Acta Scientiarum

http://www.uem.br/acta
ISSN printed: 1679-9291
ISSN on-line: 1807-8648
Doi: 10.4025/actascihealthsci.v35i2.14581

The importance of coating standardization in gastro-resistant capsules produced in magistral pharmacy

Suelen Cristina Franco[1], Flávia Cristina da Silva[1], Marcela Maria Baracat[1], Rúbia Casagrande[1], Janice Aparecida Rafael[2] and Daniela Cristina de Medeiros[1*]

*[1]Centro de Ciências da Saúde, Universidade Estadual de Londrina, Rod. Celso Garcia Cid, PR-445, Km 380, Cx. Postal 6001, 86051-980, Londrina, Paraná, Brazil. [2]Faculdade de Ensino Superior Dom Bosco, Cornélio Procópio, Paraná, Brazil. *Author for correspondence. E-mail: danielamedeiros@hotmail.com*

ABSTRACT. Gastro-resistant capsules are often used for several purposes, such as protection of unstable drugs in acid medium to the action of gastric fluids or protection of the gastric mucosa to irritants drugs. The aim of this study was to verify the variation of preparations of capsules coating with cellulose acetate phthalate and methacrylic acid copolymer, without drug addition, in 7-10% coating concentrations, prepared manually with four or five immersions in tested coating solution. Results were analyzed considering the formulation's disintegration test. Within the context of formulations under analysis, it was observed that the capsules coated with cellulose acetate phthalate 10% complied with the pharmacopeia's disintegration specifications. However, capsules coated with methacrylic acid copolymer did not show accordance with the pharmacopeia's specifications. The results emphasize the need for the standardization of coating methodology.

Keywords: methacrylic acid copolymer, cellulose acetate phthalate, enteric coating, capsules.

Importância da padronização dos revestimentos utilizados em cápsulas gastrorresistentes produzidas em farmácia magistral

RESUMO. Cápsulas gastrorresistentes são frequentemente utilizadas com diversos propósitos, como a proteção de fármacos instáveis em meio ácido à ação dos fluidos gástricos ou proteção da mucosa gástrica à fármacos irritantes. O objetivo deste trabalho foi verificar a variação da preparação de revestimento de cápsulas com acetoftalato de celulose e copolímero do ácido metacrílico, sem adição de fármaco, em concentrações que variam de 7 a 10% de revestimento, preparadas manualmente com quatro a cinco camadas da solução dos revestimentos testados. Os resultados foram analisados considerando o teste de desintegração das formulações. Das formulações testadas, foi observado que as cápsulas revestidas com acetoftalato de celulose a 10% cumpriram com as especificações farmacopeicas quanto à desintegração. No entanto, cápsulas revestidas com copolímero de ácido metacrílico não mostraram conformidade com as especificações farmacopeicas. Os resultados obtidos enfatizam a necessidade de padronização da metodologia de revestimento.

Palavras-chave: copolímero do ácido metacrílico, acetofatalato de celulose, revestimento entérico, cápsulas.

Introduction

The production of hard gelatin capsules is on the increase. In fact, the above pharmaceutical mode is highly accepted and, similar to tablets, it is currently the most common mode of oral drug administration (MARTINS; OLIVEIRA, 2003; PINA et al., 1996, 1997).

Gastrointestinal resistant-capsules are frequently employed to protect unstable drugs against gastric fluids in an acid medium. They are also used in drugs that cause nausea or vomit, or in drugs that irritate the gastric mucous when released in the stomach. They may also be used in drugs that should only produce their greatest effect in the duodenum or the jejunum and when it is necessary that the active substances are available after a certain period (FERREIRA, 2002).

The release speed of the hard gelatin capsule should be modified so that the drugs could be encapsulated. This may occur through the disintegration of the capsule and the dissolution of the drug in neutral and/or base pH (rates may be found in the enteric medium) which may be obtained by applying a gastro-resistant coating. Since the literature provides few studies on coating application in such pharmaceutical forms, the development of methods for the coating of hard gelatin capsules is a promising research field (MARTINS; OLIVEIRA, 2003).

Pharmaceutical film-coating technology is foregrounded on polymers in solution or dispersed in an aqueous medium or in organic solvents. During the last years several varieties of film-forming polymers have been evaluated and employed for the coating of solid oral capsules (BUNHAK et al., 2007). Although

manufacturing procedures in coating technology have been highly improved in the pharmaceutical industry due to automated apparatuses, there is a lack of standardization in the above-mentioned technology within the context of magistral pharmacies.

Cellulose acetate phthalate is a polymer used in the manufacturing of an enteric coating film or as agglutinant for tablets and capsules in which approximately one half of the hydroxyl groups is acetylated and approximately one fourth is esterified by one of the two acid groups (PODCZECK; JONES, 2004; ROWE et al., 2003). According to the USP (2005), a polymer is the product of the partial reaction of phthalic anhydride and cellulose ester acetate with 21.5 – 26% of acetyl groups (C_2H_3O) and 30 - 36% of phthalic ones ($C_8H_5O_3$). It was the first polymer produced with soluble characteristics that favored its use in the enteric coating solutions of capsules (PODCZECK; JONES, 2004). The USP (2008) describes polymethacrylates, copolymers of methacrylic acid, as cation and anion synthetic polymers of dimethylaminoetylmethacrylates, methacrylic acid and methacrylic acid esters in several proportions. Different polymethacrylic types are available commercially for several applications in pharmaceutical formulations.

The present study investigated the variation in the preparation of cellulose acetate phthalate and methacrylic acid copolymer coating (Rheapol L 100®), without drug addition, in a magistral pharmacy: standardized the pharmacotechnical procedures to coat hard gelatin capsules and evaluated the efficiency of such coating through disintegration tests.

Material and methods

Material and coating preparation

Samples of coated capsules, codified by letters, were donated by a magistral pharmacy (Table 1).

Coating compositions comprised 8% (p/v) cellulose acetate phthalate, 1.5% (p/v) castor oil, 3% (p/v) propylenoglycol, 45% acetone and alcohol 96 GL to complete 100 mL (Formulation A/8). Concentrations with 9 and 10% (p/v) of cellulose acetate phthalate were also employed (Formulations A/9 and A/10).

Hard gelatin capsules, size 0, with inert matter, were also used for coating.

Acetate phthalate was solved in acetone and propylenoglycol, castor oil and ethyl alcohol were subsequently added. Capsules were given four coating applications with cellulose acetate phthalate solution 8% (p/v)(A/8/4) and 4 and 5 applications with solutions 9 (A/9/4 and A/9/5) and 10% (p/v) (A/10/4 and A/10/5), respectively.

The second coating type tested comprised Rheapol L 100® 7% (p/v) and was composed by 1.9% carbowax 400, acetone/alcohol 96 GL (50:50-v:v) in sufficient amount to complete 100 mL. Methacrylic acid copolymer was dissolved in 90 mL of the acetone/alcohol mixture. Carbowax 400 was added and final volume was adjusted to 100 mL. Capsules were immersed four times in the coating solution and dried, obtaining Formulation B/7/4. Rheapol L 100® was also tested at concentration 9% (p/v) with four or five applications to capsules, obtaining Formulations B/9/4 and B/9/5, respectively.

There was a 30 min.-interval between applications and room temperature was used for drying on a plane surface.

Coating preparation was made by manual shaking at room temperature.

Table 1. Procedures and descriptions of pharmaceutical formed used.

Formulation	Coating material	Procedure
A/8/4	cellulose acetate phthalate	8% coating with 4 layers
A/9/4	cellulose acetate phthalate	9% coating with 4 layers
A/9/5	cellulose acetate phthalate	9% coating with 5 layers
A/10/4	cellulose acetate phthalate	10% coating with 4 layers
A/10/5	cellulose acetate phthalate	10% coating with 5 layers
B/7/4	Rheapol L 100® Copolymere	7% coating with 4 layers
B/9/4	Rheapol L 100® Copolymere	9% coating with 4 layers
B/9/5	Rheapol L 100® Copolymere	9% coating with 5 layers

Experimental methods

Mean weight of content

Weight of capsules followed criteria established by the Brazilian Pharmacopeia (BRASIL, 2010) for hard capsules. Twenty units were separated and weighed; contents were removed; they were adequately cleansed and weighed again. Content weight was the difference between the full and empty capsule. Allowed variation was ± 10% (mean weight less than 300 mg) when compared to mean weight. No more than two units which did not comply with specific limits may be tolerated. However, no unit could be double the percentages indicated either for more or for less.

Gastro-resistance assays

Disintegration assays verified the gastro-resistance characteristics of the coated products. Six capsules were placed in chlorohydric acid 0.1 mol L^{-1} and maintained at 37°C ± 1°C. After 60 minute in the acid medium, the capsules were immersed in a phosphate solution pH 6.8 ± 0.1 and maintained at 37°C ± 1°C till total disintegration. In current assay disintegration was complete when no residue remained, except fragments of insoluble coating or matrix. Gastro-resistant capsules were those that remained intact, without any cracks or mollification during the 60 min.-period they were exposed to the simulated gastric fluid and failed to disintegrate in the simulated intestinal fluid up to 45 min. Results were undertaken in triplicates following

the disintegration test prescribed in the Brazilian Pharmacopeia (BRASIL, 2010).

Results and discussion

Prior to coating application, capsules were characterized by mean content weight. Table 2 shows the rates of mean weight and its lower and higher limits. According to the Brazilian Pharmacopeia (BRASIL, 2010), acceptable variation of capsule content with less than 300 mg was ± 10%. All tested capsules were within the specified limits.

The disintegration assay verified whether tablets and capsules disintegrated within specified time when six units were exposed to specific apparatus in the experimental conditions described above (BRASIL, 2010). According to the Brazilian Pharmacopeia (BRASIL, 2010), complete disintegration occurred when no capsule residue remained in the metallic sieve of the disintegration apparatus, except fragments of insoluble capsules. Units were disintegrated when they were transformed into a pasty mass during the test and remained on the apparatus's sieve.

All capsules disintegrated in Formulation A/8/4 during their exposure to chlorohydric acid in the test done in triplicate.

Capsules in Formulation A/9/4 showed disintegration signs when exposed to chlorohydric acid, although all capsules of the same formulation disintegrated in the enteric medium.

Regarding formulation A/9/5, one capsule showed signs of disintegration when exposed to chlorohydric acid, whereas all capsules of the same formulation disintegrated in the enteric medium.

The capsules of Formulations A/10/4 and A/10/5 complied with the specific requirements of the Brazilian Pharmacopeia (BRASIL, 2010) since no signs of disintegration in the acid medium occurred and all capsules disintegrated in the buffer medium at pH 6.8. On the other hand, of the three samples (B/7/4; B/9/4; B/9/5) capsules coated with Rheapol L 100®, at least one not resist in the acid stage, but totally disintegrated in the buffer stage in less than 45 min when test was undertaken in triplicate.

Capsules of Formulation A (coated with cellulose acetate phthalate) were more gastro-resistant than those in Formulation B (methacrylic acid copolymer), especially those of stocks A/10/4 and A/10/5, that complied with the requirements of disintegration tests.

Data suggest that only cellulose acetate phthalate among the gastro-resistant agents employed by the magistral pharmacy was enterically adequate for capsule coating.

The process of obtaining extemporarily enteric capsules adequate has many variables conditioned to technique and to handling which may impact the performance of other stocks.

It is thus recommendable that each formulation or batch to gastrointestinal resistant-capsules obtained extemporarily in a magistral pharmacy should undergo a disintegration and/or dissolution test to evaluate its performance and to verify whether the criteria of pharmacopeia acceptance are attended to (ROCIO et al., 2012).

Several polymeric compounds are used in the enteric coating of pharmaceutical product. The compounds should be resistant to the pH of the stomach acid and sensitive to that of the intestine tract, which will guarantee the disintegration of the polymer followed by dissolution of the drug in the pharmaceutical form.

Table 2. Average weight of capsules (g).

Capsules	A/8/4	A/9/4	A/9/5	A/10/4	A/10/5	B/7/4	B/9/4	B/9/5
1	0.2261	0.2124	0.2043	0.2050	0.2109	0.2234	0.2043	0.2067
2	0.2174	0.2137	0.2238	0.2121	0.2166	0.1992	0.2056	0.2159
3	0.2011	0.2262	0.2066	0.1998	0.2287	0.2225	0.2229	0.2302
4	0.2286	0.2322	0.2199	0.2201	0.2263	0.2181	0.2049	0.1989
5	0.2092	0.2122	0.2289	0.1996	0.2255	0.2023	0.2198	0.2234
6	0.2155	0.1963	0.2249	0.2344	0.2078	0.1983	0.1987	0.2122
7	0.2060	0.2133	0.2112	0.2018	0.2245	0.2288	0.2011	0.2049
8	0.2235	0.2138	0.2166	0.2226	0.2187	0.2094	0.2163	0.1998
9	0.2031	0.2234	0.2069	0.2334	0.2166	0.2074	0.2169	0.2266
10	0.2087	0.2256	0.2123	0.2311	0.2069	0.2150	0.2045	0.2011
11	0.2040	0.2181	0.2145	0.2104	0.2169	0.2143	0.2283	0.2144
12	0.2226	0.2311	0.1988	0.2066	0.2312	0.1967	0.1998	0.2079
13	0.2045	0.2012	0.2154	0.2257	0.1967	0.2251	0.2269	0.2098
14	0.2157	0.2088	0.2192	0.2121	0.2255	0.1933	0.2154	0.2215
15	0.2011	0.2177	0.2263	0.2223	0.2135	0.2333	0.2067	0.2061
16	0.2211	0.1993	0.2311	0.2278	0.2089	0.1976	0.1958	0.2133
17	0.2184	0.2161	0.2144	0.2254	0.1997	0.2304	0.2288	0.1939
18	0.2118	0.2083	0.1981	0.2158	0.2234	0.2336	0.2089	0.2018
19	0.2015	0.2051	0.2183	0.2167	0.2039	0.2334	0.2081	0.2129
20	0.2245	0.2193	0.2123	0.2049	0.2128	0.2120	0.2303	0.2156
Mean	0.2132	0.2147	0.2152	0.2164	0.2157	0.2147	0.2122	0.2108
Lower limit	0.1919	0.1932	0.1937	0.1948	0.1941	0.1932	0.1910	0.1897
Higher limit	0.2345	0.2362	0.2367	0.2380	0.2373	0.2362	0.2334	0.2319

The compounds should be resistant to the pH of the stomach acid and sensitive to that of the intestine tract, which will guarantee the disintegration of the polymer will guarantee the disintegration of the polymer followed by dissolution of the drug in the pharmaceutical form.Studies by Rowe et al. (2003) showed that filmogenic polymers used in enteric coating of capsules were cellulose acetate phthalate and methacrylic acid copolymer which were only soluble in intestine fluids as from pH 6.0.

In the experiments by Prista et al. (1995) with solutions composed of 8 parts cellulose acetate phthalate, 4 parts ethyl phthalate and 88 parts acetone, capsules were immersed four times in the solution and hot air-dried between applications of each two successive layers. Results showed that cellulose acetate phthalate coating is adequate to obtain gastro-resistant and entero-soluble hard gelatin capsules.

Disintegration test applied to hard gelatin capsules with gastro-resistant contents performed by Marques-Marinho et al. (2009) showed that only capsules coated with A-type methacrylic acid copolymer complied with the requirements of disintegration tests. However, stocks of cellulose acetate phthalate coated capsules were not gastro-resistant.

Conclusion

Current research shows that magistral pharmacies need comply with rules in the manufacture of gastro-resistant capsules. The latter should be protected up to the time they reach the activity site and thus their therapeutic efficiency may be guaranteed. When pharmacists make available a drug, they should be absolutely sure that they are complying with quality rules; otherwise, they should not dispense the drugs.

The present study suggested standardization of gastro-resistant capsules with two types of coating, however, of the eight stocks tested, only the formulations A/10/4 and A/10/5 are a delayed release system. Results show that the preparation of capsules by alternative processes produced a 75% gastro-resistant failure of the produced stocks.

Acknowledgements

We would like to thank the magistral pharmacy which took part in current project.

References

BUNHAK, E. J.; MENDES, E. S.; PEREIRA, N. C.; CAVALCANTI, O. A. Influência do sulfato de condroitina na formação de filmes isolados de polimetacrilato: avaliação do índice de intumescimento e permeabilidade ao vapor d'água. **Química Nova**, v. 30, n. 2, p. 312-317, 2007.

BRASIL. Agência Nacional de Vigilância Sanitária. **Farmacopéia brasileira**. 5. ed. Brasília: Anvisa, 2010. v. 1

FERREIRA, A. O. Revestimento gastro-resistente. In: FERREIRA, A. O. (Ed.). **Guia prático da farmácia magistral**. Juiz de Fora: Pharmabooks, 2002. p. 135-142.

MARQUES-MARINHO, F. D.; VIANNA-SOARES, C. D.; CARMO, V. A. S.; CAMPOS, L. M. M. Avaliação da qualidade de pantoprazol cápsulas manipuladas gastro-resistentes. **Latin American Journal of Pharmacy**, v. 28, n. 6, p. 899-906, 2009.

MARTINS, G. Z.; OLIVEIRA, W. P. Utilização do leito de jorro para aplicação de revestimento entérico em cápsulas gelatinosas duras. **Revista Brasileira de Ciências Farmacêuticas**, v. 39, n. 3, p. 299-307, 2003.

PINA, M. E; SOUSA, A. T.; BROJO, A. P. Coating of hard gelatin capsules. 1. Application of hydroalcoholic solutions of formaldehyde in preparation of gastro-resistant capsules. **International Journal of Pharmaceutics**, v. 133, n. 1/2, p. 139-148, 1996.

PINA, M. E; SOUSA, A. T.; BROJO, A. P. Enteric coating of hard gelatin capsules. 2. Lioavailability of formaldehyde treated capsules. **International Journal of Pharmaceutics**, v. 148, n. 1, p. 73-84, 1997.

PODCZECK, F; JONES, B. E. **Pharmaceutical capsules**. 2nd ed. London: Pharmaceutical Press, 2004.

PRISTA, L. N.; ALVES, A. C.; MORGADO, R. M. R. **Tecnologia farmacêutica e farmácia galênica**. 4. ed. Lisboa: Fundação Calouste Gulbekian, 1995.

ROCIO, K. H.; OLIVEIRA, B. A. M.; MOREIRA, M, L.; SILVA, T. D. Manipulação e validação de revestimento gastrorresistente de cápsulas contendo ácido acetilsalicílico. **Farmácia e Ciência**, v. 3, p. 46-54, 2012.

ROWE, R. C.; SHESKEY, P. P.; WELLER, P. J. **Handbook of pharmaceutical excipients**. 4th ed. London: Pharmaceutical Press, 2003.

USP-United States Pharmacopoeia. **US Pharmacopeial Convention**. 28th ed. Rockville: The United States Convention, 2005.

USP-United States Pharmacopoeia. **US Pharmacopeial Convention**. 31th ed. Rockville: The United State Convention, 2008.

Received on September 24, 2011.
Accepted on April 3, 2012.