Preparation of flurbiprofen loaded PLGA microspheres using a membrane emulsification method

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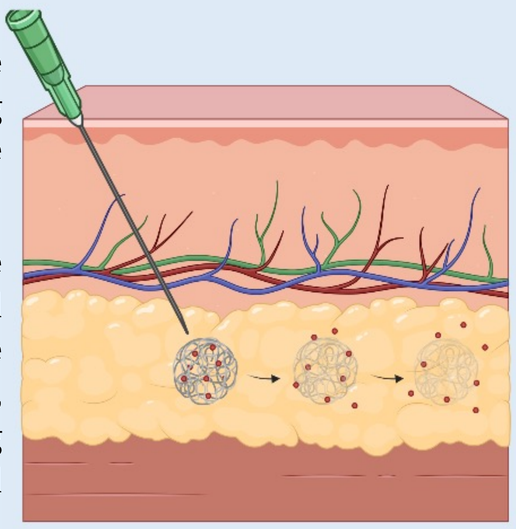
Introduction

PLGA-based formulations account for the majority of marketed biodegradable long-acting injectables [1] and most of these are **microspheres** (MS).

In the optimization of formulation as well as the development of copies, several formulation and process variables impact on the biopharmaceutical performances of the product, including PLGA features and manufacturing process which can affect the size distribution and MS microstructure.



To screen the effect of these parameters, the drug release studies performed using conventional media are not suitable, since the macromolecular components, osmolarity and pH of interstitial fluids can modify the surface and therefore they can provide a further barrier to drug diffusion.

Aim

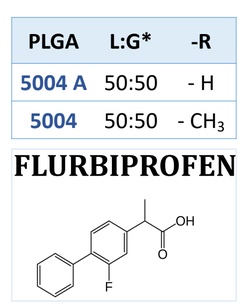
This work aims to provide preliminary data on the development of drug release test based on biorelevant media suitable to mimic the SC environment.

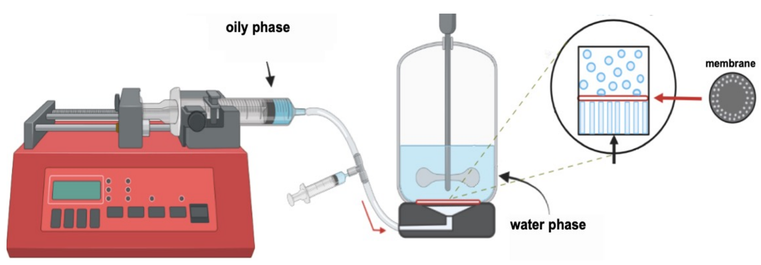
PREPARATION OF FLURBIPROFEN MICROSPHERES

PLGA MS were prepared by membrane emulsification/solvent evaporation method (Micropore Technologies Ltd, UK) using two types of PLGA and loading flurbiprofen as model of lipophilic drugs. All parameters were optimized to have the target size of about 50 µm and a narrow size distribution.

PLGA	L:G*	-R
5004 A	50:50	- H
5004	50:50	- CH_3

FLURBIPROFEN





MS were collected, washed and resuspended in MilliQ® water before freeze-drying.

MEDIA OPTIMIZATION

Four biorelevant media [2] were prepared simulating the saline composition of SC interstitial fluid at pH=7.4 and differing in terms of osmotic/oncotic pressure, and viscosity by the presence of:

- proteins (albumin);
- hyaluronic acid (HA)(2)
- both macro molecules.

The release test was performed statically in a thermostatic chamber at 37±0.5 °C upon 4 weeks.

Component	Concentration (mg/L)			
	SIB**	ALBU	HA	ALBU + HA
Albumin	-	50	-	50
HA	-	-	10	10
$CaCl_2$	0.144	0.144	0.144	0.144
$MgCl_2$	0.047	0.047	0.047	0.047
CH_3COONa	0.410	0.410	0.410	0.410
NaCl	6.393	6.393	6.393	6.393
Na_2SO_4	0.071	0.071	0.071	0.071
$NaHCO_3$	2.234	2.234	2.234	2.234
K_2HPO_4	0.174	0.174	0.174	0.174
KCl	0.141	0.141	0.141	0.141
Tris	7.880	7.880	7.880	7.880

PARAMETERS SELECTION

Solvent	PLGA (%)	HPMC (%)	D10 (µm)	D50 (µm)	D90 (µm)	SPAN
DCM	12	2.5	13.8	23.2	37.6	1.02
CF	12	2.5	22.6	41	75.8	1.3
DCM	12	2	18	31.9	54.6	1.14
CF	12	2	28	75.1	158	1.7

1 Organic solvent:
- Dichloromethane (DCM)
- Chloroform (CF)

Solvent	PLGA (%)	HPMC (%)	D10 (µm)	D50 (µm)	D90 (µm)	SPAN
DCM	**4**	2.5	7.5	13.2	21.7	1.07
CF	**8**	2.5	10	18.3	29.9	1.08
DCM	**12**	2.5	13.8	23.2	27.6	1.02
CF	**15**	2.5	11.4	21.3	38	1.25

2 PLGA concentration:
PLGA % (4-15)

Solvent	PLGA (%)	HPMC (%)	D10 (µm)	D50 (µm)	D90 (µm)	SPAN
DCM	8	**3**	6.8	12.7	23.1	1.3
DCM	8	**2.5**	10	18.3	29.9	1.08
DCM	12	**2.5**	13.8	23.2	37.6	1.02
CF	12	**2.5**	22.6	41	75.8	1.3
DCM	12	**2**	18	31.9	54.6	1.14
CF	12	**2**	28	75.1	158	1.7

3 Stabilizer concentration:
HPMC % (2-3)

Solvent	PLGA (%)	O/W ratio	D10 (µm)	D50 (µm)	D90 (µm)	SPAN
DCM	8	**1:12**	8.8	29.8	504	16.6
DCM	8	**1:60**	10	18.3	29.9	1.08

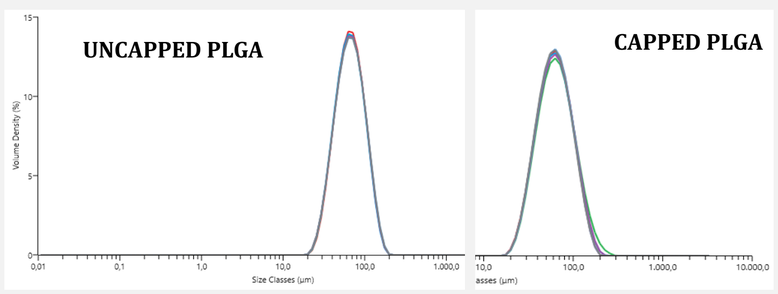
4 O/W ratio: (1:12 - 1:60)

5 Stirring speed:
330-1240 rpm

Solvent	PLGA (%)	HPMC (%)	Stirring speed (rpm)	D10 (µm)	D50 (µm)	D90 (µm)	SPAN
DCM	4	2.5	**1240**	3.7	7.9	22.6	2.4
DCM	4	2.5	**550**	6.1	13.4	33.8	2.1
DCM	4	2.5	**330**	7.5	13.2	21.7	1.07

OPTIMIZED FORMULATIONS

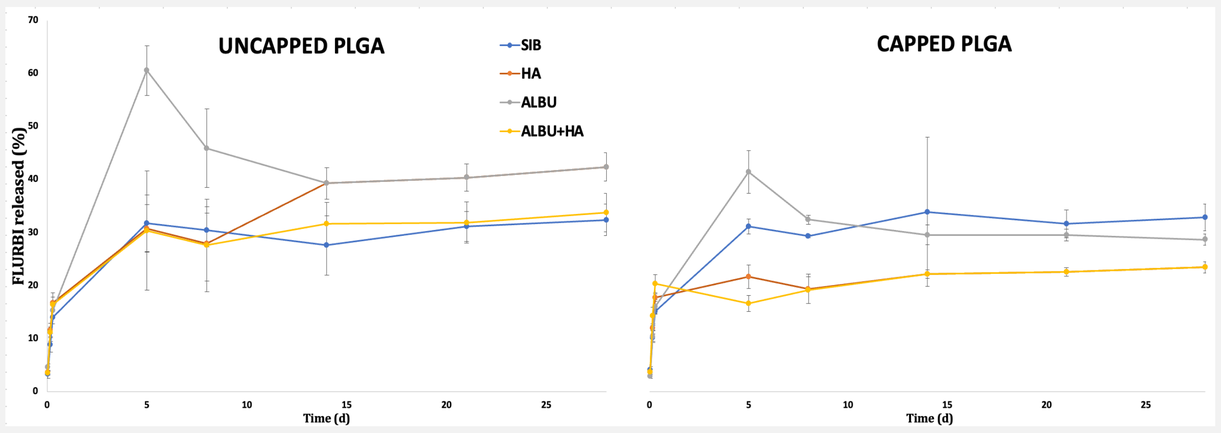
Independently of PLGA type, the membrane emulsification solvent evaporation technique allowed to prepare PLGA MS with a narrow size distribution.



- O phase: 12% (w/v) PLGA in DCM;
- W phase: 2% (w/v) HPMC;
- 330 rpm = stirring speed.

IN VITRO RELEASE PROFILE

PLGA	D_{10} (µm)	D_{50} (µm)	D_{90} (µm)	SPAN	FLURBI (%)	Drug loading (%)	EE (%)
5040 A	34.3	61.7	111	1.1	20	12.4 ± 0.0	61.3 ± 0.1
5004	37.9	65.4	110	1.2	20	12.0 ± 0.2	59.8 ± 1.1



- Flurbiprofen release was slower for MS made of capped PLGA;
- Macromolecules strongly influenced the drug release:
  - **albumin** increased the drug released;
  - **HA** slowed it down with respect to the saline solution.

Under these conditions, differences were particularly evident for capped PLGA MS.

Conclusion

The **composition** of dissolution medium, and in particular the presence of proteins, **influences the release profile** of flurbiprofen from PLGA MS;
These data emphasize the relevance of release media closely mimicking the environment of SC tissue.

References: [1] Selmin F. *et al.,* Drug Discovery Today 25(2): 321-329, 2020; [2] Torres-Terán I, *et al.,* Int J Pharm. 610:121257, 2021.