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Research Paper

A Review Article on Novel Drug Delivery System

Saurabh Pandey*
Institutional Affilation- SAM College of Pharmacy Bhopal Madhya Pradesh
Gmail ID:pandeysaurabh1412@gmail. Com
ADDRESS :Kolua, Gram Adampur Chawni, Raisen Road, Bhopal (M.P.) 462021
Corresponding Author: Saurabh Pandey,*

ABSTRACT
The science and technology has emerged in pharmaceutical research with focus on developing novel drug delivery systems for oral administration. Conventional dosage forms like tablets and capsules are associated with a low bioavailability, frequent application, side effects and hence patient noncompliance. By developing novel strategies for drug delivery, researchers embraced an alternative to traditional drug delivery systems. Out of those, fast dissolving drug delivery systems are very eminent among pediatrics and geriatrics. Orally disintegrating films are superior over fast dissolving tablets as the latter are assigned with the risk of suffocation. Due to their ability of bypassing the dissolution and the first pass effect after oral administration, self-emulsifying formulations have also become increasingly popular in improving oral bioavailability of hydrophobic drugs. Osmotic devices enable a controlled drug delivery independent upon gastrointestinal conditions using osmosis as driving force. The advances in nanotechnology and the variety of possible materials and formulation factors enable a targeted delivery and triggered release. Vesicular systems can be easily modified as required and provide a controlled and sustained drug delivery to a specific site. Today's drug delivery technologies enable the embodiment of the drug into novel delivery devices and hence facilitate various therapeutic and commercial benefits. Ranging from fast dissolving to Nano particulate drug delivery systems, a variety of novel delivery systems have been developed and evaluated and numerous strategies for a controlled drug delivery to a specific target-site have been researched. However, there are several challenges remaining. One of the permanent features of drug delivery technologies, is the important part that polymers play in navigating the drug liberation as well as in manufacturing drug carriers. Progress, especially in the field of nanotechnology, is limited by the availability of suitable biocompatible polymers. An ongoing interest in new polymer synthesis has occurred due to the demand for polymers with aimed physical and biological features. For this reason, a wide array of biodegradable polymers form natural or synthetic origin has been studied for their ability of an extended drug liberation and targeted drug delivery. So far, only a small number of them are found to be biocompatible. From the manufacturing perspective, conventional methods have the merit of easy scale-up but are likely to lose conciseness in monitoring over particle characteristics. Although top-down techniques would allow to regulate size and shape, they are only applicable to a few drug delivery systems. Several other approaches have been made including in the treatment of diabetes mellitus to address the limitations with the administration of insulin. By using the glucose modulation, the insulin delivery rates can be regulated enabling a self-regulated drug delivery. The major challenge is to develop a delivery system that exhibits the natural pattern of insulin release in vivo. Critically concluded, the need for new materials for their quality of being biodegradable, biocompatible and low toxicity will be met in future and in combination with novel fabrication techniques will provide significant advantages in drug delivery.

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I. INTRODUCTION

Novel drug delivery system (NDDS) is an expression mainly associated with the formulation of new pharmaceutical forms which have optimized characteristics such as smaller particle size, higher permeability parameters, and selective site tar- getting. NDDSs can be used to enhance the performance of biotherapeutic agents when compared with their effect in the conventional dosage forms. This chapter will explain the concept of NDDS, the different methods of design, and some of their clinical applications. [INTRO]

Generally, the pharmaceutical drug delivery system consists of:

1. A suitable dosage form (pharmaceutical formulations) that carries the drug into the body.

2. The release mechanism of a drug from the dosage form to the organ/cells of targeting after administration.

3. An optimum medical device/pharmaceutical technique used for manufacturing the dosage form.

Therefore a NDDS could be obtained:

1. Formulation of SMART Nano carrier-based drug delivery systems to improve the cell selective for enhanced targeting.
2. Superior controlling of the duration of action (SMART extended release drug delivery systems).
3. Utilization of novel techniques of manufacturing, for example, microfluidics (MF).

II. KEY POINTS

Novel drug delivery system, Smart Nano carrier-Based, Mechanism,Stimulate, Polymericmicelles, Microfluidics,

III. SMART NANOCARRIER-BASED DRUG DELIVERY SYSTEMS

A carrier-based drug delivery system implies that drug molecules will be loaded into vesicular and/or polymeric system. Some examples of SMART Nano systems are polymeric micelles, liposomes, dendrite's, and nanoparticles (NPs) [1]. The design of a Nano system with optimum characteristics such as higher drug-loading capacity, smaller particle size (50—300 nm), and controllable release profile are the main goals for designing a successful pharmaceutical product [2].

The term "SMART" means that the Nano carrier drug delivery system can release the drug in response to physiological stimuli thereby targeting it to the diseased cells/tissue with an extended/controllable manner [3].

03. 01. MECHANISMS OF NANO CARRIER TRANSPORT THROUGHOUT THE SYSTEMIC CIRCULATION REACHING THE SPECIFIC TARGET

03. 01. 01. PASSIVE TARGETING

Passive targeting is the primary pathway for a colloidal Nano system via the enhanced permeability and retention (EPR) effect. The EPR effect has been extensively investigated in previous studies. These studies illustrated that the EPR effect highly depends on the degree of vascularity and efficiency of lymphatic drainage at the site of targeting. Increased leakage of blood vessels and inefficient lymphatic drainage might enhance the EPR effect and achieve better accumulation of Nano carriersin targeted tissues [4]. Fortunately, a crucial gain from the EPR effect is that it can be used to maximize the delivery of noncolloidal systems to tumour's or cancer- ous tissues due to their enhanced vascular permeability when compared with healthy tissues (see Fig. 1. 1) [1].

One of the biggest limitations of drug transport via passive diffusion or convection is the lack of site selectivity which might lead to several side effects and drug resistance [5]. To overcome this obstacle, some novel techniques have been designed to formulate colloidal Nano system that can actively and selectively bind with targeted cells after extravasation. This is explained as the active targeting approach [6].

03. 01. 02. ACTIVE TARGETING

Active targeting is an advanced strategy used to ensure selectivity and specificity of SMART Nano system to the targeted site/organ/cells. Commonly, targeting of antitumor drugs to the cancerous tissue has become the main strategy to reduce the effects the drugs might have on healthy tissues. The technique of active targeting should be considered during preparation of the SMART noncolloidal system via functionalization of the surface of the carrier with ligands, which specially bind with its corresponding receptor on the surface of the targeted cell. Ligand—receptor attachment can guarantee that the Nano system will be optimally delivered to the dis- eased cells rather than the surrounding healthy tissue [7]. The attached ligand on the surface of the Nano system can be classified as several subtypes including antibodies or parts of their fragments, nucleic acids (aptamers), and various classes of peptides. These ligands bind with their specific receptors that are densely localized on the surface of tumour cells. This approach also ensures higher cellular uptake through the endocentric pathway [8]. The affinity of binding between the ligand and the receptor which is overexpressed on the surface of the targeted cell is the most important factor affecting the delivery of the drug. After ligand—receptor interaction, two possible mechanisms might occur, the Nano system might start to release part of its encapsulated drug in the close proximity of the tar- get cells and act as sustained release drug reservoir or the intact Nano system is engulfed via endocytosis and the release begins inside the cell [9]. The second mechanism is desirable to ensure efficient delivery of drug inside the cells. Recently, SMART NPs have been widely used as a Nano carrier drug delivery system for cancer therapy. The surface of SMART NPs is functionalized with specific ligands for active targeting (see Fig. 1. 1). These systems take advantage of the fact that tumorous cells

highly express specific receptors that can be targeted with their ligands (see Table 1. 1). Some limitations regarding the clinical application of SMART NPs due to immunogenicity of the targeting ligands and impaired dose delivery because of lysosomal digestion following endocytosis remain as challenges that need to be resolved. Most studies investigate the optimum methods and designs that ensure higher drug efficacy and delivery to over- come these drawbacks [3]

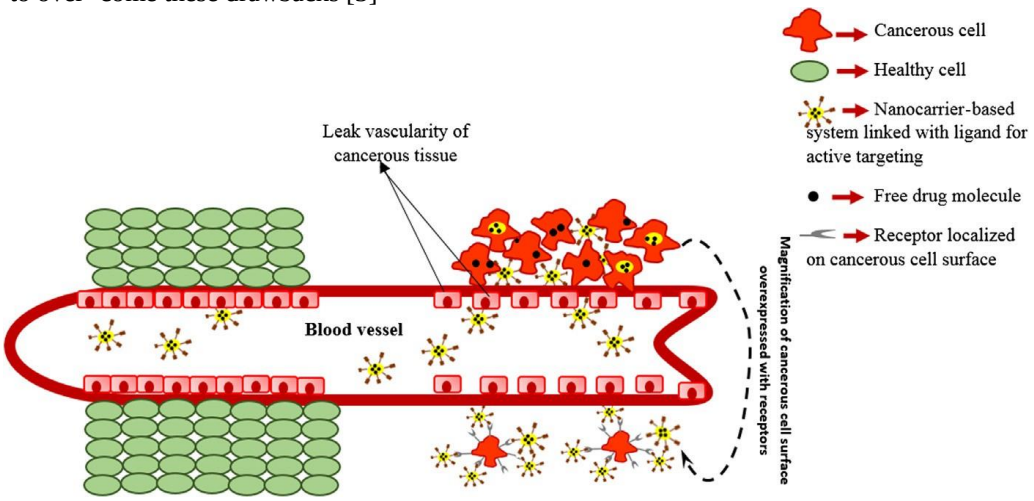

Figure 1. 1 Approaches of nanosystem transport passive and active targeting.

Table 1. 1 Some examples of SMART nanoparticles functionalized with ligands for active targeting.

SMARTNPS	LIGAND	RECEPTOR
Folate-basedNPs	Folicacid	Folatereceptors Prostate-specificmembrane antigen
Biotin-basedNPs	Biotin(vitaminH)	Biotinreceptors
Lectin-basedNPs	Galactose Jacalin	Asialoglycoproteinreceptors Thomsen—Friedenreich carbohydrateantigen
Hyaluronicacid—basedNPs	Hyaluronicacid	GlycoproteinCD44receptorIntegrin $\alpha_v\beta_6$
Peptide-basedNPs	H2009. 1peptide IL-13peptide	IL-13R$\alpha_2$receptor
Monoclonal antibody (mAB)-basedNPs	EGF HER2mABs	EGFR Anti-HER2monoclonalantibodies
Transferrin-basedNPs	Transferrin	Transferrinreceptors

NP, Nanoparticle

3. 01. 03. RESPONSIVE TO STIMULATE TARGETING

This is a newer targeting strategy, is still under investigation as several limitations have emerged after its clinical application. The main concept of this approach is that SMART nanosystems start to release their encapsulated drug content after exposure to an external trigger [3]. These triggers might be pH, temperature, light, ultrasound, or magnetic/electric field [10,20,21]. To optimally apply this technique, one or more of the nanosystem components should be sensitive to these triggers. The advantages of responsive to stimuli targeting include:

- enhancing of nanosystem internalization and binding to the targeted cells [3];
- controlling of the drug release [22];
- reducing of unwanted side effects [3];
- efficient drug distribution throughout the tumor mass [23]; and
- improving the bioavailability of some insoluble class II/IV chemotherapeutic agents [3]. .

03. 02. TYPES OF NANO CARRIER-BASED DRUG DELIVERY SYSTEM

03. 02. 01. LIPOSOMES

Liposomal structure is based on the presence of internal and external zones which have different affinity to the drug molecules (see Fig. 1. 2). A liposome is composed of uni/multilayers of phospholipids organized in vesicular form. The center of this vesicle has a higher affinity to encapsulate hydrophilic drugs, whereas the hydro- phobic drug is incorporated in the peripheral zone between the lipid—phospholipid layers [1,24]. Liposomes are classified into noisome, phytosomes, ethosomes, and transfersomes. The presence of non-ionic surfactant with no or very low concentration

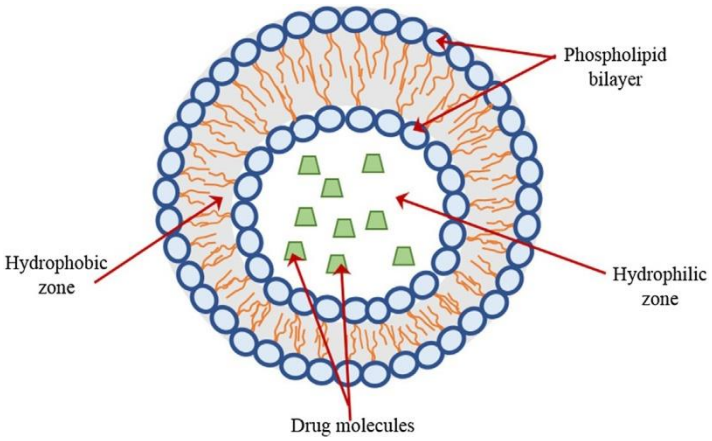

Figure 1. 2 Basic structure of classical unilayer liposome.

of phospholipid leads to formation of niosomes, which have good aqueous dispersibil- ity and stability [7]. Transferomes are considered flexible liposomes with higher elas- ticity due to the presence of single chain surfactant acting as an edge activator. If ethanol is used as a main component in the preparation of liposomes, ethosomes will be produced [25]. When the phospholipids are used to encapsulate an active compo- nent that has herbal origin or extracted from plant, they are called phytosomes [26]. The liposomal vesicular shape has become an attractive form for encapsulating different categories of biotherapeutic agents, which have varying physicochemical properties and three-dimensional (3D) structures. The ability to incorporate several peptides and proteins in liposomes makes them suitable for designing vaccines and delivering cancer therapy [27]. More recently, immunoliposomes have been applied as the liposomal surface can be linked with antibodies directly or by covalent bonds with the polyethylene glycol (PEG) chain of PEGylated liposomes. The presence of PEG chain on the surface of liposomes is a new method used to protect liposomes from the reticuloendothelial system (RES), which will be discussed later. Currently, several liposome-based pharmaceutical products are available in the market (see Table 1. 2) and the development of various liposome-manufacturing techniques has led to the growth of a large industry.

03. 02. 02. POLYMERIC MICELLES

The configuration of polymeric micelles is composed of an external hydrophilic shell and central hydrophobic core suitable for incorporating water-insoluble drugs. The principle of this delivery system is that the hydrophilic shell can mask the nanosytem and protect it from being attacked by the immune system. This is known as the so-called Stealth effect. The Stealth effect enables the nanosytem to pass through the blood vessels with less immunogenic reaction and less uptake by macrophages of RES. This results in a longer circulating time and better kinetic

Table 1. 2 Some of the FDA-approved liposome-based pharmaceutical products available in the market

DRUG	DRUG ROUTE OFADMINISTRATION	CLINICAL INDICATION	TRADE NAME
Vincristine	IV	Acute lymphoblastic leukemia	Marqibo
Verteporphin	IV	Macular degeneration	Visudyne
Cytarabine	Spinal	Neoplastic/lymphomatous meningitis	DepoCyt
Doxorubicin	IV	Breast/ovarian cancer and Kaposi's sarcoma	Doxil/Lipodox/ Myocet
Morphone sulfate	Epidermal	Severe pain	DepoDur
Amphotericin B	IV	Severe fungal infections	Amphotec/Abelcet/Ambisome
Daunorubicin	IV	Leukemia	DaunoXome

[28].

IV, Intravenous

Stability [29]. As a result, the presence of polymeric micelles in systemic circulation will be extended, thereby enhancing the drug bioavailability for Class II and IV candidates (drugs with low solubility) [30]. The major difference between polymeric micelles and the traditional surfactant micelles is that the central core of the polymeric micelle is much larger, which leads to higher power of solubilisation [31].

Polymeric micelles can be functionalized to be "SMART" for active targeting as discussed previously via linkage with targeting ligands [7]. SMART polymeric micelles could be localized into the cell, thereby enabling the modulation of cellular functions such as activity of efflux transporters, gene expression, and apoptotic signal transduction. This property of polymeric micelles has led to their wide use in delivering cancer therapy [7].

03. 02. 03. DENDRIMERS

Dendrites are a less common type of carrier-based Nano system. It differs from most other vesicular systems in its 3D structure (see Fig. 1. 3). It is mainly composed of a central core surrounded by a peripheral zone consisting of densely hyper- branched chains arranged to look tree-like. Dendritic components can be arranged symmetrically as building blocks and the chains can be further functionalized with targeting ligands to form "SMART" dendrimers [32] or attached with imaging contrasting agents for application in diagnostics [33]. Dendrimers are monodispersing macromolecules with nano/microsize. The central cavity of dendrimers might be hydrophilic or lipophilic depending on the nature of its individual units [7]. Dendrimers can be classified into amphiphilic dendrimers, tecto dendrimers, chiral dendrimers, and peptide dendrimers based on the structure [33]. Recently dendrimers have been used for gene delivery and transfection applications.

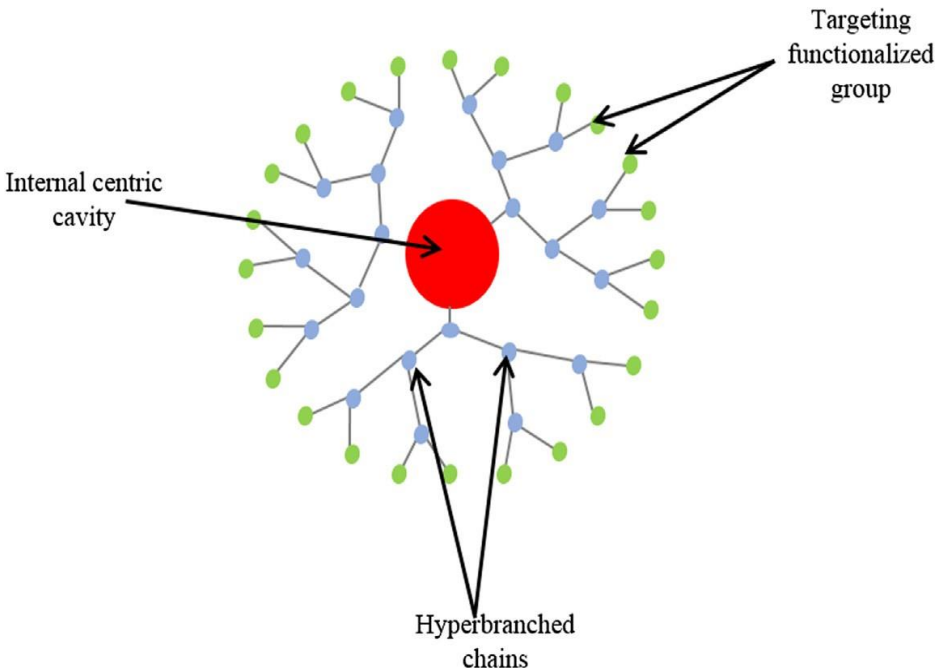

Figure 1. 3 Classical structure of dendrimers.

03. 02. 04. NANOPARTICLES

NPs are classified into several categories of nanomaterials with different configuration such as nanocapsules, nanospheres, nanopores, and Nano shells with particle size ranging from 20 to 250 nm [1]. Polymeric NPs can either encapsulate the drug into their internal phase, or in some cases, free drug molecules might be adsorbed on their surface for initial burst release a short time after administration [34,35]. Polymeric materials such as polylactic-co-glycolic acid (PLGA) and its coblock (PLGA-PEG-PLGA or PEG-PLGA-PEG) have been widely used in NPs preparation due to their biocompatibility and biodegradability [21]. The surface of NPs can also be bound with functionalized groups that can attach to their specific receptors on the cell membrane. The resulting SMART NPs would be actively transported to the targeted cells with higher cellular uptake capacity and better selectivity and without any negative effects on the surrounding healthy tissues [3].

SMART NPs have been improved and developed through several stages with the aim of increasing site selectivity, specificity, and cellular uptake. The first stage includes NPs transported via passive diffusion with no selectivity such as those encapsulating peptides or anticancer drugs [35,36]. Then, an active targeting approach is employed via binding with the targeting ligand attached to its specific receptors overexpressed on the surface of targeted cells. A recent trend in SMART NPs design is to combine more than one drug release mechanisms for emphasis on internalization into the targeted cells [20].

For cellular targeting, the first step is to activate the surface of SMART NPs with functionalized groups for cell targeting. Then, a linkage is formed between the targeting ligand and receptors on the cell surface. A second mechanism that uses pH-responsive polymers for encapsulating anticancer drugs can also be employed. The polymeric matrix starts to lose its architecture in the acidic medium of cancerous tissue, enabling the drug molecules to move freely after localization inside the cancerous cell. The third targeting mechanism is to use densely positively charged polymers that will be attracted to infected cells [37]. PEG chains can also be added on the surface of NPs to extend its presence in the systemic circulation via the Stealth effect (discussed previously) [35]. In recent years, a synthetic polymeric material composed from amphiphilic copoly- mer polystyrene-alt-maleic anhydride functionalized with folic acid using a linkage of 2,4-diaminobutyric acid (FA-DABA-SMA) has gained widespread attention. This is a multifunction polymer that can potentially achieve maximum targeting with lower or no side effects. This polymer exhibits the three possible strategies of targeting: passive targeting, active targeting, and responsive to trigger [10,22]. FA-DABA-SMA has a hydrophobic core that encapsulates low-soluble drugs which include most of the che- motherapeutic agents and a hydrophilic shell that enable it to circulate in the blood vessels with lower immune interaction or macrophage engulfment (RES effect). The surface of the polymer is linked with folic acid to enable active targeting via binding with folic acid receptors that exist on the cell. This polymer is sensitive to pH change and at acidic pH, the microenvironment of cancer tissue, its interior chains begin to open allowing the drug particles to travel out to the nanosystem (see Fig. 1. 4) [3]. The synthesis and clinical applications of FA-DABA-SMA has been widely described in the literature. The initial polymeric material is polystyrene-alt-maleic anhydride that forms the main spherical nanoshape. The ligand (folic acid) is com- bined with a linker (DABA) by a chemical interaction between folic acid, dicyclo- hexylcarbodiimide, and hydroxy succinimide to form a stable functionalized group [22]. FA-DABA-SMA has been used to encapsulate curcumin as an example of a hydrophobic anticancer drug and also because of its intense fluorescent property [38,39]. FA-DABA-SMA encapsulates curcumin into its hydrophobic core to form an advanced SMART nanocarrier-based drug delivery system [40]. Preclinical stud- ies have shown that FA-DABA-SMA NPs loaded with curcumin can be selectively targeted to pancreatic cancer cells with no toxic effect and good therapeutic out- comes [10]. It is hoped that this promising approach of using SMART FA-DABA- SMA NPs will be extended to clinical trials in the future.

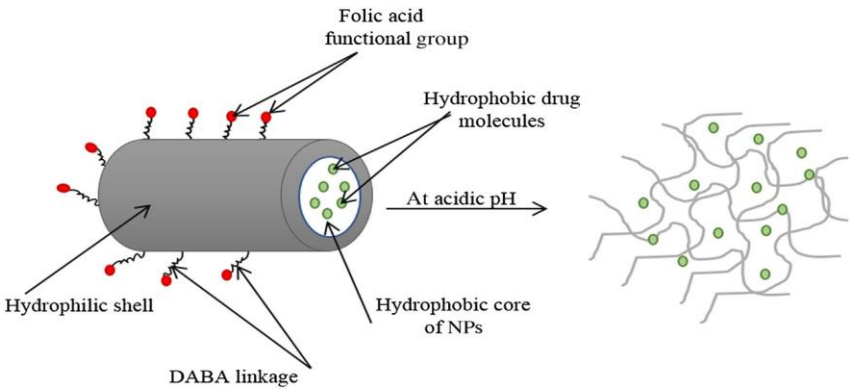

Figure 1. 4 graph showing the configuration of folic acid-2,4-diaminobutyric acid-poly(styrene-alt-maleic anhydride) (FA-DABA-SMA) nanoparticles (NPs) at neutral/ acidic pH.

04. SMART EXTENDED RELEASE DRUG DELIVERY SYSTEM

Controlling the release of drugs from conventional dosage forms has been a point of interest for reducing the frequency of administration and increasing patient com- pliance. Several pharmaceutical techniques such as dissolution matrix/reservoir [41,42], diffusion matrix/reservoir [43,44], floating systems [45], and osmotic sys- tems [46] have been developed in this area. However, several drawbacks have been found after clinical applications including [3]:

- sensitivity to first pass metabolism.
- high cost of preparation.
- Difficulty to deal with drugs of high molecular weights or low-soluble drugs.
- Irritation of gastrointestinal tract.

The EPR effect is the favorable pathway for nanocarriers to be saved from immune response and stay in the circulation for a longer time. Nanocarrier-based drug delivery formulations are usually sterically hindered and therefore they are easily detected by RES and engulfed by macrophages [47]. PEGylation is a strategy that can be used to overcome this obstacle. Addition of PEG chains to the surface of a nanocarrier system stabilizes it and enhances its circulation throughout the blood vessels via the Stealth effect. The immune system is unable to recognize the nanosystem and so no immune reaction against the nanocarrier is elicited. This enables the nanocarrier to be directed to the targeting site with an extended time [48].

A combination of PEGylation and active targeting or responsive to stimuli approaches Is a novel strategy which can ensure higher selectivity and extended release. For example, immunoliposomes, used for vaccines, are linked with monoclonal antibodies for active targeting. Also, PEG chains could be bound on the surface of immunoliposomes to for- mulate PEGylated immunoliposomes which can escape destruction by RES and stay for prolonged time in the circulation [27]. SMART PEGylated NPs conjugated with antibo- dies for active targeting have shown promising results in the treatment of various types of cancers due to their extended availability in the systemic circulation [3].

05. NOVEL TECHNIQUE FOR NANOCARRIER FABRICATION: MICROFLUIDICS

MF is a novel technique that has been developed to fabricate carrier-based drug delivery system and offers several advantages over the traditional pharmaceutical methods of preparation. Nanocarriers DDS prepared by MF technique have opti- mum in vitro characterizations such as higher drug-loading capacity, smaller parti- cle size, uniform size distribution, typical spherical morphology, controllable release pattern, and less side effects [49]. MF technology can be used to fabricate NPs using a single or multiple emulsion technique and incorporate the bioactive agent depending on its hydrophilic/lipo- philic nature in the aqueous or the organic phase [50]. Also, MF technique can combine more than one drugs with different physicochemical properties (solubility and partition coefficient) in the same carrier [49]. The in vitro characteristics of resulting NPs can be well controlled via manipulation of the flow rate of the immis- cible solvents through the MF channels and adjusting geometric parameters of the device [51]. T-junction and coflowing rate are the main operating factors that should be optimally adjusted prior to the beginning of fabrication process [52,53]. This means that each single phase containing its soluble drug of nanoemulsion would flow in a separate microchannel till they reach a point of intersection to then complete the flow in a united channel to the end of process. The shape of these channels looks like the letter "T" [52]. Recently, MF has been widely used in the area of nano/micro carrier—mediated formulations. For example, niosomes are fabricated using MF via vagarious mixing of the two immiscible solvents in MF channels producing niosomal structure with smaller vesicular size than those resulting from the traditional methods [54]. Common polymeric materials such as polycaprolactone, PEG, polyvinyl alcohol [55], and PLGA and its initial components of poly-lactic acid (PLA) [56,57] that are already used in nano/micro formulations due to their biocompatibility, biodegrad- ability, and extended/controlled release behavior could be utilized in MF. Optimum NP configurations can be produced via good modulation of the flow of viscous polymeric materials composed of PLGA and PLGA-PEG [51]. Micro particles of PLGA loaded with bupivacaine have been prepared using a modified single emulsion solvent evaporation technique combined with the flow focusing genome- try of the MF device [58]. Another technique called cross-flow membrane emulsificationhas also used the MF device to produce microsphere of haloperidol (psychiatric drug, dopamine antagonist) encapsulated into PLGA [59]. MF techniques might also be used for manufacturing DDS containing sensitive biological agents such as peptides/proteins. Chitosan microsphere encapsulating insulin has been prepared using MF cross-linkage technique combined with the membrane emulsification method. The resulting microspheres possess optimum particle size and maintain peptide integrity [60]. For liposomes fabrication, the flow rate and the ratio of ethanol to water solution are the main controlling factors affecting the features of the resulting liposomes [61]. Liposomes produced from MF devices have smaller particle size and higher entrapment efficiency when compared to those prepared by the thin film hydration method [62]. Functionalizing of nanocarriers with targeting ligands to form "SMART" system can also be implemented using the MF technique. MF could combine two drugs, each one entrapped in outer or inner zone depending on its hydrophilicity/lipophilicity properties and the whole system can then be transported

via active targeting due to the attached ligand on its surface. Such complicated nanosystems are widely employed in the treatment of cancer [63,64]. For example, a combination of doxorubicin hydro- chloride (hydrophilic) and paclitaxel (hydrophobic) anticancer drugs were encapsulated into PLGA NPs using modified nanoprecipitation MF technique [64]. For prostate cancer, docetaxel and prodrug of cisplatin were incorporated into PLA poly- mer and the surface of SMART NPs was functionalized with 10-Aptameter for active targeting [63]. MF has no found use in clinical applications other than pharmaceutical nano for- mulations. It is used to model and detect in vitro drug toxicological side effects and its influences on body organs. Each organ is represented as a chamber in an MF sys- tem, the drug starts to flow throughout MF channels into these chambers and any pathological/physiological changes occurring in the organs can be detected. Also this method can be applied for an individual drug or a combination of drugs [49]. The Implementation and clinical applications of MF have had a great impact on the pharmaceutical industry. The MF technique has resulted in many new innova- tions in the manufacturing of drug delivery systems. Also MF has been used to screen therapeutic/toxicological effects of bioactive agents via its application at the level of tissue culture studies.

06. IMPORTANCE OF NOVEL DRUG DELIVERY SYSTEM

- *Enhanced drug efficacy:* Novel drug delivery systems can improve the therapeutic effect of drugs by delivering them to the target site in a controlled and sustained manner.
- *Reduced side effects:* By targeting drug delivery, these systems can reduce the exposure of healthy tissues to the drug, minimizing side effects.
- *Improved patient compliance:* Systems that reduce dosing frequency or simplify drug administration can improve patient adherence to treatment regimens.
- *Enhanced drug stability:* Some delivery systems can protect drugs from degradation, improving their stability and shelf life.
- *Targeted drug delivery:* These systems can deliver drugs specifically to the site of action, increasing their concentration at the target and reducing systemic exposure.
- *Controlled drug release:* Novel delivery systems can provide controlled release of drugs, maintaining therapeutic levels over an extended period and reducing the need for frequent dosing.
- *Improved bioavailability:* Some delivery systems can improve the bioavailability of poorly soluble drugs, increasing their absorption and effectiveness.
- *Potential for combination therapies:* Novel delivery systems can enable the delivery of multiple drugs simultaneously or sequentially, allowing for synergistic effects and improved treatment outcomes.
- *Tailored treatments:* These systems can be designed to deliver drugs according to individual patient needs, allowing for personalized medicine approaches.
- *Facilitation of drug development:* Novel drug delivery systems can facilitate the development of new drugs by improving their delivery and efficacy, potentially leading to the development of new treatments for various diseases.

07. SUMMARY AND CONCLUSION

Multifunctional SMART nanotechnology that combines more than one targeting mechanism and provides extended release behavior results in higher selectivity, fewer side effects, better therapeutic index, and improved patient compliance. Therefore future research should focus on nanomedicine and the clinical implemen- tation of these SMART nanocarrier-based drug delivery systems. Nanomedicine can be optimally used for therapeutic purposes and has the potential to be applied in biomedical and diagnostic objectives.

LIST OF ABBREVIATIONS

•	EPR	Enhanced permeability and retention
•	FA-DABA-SMA	Folic acid-2,4-diaminobutyric acid-poly(styrene-alt-maleic anhydride)
•	MF	Microfluidics
•	NDDS	Novel drug delivery system
•	NPs	Nanoparticles
•	PEG	Polyethylene glycol
•	PLA	Polylactic acid
•	PLGA	Polylactic-co-glycolic acid

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