# Synthesis and application of magnetic nanoparticles (MNPs) in drug delivery to the retina

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## INTRODUCTION

The development of an innovative drug delivery system to target, after topical administration, the retina with bioactive agents against retinal pathologies and degenerations is a major challenge[1]. Currently, the sole approach to target these tissues is through intravitreous injection, but this is not free from problematics such as severe side effects and, rapid clearance of small molecules form the vitreous requiring repetitive injections; additionally this is not permitted for treating children[2].

In this respect, **we aim to develop a new magnetic nanoparticle-mediated delivery technology that shall allow achieving needle-free delivery of active drugs (small molecules) to the retina by topical administration.**

In this study we have used magnetic nanoparticles loaded with a combination of two drugs, Guanabenz (GBZ) and Valproic Acid (VPA) which have been proved to slow down the retinal degeneration in the Bardet Biedl Syndrome (BBS)[4] (Cilia-related retinal dystrophies).

## MATERIALS AND METHODS

1- MNPs synthesis & preliminary characterization

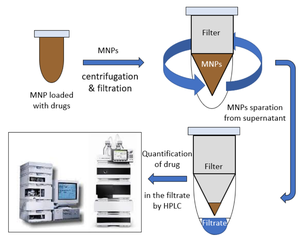
Magnetic decantation of MNPs

2- MNPs screening

| MNP | Coating |
|---|---|
| NP01 | Inorganic |
| NP02 | Polymeric |
| NP03 | Polymeric |
| NP04 | Lipid |
| NP05 | Polymeric |
| NP06 | Organic |
| NP07 | Inorganic |
| NP08 | Lipid |
| NP09 | Inorganic |

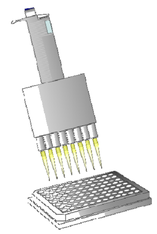
List of MNPs synthetized

3- Candidate's characterization




Representation of drug loading procedure

4- MNPs biocompatibility *in vitro*



Representation of an *in vitro* assay

## RESULTS

MNPs synthesis

METHODOLOGY:

Co-precipitation of iron salts with alkaline solution.

$$2Fe^{3+} + Fe^{2+} + 8OH^- \rightarrow 2Fe(OH)_3Fe(OH)_{2\,(s)} \rightarrow Fe_3O_{4\,(s)} + 4H_2O$$

COATING AGENTS:
inorganic, organic , natural and synthetic, polymers.

PURIFICATION:
magnetic decantation, dialysis, centrifugation.

FIRST CHARACTERIZATION:
Iron content, hydrodynamic size distribution and electrostatic charge profile.

Several MNPs have been synthesized & primary

selection performed based on size, charge and stability

Figure 1: description of the synthesis methodology selected to produce the MNPs used in the study.

MNPs selection on drug loading efficiency & stability

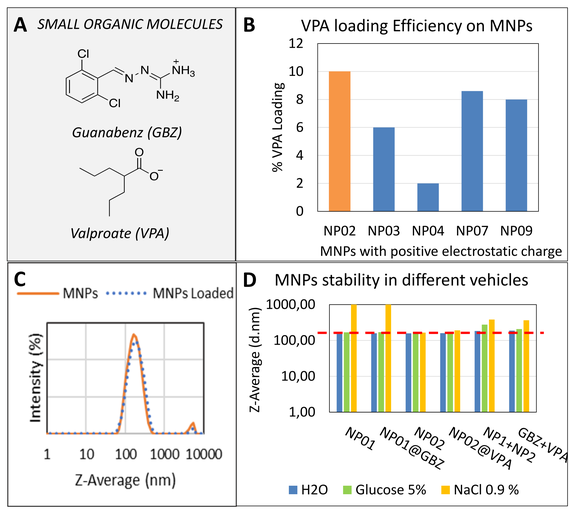



Figure 2: structure of the two small organic molecules used in collaboration with UMR_S1112 (A); loading efficiency of VPA on the surface of cationic MNPs by electrostatic interactions (B); hydrodynamic size of NP01 mixed with NP02 in loaded and unloaded conditions at 24h from mixing them together (C); stability study of NP01 and NP02, for the loading of GBZ and VPA respectively (D).

NP01 and NP02 load efficiently GBZ and VPA

Also they allow to obtain stable formulation upon mix

NP01 and NP02 complete physico-chemical characterization

| A Feature | NP01 | NP02 |
|---|---|---|
| Size (TEM) | 10 nm | 10nm |
| Hydrodynamic size (DLS) | 137 nm | 143 nm |
| Surface charge | -28 mV | +33 mV |
| Chemical composition | Magnetite | Magnetite & Ghoetite |
| Morphology | Spherical | Spherical |
| Loading efficiency | 40% (GBZ, 7µM) | 10% (VPA, 2mM) |

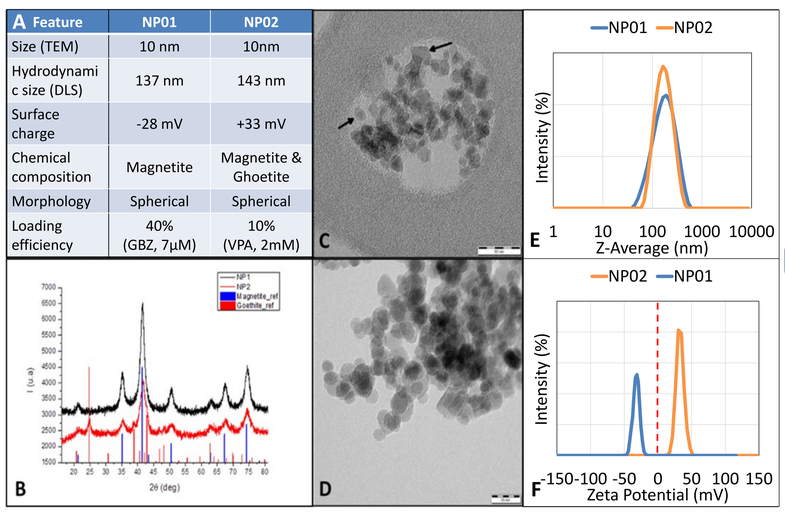



Figure 3: list of NP01 and NP02 physico-chemical features (A); Powder X-ray diffraction of NP01 (black) and NP02 (red); vertical lines correspond to the diffraction pattern of bulk magnetite (blue) and ghoetite (blue) (B); TEM images of NP01 (C) and NP02 (D); hydrodynamic size (E) and zeta potential (F) of NP01 (blue) and NP02 (orange).

NP01 and NP02 loaded

have correct features *for in vitro* & *in vivo* application[3]

*In vitro* biocompatibility

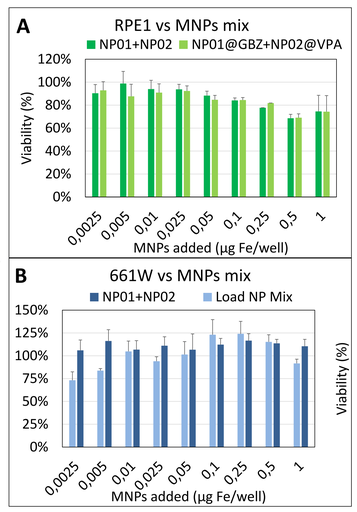



Figure 4: RPE1 cell viability using OZ Blue assay kit at 24h from MNPs exposure, n=3 (A); 661W cell viability using OZ Blue assay kit at 24h from MNPs exposure, n=3 (B).

## CONCLUSIONS

- **MNPs can efficiently load small organic molecules on their surface by electrostatic interactions**
- **Two MNPs have been fully characterized and formulated for the delivery of GBZ and VPA**
- **The formulations are biocompatible and tolerated by retinal cells *in vitro***
- **The formulation showed positive biological effect in BBS mice model (see Daniel Ajoy Moreno poster)**

## REFERENCES

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4. Mockel A. et al; Pharmacological modulation of the retinal unfolded protein response in bardet-biedl syndrome reduces apoptosis and preserves light detection ability. *Journal of biochemistry. 2012, 287, 44, 37483–94*

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