

CHALLENGES IN DRUG DEVELOPMENT IN THE USE OF INCLUSION COMPLEX WITH CYCLODEXTRINS

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Introduction

Cyclodextrins are cyclic oligosaccharides composed of glucose units linked by α -1,4 bonds, obtained by the enzymatic degradation of starch through the microorganism *Bacillus macerans*, having as main characteristic the formation of inclusion complexes with drug in a total, partial way, or as non-inclusion complexes (FERREIRA et al., 2016; JACOB; NAIR, 2018). The use of inclusion complexes in cyclodextrins by pharmaceutical industries has as main objective to solve the problem of low solubility and bioavailability of several drugs that are available in the world market (CONCEIÇÃO et al., 2018). This study evaluated the market for the production of cyclodextrins for pharmaceutical use and the supply of medicines using this strategy in three countries, the USA, Portugal and Brazil.

Material and Methods

The electronic addresses of 16 cyclodextrin producers were consulted to obtain information about their industrial production. The research results revealed that the produced cyclodextrins of pharmaceutical interest are used as an inclusion complex with the drug, as an excipient and as an active ingredient.

A literature search was carried out for references that related which drugs are available in the pharmaceutical market using cyclodextrins. Based on this relationship, the database of 3 drug registration agencies was consulted in order to verify the current status of the information presented and gather more details about the preparations. The Food and Drugs Agency (FDA) of the United States of America was consulted (<https://www.accessdata.fda.gov>) accessed on: 06/09/2021, National Authority of Medicines and Health Products (Infarmed) from Portugal (<https://extranet.infarmed.pt>) accessed on 10/06/2021, and the National Health Surveillance Agency (ANVISA) from Brazil (<https://consultas.anvisa.gov.br/bulario>) acesso em 11/06/2021.

Results and Discussion

The search results revealed that the produced cyclodextrins of pharmaceutical interest are used as an inclusion complex with the drug, as an excipient and as an active ingredient. The cyclodextrins producers around the world are 16 companies located in the following countries: Japan, China, United States, Germany and Hungary. China comprises 50% of the manufacturers surveyed, and the US has the largest market for cyclodextrins. The cyclodextrins that the pharmaceutical industry produced for the inclusion complex with drugs are: α -CD, β -CD, γ -CD, DM- β -CD, HP- β -CD, SBE- β -CD, e HP- γ -CD, meeting the pharmacopoeial specifications, preferably the American, European and Japanese pharmacopoeias. Cyclodextrin industries also produce and market to pharmaceutical industries cyclodextrin conjugated polymers and pre-prepared inclusion complexes.

The bibliographic survey resulted in 14 literature reviews related to pharmaceutical products that employ cyclodextrins available in the world market from 1997 to 2020. The search for drug registration data using cyclodextrins available in the American, Portuguese and Brazilian markets. It was observed that the most used cyclodextrins for the inclusion complex with drugs are β -CD, HP- β -CD and SBE- β -CD.

The research showed that the Portuguese pharmaceutical market offers 20 medicines using cyclodextrins and the North American market has 23 medicines in this condition, while in Brazil this

technological strategy is applied in only 09 medicines. Only 07 drugs are available for sale in the three countries. The produced cyclodextrins of pharmaceutical interest are used as an inclusion complex with the drug, as an excipient and as an active ingredient. The intravenous (IV) dosage form is the most used in drug formulations containing cyclodextrins with 20 presentations. In intravenous preparations, cyclodextrins work with excipients

Brazil does not offer all the alternatives available on the world market. Several drugs whose dosage forms that contain cyclodextrins are available in the American and European markets, especially in Portugal, are not available in the Brazilian market, having only dosage forms that do not contain cyclodextrin.

There is an expectation of approval for the market in the 3 countries consulted, and for the world market, of new drugs of various pharmacological activities containing cyclodextrins that are in clinical development. Some cyclodextrin-containing vaccines for the treatment of SARS-CoV-2 are in clinical development. Also noteworthy are polymers based on cyclodextrins and antiviral drugs in cyclodextrin inclusion complex (BRAGA et al., 2021). HP- β -CD has been studied for the treatment of Alzheimer's and Niemann-Pick Type C diseases, a genetic disease that results in abnormal cell lipid metabolism, which can cause fatal neurological and hepatic manifestations (CYCLOTHERAPEUTICS, 2021). Research in Brazil is focused on the development of inclusion complexes with drug candidates with activity against neglected diseases, in addition to antimicrobials and antitumours.

Conclusion

The present study showed that there are great differences in the supply of medicines with cyclodextrin in the American, European and Brazilian market. Cyclodextrin is a well-accepted technological strategy for solving drug solubility and bioavailability problems.

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