

## METHODS TO ANALYZE MUCOADHESION OF GRANULES AND THEIR DEGREES OF ADHERENCE BY THE SCIENTIFIC COMMUNITY

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### Introduction

Through the development of modified-release pharmaceutical formulations, it was possible to decrease the frequency of dosage and adverse effects on the treatment of conditions that require constant control [1], such as heart disease, diabetes, and psychological conditions. More recently, mucoadhesive modified-release formulations are being developed.

There is still no official pharmacopoeial method for the analysis of mucoadhesion, but those described in the literature are divided into two groups: direct and indirect methods. Direct methods measure the force or time required to displace the pharmaceutical form of the mucosa, while indirect methods determine the interaction between the formulation and the mucins (mucosal glycoproteins) or through interaction with a polypropylene plate [2, 3]. However, in this work, the methods were categorized into three groups: *in vivo*, *ex vivo*, and *in vitro*. Any method that uses biological tissue from animals previously slaughtered was classified as an *ex vivo* analysis.

To assist in the decision-making regarding the selection of which type of method to use, this study aims to characterize the general profile of the literature indexed by the Web of Science core collection through basic bibliometric techniques, to determine which types of methods are more commonly adopted by the scientific community to evaluate mucoadhesive granules. It is worth mentioning that the same method can often be used for more than one specific type of solid pharmaceutical formulation.

### Method

The research was carried out on July 18<sup>th</sup>, 2020 on the core collection of the Web of Science platform. The string used in the advanced search was: "*TS = (mucoadhesi\* AND beads OR mucoadhesi\* AND granules)*". The term microsphere was accepted as a granule synonym.

Zotero (version 5.0.86) was used to export metadata from the Web of Science to perform an advanced search to separate articles that contained the words related to mucoadhesiveness in the title and/or in the abstract. These articles were chosen for individual evaluation. Exclusion criteria included: (i) studies that were not found complete; (ii) secondary studies; (iii) studies that mentioned the searched terms but did not perform mucoadhesion tests; (iv) studies citing other types of pharmaceutical formulations.

### Results / Discussion

According to the Web of Science's core collection, there are few published studies between 1990 and 2009. Most works were published in the last decade. Moreover, most publications on the topic were from India (116 of 267), with an overwhelming difference of approximately +84% compared to the United States (18), which appears shortly thereafter. Of the 267 articles, Zotero signaled 186 through its advanced search. These were individually evaluated, resulting in 85 (45%) selected studies.

Ninety-five percent of all the selected studies (81) used animal tissues in their mucoadhesion tests, either in *in vivo* and/or *ex vivo* analysis. Among these studies, 9 (10%) also used an *in vitro* method. Twenty-nine percent of all the selected studies (25) included some type of *in vivo* analysis after the *in vitro* or *ex vivo* mucoadhesion analysis, not necessarily as just a follow-up mucoadhesion test, but also aiming to evaluate pharmacodynamics. The preference to use biological tissues in *ex vivo* and/or *in vivo* analysis occurs due to their greater reliability, since contemporary *in vitro* methods have inconsistent results, and therefore are not recommended as a standalone analysis [2, 4, 5].

The biological tissue was mostly obtained from goats (32 (42%)), followed by rats (26 (34%)) and pigs (10 (13%)), while sheep, chicken, bovine, and rabbits added up to 9 citations (12%). The choice is based on the animal's mucosa similarity with the human mucosa. However, since a good part of the biological tissues are obtained in local slaughterhouses, it can also be subject to the meat consumption profile of the country where the study is developed. In addition, the decision is also impacted by the administration route of the formulation. Most researchers used gut tissues (47 (59%)), followed by stomach tissue (20 (25%)), gastrointestinal tract tissue (8 (10%)), buccal tissue (3 (4%)), and chicken eggshell membrane (2 (3%)).

## Conclusion

The overwhelming majority of the evaluated articles used biological tissue to assess the mucoadhesiveness of granules, due to their greater reliability compared to *in vitro* methods. Goats were the animals predominantly used in these studies. This fact may be related to the origin of most of the evaluated studies, India, where it is probably easier to get goats' tissues locally, since Hinduism prohibits the consumption of beef and Islam bans consumption of pork. However, Brazilian researchers probably have more access to pigs' tissues from local slaughterhouses. Moreover, the most used type of mucosa was obtained from the gastrointestinal tract (94%), since it is the site of action of most of the evaluated granules.

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