NEW PHARMACOLOGICAL DOSAGE FORMS

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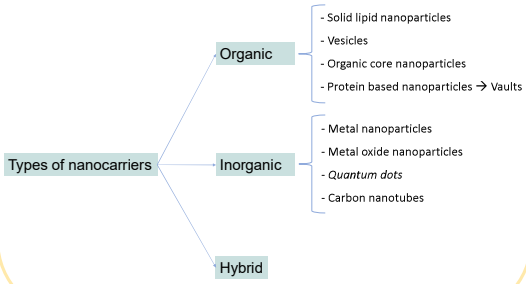
Nanoparticles as drug delivery system (DDS) have received much attention throughout the last decades. Its capabilities to increase solubility, pharmacokinetics and bioavailability of the administrated drug lead to improve the therapeutic efficacy of conventional drugs. In addition, therapeutic nanoparticles are target tissue specific so toxicity and collateral effects of drugs are reduced, making them an excellent alternative for traditional anticancer drugs.

Objectives: 1. Learn about new dosage forms. 2.Discover how nanoparticles are produced and its mechanism of action. 3. Confirm if nanoparticles are more useful for drug administration

1.1 TYPES OF NANOPARTICLES

It has been discovered that a large number of biomolecules and cell components can be used as an effective drug release system. Although they can also be synthesized *de novo* from inorganic materials.



1.2. DESIGN OF NANOVEHICLES

Physicochemical properties of the nanoparticle allow to estimate the interactions with other molecules though also pharmacokinetics, pharmacodynamics and excretion of the nanoparticle.

Strategies for driving the nanoparticle to the biophase based on: tumor micro-environment, intracellular signals of target cells or overexpression of different molecules on the surface of tumor cells.

Size: related to the loading and the rate of release of drugs as well as to the stability of the nanoparticle + drug, the biological destination of the nanoparticle, toxicity, distribution and orientation.

Modifications in the nanoparticle's surface: key factors to guide them to the biophase. Some modifications allow crossing the blood-brain barrier

2. VAULT PARTICLES

-Cytosolic ribonucleoproteins which are composed of two subunits.

-Ovoid morphology.

-Stable structure.

[4]

	Numbers of residues or bases	Molecular weight (kDa)
MVP		
rat	861	95,798
human	893	99,327
vPARP		
human	1,724	192,595
TEP1		
rat	2,629	291,708
human	2,627	290,490
vRNA		
rat	141	47,686
human		
hvg1	98	32,994
hvg2	88	29,612
hvg3	88	29,544

[5]

Each subunit ➡ 39 identical MVP ➡ main structural component of the nanoparticle.

MVP: Naturally synthesized by humans and many other mammals, birds and even insects.

MVP in humans ➡ located on chromosome 16 and is expressed in most normal tissues. Its subcellular location is in the cytoplasm, although it is also found in the nuclear pores.

3. RESULTS

1

MVP is the key factor for the development and synthesis of the protein cover of the nanoparticle. It has the ability to self-assemble forming a very stable protein structure with empty lumen.

The synthesis of the nanoparticle is given through a plasmid which contains the following sequences:

- Protein with self-assembling capacity (MVP)
- Peptide that guides de nanoparticle to the target tissue → biomarker
- Histidine tag→ Prevents the nanoparticle from being degraded and prematurely excreted

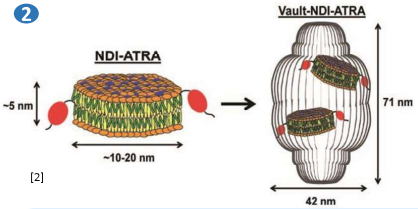
C-terminal of MVP is the outer part of a Vault's subunit while N-terminal is the inner part. Regarding its functions, N-terminal is related to the union of the two Vault's subunits forming a closed structure whereas C-terminal is where the biomarker is joined.

Therapeutical nanoparticles are target specific so have the capacity to accumulate in the tumour through two targeting strategies (active or passive mechanism) without damaging healthy tissues.

Once the nanoparticle is formed a drug can be introduced within the lumen. Another option is incorporating the sequence of a pro-apoptotic peptide such as PUMA or BAK 1 in the plasmid above to create nanoparticles intrinsically toxic.

A strategy to incorporate the drug is introducing a nanoparticle of 10-20 nm to the lumen of the Vaults, this nanoparticle is called Nanodisk (ND).

2



[2]

NDs are diskoidal molecules formed by lipid bilayer fragments derived from Apolipoprotein-AI, which contain amphipathic helixs that surround the circumference of the disk. They contain a lipophilic domain that allows the absorption of hydrophobic components such as drugs promoting that the active principle remains trapped inside the Nanodisk

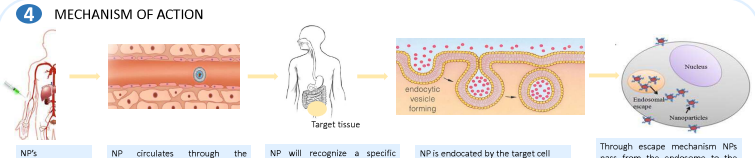
3

A domain of the C-terminal of the VPARP protein which is naturally associated to the lumen of the Vaults has been used to encapsulate the ND into the nanoparticle.

This domain has been called INT and it has been discovered that it acts as a carrier of substances to the lumen of the protein structure *in vivo*. By conjugation the ND + drug in the INT, it will be transported to the lumen of the Vaults.

Because of the large size of Vaults, it has been seen that multiple NDs can be encapsulated, which can help increase the concentration of the drug.

4 MECHANISM OF ACTION



NPs administration

NP circulates through the bloodstream guided by the biomarker to the target tissue.

NP will recognize a specific overexpressed receptor in target cells.

NP is endocated by the target cell

Through escape mechanism NPs pass from the endosome to the cytoplasm where the active principle is released.

4. CONCLUSIONS

- Improve the viability and therapeutic efficacy of drugs by promoting an accumulation of the active principle in the target tissue.
- Reduce the dose of administration and toxicity.
- Increase the solubility and biodistribution of drugs → improve their pharmacokinetics
- Ensure circulatory persistence.
- Increase the safety of drugs through systemic release directed to the biophase so, healthy tissues should not be damaged.
- Prevent premature degradation and excretion of drugs.
- Vaults are biocompatible so should not cause any immune response and show biodegradability.

5. STATE OF ART

So far, most nanoparticles have only been studied *in vitro* or in animal models but their efficacy has not been clinically proven, therefore, there is still much research to be done. It is believed that they can be a first step towards individualized directed therapies.

Different articles point out that *in vivo* experiments must be done to ensure that nanoparticles release the drug into the biophase and reduce the adverse effects.

It should be emphasized that several studies made with the molecular bases of different tumors have given enough information to be able to think that nanovehicles can be a way to overcome the resistance that certain populations of tumor cells develop to drugs.

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