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“Breaking Paradigms: Towards a Multi-, Inter- and Transdisciplinary Science” In commemoration of the 250th Anniversary of Alexander von Humboldt

REVISION/REVIEW

General Approach to Drug Delivery Systems (DDS)

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ABSTRACT

The field of drug discovery drives to find out efficient, selective, stable and biocompatible new drugs. The purpose of drug delivery systems (DDS) is to reduce the side effects that treatments usually cause to mitigate some diseases, especially cancer. Cancer treatments are usually so strong and invasive that they end up weakening the patient, so the cure became as dangerous as the disease. That is the reason that DDS try to maximize the effectiveness of the drugs administered by wanting them to reach specifically to the area affected by the disease (High specificity). In this regard, the fruitfully use of liposome-, erythrocytes-, nanoparticles- or antibodies-based therapies became a choice for the treatment of a huge range of diseases, due to the biocompatibility that these macromolecular systems present. In the last five years, a broad range of DDS have been developed, and some of them, specifically four ADC's are approved by the FDA and commercializing. In this work, we summarized the most important approach to DDS obtained through chemical conjugation, highlighting ADC's like the most promising controlled release systems.

keyword: Drug delivery systems, Nanocarriers, Biocarriers, therapeutic agents, Antibody Drug Conjugates.

INTRODUCTION

Drug discovery field drives to find out efficient, selective, stable and biocompatible new drugs, also looking for avoiding side effects. Current advances in the mechanistic understanding of the molecular drivers of malignancy have led to many new drugs, which are targeted directly at the malignant cells or therapeutic targets, and not the neighbouring healthy cells. Thus, in order to enhance the efficacy of existing drugs or therapies, several drug delivery approaches have been developed.

In this regard, the fruitfully use of liposomes-, erythrocytes-, nanoparticles- or antibodies-based therapies (Drug Delivery Systems) became an actual choice and closer future for the treatment of a huge range of diseases, due to the biocompatibility that these macromolecular systems presents. In the last five years, a broad range of DDS have been developed, and some of them, basically ADC are already being commercialized. In this paper, we summarized the most important approach to DDS based on Liposomes, Erythrocytes, Nanoparticles and Antibodies, highlighting ADC's as the most promising controlled release systems (**Figure 1**).

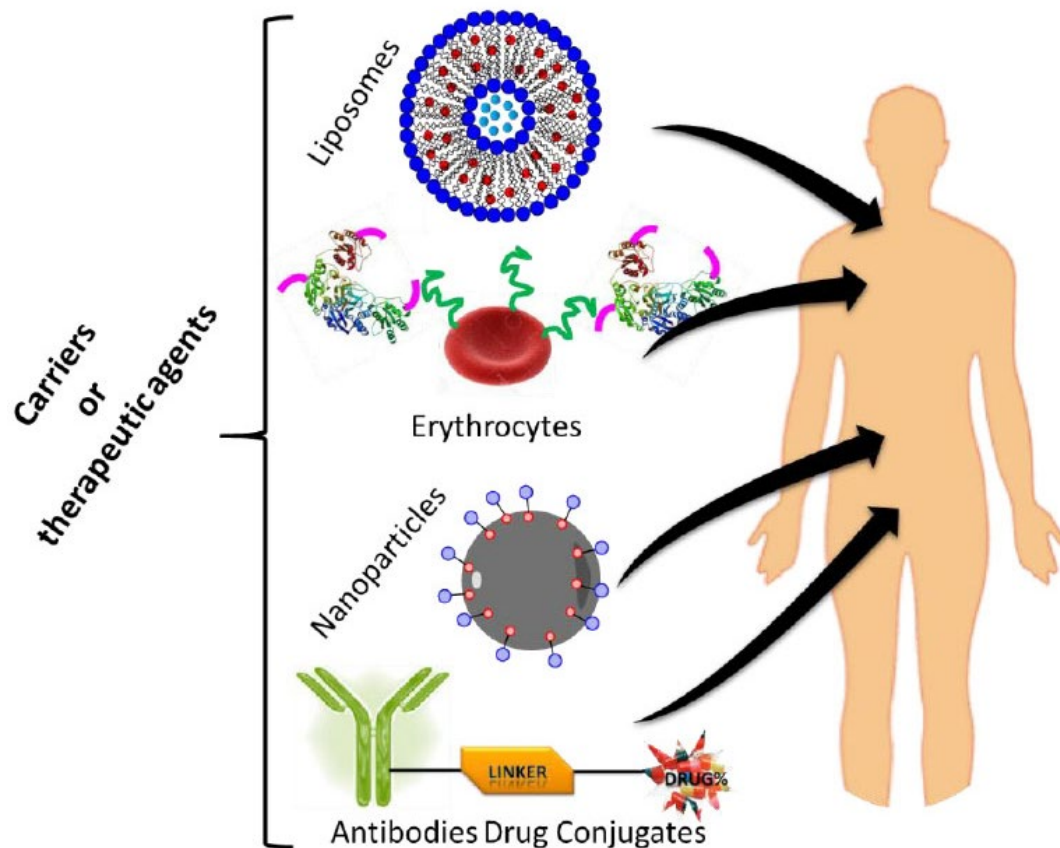


Figure 1. DDS based on Liposomes, Erythrocytes, Nanoparticles and Antibodies Drug Delivery Systems (DDS) to introduce therapeutic agents into the body

Liposomes

DDS based on liposomes has demonstrated a high drug loading capacity as well as improved antitumor efficacy in vivo. Liposomes are useful in the administration of both, hydrophobic or hydrophilic drugs.¹ This carrier is one of the most studied to be used in DDS due to some positive features that liposomes have, for example, they have a high level of loaded and in turn, a long period time in circulation, changing drug pharmacokinetics in comparison of the drug administered alone.² Liposomes as carriers are safe, biodegradable and biocompatible, which made of them very useful to theranostics and even with imaging purpose when these are conjugated with quantum dots or gold nanocluster.^{2,3}

Erythrocytes

Erythrocytes are the most numerous cell in the blood. Some characteristics such as its biocompatibility, biodegradability, and non-immunogenicity, make these entities interesting to be used in as DDS.⁴ For instance, ASNase was conjugated with some copies of a glycoprotein A- through of binding peptide and then binding to erythrocytes to get high affinity. This procedure allows to reduce the development of antibodies and increase the effect pharmacodynamics of the drug.⁴ Nowadays, conjugated erythrocytes there is neither in the pharmaceutical market (nor approved by the FDA), but there are studies about non-conjugated erythrocytes in phase I, II and III.⁵ Erythrocytes as carriers of DDS is

complicated to bring to market because of implicating be careful with the parameters that a clinical product must have in both, conjugated and non-conjugated biomolecules. Among parameters that make difficult their market development are: i) cell material source, which refers if the erythrocytes to use come from analogous or homologous donated blood; ii) manufacturing process, which refers to the sterility of the cell suspension and the reduction of leukocytes; iii) product storage, regarding the solution where the erythrocytes are reserved to theirs prompt administrated because they tend to degrade.⁶

Nanoparticles (NPs)

The use of nanoparticles in DDS would be a good alternative for cancer therapy or diagnosis. In this regards, polymeric nanoparticles have been prepared, and its characteristics, such as its biodegradability, biocompatibility, and nontoxicity are demonstrated at in vitro phase. Size and shape of these systems are particularly essential to penetrate the tissues. The nanoparticles were conjugated either within or onto the surface of the polymeric nanoparticles with the drug, e.g. Doxorubicin.⁷

Nanoparticles could be classified taking into account its origin as biological (i.e. biomolecules), or as non-biological. Regarding nanoparticles generated through non-biological materials, several materials i.e. metallic or metal oxide materials, and polymeric substrates (i.e. PLGA, PLA, PEG, hydrogel, chitosan analog) have been used to generated nanoparticles (NPs). Surface NPs are covalently modified taking into account the therapeutic agent, the ligand and the NP material (**Figure 2**). The most studied reactions in the conjugation with NPs are: hydrazide-aldehyde, amide, thiol-meleimide, thiol-thiol, gold-thiol and click chemistry.⁸

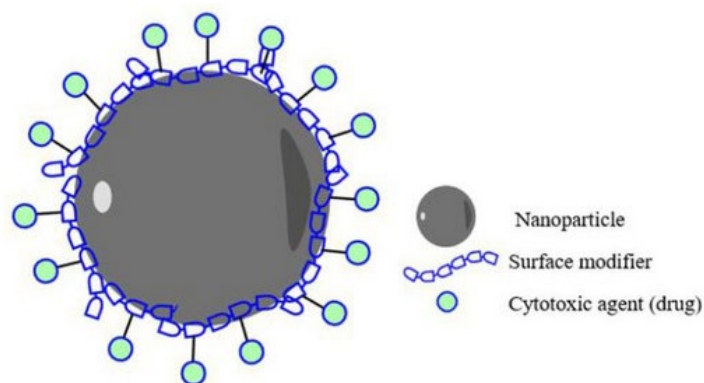


Figure 2. General structure of nanoparticles as DDS.

Antibody Drug Conjugates (ADC's)

Focusing on ADCs, there have been many academic, but also industrial efforts, aimed at the design of antibodies armed with drugs, cytokines, toxins and radionuclides, all of them with application in cancer therapy.⁹

The possibility to combine the favorable binding properties of mAbs with the biocidal activity of potent cytotoxic agents promises to increase the therapeutic index of therapeutic payloads. ADC systems use a bifunctional linker to conjugate the drug and the antibody, which should be specific for determined cancer cells or target. ADC's applications would be extended to the therapies of other diseases.⁹

At present, four ADC products hold market authorization for the therapy of certain types of cancers: AdcetrisTM,^{10,11} KadcylaTM,¹² BesponsaTM,^{13,14} MylotargTM.¹⁵ (**Figure 3**) AdcetrisTM (Brentuximab Vedotin, BV) is an anti-neoplastic agent used in the treatment of Hodgkin lymphoma and systemic anaplastic large cell lymphoma. BV is obtained through the covalent conjugation of the mouse-human chimeric monoclonal antibody IgG1 antiCD30 (cAC 10), with monomethyl auristatin E (MMAE), a toxin which is a synthetic antitubulin analog, using an enzymatically cleavable dipeptide linker. (**Figure 3A**) On average each antibody molecule was conjugated to four groups of MMAE.^{10,11}

On the other hand, KadcylaTM (Trastuzumab emtansine) is an innovative, unique and selective antineoplastic drug used in patients with advanced breast cancer (HER2+).⁷ This ADC is composed of the antiHER2 antibody trastuzumab (Herceptin®) and the cytotoxic agent microtubules, DM1, bound through a bifunctional succinimidyl 4-(N-maleimidomethyl)cyclohexane-1-carboxylate (SMCC) as noncleavable linker. This drug acts selectively on HER2 + tumors cells, exercising, on one hand, the mechanisms of action of the trastuzumab, and on the other hand the powerful cytotoxic effect of DM1. (**Figure 3B**) The main advantage of this ADC is that it has a selective release,

allowed to minimize its side effects in comparison to other agents for the same pathology.¹²

Besponsa™ (Inotuzumab ozogamicina) is prescribed for adults with acute lymphoblastic leukemia (ALL) whose disease has stopped responding to conventional chemotherapy (recurrence), or never responded to it (refractory). The carrier of Inotuzumab ozogamicina is a monoclonal antibody that attacks the CD22 protein, which is produced in excess on the surface of lymphoblastic leukemia cells. The antibody binds to a compound called calicheamicin that kills cancer cells using hydrazone linker (Figure 3C). Once inotuzumab antibody binds to CD22 in the cancer cells, the calicheamicin is released into the cell where it damages cellular DNA and causes its death.^{13,14}

Finally, Mylotarg™ (Gemtuzumab ozogamicin) has been prescribed for the treatment of acute myeloid leukemia (AML), a bone marrow cancer. Structurally it is similar to Besponsa, varying only the antibody used. In this case, Inotuzumab ozogamicin consists of a recombinant humanized IgG4 kappa CD22-targeting monoclonal antibody covalently attached to calicheamicin derivative, which is a potent DNA-binding cytotoxic agent (Figure 3C).¹⁵

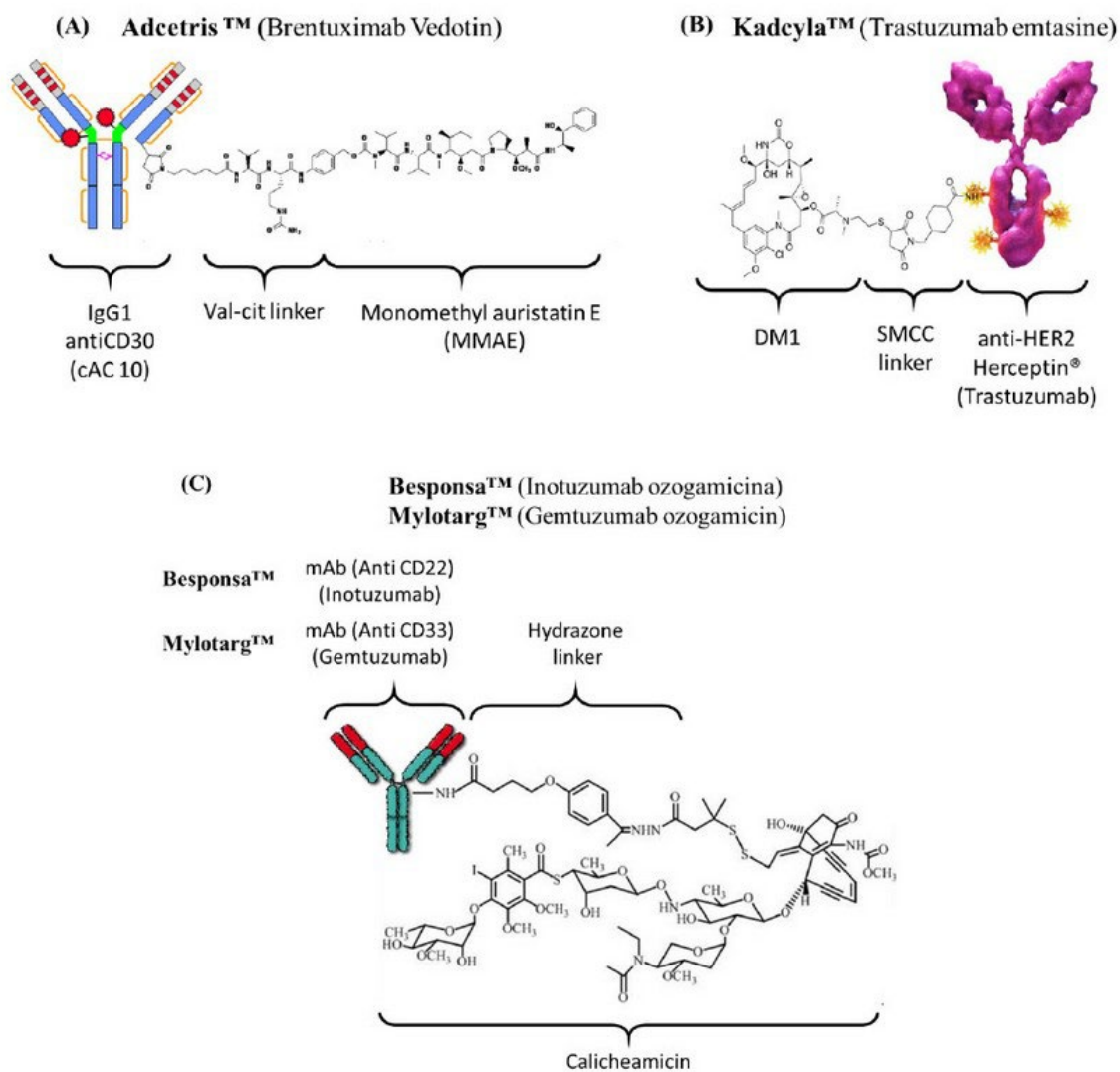


Figure 3. General structures of ADC's approved by FDA. A, Adcetris™ (Brentuximab Vedotin, BV); B: Kadecyla™ (Trastuzumab emtansine); C: Besponsa™ (Inotuzumab ozogamicina) and Mylotarg™ (Gemtuzumab ozogamicin).

CONCLUSIONS

DDS based on biomolecules as liposomes, erythrocytes, or antibodies, but also nanoparticles, have been extensively reported in scientific bibliography in the last five years. Because of the high impact of conjugates as potential medical treatments, it is always desirable the development of new synthetic methodologies which allowed to obtain novel entities.

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