SOFT GELATIN CAPSULES-REVIEW

Cristina Bazbanela[1], Olimpia Dumitriu Buzia[1], Irinel Lungu[1]*, Monica Dinu[1]*, Dorin Ioan Cocoș[1]

1. Faculty of Medicine and Pharmacy, Centre in the Medical- Pharmaceutical Field, University "Dunarea de Jos" Galati, Romania
* Corresponding authors: email: Monica Dinu, e-mail: monica.dinu24@gmail.com
Irinel Lungu, e-mail: LUN_IRI@yahoo.com

#Aknowledgements: All authors had an equal contribution to this work

ABSTRACT

Our paper aims at a brief presentation of a drug coating material, namely soft gelatin capsules (CGS). Soft gelatin capsules can be used both in gastrointestinal administration and in enterosoluble administration. Gastro-resistant CGS can prove useful in the oral administration of drugs of an irritant or lable nature, also having an improved bioavailability in liquid form. The novelty of our study is the presentation of these gastro-resistant capsules as selected coatings by the applied technology of gelatin coating with copolymers of methyl methacrylic-acrylate acid (for example, Eudragit L or S ®). The challenge of this study is to identify physicochemical phenomena that can be used in the design and manufacture of modified-release gelatin films.

Keywords: capsule, gelatin, coating

1. INTRODUCTION

Gelatin capsules have been known since the middle of the 19th century, their importance increasing in recent decades. Gelatin capsules are currently considered particularly advantageous and are widely used especially for the manufacture of pharmaceutical preparations in industry.

The solid dosage form has retained its importance in the pharmaceutical industry due to its light production and handling and because it is the safest way to deliver the drug.

2. MATERIALS AND METHODS

The paper was used as study materials, and works indexed in scientific journals belonging to the PubMed, and FRX databases, and specialized works.

Capsules are one of the solid dosage forms that are available on the market in the form of soft and hard capsules. Soft capsules are dosage forms that are prepared as a single unit, and capsules are usually a double dosage form. Depending on the preparation material, soft capsules are classified as soft gelatin capsules and non-gelatin soft capsules. The composition of soft gelatin capsules is gelatin, plasticizers, water, preservatives, coloring agents, opacifiers, flavoring agents, and sweeteners [1,2]

Moreover, if the soft gelatin capsule is intended for intrinsic release, then the intrinsic coating could be an additional composer of the capsule. The decay time for these capsules is faster compared to the decay time of non-gelatin capsules [3.4]. Although the soft gelatin capsule covers most of the soft capsule market, soft, gelatin-free capsules also gain consumer interest. This is due to a variety of reasons, such as consumer choice [5], unchanged gelatin reaction with aldehydes [5,6], problems in intrinsic release and temperature sensitivity [2.6].

Gastro-resistant formulations are the most common type of modified drug release system.

2.1 Gastro-resistant forms of drug administration allow:

a) minimizes side effects such as nausea and bleeding associated with irritation of the gastric mucosa that may be caused by some active substances;
b) administration of the drug intended for local action in the intestines;
c) protects the degrading drug in an acidic stomach medium [7.9].

Gastro-resistant soft gelatin capsules can prove their usefulness in the oral administration of irritating or acid-label medicines, often having improved bioavailability in liquid form, which can be considered an advantage for film-coated tablets [8.9]. The most obvious examples of substances to be formulated in gastro-resistant dosage forms are non-steroidal anti-inflammatory drugs (NSAIDs), which are irritating to the gastric mucosa.

Products in the form of gastro-resistant capsules are usually designed as conventional coatings of hard capsules filled with enteric-coated pellets or mini-tablets. The manufacture of soft gastro-resistant capsules is, however, a challenge. Due to the filling with liquid, the change in the rate of release of the drug from the soft capsules can only be achieved by changing the capsule shell to make it resistant to acid pH. This issue can be addressed by covering standard capsules with acid-resistant polymers, such as methacrylic acid-methyl acrylate copolymers (for example, Eudragit L or S ®) [10].

A less popular alternative is to incorporate gastro-resistant polymers into the coating material used to form capsules [11]. Both approaches are technologically perplexing at some points, although changing the coating material may be considered more beneficial both economically and technologically. However, it is not yet used in commercial products. It is essential to take into account that any change in the composition of the film open mixture may lead to a significant change in the general physicochemical properties of the films prepared, which can lead to the loss of their potential to be formed in capsules in a conventional manufacturing process.

A very important issue associated with the development of a new capsule shell composition is the identification of physicochemical phenomena that can be used in the design and manufacture of modified-release gelatin films. Changes in the composition of the coating material were performed and their microstructure and barrier properties [12.13] were described. However, there are still some unexplained problems in describing the phenomena that lead to the formation of films, as well as the changes that films undergo when exposed to different conditions. Therefore, in the present paper, a more detailed investigation of the events associated with the formation of the gastro-resistant film was carried out, and, further, structural changes are made when immersing such films in the acid dissolution fluid. For a better characterization of films and film formation processes, several modern techniques can be used.[9]

3. SGC (SOFT GELATIN CAPSULES): ADVANTAGES AND DISADVANTAGES

GSCs offer several advantages compared to traditional solid oral dosage forms, and their popularity as a dosage form is growing for several reasons, including:
a) Consumer preference: GSC dosage forms have been developed to hide the unpleasant taste and smell of drugs. Compared to tablets, GSCs are more comfortable to swallow when used with water, as the soft gelatin capsule is self-lubricating [14,15].
b) SGCs seem more attractive and enjoyable for consumers, as they can be easily produced in various shapes, sizes, and colors, and different drug management systems, such as

chewable soft capsules and soft melt capsules [16,17].

3.1 Technical advantages:

GSCs have high accuracy and uniformity of dosing [14,15], **as** well as more consistent manufacturing requirements and product stability. It is possible to deliver an API with a higher degree of accuracy and greater consistency between different production batches due to the combination, more precise mixing, and distribution of liquid fillers.

GSC products tend to have greater stability, as the entire encapsulation process can be performed in inert conditions to protect drugs against oxidation and degradation. This is especially important for medicines that are subject to hydrolytic and oxidative degradation.

3.2 Safety aspects:

Sealed sealing of the gelatin coating protects the air and environmental contamination filler. The housing can be formulated to block ultraviolet light (UV), as well as visible light. The GSC formula also helps to avoid contamination by dust handling and increases the safety of the operator [15].

3.3 Advantages of bioavailability:

GSCs can increase the bioavailability of poorly soluble drugs by improving solubility and improving GIT absorption [18,19]. Water-insoluble drugs are formulated as GSCs using lipophilic vehicles as a portion of the filler material, significantly improving the absorption of these drugs in GIT [20].

Despite these advantages, GSCs are not a first-line form of oral dosage of choice for most pharmaceutical companies for the following reasons: GSC technology is believed to be relatively expensive to produce, and this can increase consumer prices. Many pharmaceutical companies do not have the specialized equipment needed to fill GSCs, and most rely on laboratories/contract manufacturers to supply them.

Unlike solid dosage forms, GSCs can also be affected by moisture and microbial contamination. This can cause problems with product stability if the medicines are not stored in sealed containers or a cool, dry place.

Depending on the nature of the medicine that is dissolved in the lipophilic vehicle, there is a chance that the medicine will migrate to the capsule shell. This migration can cause problems during absorption into the body, as the rate of release of the drug would be changed. SGCs are also not generally able to retain water-based liquids, as the medicine may spread out of the soft gelatin capsule [14.15].

Another problem with the use of soft gelatin medicinal products is that some groups have food restrictions that prevent them from consuming products of animal origin found in the GSC. Gelatin is mainly obtained from bones, skins, and other parts of animals, such as pigs and cows. Because capsule shells are made of animal parts, many vegetarians also choose not to use them. Due to this, there are developing technologies for replacement gelatin capsules without animals, made from seaweed extract or other sources, but they are generally more expensive and harder to find [21].

Gelatin is extremely soluble in water, which helps it dissolve in the body. The disadvantage of this property is that GSCs are sensitive to heat and humidity. In hot or humid climates, the capsules may stick or even open before consumers have a chance to use them [15,22].

Alkaline or acidic solutions are not good candidates for filling with soft gelatin, as they can cause hydrolysis and leakage of the gelatin coating unless their pH is adjusted to neutral [18].

4 PHYSICO-CHEMICAL INFLUENCES OF GELATIN PROPERTIES ON THE DISSOLUTION OF GSC MEDICINAL PRODUCTS

Gelatin is a natural product obtained by partial hydrolysis of collagen derived from leather, white and bone connective tissues of animals [23] and is a food ingredient generally recognized as safe (GRAS). The most abundant source of gelatin is pig skin [24]. Gelatin is classified according to its method of preparation. Gelatin derived from an acid pretreatment is known as type A, while gelatin derived from an alkaline pretreatment process is known as type B. There are no vegetable sources of gelatin; however, gelatin substitutes [21, 25] are available.

In pharmaceutical applications, it is important to understand how the physicochemical properties of gelatine can affect the rate of dissolution of the GSC. Gelatin that is used for pharmaceutical applications must meet the requirements set by official pharmacopoeias, such as the United States Pharmacopoeia (USP) and the European Pharmacopoeia (Ph. Eur).

Gelatin must be able to secure at a fast pace in strips of defined thickness and sufficient mechanical characteristics to tolerate all processes on the encapsulation machine. The strength and functionality of the gelatin are derived from its structure with a triple helix in an aqueous solution, the critical functional property being the ability to form a thermo-reversible gel. This triple helix structure is the foundation of the intrinsic strength of the capsule seal and coating.

Given these aspects, the technologically relevant gelatin parameters are gel / Bloom resistance, viscosity, solubility, melting point, socket point, particle size and molecular weight distribution.

5. THE VISCOSITY OF THE GEL

Viscosity is probably the second most important property of gelatin and depends on its degree, Bloom resistance, and molecular weight [26,27,28].

Its value generally increases as Bloom's power increases. For use in GSC, the gelatin solution should ideally have a viscosity of 2.8 to 4.5 mPas at 60 ° C, depending on the gelatin type [15].

Gelatin solutions used for encapsulating active pharmaceutical ingredients (API) must have sufficient viscosity stability, also known as viscosity retention, so that it can remain at the temperature of the ribbon casting during the stage. The thickness of the soft gelatin capsule is normally a function of the viscosity of the gelatin solution. Therefore, based on the explanation given in point 1 above, there is a significant relationship between the viscosity of the gelatin, the resistance of Bloom, and the rate of dissolution of the GSC.

6.POSSIBILITIES FOR DISTRIBUTION OF HEAVY MOLECULES

Gelatin has a molecular weight distribution between 10 and 400 kDa [29,30,31,32]. High proportions of low molecular weight gelatin shorten storage time and poor capsule sealing, while high proportions of high molecular weight gelatin cause greater viscosity and encapsulation problems. Available data showed that the higher the reticulation of gelatine, the higher the molecular weight, and this is inversely proportional to the dissolution rates of gelatine [33].

A molecular weight profile provides useful information about the functional performance of gelatin, such as encapsulation and dissolution [29,30,31,32].

7. FORMULATION OF THE COATING AND FILLING OF THE GSCS

When developing an SGC formulation, the possible interaction between the filler and the gelatin coating must be considered. These interactions may occur during production, drying, or the shelf life of the product. Interactions may include a chemical reaction between the fillers / and their oxidation or degradation products and coating or physical interaction, such as migration of filler into or through the coating and vice versa [34,35]. The magnitude of these interactions depends on many factors. These include the amount of each component in the coating and the filling formula. One of the most popular problems with the formulation of the coating is associated with API or excipients containing reactive functional groups, such as carbonyl, which can lead to crosslinking of gelatine [33,36,37].

The shell formulation for GSC usually consists of gelatin, plasticizer (i), water, and other minor additives, such as dyes, flavors, spacers, sweeteners and possibly sugar, preservatives, and, in rare cases, even active ingredients [38]. Water serves as a solvent to make a liquefied gelatin formulation with a castable viscosity at 60-70 ° C. To obtain protection for light-sensitive ingredients or a more attractive appearance for consumers, the coating may be formulated with pigments such as titanium dioxide and iron oxides [39,40].

8. CONCLUSIONS

Gelatin capsules in general and soft gelatin capsules in particular, are coatings used in pharmaceutical technology on a very large scale.

Gastro-resistant formulations are modified drug release systems, used in therapy due to their multiple advantages: they are commodes in administration, minimize side effects, and protect the active substances from the action of hydrochloric acid in the stomach.

The gelatin coating ensures a watertight sealing of the filler by the action of the air and the environment and can block ultraviolet light (UV), as well as visible light.

GSCs may increase the bioavailability of poorly soluble drugs; the physicochemical properties of gelatin may affect the rate of dissolution of the GSC.

Despite these advantages, GSCs are not yet a first-line form of oral dosage of choice for most pharmaceutical companies. The future can preserve their use more and more, as is demonstrated through research, their importance, and efficiency in technology.

References

1. Forme de dozare cu capsule Gullapalli RP, Mazzitelli CL gelatină și non-gelatină. *J.Pharm. Sci.* 2017; 106 :1453–1465. doi:10.1016/j.xphs.,2017.02.006. [PubMed] [CrossRef] [Google Scholar]

2. Joshi S, Sahu R, Dennis VA, Singh SR. Nanofiller-Enhanced Soft Non-Gelatin Alginate Capsules for Modified Drug Delivery. Pharmaceuticals (Basel). 2021 Apr 13;14(4):355. doi: 10.3390/ph14040355. PMID: 33924320; PMCID: PMC8069733

3. Prakash A., Soni H., Mishra A., Sarma P. Sunt capsulele tale vegetariene sau nevegetare: O justificare etică și științifică. *Indian J. Pharmacol.* 2017; 49 :401–404. doi: 10.4103/ijp.IJP_409_17. [Articol gratuit PMC] [PubMed] [CrossRef] [Google Scholar]

4. Podczeck F., Jones BE *Pharmaceutical Capsules.* a 2-a ed. Presă farmaceutică; Londra, Marea Britanie: 2004. pp. 1–272. [Google Scholar]
5. Khakalo A., Filpponen I., Johansson L.-S., Vishtal A., Lokanathan AR, Rojas OJ, Laine J. Utilizarea proteinei de gelatină pentru a facilita termoformabilitatea hârtiei. *Reacţiona. Funct. Polim.* 2014; 85 :175–184. doi: 10.1016/j.reactfunctpolym.2014.09.024. [CrossRef] [Google Scholar]
6. Liu WG, Yao KD, Wang GC, Li HX Investigație de fluorescență intrinsecă asupra modificării conformației gelului de gelatină reticulat în timpul tranziției fazei de volum. *Polimer.* 2000; 41 :7589–7592. doi:10.1016/S0032-3861(00)00015-X. [CrossRef] [Google Scholar]
7. Soni H., Patel VA Sistem gastro-retentiv de livrare a medicamentelor. *Int. J. Pharm. Sci. Rev. Res.* 2015; 31 :81–85. [Google Scholar]
8. Benameur H. Tehnologia de administrare a medicamentelor cu capsule enterice — Obținerea protecției fără acoperire. *Drug Dev. Livr.* 2015; 15 :34–37. [Google Scholar]
9. Maciejewski, B., Arumughan, V., Larsson, A., & Sznitowska, M. (2020). Prototype Gastro-Resistant Soft Gelatin Films and Capsules-Imaging and Performance In Vitro. *Materials (Basel, Switzerland), 13*(7), 1771. https://doi.org/10.3390/ma13071771
10. Felton LA, Haase MM, Shah NH, Zhang G., Infeld MH, Malick AW, Mcginity JW Proprietățile fizice și enterice ale capsulelor moi de gelatină acoperite cu Eutragit L30 D-55. *Int. J. Pharm.* 1995; 113 :17–24. doi: 10.1016/0378-5173(94)00169-6. [CrossRef] [Google Scholar]
11. Hassan EM, Fatmi AA, Chidambaram N. Compoziție enterică pentru fabricarea peretelui capsulelor moi. 8.685.445. *Patent SUA.* 1 apr 2014;
12. Maciejewski B., Ström A., Larsson A., Sznitowska M. Filme moi de gelatină modificate cu dispersie de pseudolatex de ftalat de acetat de celuloză — structură și permeabilitate. *Polimeri (Basel)* 2018; 10 :981. doi: 10.3390/polym10090981. [Articol gratuit PMC] [PubMed] [CrossRef] [Google Scholar]
13. Maciejewski B., Sznitowska M. Filme de gelatină modificate cu polimeri acizi și polielectroliți - selecția materialului pentru capsule moi gastrorezistente. *Polimeri (Basel)* 2019; 11 :338. doi: 10.3390/polym11020338. [Articol gratuit PMC] [PubMed] [CrossRef] [Google Scholar]
14. Augsburger LL capsule tari și moi. În: Banker GS, Rhodes CT, editori. *Farmaceutică modernă.* Marcel Dekker, Inc.; New York, NY, SUA: 2002. pp. 512–575. [Google Scholar]
15. Reich G. Formularea și proprietățile fizice ale capsulelor moi. În: Podczeck F., Jones BE, editori. *Capsule farmaceutice.* Presă farmaceutică; Londra, Marea Britanie: 2004. pp. 201–212. [Google Scholar]
16. Hassan EM, Kindt WW, Gordon R. *Chewable Soft Capsule.* Patheon Softgels Inc.; High Point, NC, SUA: 2012. [Google Scholar]
17. Schwab E. *Capsule moi umplute cu topitură la cald.* Swiss Caps Rechte und Lizenzen AG; Kirchberg, Elveția: 2010. p. 15. [Google Scholar
18. Bekerman T., Golenser J., Domb A. Cyclosporin nanoparticule lipospheres pentru administrare orală. *J. Pharm. Sci.* 2004; 93 :1264–1270. doi: 10.1002/jps.20057. [PubMed] [CrossRef] [Google Scholar]
19. Lissy M., Scallion R., Stiff DD, Moore K. Comparația farmacocinetică a unei capsule de gelatină moale umplută cu lichid de diclofenac de potasiu cu o tabletă de diclofenac de potasiu. *Opinia expertului. Pharmacother.* 2010; 11 :701–708. doi: 10.1517/14656561003614773. [PubMed] [CrossRef] [Google Scholar]
20. Bende G., Biswal S., Bhad P., Chen Y., Salunke A., Winter S., Wagner R., Sunkara G. Biodisponibilitatea relativă a diclofenacului de potasiu din capsulă softgel versus pUlbere pentru soluție orală și cu eliberare imediată formularea tabletei. *Clin. Farmacia. Drug Dev.* 2016; 5 :76–82. doi: 10.1002/cpdd.215. [PubMed] [CrossRef] [Google Scholar]

21. Fonkwe LG, Archibald DA, Gennadios A. *Non-Gelatin Capsule Shell Formulation în Greensboro, NC.* Patheon Softgels Inc.; High Point, NC, SUA: 2005. [Google Scholar]
22. Jones BE, Podczeck F., Lukas P. Fabricarea învelișului capsulei. În: Augsburger LL, Hoag SW, editori. *Forme de dozare farmaceutică: capsule.* Taylor & Francis Group; Londra, Marea Britanie: 2018. pp. 75–110. [Google Scholar]
23. Duconseille A., Astruc T., Quintana N., Meersman F., Sante-Lhoutellier V. Structura și compoziția gelatinelor legate de dizolvarea capsulelor dure: o revizuire. *Hydrocoll alimentar.* 2015; 43 :360–376. doi: 10.1016/j.foodhyd.2014.06.006. [CrossRef] [Google Scholar]
24. Lin L., Regenstein JM, Lv S., Lu J., Jiang S. O prezentare generală a gelatinei derivate din animale acvatice: Proprietăți și modificare. *Trends Food Sci. Tehnol.* 2017; 68 :102–112. doi: 10.1016/j.tifs.2017.08.012. [CrossRef] [Google Scholar]
25. Stegemann S. Capsule fără gelatină. În: Augsburger L., Hoag S., editori. *Forme de dozare farmaceutică: capsule.* CRC Press; Boca Raton, FL, SUA: 2017. pp. 110–130. [Google Scholar]
26. Qiao C., Chen G., Li Y., Li T. Proprietățile de vâscozitate ale gelatinei în soluții de săruri monovalente și bivalente. *Coreea-Aust. Rheol. J.* 2013; 25 :227–231. doi: 10.1007/s13367-013-0023-8. [CrossRef] [Google Scholar]
27. Davis CE, Oakes ET, Browne HH Viscozitatea soluțiilor de gelatină. *J. Am. Chim. Soc.* 1921; 43 :1526–1538. doi: 10.1021/ja01440a013. [CrossRef] [Google Scholar]
28. Horský J., Švantner J. Renaturarea gelatinei și vâscozitatea soluțiilor de gelatină diluată. *Polim. Int.* 1993; 32 :159–164. doi: 10.1002/pi.4990320208. [CrossRef] [Google Scholar]
29. Cho SM, Gu YS, Kim SB Optimizarea extracției și proprietățile fizice ale gelatinei de piele de ton galben (Thunnus albacares) comparativ cu gelatinele de mamifere. *Hydrocoll alimentar.* 2005; 19 :221–229. doi: 10.1016/j.foodhyd.2004.05.005. [CrossRef] [Google Scholar]
30. Lim YP, Mohammad AW Proprietățile fizico-chimice ale melatinei de mamifere în raport cu cerințele procesului membranar. *Tehnologia bioproceselor alimentare.* 2009; 4 :304–311. doi: 10.1007/s11947-009-0285-9. [CrossRef] [Google Scholar]
31. Ninan G., Joseph J., Abubacker Z. Proprietățile fizice, mecanice și de barieră ale filmelor de gelatină a pielii de crap și mamifer. *J. Food Sci.* 2010; 75 :E620–E626. doi: 10.1111/j.1750-3841.2010.01851.x. [PubMed] [CrossRef] [Google Scholar]
32. Ninan G., Joseph J., Aliyamveettil Z. Un studiu comparativ asupra proprietăților fizice, chimice și funcționale ale pielii de crap și gelatinelor de mamifere. *J. Food Sci. Tehnol.* 2014; 51 :2085–2091. doi: 10.1007/s13197-012-0681-4. [Articol gratuit PMC] [PubMed] [CrossRef] [Google Scholar]
33. Digenis GA, Gold TB, Shah VP Legătura încrucișată a capsulelor de gelatină și relevanța acesteia pentru performanța lor in vitro-in vivo. *J. Pharm. Sci.* 1994; 83 :915–921. doi: 10.1002/jps.2600830702. [PubMed] [CrossRef] [Google Scholar
34. Armstrong NA, James KC, Pugh WK Migrarea medicamentelor în învelișurile capsulelor moi de gelatină și efectul acesteia asupra disponibilității in vitro. *J. Pharm. Pharmacol.* 1984; 36 :361–365. doi: 10.1111/j.2042-7158.1984.tb04399.x. [PubMed] [CrossRef] [Google Scholar]
35. Serajuddin AT, Sheen PC, Augustine MA Migrarea apei din învelișul capsulei de gelatină moale la materialul de umplutură și efectul acesteia asupra solubilității medicamentului. *J. Pharm. Sci.* 1986; 75 :62–64. doi: 10.1002/jps.2600750114. [PubMed] [CrossRef] [Google Scholar]
36. Eldridge JE, Ferry JD Studii ale procesului de reticulare în geluri de gelatină. III. Dependența punctului de topire de concentrație și greutate moleculară. *J. Fiz. Chim.* 1954; 58 :992–995. doi: 10.1021/j150521a013. [CrossRef] [Google Scholar]
37. Meyer MC, Straughn AB, Mhatre RM, Hussain A., Shah VP, Bottom CB, Cole ET, Lesko LL, Mallinowski H., Williams RL Efectul reticulării gelatinei asupra bioechivalenței capsulelor de

acetaminofen gelatină tare și moi . *Farmacia. Res.* 2000; 17 :962–966. doi: 10.1023/A:1007579221726. [PubMed] [CrossRef] [Google Scholar

38. Gullapalli R. Capsule gelatinoase moi (Softgels) *J. Pharm. Sci.* 2010; 99 :4107–4148. doi: 10.1002/jps.22151. [PubMed] [CrossRef] [Google Scholar]
39. Poppe J. Gelatina. În: Imeson A., editor. *Agenți de îngroșare și gelificare pentru alimente*. Springer; Boston, MA, SUA: 1997. pp. 144–168. [Google Scholar]
40. Damian, F., Harati, M., Schwartzenhauer, J., Van Cauwenberghe, O., & Wettig, S. D. (2021). Challenges of Dissolution Methods Development for Soft Gelatin Capsules.Pharmaceutics,13(2),214.Https://doi.org/103390/pharmaceutics13020214