Pharmaceutical development of a capsule for the treatment of acute coronary syndrome

ABSTRACT

Aims: The main objective of this work has been the development of delayed-release hard capsule containing mini-tablets of two-platelet antiaggregant, acetylsalicylic acid and clopidogrel, for the treatment of patients suffering from acute coronary syndrome at risk of gastrointestinal bleeding, therefore jointly is administered an inhibitor of gastric acid secretion, the ranitidine.
Study design: Design of mini-tablets into a capsule for the treatment of acute coronary syndrome.
Methodology: For the galenic preparation of the three mini-tablets, an in-depth study of the choice of excipients and the most appropriate manufacturing methodology was carried out. Once the suitability of the mixture for use in direct compression was determined, which is the selected technological method, as it is the most profitable and involves less time, the mini-tablets were prepared and their physical characterization. Tablet appearance and physical characteristics such as dimensions, thickness, mass, resistance to crushing, friability, disintegration time and content uniformity met the requirements established according to pharmacopoeia to ensure the quality of the tablets.
Results: The final formulation consists of the grouping of mini-tablets of three drugs in a delayed-release hard capsule ("tablets-in-capsule") for the treatment of patients suffering from acute coronary syndrome at risk of gastrointestinal bleeding. All tablets show resistance to crushing, disintegration, and friability features that strictly meet pharmacopoeia requirements.
Conclusion: Adherence to treatment is increased because the concomitant administration of three active ingredients is unified in a single pharmaceutical dosage form.

Keywords: Acute coronary syndrome, acetylsalicylic acid, clopidogrel besylate, ranitidine HCl, mini-tablets in capsule, direct compression, adherence to treatment.

1. INTRODUCTION

Cardiovascular disease is a major cause of disability and premature death throughout the world and contributes substantially to the escalating costs of health care. The underlying pathology is atherosclerosis, which develops over many years and is usually advanced by the time symptoms occur, generally in middle age. Acute coronary and cerebrovascular events frequently occur suddenly and are often fatal before medical care can be given (World Health Organization, 2007). Acute coronary syndrome (ACS) is caused by an acute complete or incomplete thrombosis resulting from a vascular, cellular, and plasmatic response to atherosclerotic plaque rupture or erosion (Zeitouni et al., 2018). The benefit of dual antiplatelet therapy (DAPT) in patients presenting with ACS is both clinically important and unequivocal. The latest clinical practice guidelines agree on the usefulness of DAPT both as part of the treatment of ACS and as a measure to prevent recurrence (El-Toukhy et al., 2017; Anastasius et al., 2016; Fuertes et al., 2019; Tersalvi et al., 2020). DAPT comprising acetylsalicylic acid plus a platelet ADP P2Y12 receptor inhibitor (clopidogrel, prasugrel or ticagrelor) is key in avoiding thrombosis following balloon angioplasty, or angioplasty with stent implantation. The main risk of DAPT is gastrointestinal bleeding, thus concomitant administration of an inhibitor of gastric acid production is frequently prescribed (Saven et al., 2022).

Single unit formulations can contain the drug(s) within the single tablet or capsule or comprise several discrete dosage units such as beads, granules, ion exchange resin-particles, powders, mini-tablets (diameter equal to or smaller than 2-3 mm) or even multiple small standard tablets (Clarke et al., 1995; Lennartz et al., 1998). These dosage units can be filled into capsules directly or after film coating (Seo et al., 2020). Manufacturing methods of mini-tablets are like traditional sized tablets, being occasionally more challenging in terms of weight control, content uniformity and measurement of physico-mechanical attributes (i.e., tensile strength, friability, disintegration time and solid fraction) (Baseer; Aleksovsky; Mitra). Filling standard tablets into hard capsules may offer some advantages over other smaller dosage units such as achieving higher doses within the same footprint (Markl, 2017). Small standard tablets and mini-tablets can be formulated and designed independently. Encapsulated small standard tablets, mini-tablets, or their combination, provide the formulator the chance to combine different incompatible API (active pharmaceutical ingredients) and/or customize the release site of the drug. As a result, the therapeutic outcome is improved, and patient adherence is enhanced.

The small standard tablets present several advantages over mini-tablets and beads as related in the following:

- Follow standard manufacturing; special equipment/tooling is not required.
- They offer consistent dimensions and smooth surface for subsequent coating or filling steps.
- The drug loading capacity is higher than mini-tablets and beads.
- Coating process is less challenging compared to mini-tablets or beads. Moreover, less coating material is required due to the smaller surface area.

Nowadays, fixed-dose combinations polypills are available with differing active components. They involve a better adherence to medications, simplification of treatment strategies and a reduction of economic burden of pharmacological treatments (Lombardib et al., 2018; Castellano et al., 2014; Baumgartner et al., 2020; Brandon). The concept of the polypill is quite simple, instead of taking two or more pills (each containing one drug); multiple drugs are combined into one formulation.

The primary objective of this study was to develop an alternative hard capsule formulation comprising a fixed dose combination (FDC) of small standard tablets for the secondary prevention of atherothrombotic events in adult patients with risk of gastrointestinal bleeding. For this, was developed a delayed-release hard capsules containing mini-tablets of two platelet antiaggregant, acetylsalicylic acid and clopidogrel, and jointly, an inhibitor of gastric acid secretion, like the antihistamine H_2, ranitidine.

2. MATERIAL AND METHODS

2.1 Materials

Acetylsalicylic acid, clopidogrel besylate and ranitidine clorhydrate form II were purchased from Zydus Cadila Healthcare Ltd, Cofares and Laboratories Liconsa S.A, respectively. **Figure 1** shows the molecular structures of these drugs.

Microcrystalline cellulose (Vivapur® 101, 102 & 12, JRS Pharma, Germany), Mannitol (Pearlitol® 200 SD, Roquette, France), L-HPC (LH-11 Shin-Etsu Chemical Co, Ltd), Partially pregelatinized maize starch (Starch 1500®, Colorcon U.S.A), Croscarmellose sodium (Vivasol® JRS Pharma, Germany), Hyprolose (HPC SSL-SFP, Nippon Soda Co., Ltd, Japan), Talc (Laboratories Guinama, Spain), Stearic acid (Ligamed® SA-1-V, Peter Greven GmbH & Co.KG, Germany), Magnesium stearate (Ligamed® MF-2-V, Peter Greven GmbH & Co.KG, Germany), Glyceryl dibehenate (Compritol® 888 ATO Gattefossé, Germany), were the excipients used.

2.2 High-performance liquid chromatography (HPLC) analysis

Assay of API were determined using a validated HPLC method. The conditions are described in **Table 1.**

2.3 Formulations

One acetylsalicylic acid mini-tablet was required to obtain the therapeutic dose needed in the treatment of ACS patients, (100 mg acetylsalicylic acid), two clopidogrel mini-tablets (75 mg clopidogrel as besylate), and two ranitidine mini-tablets (150 mg ranitidine as hydrochloride). Formula is presented in **Table 2** and **Figure 2.** The pharmacological development of the polypill has been achieved thanks to the combination of different active ingredients in an only capsule that avoids

physical-chemical incompatibilities and maintains the biopharmaceutical and pharmacokinetic properties of each of its components.

2.3.1 Preparation of the small standard tablets

The APIs were deagglomerated through a 1.0 mm manual sieve, then blended manually with the rest of the excipients (previously sieved through a 0.8 mm). Lubricant were passed through a 0.5 mm manual sieve, then added to the pre-lubricated and blended manually for 2 min. The tablet blends were compressed using a single station compression press (J. Bonals 40B type MT), with 6.0 mm flat-faced beveled edge multiple tip tools. The nominal tablet weight was kept constant at 125 mg. The manufacturing flow chart is exposed in **Figure 3.**

2.4 Tablets characterization

2.4.1 Thickness and diameter

Ten tablets were used, and average values were calculated. The thickness of the final product was determined using a tablet testing instrument Pharmatest PTB 311 (Germany).

2.4.2 Weight variation

Twenty tablets were randomly selected from each batch and individually weighed using an electronic balance (balance Mettler Toledo AG 245, Switzerland). The average weight of all tablets and percentage deviation from the mean value for each tablet were determined.

2.4.3 Resistance to crushing

In the preformulation step, the resistance to crushing expressed as the force in Newton required crushing the tablets was evaluated (Ph. Eur. 2.9.8. Resistance to crushing of tablets). The resistance to crushing of the ten tablets were evaluated using a hardness tester Pharmatest PTB 311 (Germany).

2.4.4 Friability test

The tablets were accurately weighed and placed in the drum of the friabilometer (Pharmatest PTF E®, Germany). The drum was rotated 100 times at 25 rpm, and the tablets were removed, dedusted, and accurately weighed. If the tablets weigh up to 0.65 g, take 20 and if they weigh more, take 10 units. The percentages of friability were calculated. The loss of substance is expressed as a percentage and is considered satisfactory if it is not greater than 1%. For preformulation studies the limit is 0.8% (Ph. Eur. 2.9.7. Friability of uncoated tablets).

2.4.5 Disintegration studies

The disintegration time of the tablets was determined in 600 mL of deionized water at 37 ± 0.5°C, using a USP disintegration test apparatus Turu-Grau® (Spain) (Ph. Eur. 2.9.1. Disintegration of tablets and capsules).

2.4.6 Content uniformity

The test for uniformity of content of single-dose preparations is based on the assay of the individual contents of drugs of a number of single-dose units to determine whether the individual contents are within limits set with reference to the average content of the sample (Ph. Eur. 2.9.6. Uniformity of content of single-dose preparations). Using an analytical method proposed, the individual contents of 10 dosage units taken at random were determined.

3. RESULTS AND DISCUSSION

3.1. Formulation

Tables 3-5 show the individual composition of each mini-tablet. Formulations were prepared individually by direct compression method having all cores the same weight. The final formulation consists of the grouping of mini-tablets of three drugs in a delayed-release hard capsule ("tablets-in-capsule"). To achieve this, the research has focused on choice of excipients used in each formulation and selection of the manufacturing method. The manufacturing method was direct compression, due to the technological advantages it provides in terms of simplicity, reproducibility and stability. In addition, as is known, it is an economical method because it requires a smaller number of manufacturing steps.
In order to simplify the formulation as much as possible, batches were made trying to use the least amount of excipients possible and to obtain the best compressibility results.

3.2. Pharmaceutical parameters evaluation results

The study determine different physical parameters including aspect, physical characteristics: dimensions and thickness, average mass, resistance to crushing, friability, disintegration time and content uniformity. In **Table 6** is described the pharmaceutical technological characteristics of three mini-tablets obtained by direct compression, which must meet the requirements established according to European Pharmacopoeia (Ph. Eur.) (ref) to ensure that the quality of the tablets is as expected.

Acetylsalicylic acid and clopidogrel besylate tablets had a white or off-white round tablets visual appearance, and yellow round for ranitidine HCl tablets. All of them presented excellent pharmaceutical technological characteristics and satisfy with the specifications of (Ph. Eur.) (ref). The content uniformity test was developed to ensure the consistency of the content of active drug substances within a narrow range around the label claim in dosage units. This test is crucial for tablets that have a drug content of less than 2 mg or when the active ingredient comprises less than 2% of the total weight of the tablet.

Finally, the five mini-tablets weighing 125 mg each, white or yellow, flat, and with a diameter of 6 mm, are placed in a delayed-release capsule. **Figure 4** shows the result of the encapsulation of formulation in gastro-resistant capsules (V caps enteric®), showing the yellowish colour of ranitidine, inside a transparent hard gelatine capsule number 0E. The gastro-resistant capsules (V caps enteric®) used have complied with the gastro-resistant test described in the literature. In this way, the coating process of a conventional hard capsule or one of the mini-tablets is avoided.

4. CONCLUSIONS

The concept of a combination polypill composed of aspirin and, antihypertensives, has been suggested to simplify and improve the prevention and treatment of cardiovascular disease. In this paper

The development and manufacture of delayed-release hard capsules containing antiplatelet mini-tablets and a hydrochloric acid production inhibitor get adherence to treatment is increased because the concomitant administration of three active ingredients is unified in a single pharmaceutical form. The manufacture of said formulations is feasible at an industrial level since it is a simple, economical and highly reproducible manufacturing process.

On the other hand, pharmacotechnical studies of the mini-tablets were carried out, the results of which demonstrated their quality. All tablets show resistance to crushing, disintegration, and friability features that strictly meet Pharmacopoeia requirements. So, on the basis of those results, we can conclude that the mini-tablets meet the quality parameter to satisfy therapeutic efficacy.

It is very important to point out that from the economic point of view, it is a very attractive presentation since the administration finances only one individual drug instead of three, and the pharmaceutical industry would reduce registration and production costs (manufacturing and conditioning costs that reduce the environmental pollution).

Table 1. Hard capsule formulations containing small standard tablets.

Parameter	Chromatographic conditions acetylsalicylic acid	Chromatographic conditions clopidogrel besylate	Chromatographic conditions ranitidine HCl
Mobile phase	Ammonium acetate Merck ($C_2H_7NO_2$) 0.1M 60:40 ACN	Ammonium acetate Merck ($C_2H_7NO_2$) 0.1M 25:75 ACN	Ammonium acetate Merck ($C_2H_7NO_2$) 0.1M 60:40 ACN
Injection volume (µL)	10	20	10
Flow (mL/min)	1	1	1
Solvent programming	Isocratic	Isocratic	Isocratic
Chromatographic column	Kromasil 100 C18 5 µm 15 x 0.46	Kromasil 100 C18 5 µm 15 x 0.46	ACE EXCEL 5 µm
Chromatographic column temperature (ºC)	20	20	20
Detector	Diode array detection (DAD)	Diode array detection (DAD)	Diode array detection (DAD)
Wavelength (λ) (nm)	275	225	325

Table 2. Hard capsule formulations containing small standard tablets.

	API	Dose (mg)
Formulation	Acetylsalicylic acid	100
	Clopidogrel besylate	75
	Ranitidine HCl	150

Table 3. Composition of acetylsalicylic acid mini-tablets.

Raww material	mg/tablet
Acetylsalicylic acid	100.00
MCC (Vivapur® 101)	10.00
Hydroxypropyl cellulose (HPC SSL-SFP)	2.50
Pregelatinised starch (Starch 1500®)	6.30
L-HPC (LH-11)	2.50
Magnesium stearate (Ligamed® SA-1-V)	3.80
Total	125.00

Table 4. Composition of clopidogrel besylate mini-tablet.

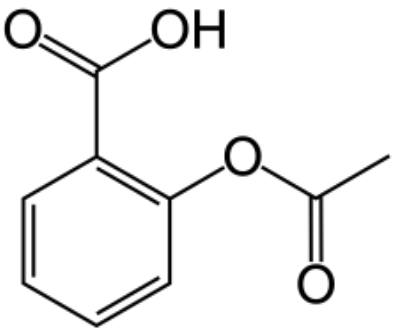
Row material	mg/tablet
Clopidogrel besylate	55.93
Mannitol (Pearlitol® 200SD)	50.52
MCC (Vivapur® 102)	12.50
Croscarmellose sodium (Vivasol®)	1.05
Talc	3.75
Glyceril behenate (Compritol® 888 ATO)	1.25
Total	125. 00

Table 5. Composition of ranitidine HCl mini-tablets.

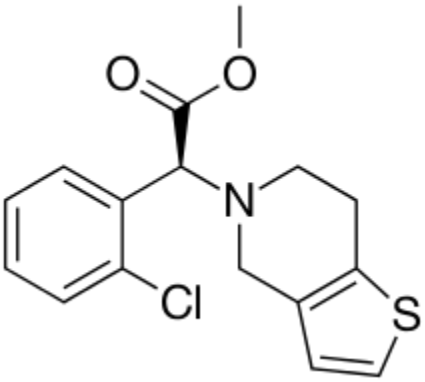
Row material	mg/tablet
Ranitidine HCL	83.75
MCC (Vivapur® 12)	40.00
Magnesium stearate (Ligamed® MF-2-V)	1.25
Total	125. 00

Table 6. Pharmaceutical technological characteristics of mini-tablets.

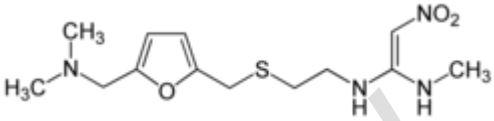
Pharmaceutical technological characteristics	Acetylsalicylic acid tablet 100 mg		Clopidogrel besylate tablet 75 mg		Ranitidine HCl tablet 150 mg	
Aspect	White or off-white round tablets	✓	White or off-white round tablets	✓	Yellow round tablets	✓
Dimension (mm)	6.0 ± 0.2	6.0	6.0 ± 0.2	6.0	6.0 ± 0.2	6.0
Thickness (mm)	3.5 ± 0.3	3.5	4.0 ± 0.3	4.0	3.5 ± 0.3	3.6
Average mass (mg)	125.0 ± 7.5% (11.6 – 134.4)	125.6	125.0 ± 7.5% (115.6 – 134.4)	125.3	125.0 ± 7.5% (115.6 – 134.4)	125.6
Resistance to crushing (N)	>30	40	>30	36	>30	40
Friability (%)	≤ 1.0%	0.3%	≤ 1.0%	0.1%	≤ 1.0%	0.2%
Disintegration time	< 15 min	3 min	< 15 min	4 min	< 15 min	3 min 40 s



Acetylsalicylic acid



Clopidogrel besylate



Ranitidine HCl

Figure 1. Molecular structures of APIs

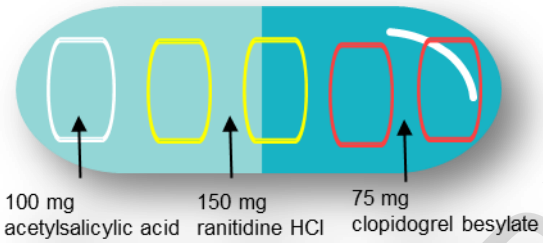


Figure 2. Polypill.

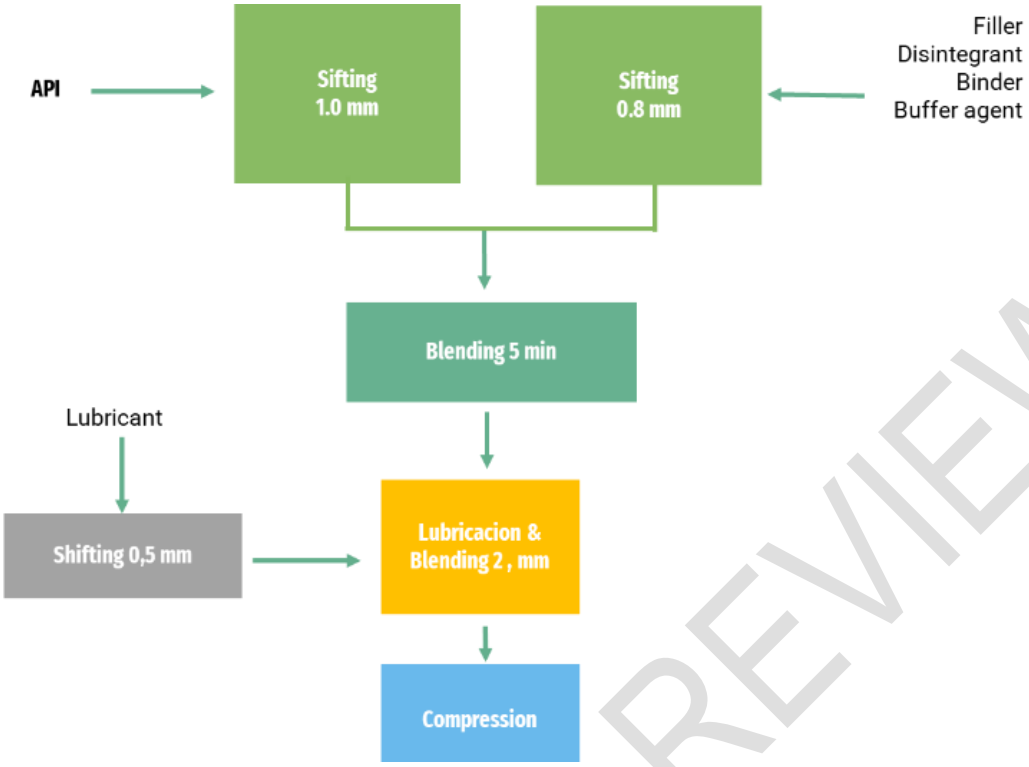


Figure 3. Manufacturing process flow chart.

Figure 4. Capsule with mini-tablets of acetylsalicylic acid, clopidogrel besylate and ranitidine HCl.

CONSENT (WHERE EVER APPLICABLE)

All authors declare that 'written informed consent was obtained from the patient (or other approved parties) for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editorial office/Chief Editor/Editorial Board members of this journal.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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