International Journal of Pharmaceutics 565 (2019) 378–390

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Mini review

Managing efficacy and toxicity of drugs: Targeted delivery and excretion

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ARTICLE INFO

Keywords:
Bioactive small molecules
Drug delivery systems
Targeted drug delivery
Drug solubilization
Drug excretion

ABSTRACT

Medicine is a natural companion of mankind in the present era for mere survival from the deadly diseases in ever-increasing polluted environments. Hence, in recent years, major focus of pharmaceutical, medicinal and biophysical research has been navigated in exploring and developing new and simple avenues to enhance the efficacy of the administered drugs on one hand and to get rid of, or at least reduce, the toxic side effects of the excess drugs accumulated in human body on the other. A potential approach to amplify the efficacy of the administered drug is to develop proficient targeted drug delivery systems (DDSs). This review provides an essence of some newly developed simple but prospective strategies on enhancing the efficacy of drugs/bioactive molecules exploiting various drug delivery systems like micelles, cyclodextrins, liposomes etc. to serve the purpose of targeted delivery towards DNA, by endogenous and/or exogenous means. Improved bio-availability and solubilization of ionic drugs within the less polar target regions from the bulk aqueous phase has also been achieved through the introduction of some physiologically permissible salts. In the other context, *in vitro* and *in vivo* studies demonstrate a simple technique for easy removal of the excess adsorbed drug molecules from the cell membranes/lipid bilayers by exploiting health-amiable supramolecular assemblies.

In this review, we summarize the recent experimental findings, mostly from our lab, encompassing the development of simple biocompatible methods to enhance the benevolent role of drugs through their safe, effective and convenient administration. It also presents easy and effective means to remove the excess adsorbed drugs from human body to diminish their malign effects. These prospective approaches of drug delivery and excretion of drug molecules have promising roles to play from both physicochemical and pharmaceutical perspectives, ensuring enhanced bioavailability of drugs as well as disposing of drug-induced adverse side effects.

1. Introduction

In 21st century, medicine has become an integral part of human race for their healthy survival in the increasingly polluted world. However, large intake of drugs invites harmful side effects and the situation is worsening day by day due to the ever-increasing health hazards caused by pollution, unhealthy lifestyle and so forth. Nonetheless, avoiding medicines in this degrading situation can put a serious question mark on the existence of mankind on this planet. The cartoon diagram, as shown in Scheme 1, best represents the present day scenario of human beings in a lighter note. Under this situation, it is a challenge for the scientific community to find a healthy balance between the intake of drug and the associated toxic side effects.

Optimization of the therapeutic activity of drugs by minimizing their adverse side effects can be implemented principally by the following three ways: firstly, by developing suitable drug delivery systems (DDSs) to deliver drug molecules selectively to the target region/s, secondly, by pushing the ionic drugs to the less polar target regions by introducing permissible salts (*electrostatic pushing*, see later) resulting in a greater solubilization of the ionic drugs and lastly, by excretion of the excess drug molecules adsorbed in the cell membranes by means of biocompatible strategies.

DDSs are secured, convenient and effective tools for the easy administration of drugs to achieve maximum availability of the drug at the diseased site and to avert harmful side effects induced by the drugs by improving their pharmacokinetics and bio-distribution profiles (Langer, 1998; Park, 1997; Rotello et al., 2009). DDSs can also endorse the safety of a drug by avoiding its partitioning into healthy cells/organs, putting the undesired release of drug in stomach on hold and thereby curbing gastric damage and subsequently reducing the side effects of the drug to a great extent (Adams et al., 2003; Babish et al., 2010; Maeda et al., 2011; Matsumura, 2011). The smart drug delivery system, called targeted drug delivery system (TDDS) delivers the pharmacologically active moiety (drug) selectively to its site of action within the body in therapeutic concentration, restricting its access to the normal cellular lining and thus, minimizing the toxic side effects

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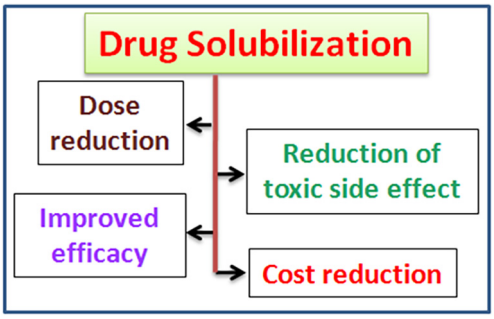
https://doi.org/10.1016/j.ijpharm.2019.04.058
Received 20 March 2019; Received in revised form 17 April 2019; Accepted 19 April 2019
Available online 07 May 2019
0378-5173/

Scheme 1. Cartoon diagram of the present day scenario of human being.

(Gupta and Sharma, 2011; Mishra et al., 2016). The important properties and benefits of targeted drug delivery are shown in Scheme 2. Considering the numerous benefits of the site-specific/targeted delivery of drugs (Scheme 2) over the conventional drug delivery systems, development of such TDDS has undeniably become a challenging and, at the same time, a promising task for the researchers over past three decades. With this realization, a wide variety of nano-sized materials like micelles, cyclodextrins, liposomes, dendrimers, carbon nanotube (CNT), quantum dots, silver nanoparticles (AuNPs), graphene, hydrogels, conjugates etc. have been employed as potential TDDSs (Culver et al., 2017; Goenka et al., 2014; Lee et al., 2015; LoRusso et al., 2011; Mehta et al., 1984; Peer et al., 2007; Ranade et al., 2004; Rotello et al., 2009; Shi et al., 2010; Soussan et al., 2009; Torchilin, 2007; Yih and Al-Fandi, 2006; Zhu and Mahato, 2010). Among the TDDSs, supramolecular assemblies like micelles, liposomes etc. are extensively exploited because of their easy availability, permeability, health friendly nature along with their extended residence time (Allen and Cullis, 2013; Hubbell, 2003; Kataoka et al., 2001; Langer and Kral, 1999; Moughton et al., 2012; Needham and Dewhirst, 2001; Petrov et al., 2009; Torchilin, 2001).

Delivery of the drug from carrier to the desired target is principally controlled by two approaches: endogenous and exogenous (Hatakeyama, 2017). For delivery through endogenous mode, definite physicochemical properties of the drug together with the nature of the microenvironments are exploited for controlling and releasing the carrier-bound drug to the desired target. On the other hand, exogenous delivery involves external stimulating agents like temperature, magnetic field, ultrasound, high energy radiation etc. or some health-friendly external agent to trigger the delivery of the drug at the preferred site (Dobson et al., 2008; Du et al., 2011; Hatakeyama, 2017; Jiang et al., 2006; Kim et al., 2006; Kono et al., 2002; Schroeder et al., 2009; Torchilin, 2009; Yatvin et al., 2013). The essential criterion for a viable DDS is that the carrier does not affect the native structure and functions of the desired target. Compared to stimulus-assisted delivery, release of drugs through endogenous activation is easier since the latter does not invite complicacies from the external stimulant and also avoiding the presence of complex equilibria involving drug, carrier, target and stimulant. This review aims to discuss both endogenous and exogenous delivery of drugs/therapeutics from the TDDSs constructed by various supramolecular assemblies to one of the most relevant biomolecular target, namely DNA.

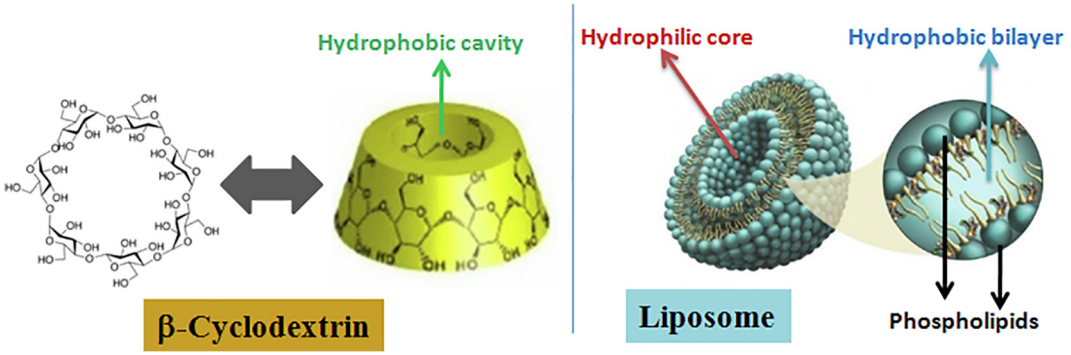


Scheme 3. Potential benefits of drug solubilization at the targeted region.

Apart from the major achievements in developing drug formulations and DDSs, the process of drug solubility, gastrointestinal permeability and dissolution are concerned parameters that control the extent of drug absorption and its bioavailability (Amidon et al., 1995). About 40% of the approved drugs and 90% of drugs in the process of discovery suffer from the drawbacks of poor water solubility, rapid metabolism, low permeability and poor elimination from the body and thereby are eliminated from appearing in the clinical trials (Amidon et al., 1995; Hodgson, 2001; Loftsson and Brewster, 2010). Thus, solubilization and dissolution of drugs into target regions are significant factors in the process of drug development. The potential advantages of enhanced drug solubilization are portrayed in Scheme 3. This review provides some simple but effective techniques for greater solubilization and effortless delivery of ionic drugs in hydrophobic target regions from the bulk aqueous phase expecting a drastic improvement in the efficiency of drugs and thereby reducing the dose of drugs required to be administered.

Beside the enhanced bioavailability of drugs, getting rid of the excess drug induced toxicity is still a serious concern to the modern day researchers. Drugs of hydrophilic nature are effectively removed *via* the common water excretory pathways like urine, sweat, saliva, exhaled air, milk etc. Buch presented some age-old chemical techniques for the removal of excess acidic and basic drugs through our urinary system (Buch, 2010). Growing interest in developing various biocompatible strategies to remove the excess unwanted drugs, particularly from the cell membrane, has stimulated us to make use of supramolecular assemblies like micelles and cyclodextrins (CDs) for this purpose. CDs, differing in size and solubility, form truncated cone like structures having hydrophilic exterior and hydrophobic interior (Scheme 4) and hence, are capable of forming non-covalent inclusion complexes with different drugs (Bender and Komiyama, 1978).

Scheme 2. Properties and benefits of targeted drug delivery systems.



Scheme 4. Structures of β-cyclodextrin and liposome.

Non-toxicity of CDs and water solubility of both CD and probe-CD inclusion complexes are supposed to provide suitability of this approach from pharmaceutical perspectives (Bender and Komiyama, 1978; Ghosh et al., 2014c). For various purposes, liposomes (Scheme 4) are widely used as models of cell membranes as they mimic the structure and geometry of cell walls. On the basis of our results of *in vitro* and *in vivo* experiments, we make a strong base of developing new strategies for the removal of deposited drugs from live/model cellular membranes.

For the purpose of targeted drug delivery and excretion of drugs preferentially from the cell membranes, fluorescent drugs or small bioactive molecules of special therapeutic significance is, in general, used and their differential spectroscopic signals in varied environments are analyzed. Scheme 5 depicts the structures of some fluorescent probes, differing in charge characteristics and active functional groups, exploited by us as models of drugs.

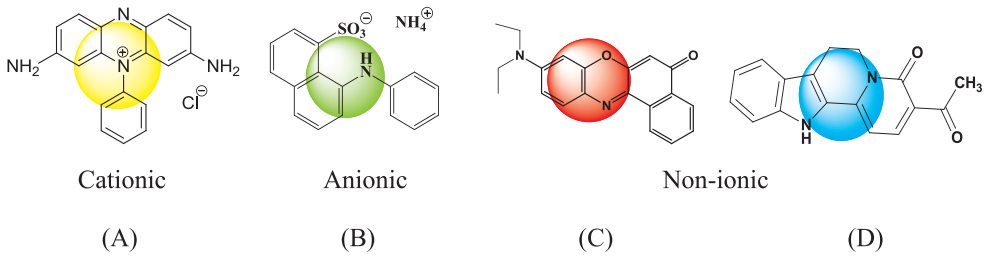
2. Targeted delivery of molecular probes/drugs using drug delivery systems

A target means an area of interest (an organ or a tissue or a cell or a protein or DNA) where drugs are to be delivered by the carrier. Scientists have reported different strategies of drug targeting to the desired organ/tissues like active targeting, passive targeting, inverse targeting, double targeting, dual targeting etc. (Bhargav et al., 2014; Mishra et al., 2016; Rani and Paliwal, 2014). Drug targeting not only increases the therapeutic effectiveness of the drugs but also minimizes toxicity associated with them because of a reduced dose requirement for the therapy. Drug carriers or drug delivery vehicles are special molecules or supramolecular assemblies or nano-particles essentially required for the effective transportation of drug molecules to the vicinity of the target by means of entrapping the drug molecules within them. An ideal drug carrier should be biocompatible, non-toxic, biodegradable, non-immunogenic and should not affect the function and structure of the target and should overcome the blood brain barriers. The drug loaded carrier should be stable in bio-fluids and should release the drug to the target after identification (Rani and Paliwal, 2014). Liposomes, micelles, plasma proteins, nanoparticles, dendrimers, lipoproteins, quantum dots, carbon nanotube (CNT), graphene, hydrogels, conjugates, cyclodextrins are well established DDSs and they are known for enhancing the efficacy of drugs and hence, used as valuable contenders in targeted drug delivery (Bhargav et al., 2014; Culver et al., 2017; Fahmy et al., 2005; Goenka et al., 2014; Khan, 2010; Lee et al., 2015; LoRusso et al., 2011; Mehta et al., 1984; Mishra et al., 2016; Peer et al., 2007; Ranade et al., 2004; Rani and Paliwal, 2014; Rotello et al., 2009; Shi et al., 2010; Soussan et al., 2009; Torchilin, 2007; Yih and Al-Fandi, 2006; Zhu and Mahato, 2010).

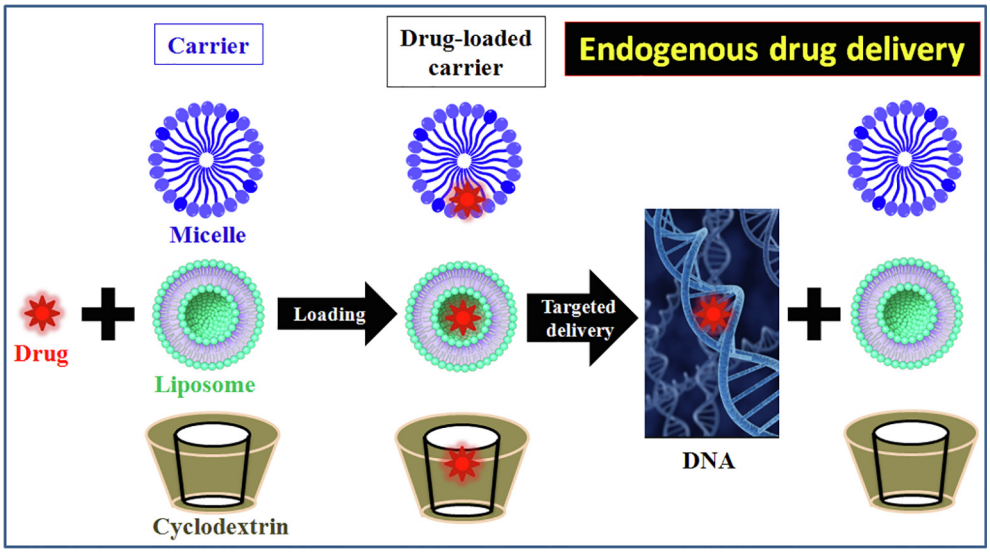
DNA is one of the extensively studied molecular targets that controls the heredity of life, and regulates numerous essential biological functions like gene transcription (Ma et al., 2012), gene expression (Yue et al., 2012; Zhou et al., 2003), mutagenesis (Fei et al., 2009), etc. A wide variety of drugs directly interact with DNA or prevent the proper relaxation of DNA to become important entities of research in medical science, chemistry and life science (Dervan, 2001; Osborne and Ellington, 1997). This review outlines the carrier-mediated targeted delivery of drugs and/or small bioactive molecules to DNA by both endogenous and exogenous mechanisms (Hatakeyama, 2017). These simple but useful strategies of targeted drug delivery are very useful from the perspective of cancer therapy.

2.1. Endogenous delivery

Being simple in mechanism, endogenous delivery of drugs have already been utilized by several research groups for targeting drugs towards cell or tissues and specially to DNA using several nano-sized materials as DDSs (Culver et al., 2017; Ghosh and Chattopadhyay, 2013; Goenka et al., 2014; Lee et al., 2015; Osborne and Ellington, 1997; Peer et al., 2007; Ranade et al., 2004; Torchilin, 2007). Sahu et al. have demonstrated delivery of curcumin, an anticancer drug, to the cancer (HeLa) cells through complex formation with the bovine casein micelles (Sahu et al., 2008). Torchilin has documented micellar carrier-induced delivery of several anticancer drugs like doxorubicin, cisplatin, adriamycin, carboplatin etc. (Torchilin, 2007). Lately, Mazzoli et al. have exploited non-ionic TX-100 micelle to act as a promising drug carrier for the endogenous delivery of anticancer azinium iodides targeted towards DNA (Mazzoli et al., 2015). Liposome and micelle based drug delivery systems have also acquired attention for their



Scheme 5. Structures of (A) phenosafranin (PSF), (B) 8-anilino-1-naphthalene sulfonate (ANS), (C) nile red (NR) and (D) 3-acetyl-4-oxo-6,7-dihydro-12*H*-indolo-[2,3-a]-quinolizine (AODIQ) respectively. Colours of fluorophores roughly correspond to their respective emission bands.



Scheme 6. Scheme of endogenous delivery of drug targeted towards DNA.

widespread applications in the field of pharmaceutical science specially in cancer therapy (Allen and Cullis, 2013; Khan, 2010; Langer and Kral, 1999). Recently, Johnsen et al. have discussed endogenous delivery of exosomes for targeted cancer therapy (Johnsen et al., 2014). Challa et al. have already discussed the utility of cyclodextrins in delivery of protein and peptide and also in gene delivery (Challa et al., 2005). Scheme 6 depicts the general mechanism of endogenous drug delivery targeted to DNA.

For drug-DNA binding, three preferred modes of binding are (i) intercalative binding (ii) major or minor groove binding and (iii) electrostatic binding (Armitage, 1998; Saenger, 1983). For endogenous delivery, the binding studies of a bio-potent cationic probe, phenosafranin (PSF), a photosensitizer with antimalarial activity (Bose et al., 2010; Broglia et al., 2005; do Nascimento et al., 2010; Vennerstrom et al., 1995), with calf thymus DNA (ctDNA) has been examined using various spectroscopic measures (Sarkar et al., 2008). Significant modifications in the steady state absorption and fluorescence studies of the charge transfer (CT) band of PSF upon addition of DNA suggests strong binding interaction between the two (Fig. 1) (Afzal et al., 2016b; Das et al., 2007; Sarkar et al., 2008). High value of the binding constant of PSF with DNA ($5.6 \times 10^4\,M^{-1}$), significant spectral changes in the circular dichoroism (CD) and appreciable enhancement in the helix melting temperature (~5 °C) of DNA in the presence of PSF (Fig. 1) unambiguously establish that the probe binds to the base pairs of ctDNA through intercalative mode (Afzal et al., 2016b; Das et al., 2007; Hildebrand and Benesi, 1949; Sarkar et al., 2008).

2.1.1. Micelle mediated delivery

Micelles, one of the mostly used class of drug carriers, are organized assemblies of the amphiphilic surfactant monomers having hydrophobic tails and hydrophilic heads (Lu and Park, 2013). Micelles have the ability to enhance the solubility and hence bioavailability of drugs by encapsulating them within the micellar core/interface (Kataoka et al., 2001; Khan, 2010; Torchilin, 2007). Enhanced solubilization of drugs also diminishes the risk of aggregation of drugs during intravenous administration (Tuncer Degim and Celebi, 2006). Cabral and Kataoka have reported the application of polymeric micelle based drug delivery systems in clinical studies (Cabral and Kataoka, 2014). In cancer therapy, micelle-based formulation has been used in various stages of clinical trials (Khan, 2010). Generally, non-ionic micelles are exploited as proficient drug carriers for the purpose of targeted drug delivery because of their low toxicity (Mohanty et al., 2013).

Afzal et al. have demonstrated simple techniques of micelle mediated endogenous delivery of drugs to the target, DNA, using non-ionic triton X micellar systems namely, TX-165 and TX-100 (Afzal et al., 2016b,a). Insignificant alteration of the circular dichroism bands of the right-handed B-DNA in the presence of triton X micelles encourages the use of these micellar systems as effective drug carriers for the safe delivery of drugs targeted towards DNA (Afzal et al., 2016b,a). From the fluorometric (both steady state and time resolved) modifications of PSF in different environments (micelles, DNA and (TX micelle + DNA)), it has been established that the probe individually binds with both the DDS and the target. However, in the composite environment, it prefers to bind with DNA leaving the micellar carrier (Fig. 2) (Afzal et al., 2016b,a; Sarkar et al., 2010b). Endogenous transfer of PSF from TX micelles to DNA has been rationalized from the higher binding affinity of PSF with DNA ($5.6 \times 10^4\,M^{-1}$) relative to that with the individual micelles ($1.1 \times 10^4\,M^{-1}$ for TX-165 and $1 \times 10^3\,M^{-1}$ for TX-100). Delivery of PSF to DNA from the TX micelles is further established from the induced circular dichroism spectra of PSF and the DNA helix melting studies in different microenvironments (Fig. 2 for TX-165 micelle) (Afzal et al., 2016b,a). Thus, bio-compatible micelle mediated delivery of drugs to DNA *via* endogenous activation has prospects from the perspective of clinical and medicinal applications because of its mechanistic simplicity (Scheme 6).

2.1.2. Liposome mediated delivery

Liposomes, reported to stabilize the therapeutic compounds, are utilized for intracellular drug delivery and gene therapies, through overcoming the obstructions to cellular and tissue uptake and enhancing the bio-distribution of drugs to the target sites (Allen and Cullis, 2013; Ghosh et al., 2016; Langer and Kral, 1999; Veerati et al., 2015; Zylberberg and Matosevic, 2016). The advantages of liposomal drug carriers are their ability to encapsulate both hydrophilic and hydrophobic chemotherapeutics; improved pharmacokinetic properties, biocompatiblity, increased efficacy and therapeutic index, reduction in drug induced toxicity, minimum antigenicity etc. (Allen and Cullis, 2013; Langer and Kral, 1999). Kraut et al. and Batist et al. have reported clinically approved liposome-based drugs like DaunoXome, Doxil etc., widely used for the treatment of colorectal or colon cancer (Kraut et al., 2005; Miller et al., 2009).

The use of anionic liposome (dimyristoyl-L-α-phosphatidyl glycerol (DMPG)) as nanocarrier for the targeted delivery of PSF to DNA has been successfully achieved by our group through endogenous mode (Ghosh et al., 2016). Circular dichroism studies ensure that DMPG lipid can efficiently serve as a safe DDS for transporting the drug to the DNA

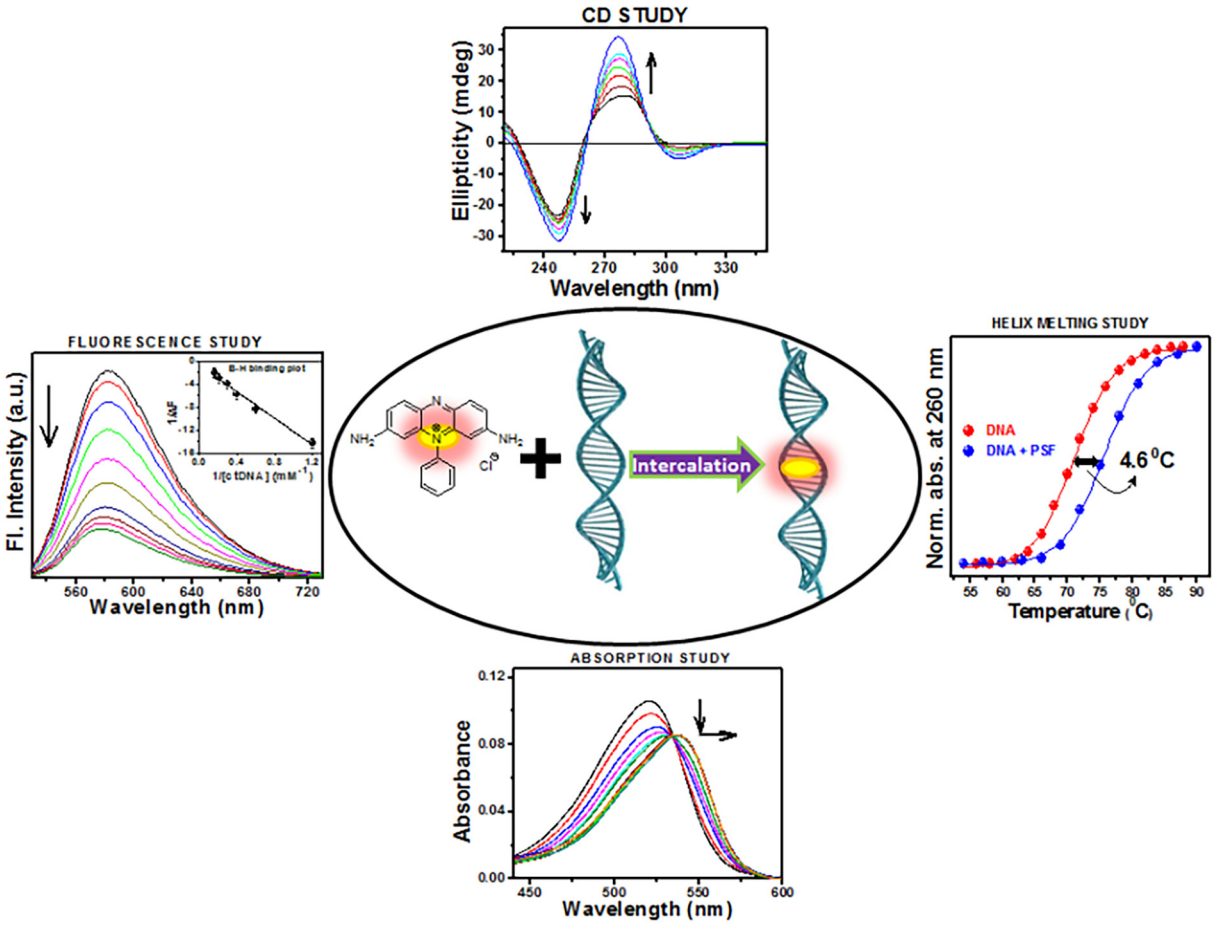


Fig. 1. Multispectroscopic evidences of intercalative binding of PSF with ctDNA. Reproduced with permission from Sarkar et al. (2008). Copyright 2008 American Chemical Society.

without affecting the structure of the latter. Fluorometric modifications (emission maxima and corresponding emission intensities) of PSF in DMPG and DNA media imply that the probe independently binds with the lipid (Sarkar et al., 2010a) and the DNA. However, in the composite medium (DMPG + DNA), PSF preferentially binds with the DNA leaving the liposomal environment completely (Ghosh et al., 2016). An order of magnitude higher binding affinity of PSF with ctDNA ($5.6 \times 10^4\,M^{-1}$) compared to that with DMPG lipid ($5 \times 10^3\,M^{-1}$) favors the endogenous transfer of the probe towards DNA. Exploitation of various spectroscopic techniques like fluorescence decay analysis, circular dichroism, thermal melting profiles of DNA, determination of micropolarity, etc. (Fig. 3) has demonstrated that upon addition of DNA to the DMPG-bound PSF, the probe molecules get dislodged from the lipid environment and bind to the DNA as depicted in Scheme 6 (Ghosh et al., 2016).

2.1.3. Cyclodextrin mediated delivery

Cyclodextrins (CDs), because of their water solubility, non toxicity and complex forming ability with various drug molecules, are successfully used as drug delivery systems in the biomedical and pharmaceutical fields. Loftsson et al. reported that cyclodextrins enhance the formulation, solubilization and stabilization of drug molecules and hence, are utilized as drug carriers (Loftsson et al., 2005). Challa et al. have discussed the applications of cyclodextrins in protein and peptide delivery and also in gene delivery (Challa et al., 2005). Tiwari et al. have reported the application of cyclodextrin as delivery systems in clinical trials (Tiwari et al., 2010). Several groups have also reported cyclodextrin-mediated drug delivery in dermatology, colon specific delivery, oral, nasal and rectal drug delivery (Chordiya Mayur and Senthilkumaran, 1970; Loftsson and Olafsson, 1998; Otero-Espinar et al., 2010). An efficient mechanism for the endogenous delivery of PSF to DNA using gamma-cyclodextrin (γ-CD) as a nano-carrier has been established by our group from the fluorescence studies of PSF in different media (γ-CD, DNA and (γ-CD + DNA)) (Fig. 4) (Kundu et al., 2019). Upon gradual addition of γ-CD, PSF shows slight enhancement in its emission intensity together with a small hypsochromic shift (~2 nm) of the band maximum, suggesting binding interaction of PSF with γ-CD. In the presence of DNA, cyclodextrin-bound PSF replicates the fluorometric pattern, obtained for PSF in pure DNA environment. This implies that in the presence of both γ-CD and DNA, the probe molecules get released from the CD cavity and are intercalated within the base pairs of DNA (Fig. 4). Delivery of the probe is rationalized from the viewpoint of larger binding affinity of PSF towards DNA relative to γ-CD. Similar microenvironments around PSF in the complex environment (γ-CD + DNA) and in pure DNA have also been confirmed from fluorescence anisotropy, fluorescence lifetime and DNA helix melting studies (Fig. 4) (Kundu et al., 2019).

2.2. Exogenous delivery

Compared to the conventional drug delivery mode, the stimuli sensitive responsive nano-materials offer control on drug release leading to a superior efficacy of the loaded drugs (Zhu et al., 2012; Zhu and Torchilin, 2013). Zhu and Torchilin have discussed the application of stimuli-responsive sensitive nanopreparations for enhanced tumor targeting leading to a better antitumor effect (Zhu and Torchilin, 2013). Yao et al. gave an overview about the challenges of certain external stimuli responsive systems in drug delivery and theranostics (Yao et al.,

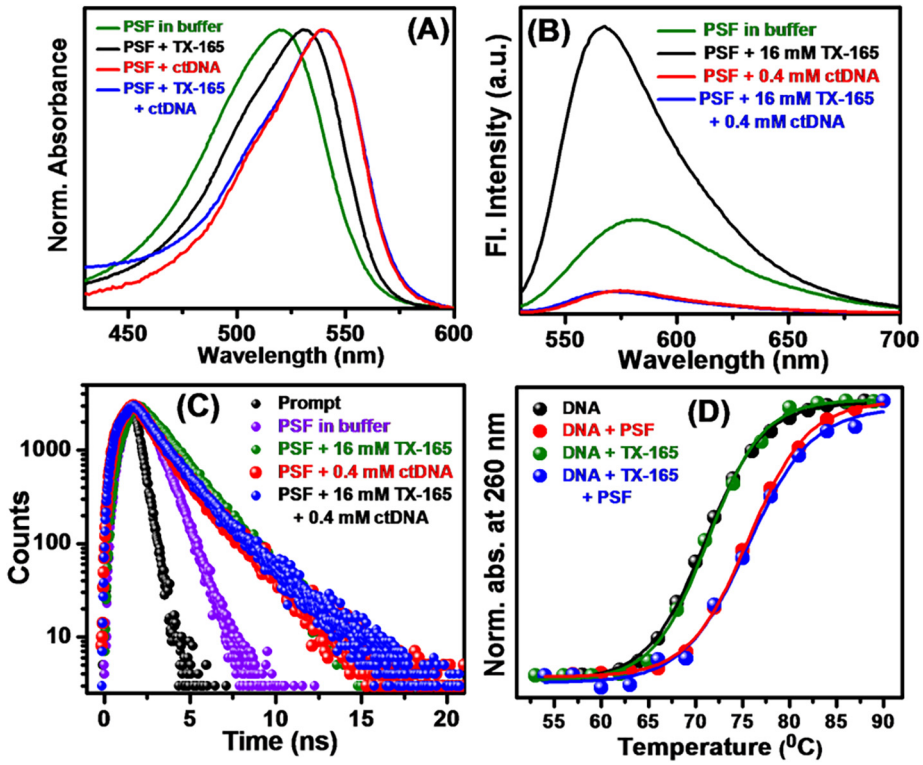


Fig. 2. Multispectroscopic observations (A: absorption; B: emission; C: fluorescence lifetime and D: DNA helix melting) for PSF in different environments as depicted in the legends. Reproduced with permission from Afzal et al. (2016b). Copyright 2016 American Chemical Society.

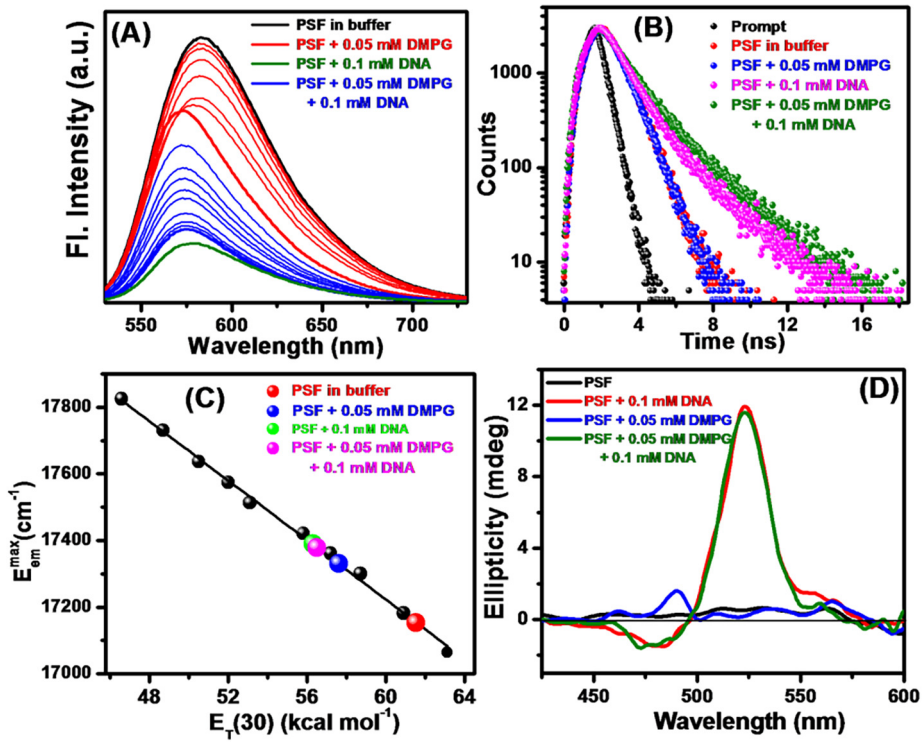


Fig. 3. Multispectroscopic observations (A: emission; B: fluorescence lifetime; C: micropolarity and D: circular dichroism) for PSF in different environments as depicted in the legends. Reproduced with permission from Ghosh et al. (2016). Copyright 2016 Elsevier Ltd.

2016). Photo-responsive release of lectin protein from amphiphilic cyclodextrin host has been reported by Samanta et al. (2012). Stimuli responsive drug delivery systems have exhibited improved therapeutic power for treatment of cancer at the clinical level.

Our group has developed a new approach with the involvement involving an external stimulant (β-cyclodextrin) on for controlled and quantitative delivery of bioactive probes from the micellar nanocarrier to the target for enhancing the drug efficacy and reducing harmful side-

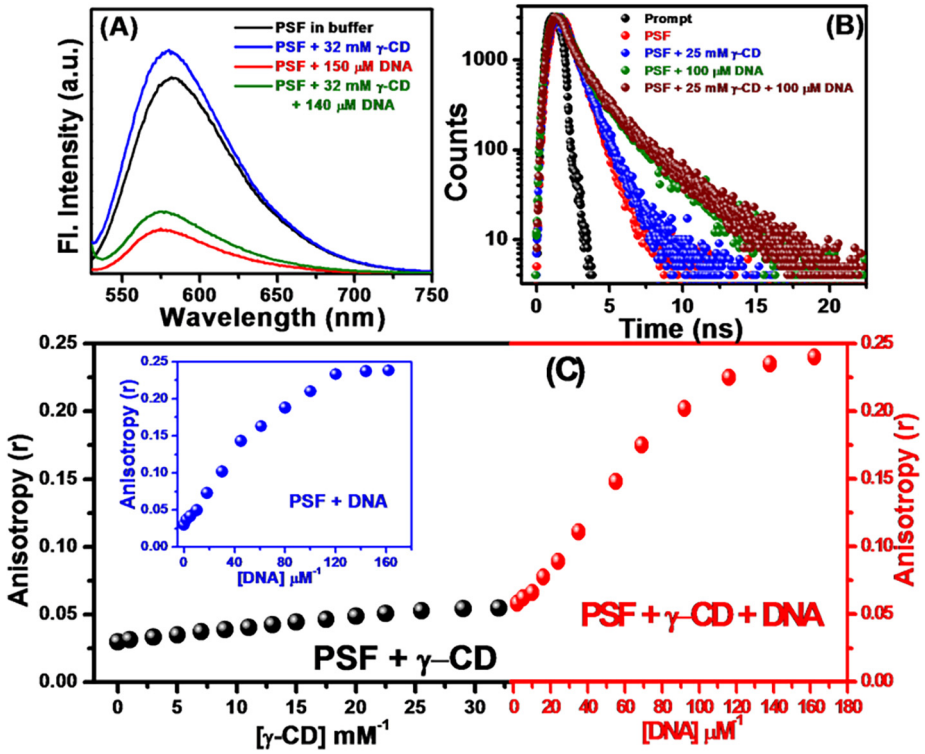


Fig. 4. Multispectroscopic observations (A: emission; B: fluorescence lifetime and C: fluorescence anisotropy) for PSF in different environments as depicted in the legends. Reproduced with permission from Kundu et al. (2019). Copyright 2019 NISCAIR.

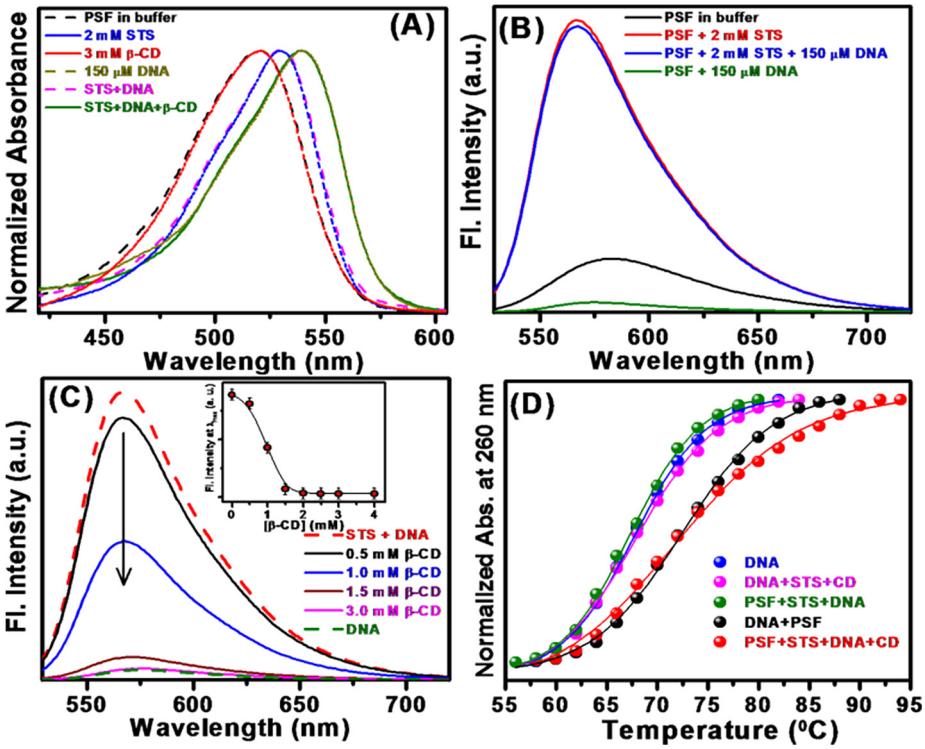


Fig. 5. Multispectroscopic observations (A: absorption; B and C: emission and D: DNA helix melting) for PSF in different environments as depicted in the legends. Reproduced with permission from Kundu et al. (2016). Copyright 2016 Royal Society of Chemistry.

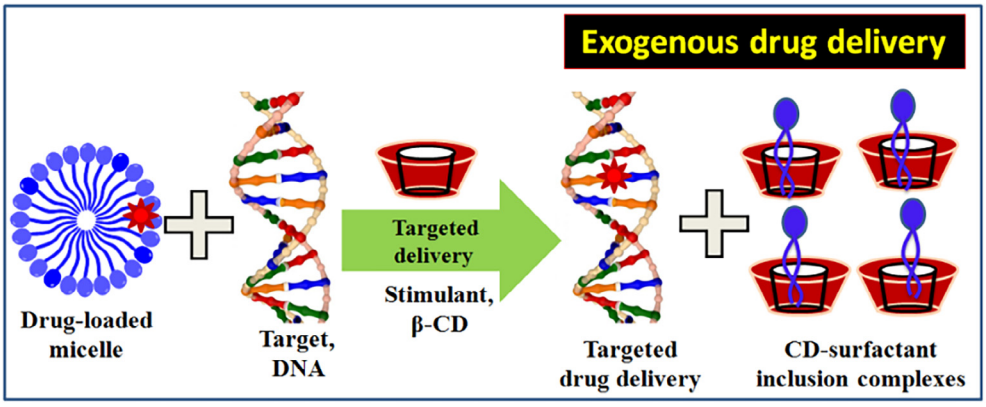
effects (Kundu et al., 2016; Kundu and Chattopadhyay, 2019). Targeted and controlled delivery of PSF to the ctDNA using sodium tetradecyl sulfate (STS) micelle as DDS and β-cyclodextrin (β-CD) as the stimulant has been successfully achieved exploiting multispectroscopic techniques including helix melting studies of DNA (Kundu et al., 2016). Water solubility and non-toxicity of β-CD, and insignificant interactions effects of both the carrier (STS) and stimulant (β-CD) on the secondary structure (as reflected from the intrinsic CD spectra of ctDNA in the absence and in the presence of STS and β-CD) and hence function of DNA reveal the potency of this strategy for clinical and medicinal

purpose (Ghosh et al., 2014c; Kundu et al., 2016). Absorption and emission spectral changes (both intensity and position of the band maximum) of PSF in the STS micelle and DNA imply that the probe binds with both the carrier and the target, independently. The spectral changes further infer that the probe resides exclusively in the micellar environment even in the presence of ctDNA (Fig. 5). Stronger binding of PSF with the STS micelle ($\sim 10^6\,M^{-1}$) (Das et al., 2007) compared to that with DNA ($5.6 \times 10^4\,M^{-1}$) is accountable for the preferred binding of the probe with STS micelle (Fig. 5) (Kundu et al., 2016). However, addition of β-CD to the composite system containing PSF, STS micelle and DNA, leads to the drastic modification of the spectral profile of PSF and at around 3 mM β-CD, intensity as well as band position of the emission spectrum of PSF match with those of the probe in pure ctDNA (Fig. 5), suggesting that the probe is fully delivered to the DNA from the micellar nanocarrier. Formation of inclusion complexes between β-CD and the hydrophobic tail of the constituents of STS micelle is believed to rupture the micellar aggregates leading to the exogenous delivery of PSF from STS nanocarrier to the DNA (Joseph et al., 2007; Lazzara and Milioto, 2008). Pertinently, by regulating the concentration β-CD, the quantum of delivery of PSF can be tuned, making the targeted drug delivery process controlled and quantitative. In another work, similar exogenous transfer of a synthesized pyrazole derivative to DNA using non-ionic micellar (TX-165) carrier has recently been reported by our group (Kundu and Chattopadhyay, 2019). Singh and Nath have also reported the stimuli-induced transfer of thioflavin T from micellar environment to DNA (Singh and Nath, 2013). The schematic representation of stimuli-responsive exogenous delivery of a drug is portrayed in Scheme 7. This strategy of exogenous transfer of drugs has the potential of revolutionizing the drug delivery process in the coming days.

3. Enhanced solubilization of ionic drugs

The therapeutic efficiency of many drugs is often limited because of their poor water solubility, rapid metabolism and low permeability (Amidon et al., 1995; Loftsson and Brewster, 2010). Efficacy of a drug can be enhanced by increasing the contact area of the drug with the target system as well as the concentration of the drug in the area of action (Afzal et al., 2017; Ghosh et al., 2014b; Sarkar et al., 2010c). Loh et al. have reported a milling technique for improving the solubility of poorly water-soluble drugs (Loh et al., 2014). Savjani et al. have given an overview of different techniques for enhancement of solubility of feebly soluble drugs involving physical (particle size reduction, drug dispersion, cryogenic techniques etc.) and chemical modifications (change in pH, complexation, salt formation, derivatization etc.) (Savjani et al., 2012). Our group has been working on improving the solubilization of ionic drugs, in less polar bio-environments from bulk aqueous medium through the introduction of some activating agents leading to an enhancement in the bioavailability of the drug (Afzal et al., 2017; Ghosh et al., 2014b; Sarkar et al., 2010c). A simple and effective strategy, coined as *electrostatic pushing* of the ionic drugs within micellar environment using permissible salts, has been developed by our group for improved cellular uptake and internalization of ionic drugs. The strategy has been demonstrated on a polarity sensitive anionic fluorophore namely, 8-anilino-1-naphthalene sulfonate (ANS) (Vanderkooi and Martonosi, 1969) (Scheme 5), which is pushed within the hydrophobic interior of the cationic cetyltrimethylammonium bromide (CTAB) micelle in the presence of halide ions (Sarkar et al., 2010c). Steady state fluorometric studies of ANS reveal that addition of KBr salt to the micelle-bound ANS leads to a significant enhancement in the fluorescence intensity together with a little hypsochromic shift (~4 nm) of the band maximum (Fig. 6), contrary to the expected bromide-induced quenching due to heavy atom effect. Addition of bromide ions to CTAB-bound probe increases the concentration of bromide ions in the immediate neighborhood of ANS (sitting in the micelle-water interface), resulting in an enhanced electrostatic repulsion operating between the anionic probe and Br^- ions forcing ANS to move further inside the micelle. Time resolved fluorometric studies (Fig. 6) also confirm that the anionic probe is pushed more into the interior of the cationic micelles by the Br^- ions and establish the proposition of the *electrostatic pushing effect* (Sarkar et al., 2010c). Another recent work from our group has established the efficiency and simplicity of this strategy by pushing cationic PSF electrostatically within the interior of anionic sodium dodecyl sulfate (SDS) micelle using cations of various permissible salts. It has been demonstrated that the degree of penetration increases with increasing the effective charge density of the cations (Afzal et al., 2017). The electrostatic repulsion between the ionic drug and the similarly charged anions/cations coming from the added salts is capitalized for the purpose. Insignificant change of the micellar size in the presence of the salts implies that this strategy of *electrostatic pushing* (depicted in Scheme 8) has the potential for successful applications in biological systems.

For enhancing the bioavailability of a drug in DNA environment, we applied our *electrostatic pushing* strategy on ANS–DNA system simply by using NaCl (Ghosh et al., 2014b). The work suggests that the increased ionic strength in the solution reduces the repulsion between the anionic ANS and negatively charged phosphate backbone of DNA, and hence favors the binding process. This is an effective strategy which evidences that a negatively charged drug can be pushed into DNA by introducing salts. Care, of course, needs to be taken in using salts to ensure that the structure of DNA is not affected beyond the tolerance limit. In another context, Yousuf et al. have shown that binding interaction of 2′-hydroxyflavone (2′HF) with ctDNA can be enhanced remarkably by complexation of the phenolic part of 2′HF with β-CD (Yousuf et al., 2012).



Scheme 7. Schematic representation of exogenous delivery of drug targeted to DNA.

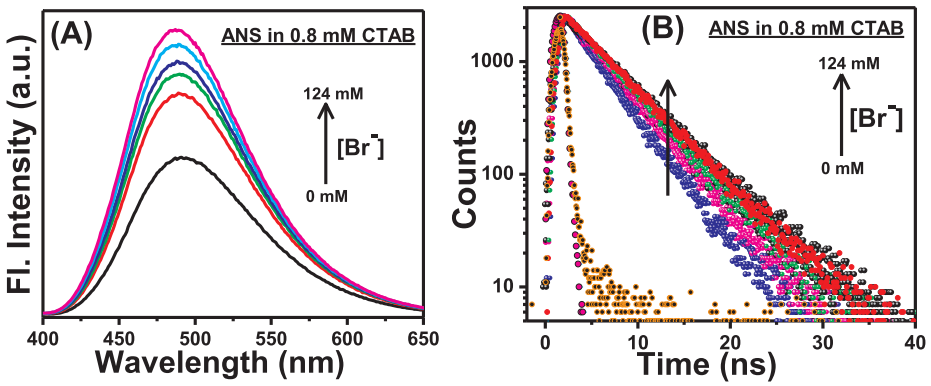
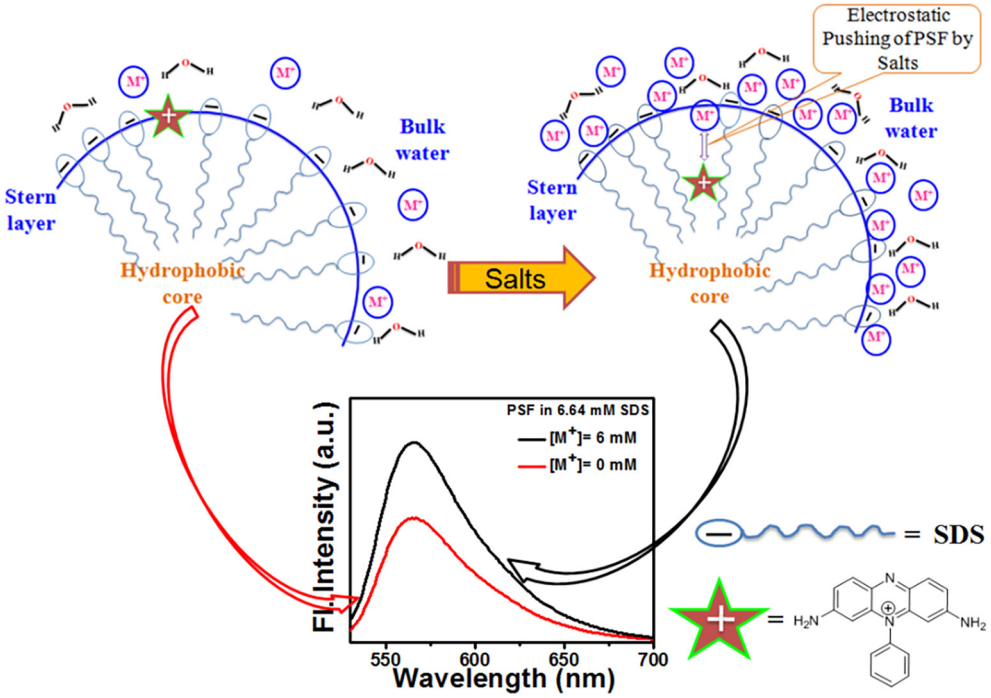


Fig. 6. (A) Fluorescence spectra and (B) time-resolved fluorescence decays of ANS in CTAB with increasing concentration of bromide ion. λ_{ex} = 370 nm. Reproduced with permission from Sarkar et al. (2010c). Copyright 2010 American Chemical Society.

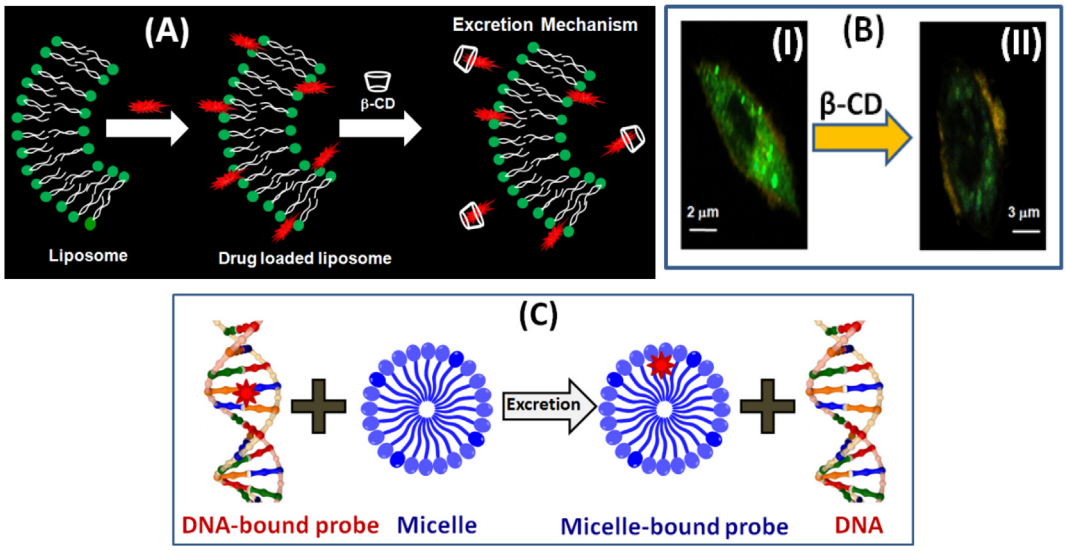
4. Drug excretion

Elimination of excess drug molecules from human body by means of a bio-friendly method is a major issue in chemotherapeutics to get rid of, or at least reduce, the toxicity of drugs. Scientists have reported a good number of excretion routes of the adsorbed drug molecules like renal excretion, biliary excretion, pulmonary excretion, excretion through breast milk etc. (Buch, 2010; Ito and Lee, 2003; Rollins and Klaassen, 1979; van Ginneken and Russel, 1989). We have developed a potential strategy to expel the adsorbed drug molecules from the model and/or real cell membranes by using health-friendly β-CD (Jana et al., 2013; Kundu et al., 2015b; Martinez and Henary, 2016; Sarkar et al., 2010a). Fluorometric studies with varieties of bioactive fluorescent probes like PSF (cationic), ANS (anionic) and nile red (NR, non-ionic) (Scheme 5) with liposomes of different charge characteristics like anionic DMPG, zwitterionic dimyristoyl-L-α-phosphatidylcholine (DMPC) and egg yolk L-α phosphatidyl-choline (EYPC) imply that addition of β-CD to the lipid-bound probe leads to its removal from the liposomal environment (Jana et al., 2013; Kundu et al., 2015b). Differential binding affinity of the probe with the two hosts (lipid and β-CD) results in its expulsion from the lipid membrane, resulting leading to the formation of probe–β-CD inclusion complex (Scheme 9A). It is pertinent to mention here that the solubility of the probe-β-CD inclusion complexes in aqueous medium allows the encapsulated drug to be expelled from the body *via* aforesaid water excretion pathways ensuring suitability of this strategy from the clinical perspective.

The strategy of excretion of drug molecules has successfully been applied *in vivo* for the excretion of nile red (NR), a non-ionic dye of phenoxazone family extensively used to stain lipid droplets and biological tissues (Martinez and Henary, 2016), from the cell membrane of a live Chinese Hamster Ovary (CHO) cell exploiting β-CD (Ghosh et al., 2014a). Confocal microscopy and fluorescence lifetime imaging microscopy (FLIM) image of an NR-stained CHO cell reveal that NR is distributed uniformly across the membrane of the cell, indicating significant binding interaction of the dye with the membrane (Scheme 9B (I)). Emission studies of NR in CHO cell also reveal the binding between the probe and the membrane (Fig. 7A). However, with the addition of β-CD, the peak in the emission profile of NR, responsible for its membrane-bound form, is reduced to a great extent and finally the emission spectrum matches with that of its CD-bound form. Scheme 9B(II) reveals complete removal of NR from the cell membrane with the addition of β-CD and unambiguously divulges that the adsorbed drug is



Scheme 8. Schematic representation of *electrostatic pushing effect.*



Scheme 9. (A) Schematic representation of drug excretion from liposome membrane using β-CD and (B) its *in vivo* application in live CHO cell (Copyright (Ghosh et al., 2014a) Royal Society of Chemistry). (C) Scheme of excretion of drug from the DNA by micelle.

successfully expelled from the membrane. The burst integrated fluorescence lifetime (BIFL) histograms also support the expulsion of NR molecules from the membrane in the presence of β-CD (Fig. 7B) (Ghosh et al., 2014a). In CHO cell, NR gives two different lifetime components and addition of β-CD to the membrane-bound probe results in the development of a third component that qualitatively agrees with the lifetime of the probe in β-CD medium (Fig. 7B(ii)), implying the drug excretion process from the live cell. The extent of expulsion may be controlled by varying the choice of CDs, since the partition of the drug depends on the comparative binding strength of the drug with the cell membrane and the CDs. This *in vivo* study provides a valid demonstration for our approach for easy removal of adsorbed drug molecules from the cell membrane leading to a significant reduction in the toxic side effects of drugs after its action.

Some other studies have recently proposed another useful mechanism namely, surfactant-induced sequestration for the excretion of drug molecules from DNA (Kundu et al., 2015a; Westerlund et al., 2003). Our group has demonstrated the dissociation of drug–DNA complex using cationic surfactant, CTAB (Kundu et al., 2015a). The probe, 3-acetyl-4-oxo-6,7-dihydro-12*H*-indolo-[2,3-*a*]-quinolizine (AODIQ) (Scheme 5), having extensive therapeutic activities (Schilitter and Bein, 1967), is reported to bind to DNA *via* groove binding mode (Kundu et al., 2015a). Stronger binding affinity of the probe with CTAB compared to DNA is accountable for the dissociation of the drug–DNA complex in the presence of the added micelle (Westerlund et al., 2003). Thus, surfactant induced sequestration can be implemented as a simple and proficient strategy to excrete the drug molecules from the DNA (Scheme 9C). One must, however, be cautious to use only lower concentrations of micelles so that the structure and hence functionality of DNA is not affected. The sequential unfolding of two major transport proteins, bovine serum albumin (BSA) and human serum albumin (HSA), by the action of urea or an anionic surfactant SDS (Ghosh et al., 2015; Ghosh and Guchhait, 2009) can also serve as a good technique to squeeze out the adsorbed drug molecules from proteins, though this method cannot be happily prescribed since the structures of the proteins are affected in the presence of added urea or SDS micelle.

5. Conclusion

In the present review we have addressed to the pertinent problems of targeted and controlled drug delivery, enhanced solubilization of ionic drugs as well as the excretion of adsorbed drugs from the living body. Some simple but prospective strategies have been demonstrated for enhanced and targeted delivery as well as excretion of drugs and related small bioactive molecules by means of biocompatible methods. Several downsides like selectivity, tunability, poor bio-distribution etc.

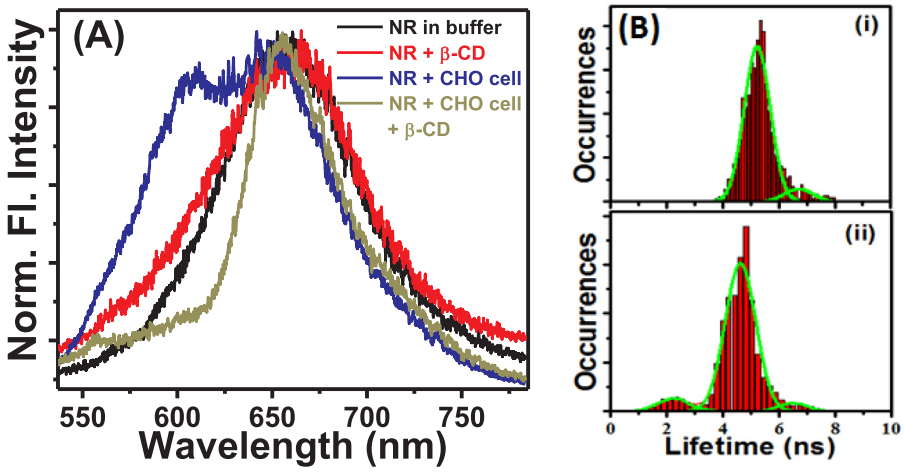


Fig. 7. (A) Normalized emission spectra of NR in buffer, β-CD, CHO cell membrane and CHO cell membrane in the presence of 6 mM β-CD. (B) Lifetime histogram of NR in CHO cell membrane in the (i) absence and (ii) presence of β-CD. Reproduced with permission from Ghosh et al. (2014a). Copyright 2014 Royal Society of Chemistry.

in direct administration of drugs can be taken care of *via* carrier-mediated delivery of drugs through endogenous and/or exogenous means. For the purpose, different supramolecular assemblies such as micelles, liposomes, cyclodextrins etc. are used as carrier or extractor as the case may be. We have also discussed on how modulation of drug–DNA interaction for of ionic drugs by the addition of bio-permissible salts can be exploited favorably for increased solubilization of ionic drugs into the hydrophobic target region. The present review also describes potential strategies that can be applied to excrete the adsorbed drugs from the biological environments simply by the application of cyclodextrins/micelles. The excretion approach exploiting cyclodextrin appears viable both *in vitro* and *in vivo*. These strategies are, expected to, give an impulse in bio-research targeting towards enhancing the drug efficacy and tackling the detrimental side effects of the excess drugs simultaneously.

Acknowledgements

Financial support from the Department of Science and Technology (grant number EMR/2016/001087), Govt. of India, is gratefully acknowledged. The authors are thankful to all the group members and research collaborators for their scientific contributions. P.K. thanks C.S.I.R and S.D. thanks U.G.C. for their senior research fellowships.

Conflict of interest

The authors declare no conflict of interest.

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