Exploring orodispersible films containing the PROTAC ARV-110 fabricated by solvent casting with PVA

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Introduction

The emerging orodispersible films (ODFs) are an efficient drug delivery system (DDS) that provides various advantages on patience compliance, cost effectiveness, and prompt assistance for emergency medication through an oral and therefore non-invasive delivery route. This project aims to provide valuable insights into formulation of ODFs for the delivery of the Proteolysis Targeting Chimera (PROTAC) ARV110. The primary objective of this drug delivery formulation is to enhance the solubility of PROTAC ARV-110, which faces significant challenges due to the low solubility of this active pharmaceutical ingredient (API), as it belongs to a molecular class that is considered to exceed the "Rule of Five" [1, 2, 3].

Manufacturing Process

Figure 1: overview of manufacturing process of PVA orodispersible films.

We employed the concept of developing a rapidly disintegrating ODF to enhance the solubility of PROTAC ARV-110 Bavdegalutamide; (MedChemExpress, Monmouth Junction, NJ, USA), utilizing polyvinyl alcohol (PVA) as the polymer of choice through solvent casting. For the film formulation the polymers PVA 4-88 "Parteck® MXP 4-88" was used, Sorbitol "SI150as plasticizer, and the Polysorbate 80, "TWEEN® 80" as surfactant from Merck KGaA, Germany. 1.775 g of PVA 4-88, 0.225 g of Sorbitol and 0.25 g of TWEEN® 80 were mixed and dissolved in 10 ml of water. Separately, 13.5 mg of API was dissolved in 2.5 ml of DMSO and and added to the excipient mixture solution in a 1:2 (2.5 ml of API solution + 5 ml of polymer solution) ratio. The film solution was then casted over a tin-coated glass plate through a casting geometry (Erichsen, Erichsen GmbH & Co. KG, Hemer, Germany) and left to dry under vacuum at 30 °C. Films with two different concentrations of ARV-110, 1.19% and 2.5% were prepared.

Ingredient	Content	Function
PVA 4-88	Polyvinyl alcohol	Polymer
Sorbitol SI 150	Sorbitol	Plasticizer
TWEEN® 80	Polysorbate 80	Surfactant
Water	H_2O	Solvent

Analytical Methods

The disintegration of the films was tested in petri dishes using artificial saliva for pharmaceutical research (Sigma Aldrich - St. Louis, Missouri,US). The strength of films was assessed performing the tensile strength test with the texture analyzer TA.XTplusC Stable Micro Systems (Stable Micro Systems Ltd, Godalming, United Kingdom), where the pieces of film were pulled through two probes at a target distance of 2 cm with a test speed at 1 mm/s. To perform the mini-dissolution test a 2x2 cm piece of film was dissolved in 0.5 ml artificial saliva. Then 7.5 ml of 0.1 M HCl was added to the suspension and stirred at 300 rpm in the shaker TH15 (IKA, Breisgau, Germany) at 37 °C reaching a pH of 1.2 mimicking the gastric environment. After 30 min 2.0 ml of 0.2 M Na3PO4 × 12 H2O was added to the solution performing the pH-shift to pH 6.8 mimicking the intestine environment with Phosphate Buffered Saline (PBS; protocol by USP, United States Pharmacopeia). The samples were filtered through a PTFE-filter (0.45 µm) and diluted with 0.1% formic acid in acetonitrile and evaluated through RT-HPLC. The sample volume was 500 µl and the samples pickup timepoints were after 5, 10, 20, 35, 50, 60, 90 and 120 minutes. An Agilent 1260 infinity HPLC system (Agilent, Santa Clara, USA) equipped with an Agilent 1260 II variable wavelength detector was used. A C8-Column (Waters XBridge Column C8, 4.6 × 50 mm, 3.5 µm) column was used for the quantification; the eluent A was 0.1% formic acid in water, eluent B was 0.1% formic acid in acetonitrile (1:1). The injection volume was 5 µl and the flow rate was 1.7 ml/min at 37°C. The wavelength was 254 nm. For each formulation sample the drug content determination was performed.

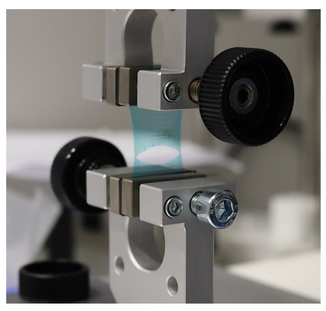

Figure 2: Placebo ODF evaluated through the Texture analyzer TA.XTplusC Stable Micro Systems.

Summary

The study demonstrated that solvent casting with PVA 4-88 effectively addresses the challenges of poorly soluble APIs like PROTAC ARV-110. This method produced rapidly disintegrating films with strong mechanical properties. The dissolution rate of the drug significantly improved over itscrystalline form, laying a foundation for further exploration of orodispersible films (ODFs) in PROTAC delivery.

References

[1] Niessen et al, JPBA, 2024.
[2] Mareczek et al, Pharmaceutics, 2024.
[3] Yang et al, AAPS J, 2020.

Results

The disintegration times of the ODFs reached an average value of ~18 s ±2 s (STDV n=3) for the formulation containing 1.19% of API, and ~35 s ± 8.89 s (STDV n=3) for the formulation containing 2.5% of API. The disintegration time is higher compared to the placebo formulation (~9 s for placebo versus ~19 s for 1.9 % API and ~35 s for 2.5 % API), which well correlates with higher thickness ranges (see Table). The average forces of the yield offset of the ARV-110 films was 6.5 N ± 0.449 N (STDV n=3) for the formulation containing 1.19% of API and 8.7 N ± 0.342 N (STDV n=3) for the formulation with the 2.5 % of API. The results from the dissolution experiments indicated dissolution enhancement of ARV-110 through processing. The raw material, ARV-110, displays no measurable dissolution, while for both ODF formulations, a highly notable enhancement is determined.

Analytics	ODFs placebo	ODFs 2.5 %	ODFs 1.19%
Thickness range (mm)	0.022-0.031	0.034-0.060	0.035-0.043
Disintegration time (sec) STDV (n=3)	9 ± 2	35 ± 9	18 ±2
Force at the Yield offset (N) STDV (n=3)	7.4 ± 1.8	8.679 ± 0.342	6.5 ± 0.5
Measured drug content (%) STDV (n=3)	/	2.00 ± 0.067	0.82 ± 0.09
Diss. max (%) after 20 min; STDV (n=3)	/	92.13 ± 0.33	99.90 ± 0.04
Diss. max (%) after 120 min; STDV (n=3)	/	54.56 ± 1.69	55.54 ± 0.48

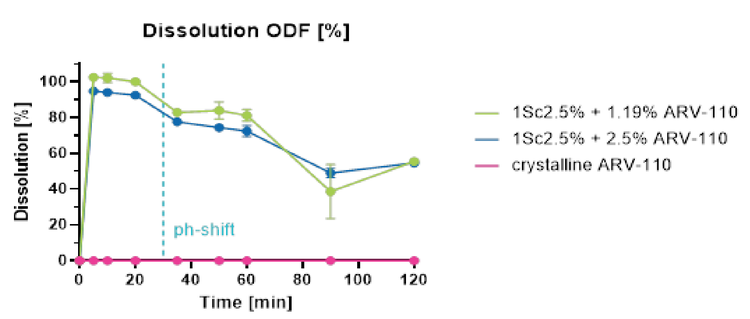

Figure 2: graphical representation of the dissolution tests of ARV-110 as crystalline, ODFs with 1.19% of ARV-110 and ODFs with 2.5% of ARV-110, with pH shift in PBS pH 6.8 at 100 rpm and 37°C.

Discussion

The raw material, ARV-110, displays no measurable dissolution during the pH shift measurements, while for both formulations, a highly notable enhancement is determined. For the formulation containing a theoretical 1.19% of API, the calculated amount of ARV-110 in the pieces of films previous the dissolution test was 0.815% ± 0.09% (STDV n=3). Meanwhile, for the formulation containing a theoretical 2.5% of API, in the single pieces of films was calculated a 2% ± 0.067% (STDV n=3) of ARV-110 before the dissolution test. Both formulations follow a similar dissolution profile over the pH-shift measurements and 120 min, in fact even if they have a different concentration, the drug release profile is very similar, probably because between 1% and 2% of ARV-110 concentration a saturation point in physiological buffer is reached. With ARV-110 being a weakly basic API, dissolution is expected to be higher in acidic pH, which can be observed in the graph. With the change to pH 6.8, dissolution values decrease, nevertheless keeping a release of ~55% after 120''.

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