestinal peptides and play key roles in homeostasis. The aim of the study was to evaluate the disintegration of Eudragit® S100 polymer-coated palm oil and glutamine capsules in simulated gastrointestinal media (pH 1.2, pH 6.0 and pH 6.8).

Material and methods

Materials used for manipulation of delayed-release gastro-resistant capsules

The following raw materials were used for manipulation of the enteric coating:
- Glutamine capsules (ErliCaps Envase Ltda®, São Paulo, Brazil);
- Palm oil capsules (Sorocaps®, Sorocaba, São Paulo, Brazil);
- Anionic copolymer based on methacrylic acid and methyl methacrylate (Rohm, Pharma Polymers, Germany);
- Distilled water (Biochemistry laboratory - Federal University of Triângulo Mineiro (UFTM), Uberaba, Minas Gerais, Brazil);
- 28-30% Ammonium hydroxide (Dinâmica®, Diadema, São Paulo, Brazil);
- Triethyl citrate (Neon®, São Paulo, Brazil);
- Pure talc powder (Synth®, Diadema, São Paulo, Brazil);
- Tartrazine yellow (Neon®, São Paulo, Brazil);
- Absolute alcohol (Ciclo farma®, Serrana, São Paulo, Brazil).

The following equipment was used for enteric coating preparation and quality control:
- Automatic stirrer (Nova Ética®, Brazil);
- Spouted bed (Labmaq®, Ribeirão Preto, São Paulo, Brazil).
- Digital scale (Gehaka®, São Paulo, Brazil);
- Calliper (ZaasPrecision®);
- Dissolution tester (Sotax AT7®).

**Modified Eudragit® s100 coating manipulation method**

The Eudragit® S100 dispersion formulation, trademarked as Quickstart® by Evonik Industries, was calculated to prepare the enteric coating, with modifications. Modifications were introduced in the amount of the following Eudragit® S100 components: ammonium hydroxide, triethyl citrate, pharmaceutical talc powder and distilled water; in addition, absolute alcohol and tartrazine yellow dye were added to the formulation (Evonik, 2016).

The coating formulation was prepared by adding 6.5% Eudragit® S100 (Rohm, Pharma Polymers, Germany) to 40% water (W/V). The dispersion was homogenised for approximately 5 minutes, slowly adding a 4.5% (V/V) solution of 1 N ammonium hydroxide (Dinâmica®, Brazil) and stirring for 60 minutes. Subsequently, 6.0% (V/V) triethyl citrate (Neon®, Brazil) was added with continuous stirring for another 60 minutes. Then, a solution containing 0.02% (W/W) tartrazine yellow (Neon®, São Paulo, Brazil), 3.0% (W/W) pharmaceutical talc (Synth®, Diadema, São Paulo) and 40% (W/V) absolute alcohol (Ciclo farma®, Serrana, São Paulo) was prepared separately and homogenised for 10 minutes (Eudragit® S100, with modifications).

Last, the talc suspension was poured into the Eudragit® S100 dispersion and stirred for 10 minutes. The mechanical stirrer speed was 20 rpm during all coating preparation phases (Eudragit® S100, with modifications). The enteric release capsules were coated with a methacrylate-based polymer (Eudragit® S100) with the goal of releasing the capsule contents 1 hour after exposure to a medium with a pH of 6.8.

**Hard and soft capsule surface area calculation**

The height and diameter of the palm oil and glutamine capsules were measured using a calliper. The cylinder equation was used to predict the total area of the capsules, thus estimating the amount of coating, in mL, to be used per cm² of capsule (Evonik, 2016; Soares et al., 2018).

The cylinder equation is shown below:

\[ At = 2\pi r (h + r) \]

where \( At \) = total area of the cylinder; \( h \) = height; and \( r \) = radius.

**Spouted bed**

The spouted bed was purchased exclusively for coating soft (palm oil) and hard (glutamine) capsules (Figure 1). The coating manipulation stage was performed at the Pharmaceutical Technology Laboratory, associated with the Gastroenterology and Clinical Nutrition Research Centre and the Gastrointestinal Surgery Department of the Federal University of Triângulo Mineiro (UFTM).

![Figure 1. Spouted bed (Labmaq®, Ribeirão Preto, São Paulo, Brazil) used to coat the palm oil and glutamine capsules, purchased by the Gastrointestinal Surgery Department – UFTM.](image-url)
The spouted bed includes a cylindrical column with a frustoconical base with a gas inlet. Air injection results in the circulation of solid particles in the central region of high porosity termed spout, where the particles are pneumatically carried, and a source of solids is formed at the top (fountain). These carrier particles are spread radially and descend through the annular space surrounding the spout. Due to the hot air, the liquid evaporates, and the solid forms a shell enclosing the kernel material (Hampel et al., 2013). The spray drying (spouted bed) coating method is an excellent technique for polymer application on capsules and tablets and can be used at an industrial scale (Martins & Oliveira, 2003).

Assessment of resistance to gastric, duodenal and jejunal pH conditions

A 6-station dissolution tester, apparatus I (baskets), was used to perform the resistance tests of the delayed-release capsules.

After adding 300 mL of 0.1 M HCl, pH 1.2, to the assessment medium, the stage was completed in 120 minutes. Immediately after, the next stage, with a volume of 363.5 mL phosphate buffer at pH 5.5, was performed for 180 minutes. Last, the final stage, with a volume of 400 mL phosphate buffer at pH 6.8, was completed in 60 minutes (Agência Nacional de Vigilância Sanitária [Anvisa], 2010).

Results

Spouted bed operating conditions

The spouted bed variables and experimental conditions used in the coating process of the pharmaceutical forms are presented below in Table 1.

| Variable | Palm oil capsule | Glutamine capsule |
|----------|------------------|-------------------|
| Capsule size | 00 | 00 |
| Eudragit® S100 dispersion amount used in the capsule coating process | 0.2 (mL cm⁻²) | 0.2 (mL cm⁻²) |
| Nozzle air pressure | 4.0 bar | 4.0 bar |
| Nozzle air flow rate | 35 L min⁻¹ | 35 L min⁻¹ |
| Spray rate | 1.8–2.2 (mL min⁻¹) | 1.8–2.2 (mL min⁻¹) |
| Temperature of the spouted bed coating process | 50°C | 50°C |

Physical characterisation of palm oil and glutamine capsules

The results from the physical characterisation of the soft (palm oil) and hard (glutamine) capsules are described in the Table 2. This analysis aimed to estimate the total coating area of each capsule.

| Capsules | Height (h) | Diameter (d) | Radius (r) | Total area (At) | Amount sprayed on each capsule |
|----------|------------|--------------|------------|----------------|------------------------------|
| Soft (palm oil) | 2.614 cm | 0.896 cm | 0.448 cm | 8.61 cm² | 0.2 mL cm⁻² |
| Hard (glutamine) | 2.28 cm | 0.854 cm | 0.427 cm | 7.27 cm² | 0.2 mL cm⁻² |

The calculation of the total coating area is an important step of the coating process to ensure its functionality. The amount of coating material required depends on the surface area of the substrate. Therefore, the coating dispersion amount is expressed as mL of polymer per cm² of substrate surface (Evonik, 2016; Soares, 2016).

Soft and hard capsules with and without eudragit® S100 coating

Soft gelatine capsules (Figure 2A) are considered one of the best pharmaceutical forms to carry active ingredients. Protection from light and humidity are among their main advantages. They are also easily administered, enable combining normally incompatible substances and can mask the unpleasant flavour and/or odour of medicines (Martins & Oliveira, 2003). Hard capsules (Figure 3A) are also easily administered, and they are versatile because they allow the extemporaneous preparation of the most diverse formulations in individual doses. Capsules inclusively allow the preparation of delayed-release coating systems (Figures 2B and 3B).
Figure 2. Palm oil capsules without (A) and with (B) enteric coating.

Figure 3. Glutamine capsules without (A) and with (B) enteric coating.

**Palm oil and glutamine capsule disintegration test**

Figures 4, 5 and 6 show the results from the disintegration test of palm oil and glutamine capsules in simulated gastrointestinal media. The results showed that coating with 0.2 mL of 6.5% Eudragit® per cm² of capsule provided resistance for 2 hours under gastric pH conditions (Figure 4) and for 3 hours under duodenal-jejunal pH conditions (Figure 5), and disintegration occurred after 60 minutes in medium at pH 6.8 (Figure 6).

Figure 4. Glutamine and palm oil capsules coated with 0.2 mL of 6.5% Eudragit cm⁻² from the first stage of disintegration in hydrochloric acid (pH = 1.2), with a test time of 2 hours.

Figure 5. Glutamine and palm oil capsules coated with 0.2 mL of 6.5% Eudragit cm⁻² after the second stage of disintegration in phosphate buffer at pH 6.0, with a test time of 3 hours.
Figure 6. Glutamine and palm oil capsules coated with 0.2 mL of 6.5% Eudragit cm⁻² after the third stage of disintegration in phosphate buffer at pH 6.8, with a test time of 1 hour, resulting in release of the active ingredient.

Discussion

Manipulation and assessment of the eudragit® s100 gastro-resistant coating

To protect the active ingredients including palm oil and glutamine, which are susceptible to degradation at low pH values, the acrylate polymer known as Eudragit® S100 was used as a coating. Eudragit® S100 is a polyanion that is insoluble in water and strongly acidic solutions. This type of polyanion results from the polymerisation of methacrylic acid and methyl methacrylate. It is a pH-dependent system because it dissolves at pH values above 6 and 7 (Thakral et al., 2013). Different capsule and tablet coating methods are used in the pharmaceutical industry, including shellac, hydroxypropyl methylcellulose phthalate, methacrylic acid/methyl methacrylate copolymers, polyvinyl acetate phthalate, cellulose acetate phthalate and formaldehyde (Ansel, Popovich, & Allen Junior, 2000; Pina, Sousa, & Brojo, 1997).

The capsules (hard and soft) were coated with an aqueous dispersion containing 6.5% Eudragit® S100 polymer and other fluid bed pharmacotechnical adjuvants. Disintegration assays were subsequently performed. The final form of Eudragit S100 after manipulation is a dispersion. Film coating takes advantage of the pharmaceutical technology used to disperse polymers in aqueous media or organic solvents (Rolim et al., 2009). The release profile was evaluated using an acceptor liquid at pH 1.2, 6.0 or a slightly neutral value of 6.8. The coated capsules withstood pH 1.2 and 6.0 for more than 120 minutes but disintegrated within 60 minutes at pH 6.8, suggesting that in vivo, release of palm oil and glutamine would occur in the distal ileum. To evaluate the release kinetics of palm oil and glutamine, adequate quantification methods are needed. Because absorption is not a limiting factor, the dissolution test is an appropriate tool to predict the bioavailability of the pharmaceutical product, as it is possible to correlate its results with in vivo conditions. The release of these compounds in the distal ileum is expected to promote the release of satiety-promoting hormones, thereby contributing to diabetes control.

The delayed-release system is applied to formulations and is designed to extend the dissolution and absorption of the medicine until the formulation reaches specific sites in the small intestine (Freire et al., 2006). Delayed release is applied to avoid the destruction of the medicine in the gastric juice or to avoid an eventual irritation of the gastric mucosa (Manadas, Pina, & Veiga, 2002). Methacrylic acid- and methyl methacrylic acid-derived copolymers (Eudragit®) meet the delayed-release criteria and are applied in the design of pH-dependent systems. Furthermore, such polymer coatings can be applied to several solid pharmaceutical forms (Thakral et al., 2013).

Enteric coating design is based on the transit time required for the pharmaceutical form to move from the stomach to the intestine. Coatings can be designed that are sufficiently thick to resist dissolution in the stomach (Ansel, Popovich, & Allen Junior, 2000). Thus, the specific surface area per unit of mass or volume of a sample is a key property that should be taken into account. Consequently, the release of the active ingredient may vary as a function of the surface area of the unit. Different techniques for calculating the surface area of solids are suggested in the literature (Santos et al., 2006).

The mathematical calculation of the surface area of a cylinder is an important tool that enables determination of the surface area of hard and soft capsules. In the present study, a calliper was used to measure the height and diameter of the unit.

The results from the physical characterisation of soft capsules containing palm oil and of hard capsules containing glutamine are outlined in Table 2. The total area of a soft capsule unit without coating containing palm oil was 8.61 cm², and the total area of a hard capsule containing glutamine was 7.27 cm². The results showed that coating with 0.2 mL of 6.5% Eudragit polymer per cm² of capsule enabled capsule disintegration at pH 6.8 after 60 minutes (Figure 6).

The main components for formulating any film coating are polymers, plasticisers, colourants and solvents. Knowledge of the properties of the polymers used is essential for preparing the coating (Rolim...
Coating with 6.0% triethyl citrate plasticiser, 40% absolute alcohol and 6.5% methacrylic acid copolymer (Eudragit S100®) proved adequate, improving the flexibility and resistance to rupture of the film formed.

The use of a plasticiser lowers the glass transition temperature. Examples of plasticisers include glycerol, propylene glycol, polyethylene glycol, triacetin, and citrate or phthalate esters, among others (Lachman et al., 2001).

Capsule coating consists of applying a coating material through a spouted bed and concomitantly using hot air to facilitate solvent evaporation (Rolim et al., 2009). In our study, 40% absolute alcohol was added to improve the drying process of hard and soft capsules. A higher temperature of the spouted bed improves the coating process of pharmaceutical forms (Lachman et al., 2001). In our study, the coating temperature was 50°C (Table 1). According to Ceream, Zheng, Young, and McGinity (2004) the main reported problem in film coating is a slow drying rate due to the high vapourisation rate of water (Ceream et al., 2004).

The coating of solid forms has numerous applications in the chemical, pharmaceutical and food industries, including controlling the release rate of the active ingredient, masking unpleasant flavours and odours, improving the aesthetics of the product, protecting the product from humid environments and providing the product with mechanical resistance (Ansel, Popovich, & Allen Junior, 2000).

This study examined the delayed-release system of soft and hard capsules containing 6.5% Eudragit® S100 for specific release in the gastrointestinal tract. In this test, the erosion and disintegration of the coated capsules were assessed. The trials were completed according to the disintegration test described in the Brazilian Pharmacopoeia, which considers capsules to be gastro-resistant capsules if they remain permanently intact in gastric fluid but disintegrate in intestinal fluid (Anvisa, 2010). The limitations of our work include the absence of dissolution tests, analytical method validation and statistical data reporting. The dissolution test aims to quantify the contents released in the disintegration medium under experimental conditions (Anvisa, 2010). Validating the method requires experimental studies using the same analytical techniques (Zepon, Fratoni, Bernardi, & Remor, 2013). Considering these parameters, it is not possible to know the concentrations of palm oil and glutamine dissolved in the gastrointestinal simulator medium, which represents a limiting factor in this experiment. Further studies should be conducted to provide complementary evidence.

Mehta et al. evaluated different concentrations of Eudragit® S100 coating on a naproxen matrix. Dissolution tests were performed at simulated gastrointestinal pH values to assess the physicochemical parameters of the formulations. The results demonstrated that tablets coated with Eudragit® S100 (2% w/v) showed controlled release for 24 hours and that this was a promising formulation for specific release in the colon region. Release of the active ingredient from pharmaceutical forms coated with Eudragit® depends on the pH of the dissolution medium and the coating thickness (Mehta, Chawla, Sharma, & Pawar, 2013).

Jain and colleagues investigated the potential of using Eudragit® S100 for insulin coating. The efficacy of insulin-containing microspheres was assessed, and the results demonstrated that in addition to depending on the pH of the medium, release also depended on the coating thickness. The study highlighted the potential of Eudragit® S100 as an insulin carrier (Jain, Panda, & Majumdar, 2005).

Onoue and colleagues developed an enteric mucoadhesive formulation containing Eudragit® S100 for the active ingredient (-)-epigallocatechin-3-gallate (EGCG), which is found in green tea, with the aim of improving its pharmacological effects. The formulation developed showed good results regarding EGCG stability and can be applied to treat gastrointestinal diseases (Onoue, Ochi, & Yamada, 2011).

The present study aimed to produce and evaluate the anionic coating of enteric-release capsules, which will allow the release of the active ingredient at a gastro-resistant pH. Palm oil capsules and glutamine capsules were coated with methacrylate (Eudragit® S100) using a spouted bed.

The use of methacrylate-based coating formulations for palm oil and glutamine capsules would be an appropriate strategy for specific release in the gastrointestinal tract and could produce promising results in studies on the mechanism of satiety and glycaemic control because the presence of undigested nutrients at the end of the gastrointestinal tract stimulates the production of intestinal hormones by enteroendocrine cells (Soares et al., 2018).

According to several studies on the mechanism of satiety (Diepvens et al., 2007; Heer, 2012; Lieverse et al., 1994; Olsson et al., 2011; Rebello et al., 2012; Van Citters & Lin, 1999), gastrointestinal hormones are released depending on the intestinal food content and nutritional status of the individual and may contribute to obesity and type 2 diabetes control.

Acta Scientiarum. Health Sciences, v. 42, e48422, 2020
Conclusion

The findings demonstrate the pharmaceutical application of Eudragit® S100 in the modification of the coating and preparation of a delayed-release system of hard and soft capsules for the ileal release of the active ingredients.

Acknowledgements

We thank Osvaldo de Freitas and Andrea Fontoura from School of Pharmaceutical Sciences of Ribeirão Preto-USP for their support and technical expertise. Supported by the National Council for Scientific and Technological Development (CNPq), the Brazilian Federal Agency for Support and Evaluation of Graduate Education (CAPES).

References

Agostoni, C., Moreno, L., & Shamir, R. (2016). Palmitic acid and health: Introduction. Critical Reviews in Food Science and Nutrition, 56(12), 1941-1942. Doi: 10.1080/10408398.2015.1017435
Agência Nacional de Vigilância Sanitária [Anvisa]. (2010). Farmacopeia Brasileira. Brasília, DF: Fiocruz.
Ansel, H., Popovich, N., & Allen Junior, L. (2000). Farmacotécnica: Formas Farmacêuticas & sistemas de liberação de fármacos (6a ed.). São Paulo, SP: Premier.
Bernardo, W., Maria Junior, J., Salomão, A., & Baracat, E. (2014). Fifteen minutes. Revista Associação Médica brasileira, 60(5), 395-397. Doi: 10.1590/1806-9282.60.05.001
Bester, D., Esterhuys, A. I., Truter, E. J. & van Rooyen, J. (2010). Cardiovascular effects of edible oils: a comparison between four popular edible oils. 2010. Nutrition Research Reviews, 23(2), 334-348. Doi: 10.1017/S0954422410000223
Ceream, M., Zheng, W., Young, C. R., & McGinity, J. W. (2004). A novel powder coating process for attaining taste masking and moisture protective films applied to tablets. International Journal of Pharmaceutics, 279(1-2), 127-139. Doi: 10.1016/j.ijpharm.2004.04.015
Chang, J., Wu, T., Greenfield, J. R., Samocha-Bonet, D., Horowitz, M., & Rayner, C. K. (2013). Effects of intraduodenal glutamine on incretin hormone and insulin release, the glycemic response to an intraduodenal glucose infusion, and antropyloroduodenal motility in health and type 2 diabetes. 2013. Diabetes Care, 36(8), 2262-2265. Doi: 10.2337/dc12-1663
Diepvens, K., Soenen, S., Steijns, J., Arnold, M., & Westerterp-Plantenga, M. (2007). Long-term effects of consumption of a novel fat emulsion in relation to body-weight management. International Journal of Obesity, 31(6), 942-949. Doi: 10.1038/sj.ijo.0803552
Edem, D. O. (2002). Palm oil: biochemical, physiological, nutritional, hematological, and toxicological aspects: a review. Plant Foods for Human Nutrition, 57(3-4), 319-341. Doi: 10.1023/a:1021828132707
Evonik. (2016). Surface area calculations and determinations. Retrieved on December 11, 2018 from https://healthcare.evonik.com/product/health-care/en/products/pharmaceuticalexcipients/EUDRAGIT/
Freire, A. C., Podczeck, F., Sousa, J. P., & Veiga, F. J. B.(2006). Colonic drug delivery. II- Types of delivery systems. Revista Brasileira de Ciências Farmacêuticas, 42, 357-355. Doi: 10.1590/S1516-93322006000300004
Galera, S. C., Fechine, F. V., Teixeira, M. J., Coelho, Z. C., Vasconcelos, R. C. d., & Vasconcelos, P. R. d. (2010). The safety of oral use of L-glutamine in middle-aged and elderly individuals. 2010. Nutrition, 26(4), 375-381. Doi: 10.1016/j.nut.2009.05.015
Hampel, N., Buck, A., Peglow, M., & Tsotsas, E. (2013). Continuous pellet coating in a Wurster fluidized bed process. Chemical Engineering Science, 86, 87-98. Doi: 10.1016/j.ces.2012.05.034
Heer, M. (2012). An analysis of the "Effect of Olibra: a 12-week randomized control trial and a review of earlier studies". Journal of Diabetes Science and Technology, 6(5), 709-711. Doi: 10.1177/193229681200600327
Jain, D., Panda, A. K., & Majumdar, D. K. (2005). Eudragit S100 entrapped insulin microspheres for oral delivery. AAPS PharmSciTech, 6(1), E100-E107. Doi: 10.1208/pt060116
Lachman, L., Lieberman, H. A., & Kanig, J. L. (2001). *Teoria e prática na indústria farmacêutica* (2 vols.). Lisboa, PT: Fundação Calouste Gulbenkian.

Lieberse, R. J., Jansen, J. B., Mascllee, A. A., Rovati, L. C., & Lamers, C. B. (1994). Effect of a low dose of intraduodenal fat on satiety in humans: studies using the type A cholecystokinin receptor antagonist loxiglumide. *Gut*, 35(4), 501-505. Doi: 10.1136/gut.35.4.501

Manadas, R., Pina, M. E., & Veiga, F. (2002). A dissolução in vitro na previsão da absorção oral de fármacos em formas farmacêuticas de liberação modificada. *Brazilian Journal of Pharmaceutical Sciences*, 38(4), 375-399. Doi: 10.1590/S1516-9532200200400002

Martins, G. Z., & Oliveira, W. P. d. (2003). Utilização do leito de jorro para a aplicação de revestimento entérico em cápsulas gelatinosas duras. *Brazilian Journal of Pharmaceutical Sciences*, 39(3), 299-307. Doi: 10.1590/S1516-9532200300300009

Meek, C. L., Lewis, H. B., Vergese, B., Park, A., Reimann, F., & Gribble, F. (2016). The effect of encapsulated glutamine on gut peptide secretion in human volunteers. *Peptides*, 77, 38-46. Doi: 10.1016/j.peptides.2015.10.008

Mehta, R., Chawla, A., Sharma, P., & Pawar, P. (2013). Formulation and in vitro evaluation of Eudragit S-100 coated naproxen matrix tablets for colon-targeted drug delivery system. *Journal of Advanced Pharmaceutical Technology & Research*, 4(1), 31-41. Doi: 10.4103/2231-4040.107498

Moustafine, R. I., Kabanova, T. V., Kemenova, V. A., & Van den Mooter, G. (2005). Characteristics of interpolyelectrolyte complexes of Eudragit E100 with Eudragit L100. *Journal of Controlled Release: Official Journal of the Controlled Release Society*, 103(1), 191-198. Doi: 10.1016/j.jconrel.2004.11.031

Olsson, J., Sundberg, B., Viberg, A., & Haenni, A. (2011). Effect of a vegetable-oil emulsion on body composition; a 12-week study in overweight women on a meal replacement therapy after an initial weight loss: a randomized controlled trial. *European Journal of Nutrition*, 50(4), 235-242. Doi: 10.1007/s00394-010-0131-x

Onoue, S., Ochi, M., & Yamada, S. (2011). Development of (−)-epigallocatechin-3-gallate (EGCG)-loaded enteric microparticles with intestinal mucoadhesive property. *International Journal of Pharmaceutics*, 410(1), 111-113. Doi: 10.1016/j.ijpharm.2011.03.020

Ortuño Sahagún, D., Márquez-Aguirre, A. L., Quintero-Fabián, S., López-Roa, R. I., & Rojas-Mayorquín A. E. (2012). Modulation of PPAR-γ by nutraceutics as complementary treatment for obesity-related disorders and inflammatory diseases. *PPAR Research*, 2012, 1-17. Doi: 10.1155/2012/518615

Pina, M. E., Sousa, A. T., & Brojo, A. P. (1997). Enteric coating of hard gelatin capsules. Part 2. Lioavailability of formaldehyde treated capsules. *International Journal of Pharmaceutical Sciences*, 148(1), 73-84. Doi: 10.1016/S0378-5173(96)04824-7

Pontes, A. L. C., Sousa, I. A., & Navarro, A. C. O. (2009). Tratamento da obesidade através da combinação de exercícios físicos e terapia nutricional visando o emagrecimento. *Revista Brasileira de Obesidade, Saúde e Emagrecimento*, 3(14), 124-135.

Rebello, C. J., Martin, C. K., Johnson, W. D., O’Neil, C. E., & Greenway, F. L. (2012). Efficacy of Olibra: a 12-week randomized controlled trial and a review of earlier studies. *Journal of Diabetes Science and Technology*, 6(3), 695-708. Doi: 11.1177/193229681200600526

Rolim, L. A., Lessa, M. M., Alves, L. D. S., Freitas-Neto, J. L. d., Alves, S. M. A., & Rolim-Neto, P. J. (2009). Coating applications of solid pharmaceutical forms in pharmaceutical industry. *Revista Brasileira de Farmácia*, 90(3), 224-230.

Santos, H. M. M., Veiga, F. J. B., Pina, E. M. S. d., & Sousa, J. J. M. S. d. (2006). Production of pellets by pharmaceutical extrusion and spheronisation. Part II. Physical characterisation of pellets. *Revista Brasileira de Ciencias Farmacêuticas*, 42(3), 309-318. Doi: 10.1590/S1516-95322006000300002

Shen, X., Yu, D., Zhu, L., Branford-White, C., White, K., & Chatterton, N. P. (2011). Electrospun diclofenac sodium loaded Eudragit R L 100–55 nanofibers for colon-targeted drug delivery. *International Journal of...*
Singh, S., Neelam, Arora, S., & Singla, Y. P. (2015). An overview of multifaceted significance of eudragit polymers in drug delivery systems. *Asian Journal of Pharmaceutical and Clinical Research, 8*(5), 1-6.

Soares, L. A., Takeuti, T. D., Terra-Júnior, J. A., Rodrigues Júnior, V., Gomes, R. A. d. S., Baptista, A. B., ... Crema, E. (2018). Influência da cápsula de liberação ileal de óleo de palma e de glutamina sobre peptídeos intestinais GLP-1 em Pacientes com Diabetes tipo 2. *Revista Brasileira de Obesidade, Nutrição e Emagrecimento, 12*(73), 615-623.

Takeuti, T. D., Terra, G. A., Silva, A. A., Terra Junior, J. A., Silva, L. M., & Crema, E. (2014). Effect of the ingestion of the palm oil and glutamine in serum levels of GLP-1, PYY and glycemia in diabetes mellitus type 2 patients submitted to metabolic surgery. *Arquivos Brasileiros de Cirurgia Digestiva, 27*(Suppl1), 51-55. Doi: 10.1590/s0102-6720201400s100013

Thakral, S., Thakral, N. K., & Majumdar, D. K. (2013). Eudragit*: a technology evaluation. *Technology Evaluation, 10*(1), 131-149. Doi: 10.1517/17425247.2013.756962

Van Citters, G. W., & Lin, H. C. (1999). The ileal brake: a fifteen-year progress report. *Current Gastroenterology Reports, 1*(5), 404-409. Doi: 10.1007/s11894-999-0022-6

Villanova, J. C. O., Oréfice, R. L., & Cunha, A. S. (2010). Pharmaceutical applications of polymers. *Polímeros, 20*(1), 51-64. Doi: 10.1590/S0104-14282010000500009

Zepon, K. M., Fratoni, G., Bernardi, L. S., Remor, V. T. R. (2013). Validação de metodologia analítica para doseamento e estudo da equivalência farmacêutica de comprimidos de sinvastatina 20 mg. *Revista Eletrônica de Farmácia, 10*(2), 43-57. Doi: 10.5216/ref.v10i2.19297