SIMPOSIO AFI 62
RIMINI 7 • 8 • 9 GIUGNO 2023

Associazione Farmaceutici Industria
Società Scientifica

FORMULATION DEVELOPMENT OF AN ORALLY DISINTEGRATING FILM LOADED WITH CLADRIBINE AS AN ALTERNATIVE TO MAVENCLAD® TABLETS

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Introduction

Tablets are the most common oral solid dosage form due to the ease of administration, the high patient compliance, and the flexibility in formulation design. However, there are several limitation for people with difficulty swallowing. To overcome these constraints, orally disintegrating films (ODF) were developed as an innovative dosage form, aiming for a fast release of the drug, without water ingestion [1].

The active pharmaceutical ingredient of Mavenclad® tablets is cladribine, which is a purine antimetabolite used for the management of relapsing forms of Multiple Sclerosis (MS), in patients who have not responded to or who are unable to tolerate alternative MS drugs [2; 3].

Cladribine (CLA) is poorly soluble in water and unstable in acidic conditions, but these problems have been addressed by employing cyclodextrin (CD) as a complexation agent in the existing formulation [4]. However, the oral bioavailability of cladribine tablets is still around 40% [5]. Since some of the advantages of ODFs are the possibility to bypass the gastric system and to avoid hepatic first-pass metabolism [6], a cladribine ODF could represent a therapeutic improvement compared to tablets.

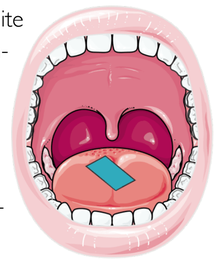

Figure 1: ODF administration example.

Aim of the project:

The aim of the present study was to develop a cladribine ODF to be tested in future pharmacokinetic studies against existing cladribine tablets. During formulation development, Differential Scanning Calorimetry (DSC) has been employed to determine the correct CLA:CD ratio that was able to grant a complete dissolution and complexation of the API [7]. Moreover, X-ray diffraction (XRD) was used to confirm the amorphous state of cladribine in the complex.

Materials and Methods:

DSC and XRD analysis:

First, cladribine and cyclodextrin were analyzed with DSC, as well as the CLA:CD intimate mixtures with ratios 1:6, 1:10, 1:12 and 1:15 (w/w). The intimate mixtures were prepared by dissolving in water the defined amount of cyclodextrin and cladribine, then drying out the solution to obtain a powdered mixture. The thermal characteristics of the samples were investigated on a differential scanning calorimeter using an aluminum non-hermetic pan. The heating rate was 10 °C/min in the range of 25-300 °C under inert atmosphere using N_2 80 ml/min.

Then, to confirm the complete complexation of the API, cladribine and cyclodextrin were analyzed with XRD, as well as the CLA:CD intimate mixture and physical mixture at the chosen w/w ratio. The physical mixture was prepared by mixing cladribine with increasing amounts of cyclodextrin until the defined ratio. An X-ray diffractometer was used to investigate the X-ray diffraction patterns of cladribine, cyclodextrin, CLA:CD physical mixture, and CLA:CD intimate mixture.

ODF qualitative formulation:

Cladribine (10 mg/dose), cyclodextrin, glycerol, pregelatinized pea starch, pullulan, water, triacetin, phospholipids.

ODF Disintegration test:

On the final dosage form, the disintegration test was performed placing 20 ml of purified water at room temperature into a weighing boat, kept in motion using an orbital shaker.

ODF Dissolution test:

The dissolution test was performed with Ph.Eur. basket apparatus. Each vessel was filled with 900 ml of dissolution media (phosphate buffer pH 6.8) at 37 °C. The rotation speed was set at 50 rpm.

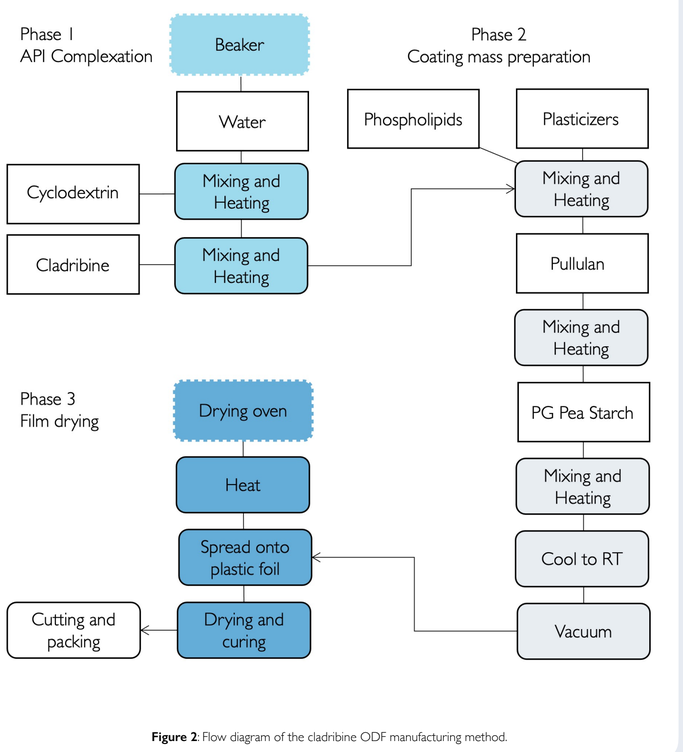

Figure 2: Flow diagram of the cladribine ODF manufacturing method.

Manufacturing process:

- **Phase 1**: it consists in the API complexation. Cyclodextrin is dissolved in warm water, then cladribine is added. Heating and stirring are kept until complex formation.
- **Phase 2**: the next step consists in the gradual addition of the remaining excipients necessary to obtain a filmable mass. The homogeneous mass obtained is kept under vacuum for several hours in order to remove air bubbles.
- **Phase 3**: the filming process consists in pouring the prepared mass onto a plastic foil, using a knife to uniform the film thickness, then drying the film at a set temperature and time. Afterward, a curing time is needed to allow the formation of structural bonds that grant the desired mechanical properties of the film.
- **Packing phase**: finally, the finished dosage forms are cut out. Then, the films obtained are sealed in their packaging, protected from light and humidity.

Results:

CLA : CD ratio determination:

In this phase, the aim was to find the correct CLA:CD ratio that could ensure a complete dissolution and complexation of the API, while using the least amount of cyclodextrin. The main issue was represented by the limited formulating space of the ODF. If too much cyclodextrin is required to dissolve the API there's no possibility to formulate an orally disintegrating film with the required mechanical properties. From bibliographic researches [7,8,9], the CLA:CD intimate mixtures with 1:6, 1:10, 1:12, and 1:15 w/w ratios were chosen and tested. In water, cladribine was not completely dissolved by an amount of cyclodextrin 6-fold greater. Instead, in the ratios 1:10, 1:12, and 1:15 cladribine was completely dissolved. The resulting dried complexes were tested, and the DSC thermograms are illustrated in Figure 3.

The DSC trace of cladribine shows two endothermic events: the first corresponds to the melting transition (around 205 °C), and the second is due to a decomposition product of cladribine (around 210 °C). [7] The DSC profile of cyclodextrin shows a broad endothermic event (from 30 to 130 °C) corresponding to the water loss. [10]

The DSC thermograms of the intimate mixtures at different ratios show both the water loss of cyclodextrin and the melting of the small amount of free cladribine. However, a new endothermic event appears at a higher temperature (around 240 °C) then cladribine melting signal. This valley is probably still referable to the decomposition of a cladribine product in which the thermal shift is caused by the interaction between cladribine and cyclodextrin to form the complex. [11] Finally, in the region of the profile where the free cladribine melting transition occurs, the line is flatter for the ratios 1:12 and 1:15 than 1:6 and 1:10 meaning that less free cladribine is present. For this reason, and since it allows to have more free formulating space than the 1:15 ratio, the CLA:CD 1:12 w/w ratio was chosen as the candidate.

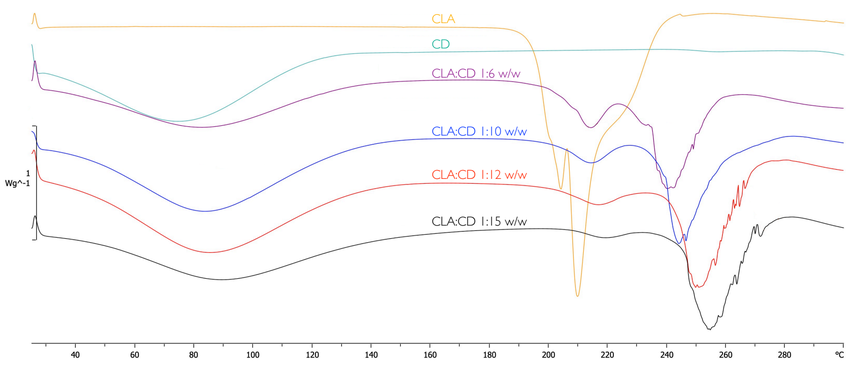

Figure 3: DSC traces of cladribine, cyclodextrin, and their intimate mixtures in different ratios.

CLA : CD ratio confirmation:

To confirm that the amount of cyclodextrin used in the intimate mixture of CLA:CD 1:12 w/w ratio was enough to complex the cladribine, and that the API solid state was amorphous, X-ray diffraction was employed, and the results are illustrated in Figure 4.

The diffractogram of cladribine shows the peaks of the crystalline form, while the profile of cyclodextrin has the typical pattern of an amorphous substance. The physical mixture of CLA:CD 1:12 w/w ratio shows the peaks of cladribine under the signal of cyclodextrin. Instead, the intimate mixture of CLA:CD 1:12 w/w ratio hasn't any peak, confirming that cladribine is in the amorphous form.

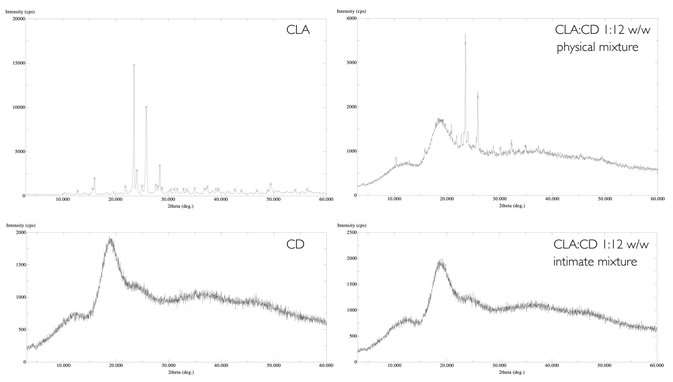

Figure 4: Diffractograms of cladribine (CLA), cyclodextrin (CD), and their physical and intimate mixture at 1:12 w/w ratio.

Disintegration of ODF:

Following the method described in the "Materials and Methods" section, the ODF has been tested. The disintegration time resulted to be less than 2 minutes.

Dissolution comparison ODF vs cladribine:

The release profile of the formulated CLA:CD complex, in the chosen ratio, has been compared to the unformulated API. The % of cumulative release of cladribine at 15 minutes for the ODF is around 85%, while for the unformulated API is around 40%.

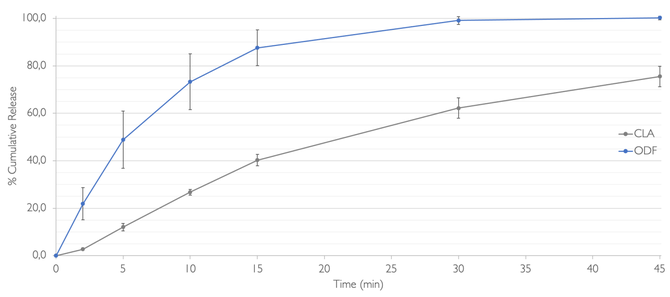

Figure 5: Dissolution rate of unformulated cladribine (CLA) against formulated cladribine (ODF) 1 dose (10 mg of cladribine) in 900 ml of phosphate buffer pH 6.8 at 37°C

Conclusions:

Cyclodextrin is a valid solution to improve cladribine solubility in water and to stabilize its amorphous form by complexation. This results in a major increase in cladribine release from the ODF compared to the unformulated API. To this, is possible to add the advantages of an orally disintegrating film in comparison to a more traditional dosage form such as immediate release tablets. In particular, the possibility to take a dose without water, simplifying the ingestion for the dysphagic population, and the opportunity to bypass the gastric system, avoiding the hepatic first-pass metabolism. [12]

Current and future development:

The developed ODF will be compared to existing cladribine tablets (Mavenclad®) in pharmacokinetic studies to determine the possibility of reducing the administered cladribine dose while maintaining comparable pharmacokinetic parameters.

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