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In situ forming implants: selection of the most suitable polymer for the administration of CBD

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1. Introduction

In situ forming implants (IFIs) that are typically made of a drug, solvent, and a biocompatible polymer, offer an interesting potential for parenteral controlled drug delivery. Also, they have the advantages of a non-complicated preparation and an easy administration using conventional subcutaneous needles. In fact, several IFIs containing doxycycline or leuprorelin are currently approved by FDA and/or EMA [1, 2].

Cannabidiol (CBD), the main non-psychotropic cannabinoid, appears as a potential anticancer drug, but it shows high lipophilicity and instability that complicates its handling and dosing and restricts its use by a parenteral route [3]. The use of IFIs could be a good strategy to develop long-active CBD formulations. The objective of this work was to evaluate, among several biocompatible and biodegradable polymer, the most suitable to develop CBD-ISFIs.

2. Materials and Methods

Poly-D, L-lactide-co-glycolic acid (PLGA) 50:50 (PLGA-502, PLGA-502H and PLGA-503), poly-D, L-lactide (PLA-202 and PLA-203), and polycaprolactone (PCL) were used as polymer, due to their biocompatibility, biodegradability and safety, and N-Methyl-2-pyrrolidone (NMP) was used as a solvent. Formulations loaded with CBD at a drug: polymer ratio of 2.5:100 were elaborated using the direct injection technique. Firstly, injectability studies (using 23G and 25G needles) were carried out to select the most suitable and manageable polymer, and the optimal polymer:NMP ratio. A polymer: NMP ratio of 100 mg:150 µL, 100 mg:300 µL and 100 mg:400 µL were used. Optimized CBD loaded implants were characterized by scanning electron microscopy (SEM) and drug release was determined.

3. Results and discussion

Injection tests that were carried out in a random way showed that PLGA-502, PLGA-502H, PLA-202 and PCL solutions exhibited good injectability properties, with an easy and continuous injection using 23G and 25G needles, as the prepared formulation would be administered subcutaneously. PLGA-503 and PLA-203 demonstrated a bad injectability properties, especially when a 25G needle was used. This could be attributed to the higher molecular weight of these resomers compared to their counterparts. Due to these injectability properties, PLGA-503 and PLA-203 were discarded. The most suitable polymer: NMP ratio of the selected polymers (PLGA-502, PLGA-502H, PLA-202 and PCL) was 100 mg:400 µl (Tab. 1).

All the selected polymers led the easy formation of CBD-loaded ISFIs when injected in phosphate buffer solution. As observed in SEM studies, a smooth surface was appreciated in recently prepared in situ forming implants (Fig 1).

Tab.1: Median score value of the injection test results. Score 1: Injection very difficult, not flow; Score 2: Injection difficult, flow initially drop wise and then continuous; Score 3: Injection easy, flow continuous; Score 4: Injection very easy, flow continuous.

Polymer	Ratio Solvent	23G Median		25G Median
502 RG PLGA	150µl	2		2
	300µl	3		2
	400µl	3		3
503 RG PLGA	150µl	1		1
	300µl	3		2
	400µl	3		2
502 H RG PLGA	150µl	2		1
	300µl	4		3
	400µl	4		4
202 RG PLA	150µl	3		3
	300µl	4		3
	400µl	4		4
203 RG PLA	150µl	1		1
	300µl	2		2
	400µl	3		2
PCL	150µl	1		1
	300µl	3		3
	400µl	4		3

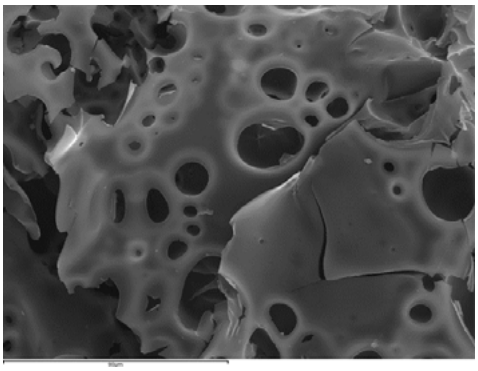

Fig 1. SEM images of a recently prepared in situ forming implant (ISFI-502).

Regarding to drug release studies, a controlled CBD release was obtained in all formulations. As we can noticed from the graphics (Fig 2), ISFIs prepared with PLGA showed a faster drug release, as the formulations prepared with PLGA-502 and PLGA-502H exhibited of around 70 % of the CBD released within 2 days. ISFIs elaborated with PLA-202 and PCL exhibited around the 50 % or 30 % of drug released at this time respectively. Except in the implants prepared with PCL, all the formulations exhibited a strong burst effect as more than 25 % of the CBD was released within the first hour. This burst effect was specially marked in the formulations prepared with PLGA-502, with more than 40 % of the CBD released at this point. However, ISFIs prepared with PCL showed a more controlled CBD release for more than 30 days, with a low burst effect (just the 6 % of CBD was released after 1 hour). Due to this better release profile, PCL seems to be the most suitable polymer to prepare a long-acting CBD-ISFI.

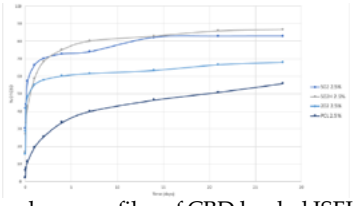

Fig 2. Drug release profiles of CBD loaded ISFIs prepared with the different polymers.

4. Conclusions

The implants prepared with polycaprolactone, using a polymer: solvent ratio of 100 mg:400 µL showed good injectability properties to be administered subcutaneously, being suitable to get a controlled CBD release for more than one month after a single administration.

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