World Journal of Pharmaceutical and Life Sciences
WJPLS
www.wjpls.org
SJIF Impact Factor: 7.409

HARD CAPSULES: THE GASTRORESISTENCE AND ENTERIC COATING IN GALENIC LABORATORY PRACTICE

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Article Received on 09/07/2024 **Article Revised on 29/07/2024** **Article Accepted on 19/08/2024**

ABSTRACT
The use of the hard gelatine capsules is considered as versatile in galenic lab related the easy way to be produced , low cost and to the simply instrument needed. This pharmaceutical form show various advantages : this can mask the unpleasant odour and taste and are in commerce various size useful for pediatric or adults therapy , not need very complex instrument. This can release in easy way the API in gastric lumen after 15 minutes and the excipent to be used are simply vs the industrial drugs production. Aim of this work is to verify the method used or suggested in order to have gastroresistence and the delayed release in galenic laboratory. A special focus is provided about some excipients used for this scope in CP and in CPS production as well as to the new innovative 3D printing systems.

KEYWORKDS: Physiology , hard gelatin capsules , gastroresistence , dealy release,enteric coating ,excipients HPMC, metilcellulose , acetoftalate cellulose,Eudragit, material science ,capsule into AR capsule method, quality control, pharmacopea, 3D printing, odontoiatry.

INTRODUCTION

The use of the hard capsules is high diffused in the galenic field for various reason : versatility, easy to use, economicity, all kind of size needed.

For the scope of this work It is of interest to investigate the various type avaiable into the commerce and the tecqnique used to produce specific release of the API : not only rapid but also delayed , gastroresistence, enteric coating and other.
In article : Paediatric oral formulations: Why don't our kids have the medicines they need?
José Eduardo Juárez-Hernández, Bruce C. Carleton
08 July 2022 https://doi.org/10.1111/bcp.15456
Is reported

“Medication use in children represents about 15–20% of total drug sales. More than 50% of children receive at least 1 prescription medication a year. Despite this, few drugs have a paediatric formulation available. Furthermore, 80% of paediatric prescriptions are considered off-label. Off-label use is defined as the use of products that differ in dose, indication or route of administration from the one established in the summary of product characteristics. Children have demograhic (height, weight, body mass index) physiological (blood flow, intestinal permeability, renal and hepatic maturational changes, and metabolism) diversity, and ontogenic changes across the age spectrum mean that these differences continue throughout the childhood. These characteristics change widely with age and have a direct impact on pharmacokinetics PK. Despite this,

pharmacokinetic and bioequivalence studies are rarely performed in children, which results in a lack of knowledge about the pharmacokinetic profile, bioequivalence, bioavailability and dosage of drugs in this population. Both the demographic and physiological differences between age groups, added to the lack of pharmacokinetic PK information leads to the use of drugs in children that may cause problems not seen in adults such as overdosage, poor medication adherence and challenges in drug administration."

When it must to be subminitrated API that are sensible to the PH acid of the gastric fluid it must to be protected by inactivation (in example PPI) and to do this various strategies are adopted by the pharmaceutical industry : production of gastro protected cps or using delay realease (cp or cps) whit matrix systems or using coated gastroresintance pellets.

Variuos API due by their specific characteristics and related the stomach PH if subministrated with hard gelatine capslues must to be produced (in the galenic lab) or in simply release or gastroresistence or in delayed release to prevent their gastric fluid degradation.

The gastroresistance cps are cps coated with cellulose acetoftalate or copolimer of metacrilic acid or other (to this FF is applicable the disgregation test by FU).

Other solution imply a normal cps filled by granule or powder covered with gastroprotective system.

In this last condition it is needed a specifi test that show the libearation of the API. (see AMOROSA).

Fig. 1: From J. Lester.

The capluses in pharmaceutical field can be divided in hard capsules and soft.
The hard Gelatins cps comes from idrolysis of the animal collagen (natural origin), and it is soluble in water.
The vegetarian cps can be HPMC hydrossipropil metilcellulose (semisyntetic product) and Pullulan cps.
Normal cps release: in 15 minutes in water environment
Acido resistance cps: HMPC shell (after 30 minutes they disgregates)
(other products: For Modified release, Delay release, Sustained release).

Release-modifying agents in use are substances used as an excipient to control drug release in a modified-release dosage form such as in prolonged-release or controlled-release tablets. They are vital excipients for modified-release tablets.
Release control in orals solid form (cp) che be obtained using various systems: reservoir systems, matrix based osmotic pump controlled, biodegradable systems and other.

It is of common knowledge that the simply hard gelatine capsules release the API in the stomach after 15 minutes . But Because the gastric PH is acid it is needed in some condition to protect API for acid degradation (PPI, pancrelipase) or to protect the stomach mucosa for irritants drugs (ferrum salts).

In Other situation is needed to release the API into the intestine to produce effect in this tract. (enteric coating, delay release) like Budesonide.

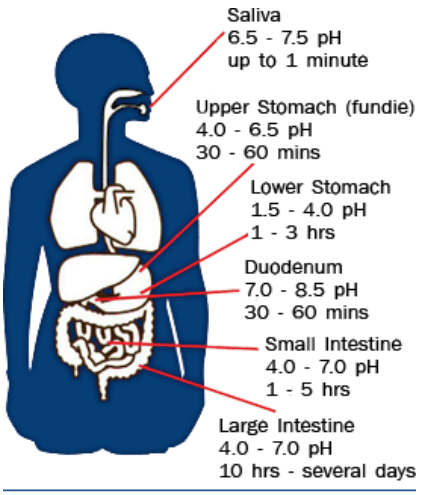

Fig. 2: From https://www.alleganynutrition.com/.

In the intestinal tract the Ph is alcaline and all of this characteristic must to be taken in consideration when producing capsules.

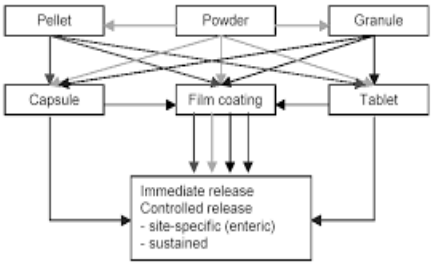

Fig. 3: From Ramu S Et Al Formulation And Evaluation Of Lansoprazole Delayed Release Pellets.

In the commerce are present capsules classified as ACIDO RESISTANCE but this characteristic due by their technical sheet are able to protect API only for 30 minutes from the gastric fluid.

The various international pharmacopeia related gastroresistence characteristics require 1 hour of resistance in acid enviroment under mixing before to release the API.

In article Galenic Laboratory: State of the Art-A Scientific and Technological Discipline, Innovation and Management is reported
"The intraluminal pH is rapidly changed from highly acid into the stomach to about pH 6 into the duodenum. The pH gradually increases in the small intestine from a pH 6 to about pH 7.4 in the terminal ileum. The pH drops to 5.7 in the caecum, but again gradually increases, reaching a pH 6.7 into rectum." So the Acid Resistance AR caps are not to be considered as gastro resistance because in 30 minutes this starts to release API in gastric environmentThe Italian pharmacopeia FU XII for gastro resistance require at least 1 hour of integrity in HCL 0.1N solution under mixing. Then in phosphate buffer at 6.8 pH they must to disaggregate in 1 hour. The classic hard gelatin capsule starts to disaggregate in 15 minutes about".

So it is clear that the acido resistence characteristic is not equal to gastro resistance.

Gastro resistance cps according pharmaceutical tecqnique can be obtained or trhought coated film , or filled with gastroresistance materials (powders and pellets).

In italian national TARIFFARIO for pharmacy related gastroresistence are classifyed two technological methods

1) Capsula into other AR capsula method
2) Dipping method with bath of acetoftalate 8% in aceton

Related phisyology: According Frank J. Dowd
"A mixed meal of solids and liquids usually begins to enter the duodenum in about 30' and requires about 4 hours to leave the stomach completely."
Other methods to produce delayed release use varius kind film based on the EURDAGIT acrilate polymers.

EUDRAGIT L and S gastroresistance (but soluble in the intestinal environment) or EUDRAGIT RL RS (PH INDEPENDENT) prolonged release.

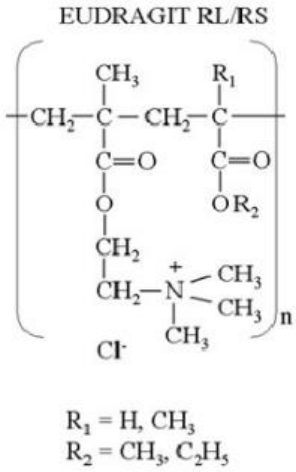

Fig. 4.

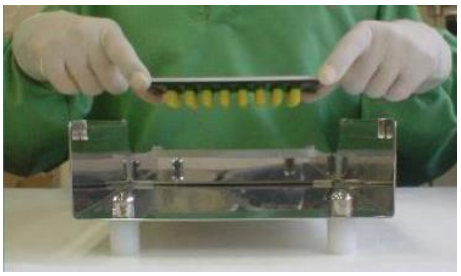

Fig. N. 5: Dipping method.

(It is necessary to coat before the body of the caplues then the heads.)

Other methodology (BETTIOL) to produce omeprazole casplues use as eccipient metolose or other metil cellulosa with high vsicosity to reduce the acid DEGRADATION of the API.

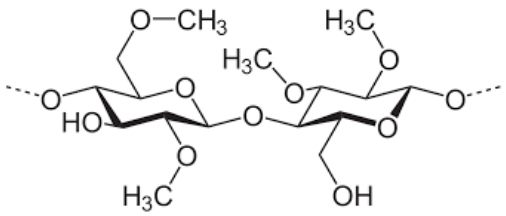

Fig. N. 6: metilcellulose, for hydrophilic matrix systems, providing a robust mechanism for the extended/controlled release of drugs from oral solid dosage forms.

Gastro resistance is needed in exampe for: API destroyed by acid environment like Pancreatin, eritromicin
Gastro lesive API in example FANS, aspirin, ferrum salts
API the require and intestinal release like Budesonide.
Gastro resitance drugs (cp or cps) are drugs that resist into the gastric secretion but disgregate into the PH of the intestine (PH from 6,8-7,5).

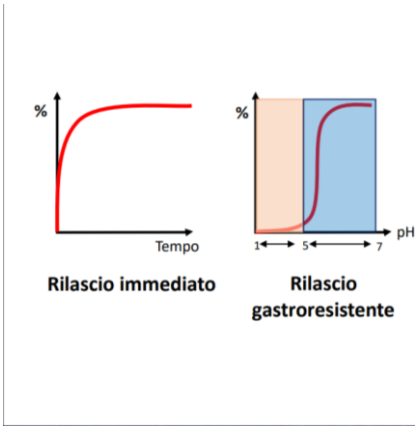

Fig. N. 7.

HPMCP: Hydroxypropil metilcellulosa-ftalate (excipient for enteric preparations)

Fig. N. 8 Capsula into other AR capsula method : there are evidence of this performance.

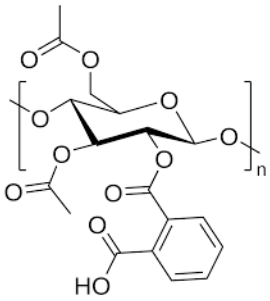

Fig. N. 9: Cellulose acetoftalate , insoluble in water and in acid medium, soluble in alcaline environment.

DIPPING METHOD: the caspules filled are then filmed in a dipping bath with acetoftalate 8% in aceton
If used normal gelatine cps 2 dipping phases , instead if used acido resistence cps only 1 cycle is needed.

Every dipping phase: 40 seconds, in continous movement and then dryed , filter on gauze , then put the capluse in a PETRI glass capsule and mantain in rotation movement since dry.

Fig. N. 10: From Santarelli.

Other method imply the use of acido resistance capsule using as eccipient metolose 90 SH idrossipropilmetilcellulosa at high viscosity at 10% in order to delay the entry of the gastric secretion into the capsule.

Omeprazolo capsule gastroresistenti (Omeprazole Capsule, Gastro-resistant B.P. 2024)	
Composizione:	
omeprazolo Metolose 90SH ® (idrossipropilmetilcellulosa)	mg 10-20 mg 40
amido di mais pregelatinizzato q.b. per 1 cps in DR-caps ®	

Fig. N. 11: Form Bettiol.

Of interest the kind of excipient used for CP : diluents , disgregants , lubrificants but also polymer for controlled release (matrix systems).

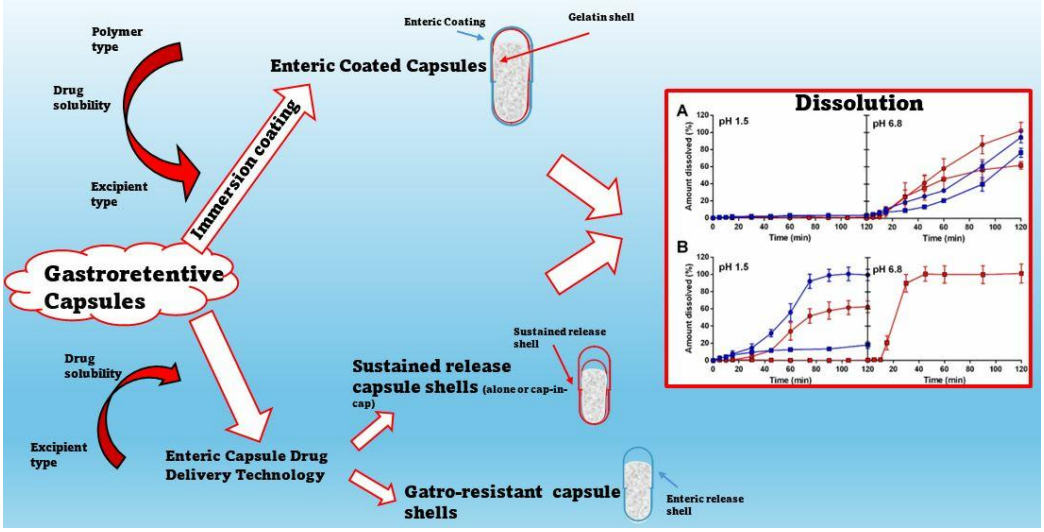

Fig. N. 12: From https://doi.org/10.3390/ph17040433.

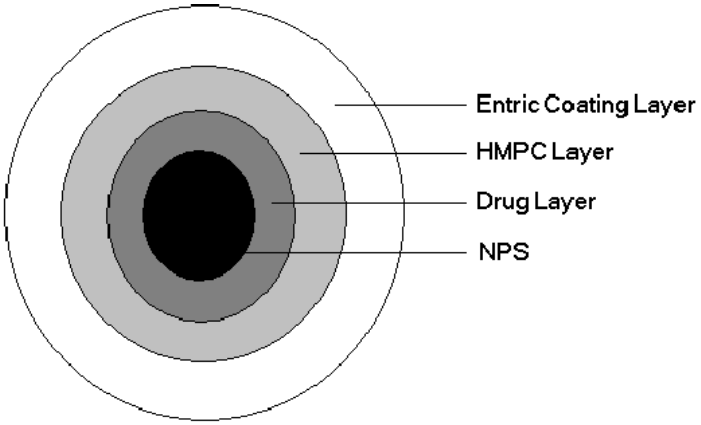

Fig. N. 13: Schematic of the multi -layer firlm coated pellets of Omeprazole . From Karim Mousavimarandi et al (Nps : nanoparticle).

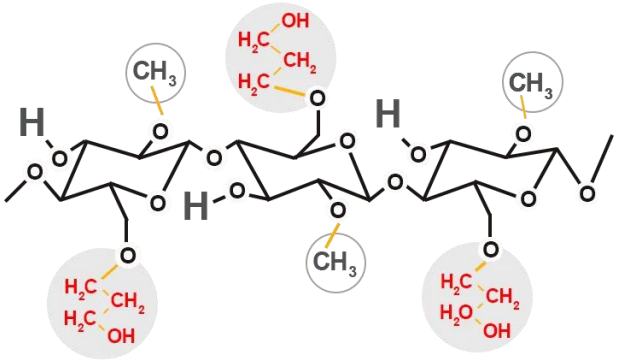

Fig. N. 14: HMPC hydroxypropilmetilcellulose.

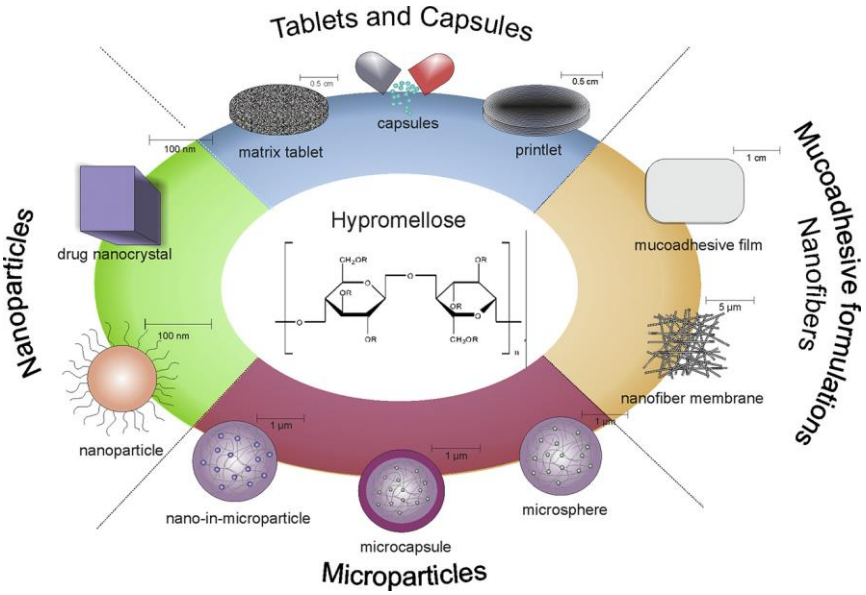

Fig. N. 15: HMPC or hypromellose, Methocel, Metolose and other branded name. From https://doi.org/10.1016/j.jconrel.2020.05.045.

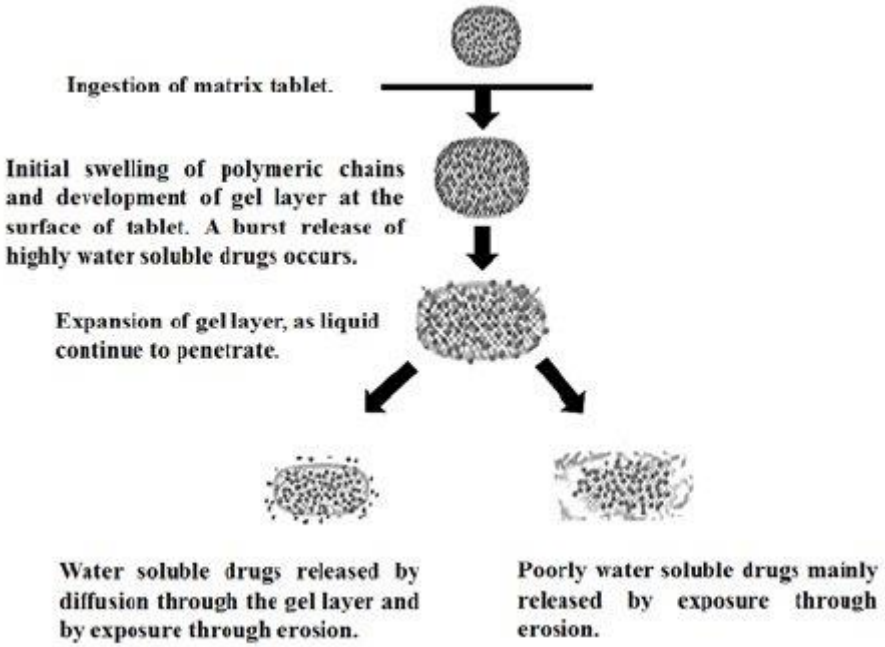

Fig. N. 16: From Ghori et al "Commonly, hydrophilic matrices HM are compressed matrix tablets and can easily be prepared by a direct compression of a powder mixture of drug with a release retardant, swellable polymer and other additives to aid processing. Among the swellable polymers usually used to develop.

These hydrophilic matrices, cellulose ethers, specifically methylcellulose and hypromellose (hydroxypropyl methylcellulose, HPMC), have provoked extensive interest. arious authors have studied the impact of MC/HPMC viscosity on drug release from hydrophilic matrices HM . It can be concluded from these studies that the higher the viscosity of a polymer, the faster the swelling of its side chains, forming a very strong gel, which decreases the drug release rate.

Of interest it is also to verify some formulations available in the commerce

Omeprazol 10 mg cps GR: **Generic drug technical sheet** indication children > 1 year and body weigth >= 10 kg Chilren and adolescent > 4 years

Capsule content: sugars spheres (made of mais starch and saccarose) Sodio laurilsolfato, Fosf ato disodico, Mannitolo, Ipromellosa 6 cP, Macrogol 6000, Talco Polisorbato 80, Titanio diossido (E171), Copolimero dell'Acido Metacrilico-Etil Acrilato (1:1).

Body cps
Gelatin Giallo chinolina (E104),Titanio diossido (E171)

"For the patients with swallows difficulties and for children that can drink or **swallow semisolids foods: The patients can open the cps and swallow the contained with hald glass of water** , or after mixing the content with liquid sligthly acid juice fruit in this case the dispersione must to be ingested immediatly or into 30 minutes.The is is needed to rinse well the bottom of the glass with water and drink all.

In alternatie way patients can dissolve in mouth the capsule and swallow the granule contained with half glass of water, the granule must not to be chewed."

And From lansoprazole Rising Pharma Holdings, Inc.

"Each delayed-release capsule contains **enteric-coated pellets** consisting of 30 mg of lansoprazole USP (active ingredient) and the following inactive ingredients: acetone, hypromellose, isopropyl alcohol, light magnesium carbonate, methacrylic acid copolymer, polyethylene glycol, polysorbate 80, sugar spheres (which contain sucrose and corn starch), talc, and titanium dioxide. Components of the gelatin capsule include D&C Red No. 28, FD&C Blue No. 1, FD&C Red No. 40, gelatin, sodium lauryl sulfate, and titanium dioxide."

Budesonide USP cps

"Each capsule for oral administration contains 3 mg of micronized budesonide with the following inactive ingredients: acetyltributyl citrate, ethylcellulose aqueous dispersion, gelatin, iron oxide red, iron oxide yellow, methacrylic acid copolymer dispersion, polysorbate 80, simethicone emulsion, sodium lauryl sulfate, sugar spheres, talc, titanium dioxide and triethyl citrate. The capsule shell is printed with black pharmaceutical ink which contains following ingredients: iron oxide black, potassium hydroxide, propylene glycol and shellac."

Table 1: size chart.

Size	Overall Capsule Lenght (in)	Average Mg Capacity	Volume Capacity
000	1.029	800 -1600 mg	1.37 ml
00E	0.996	600 - 1200 mg	0.90 ml
00	0.921	600 - 1100 mg	1.00 ml
0E	0.909	462 - 924 mg	0.78 ml
0	0.85	400 - 800 mg	0.68 ml
1	0.764	300 - 600 mg	0.48 ml
2	0.693	200 - 400 mg	0.36 ml
3	0.618	162 - 324 mg	0.27 ml
4	0.563	120 - 240 mg	0.20 ml

Related the size of capsules in pediatry

If In children more then 6/8 year it is possible to think the use of cps or cp , below this age it is necessary to pay attenyion to the size and the clinical condition of the patient for the possibility of obstruction of the airways. (Frongia et al).

Table 5 Proposed acceptable tablet/capsule parameters based on ages of paediatric populations. Strong evidence is coloured green; medium evidence is orange; weak evidence blue and no evidence is grey

Product attribute	Available evidence of acceptability			
	Neonates (<1 month)	Infants (1 month – 2 years)	Child (2–5 years)	Child (6–11 years)
Size	2 mm[23]	2 mm[17]	2 mm[14,17] 3 mm[18] 5 mm[16] 7 mm[21] 17.6 mm[20]a	3 mm[18] 7 mm[22] 9 mm[46] 12.1 × 4.2 mm
Shape	Not appropriate	Round[46]	Round[46]	Round/oblong/ caplet/oval[47]
Number of units per dose	Not appropriate	1[52] 3[47]	1[52] 3[47] 10 (minitablets in jelly; total volume < 5 ml)[15]	1–2[52] 3[47]
Taste and aftertaste of uncoated dosage forms	Not appropriate	Neutral[27]	Neutral[27]	Neutral[27]

[a]This size capsule was acceptable to children with cystic fibrosis who are used to taking monolithic dosage forms; there is no evidence on acceptability in other paediatric populations.

Fig. 17: From doi: 10.1111/jphp.12610.

BP capsules disintegration test

"For capsules with a gastro-resistant shell carry out the test for disintegration with the following modifications. Use 0.1 M hydrochloric acid as the liquid medium and operate the apparatus for 2 h, or other such time as may be authorised, without the discs. Examine the state of the capsules. The time of resistance to the acid medium varies according to the formulation of the capsules to be examined. It is typically 2 h to 3 h but even with authorised deviations it must not be less than 1 h. No capsule shows signs of disintegration or rupture permitting the escape of the contents. Replace the acid by phosphate buffer solution pH 6.8 R. When justified and authorised, a buffer solution of pH 6.8 with added pancreas powder (in example, 0.35 g of pancreas powder R per 100 ml of buffer solution) may be used. Add a disc to each tube. Operate the apparatus for 60 min. If the capsules fail to comply because of adherence to the discs, the results are invalid. Repeat the test on a further 6 capsules omitting the discs."

Quality control in the finished products magistral formula: cps and GR cps.

Procedure Following

Aspects, number os doses forma produced, mass uniformity (on a significative number of prepared cps: no more then +/- 10% difference vs medium cps mass, on filled cps).

Label check, final pakaging

(FU require for AR CPS the disgregation – dissolution test)

MATERIAL AND METHODS

With an observational point of view various relevant literature is reported for the aim of the work.

Figure reported help in showing material characteristics.

The same the characteristics of products like hard capsules or some excipient are analyzed.

It is reported the pharmacopeia requirement for GR cps and the quality control for the capsules prepared as magistral formula.

After analysis all this and after submitting an experimental project for local use a global conlusion is provided related the various methods avaiable for obtaining gastro resistance or enteric coating.

RESULTS

FORM LITERATURE

Beatrice Sabbatini et al

"The s 2 nd approach is represented by equipment based on the immersion coating procedure (such as the ProCoater® by Torpac, USA), which allows the coating of small batches of oblong tablets or capsules by dipping these dosage forms into the coating solution.[4]"

The time required is about 60 minutes

Cristina Maderuelo et al

"The main advantage of enteric coating EC is that it protects the drug from acidic pH and enzymatic degradation in the stomach while protecting it from the undesirable effects of some drugs.[5]"

Mosab Arafat et al

"Enteric coating EC films play a crucial role in pharmaceutical formulations as they are specifically designed to provide protection from premature releases of the drug molecule in acidic media. This protective function is particularly essential for drugs that are susceptible to degradation in acidic conditions, like as

erythromycin, ampicillin, and penicillin G antibiotics, as well as certain proton pump inhibitors class of drugs, including omeprazole, Pantoprazole , and esomeprazole. By forming a protective barrier, enteric coating films ensure the drugs reach their intended site of action intact.Enteric coating EC films also serve to prevent local irritation of the stomach mucosa caused by certain acidic drugs, including NSAIDs, like diclofenac and valproic acid. This feature is particularly important for enhancing patient tolerance and reducing potential side effects.[6]"

Peter Fentz Haastrup et al
"Low-dose acetylsalicylic acid is widely used as antithrombotic prophylaxis. Enteric-coated ASA has been developed to decrease the risk of gastrointestinal side effects. The consequences of enteric coating on pharmacokinetics and antiplatelet effect of ASA have not systematically been assessed. This Review demonstrates that data from clinical trials CT indicate that enteric coating can reduce the antiplatelet effect of ASA compared to plain ASA. This is possibly due to decreased bioavailability of ASA caused by prolonged solvation and absorption of the enteric-coated formulations. Therefore, low-dose enteric-coated ASA might not be bioequivalent to plain ASA, entailing the risk of insufficient cardiovascular prophylaxis.[7]"

Cristina Maderuelo et al
"The enteric coating EC prevents the delivery of a drug in the stomach but permits release of the drug in the small intestine. To achieve this, a polymer insoluble at acid pH but soluble at intestinal pH is used. When the drug reaches the upper small intestine, the coating dissolves allowing drug release DR.

The polymers commonly used to obtain enteric coatings are, among others, cellulose acetate phthalate, methacrylic acid copolymers and hydroxypropyl methylcellulose phthalate.

Technological procedures that can be used for these types of covers include film coating and sugar coating.[8]"

Anroop B Nair et al
"Esomeprazole core tablets were prepared and stabilized using Na bicarbonate as a stabilizer. A seal coat of 3% weight gain using opadry® was sufficient to protect the tablets from the acid coat of the enteric layer. Enteric coating EC was done using four different enteric coating materials (Eudragit L-30 D-55, hydroxy propyl methylcellulose phthalate, cellulose acetate phthalate.[9]"

Joao A. C. Barbosa et al
"Coating gelatin capsules is not a common industrial practice and a more common approach is to fill enteric coated granules or pellets into a conventional hard gelatin capsule.[10]"

Sarah J. Trenfield et al
"Medicines used to treat inflammatory bowel diseases IBD(budesonide) also use delayed-release coatings using polymers to enable targeted in specific regions in the GI tract.

Several studies have shown that enteric-coated products designed to release in the proximal small intestine SI do not disintegrate rapidly after emptying from the stomach.[11]"

Hannah K Batchelor,et al
"Draft EMA guidance proposed that, 'small tablets (3 to 5 mm diameter, width or length whichever is the longest) will not be considered acceptable for children below the age of 2 years, medium sized tablets tablets from 5 to 10 mm) for children below the age 6 years, large tablets (tablets from 10 to 15 mm) for children below the age of 12 years and very large tablets . tablets from 15 mm) for children below the age of 18 years' 11, This recommendation was removed from the updated guidance document . Studies that investigated the use of mini-tablets (tablets ≤3 mm) found that mini-tablets were a potential dosage form suitable for 2–6 year olds (based on placebo tablets 3 mm in diameter). Spomer and co-workers found that very young children (6–12 months) were fully capable of swallowing mini-tablets of 2 mm diameter, often accepting them in preference to sweet liquid formulations.

Standardized capsule sizes range from 11.1 mm (size 5) to 23.3 mm (size 00) in length. There are no data on acceptability of cps size in children although this should be considered to be equivalent to tablets. Capsules can be opened and the contents taken to improve acceptability in children. This should only be undertaken when justified. However, the capsule contents may taste unpleasant and the bioavailability of the opened capsule may differ from that of the intact product.[12]"

Thomas Dürig et al
"METIL CELLULOSE MC is listed in the USP/NF, pH.Eur., JP, and FCC. MC is used widely in oral solid pharmaceutical formulations as a binder, coating agent, and as a controlled release matrix.[13]"

E. Moussa et al
"Hydroxypropyl methylcellulose (HPMC) is a frequently used matrix former for controlled release tablets.[14]"

Stefan Almeling
"Hydroxypropylmethylcellulose (HPMC) is widely used as : tablet binder, film-coating, extended-release tablet matrix, capsule shell.[15]"

Polonini HC, et al.
"Paediatric patients are often unable to swallow PPIs in a solid dosage form (tablets or capsules) and critically ill patients frequently rely on enteral nutrition EN.

SyrSpend SF Alka is a starch-based powder that can be reconstituted to make a taste-masking oral liquid vehicle whose composition is detailed in table 1. It includes calcium carbonate to adjust the pH to >7 to prevent PPIs from degradation.[18],,

Table 1 SyrSpend SF Alka composition

Ingredient	Function	Safety references
Modified food starch	Suspending agent	FDA 21CFR 172.892[59]
Calcium carbonate	pH adjustment	FDA GRAS listed[60]
Sucralose	Sweetener	FDA, EC Scientific Committee on Food[61 62]

Fig. N. 18: From doi:10.1136/ejhpharm-2016-001034.

Justyna Srebro et al

"Other forms of drugs used for pediatric patients include capsules, orally disintegrating tablets, film-coated tablets, MUPS tablets, and granules for oral suspension OS . To simplify administration, the contents of capsules or a sachet containing enteric-coated granules can usually be sprinkled on soft food or, like ODT, suspended in water or fruit juice. An oral syringe can be used for easier administration of the drug in an aqueous dispersion. Enteric coated tablets ECT used in pediatrics usually have a small diameter and should not be crushed or chewed due to the protective layer.[19],,

Okwuosa, Tochukwu Chijioke et al

"The technology proved viable for incorporating different drug candidates; theophylline, budesonide and diclofenac sodium. XRPD indicated the presence of theophylline as crystals whilst budesonide and diclofenac remained in the amorphous form in the PVP matrix of the filaments and 3D printed tablets. Fabricated tablets demonstrated gastric resistant properties and a pH responsive drug release pattern in phosphate and bicarbonate buffers.

Despite its relatively limited resolution, FDM 3D printing proved to be a suitable platform for a single-process fabrication of delayed release tablets DRT.[22],,

Form Aleš Franc et al

"Vcaps® Enteric Capsules

The capsules were launched in 2015 . They consist of HPMC and HPMCAS, contain less than 6.0% water, and are not subject to cross-linking . The manufacturer, Capsugel®, declares that the capsules have been evaluated in vitro and in vivo with various substances, such as paracetamol, dimethyl fumarate, budesonide, or bisacodyl compliantly with USP, Ph. Eur., and JP requirements for delayed release.[23]

EXPERIMENTAL PROJECT HYPOTESYS

To be tested in the local galenic lab the respect of the pharmacopeia requirement for gastroresistence cps for the methods: disgregation assay : HCL 0, 1 N and then buffer phosfate PH 6,8.

1capsule into the capsule

2 dipping method with acetoftalate in aceton

Mandatory required 1 hour of resitence in acid environment and after 60 minutes all cps must to be disaggreated in buffer.

Instead if using metilcellulose 10% as eccipient in an acido resistence cps it is suggested to test the amount of free API avaiable after 60 minutes at PH gastric with specific quantitative analitical methods.

To be registered the global time required for this 3 procedure to evaluate cost / efficiency.

Fig. 19: Normal gelatine hard cps type 4 in HCL 0,1 N bath : after 15 minutes full dissolved.

Fig. N. 20: ACIDO RESISTENCE cps filled with eccipient based on 10% metilcellulose and with a fragment of gelatine head red(as control) : bath in HCL 0,1 N solution (after 1 hour).

DISCUSSION

In this work are reported the various strategies to protect API in cp and cps industrial production and also.

The characteristic of some excipient used.

Some specific formulation are also reported (omeprazole Gastro resistance cps, budesonide DR) to verify the excipient used.

Industrial producer can protect GASTRO SENSIBLE API in cps or using gastroresistence cps or filling the normal capsules with pellets gastroresistence or adding specific excipients.

The same for cp are in use also matrix methdos with API mixed with excipients (like metil cellulose and other) in order to get a controlled release (not rapid release).

For cps the acido resistence product can be made of HMPC.

Related the gastroresistence for cps in galenic lab. it is mandatory to evaluate the characteristics of the hard capluses needed (acido resistence or not) and the strategy used to obtain this properties: dipping methods (for enteric coating) or using specific excipient to delay the aggression of the gastric acid fluid.

Into the various method to get capsule gastroresistence it is to be evalaute also the use of ACIDORESISTENCE cps (with only 30 minutes of resitence with gastric fluids) mixing the API with a mix of meticellulose (10%) of adequate viscosity with cellulose microcristalline : in this way it is possible to delay the acid attack.

Metilcellulose is an excipient used also for cp delayed release as matrix for API.

Mandatory is to follow the pharmacopeia requirement: if used the methods capusle into the AR capsule and the dipping methdos this must follow the requirement for test of disintegration first in acid and the in buffered PH.

Instead if it is used the acido resistence caspsule filled with the API mixed with specific eccipient (10 % metolose at least) in order to verify the efficiency of the process it is suggested to test the free API amount present after the acid-buffered solution after the time required.

CONCLUSION

Related subminitration of gastroinactivable API are used by pharmaceutical industry various technology

From gastro resitance cps, to delayed release cp or cps (using matrix or gastroresistence pellets).

All this in order to avoid the acid environment and make possible disgregation into the intestine. (The common purpose of this).

It is clear that The acido resitance cps characteristic of the products in the market is not the gastro resitence concept required by the FU.

Acido resistence imply only 30 minute or resistance with gastric fluid instead the gastroresistence requirement for the Pharmacopeia need almost 60 ‘ of resistence.

It is clear that the method capsula into other capsula AR is the more easy method and more rapid in the current galenic practice, this method is officially reconized in italy as galenic technological operation allowed and to be reimbursed.

The same in TARIFFARIO NATIONAL italy the dipping method for gastroresitence is reported and so allowed.

But it is also to be considered also the formulation that use Metolose or similar eccipient to be added to API gastrosensible during the filling of acido resistance cps .(this make possible to reduce the aggression by the gastric secretion).

Metilcellulose of adequate viscosity is currently used as excipient for matrix in CP gastroresistence.

So based on what reported before In choosing the right procedure it must to be considered the easy to use methods, time , and costs and the global efficacy of the process.

All in order to follow the pharmacopeia requirement (Italian, PE, BP, USP) producing efficacy and safety drugs.

Crucial is to ask to the pediatry phisician to consider to shift from the cps as pharmaceutical form vs an oral suspension when possible because avaiable various eccipient basis ready for use in commerce also for gastro sensible products.

Of great interest the introduction in practice of th 3D printing systems for cp and CPS also for delay release. An innovative tool for personalized therapy.

Conflict of interest: No.

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