Supramolecular assemblies for drug delivery

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Supramolecular chemistry is the branch of chemistry which emphases on the self-aggregation of a discrete number of molecules in a controlled and desired fashion.Supramolecular chemistry has gain much more attention in medicine for their enhance drug delivery to the target cells and therefore minimizing the off-target taken by the cell which causes side-effects. In this review, three major macrocyclic host molecules: block co-polymeric self- assembles, niosome, and cucurbit[n]urils (CBs) as for the application in biomedical applications has been discussed.

I. INTRODUCTION

Supramolecular chemistry is the branch of chemistry which emphases on the self-assembly on a discrete number of molecules [1]. Unlike ordinary molecules comprised of entirely covalent bonds, supramolecule is comprised of non-covalent and weak bonds such as hydrogen bond, dipole-dipole interaction, hydrophobic forces etc. [2]. The use of macromolecular assemblies in the field of medical devices or therapeutics has led to the growing research area of supramolecular biomaterials [3-5]. Supramolecular chemistry has gain much more attention in medicine for their enhance drug delivery to the target cells and therefore minimizing the off-target taken by the cell which causes side-effects [5, 6]. A substantial advantage of supramolecular assemblies in the context of designing of biomaterials is that their properties often follow their molecular-level building blocks; i.e., properties that are predictable, reversible, and tunable [3]. The formation of self-assembly does not require any additional reagents from outside and the process is reversible. In addition to the dynamic and reversible character, these supramolecular systems characteristically exist as a result of a delicate balance of intermolecular interactions. As such, minor alterations in pH, ionic strength, temperature, solvent polarity etc. are enough to cause dramatic changes in these materials.

Drug delivery denotes to the method, formulation technology by which a drug is encapsulated, directed and transported in the body and reaches its target to achieve its therapeutic effect [6,7]. Currently, this field has expanded in the area of nanomedicine, the use of nanoparticle carriers to encapsulate the drug, enhance solubility, protect drug from harsh environmental conditions, improve drug localization towards the disease site and biocompatible [8, 9]. Nanoscale drug carriers can be explicitly targeted, such as in case of cancerous cells, nanocarriers may show preferential accumulation in tumors due to higher permeation and retention effect which results in extravasation of nanocarriers through leaky tumor vasculature [10, 11]. Another significant part in drug delivery has focused on controlled release of drugs from localized depots [1215]. As the supramolecular assemblies form by the noncovalent attachments with its monomeric unit, they can be easily dissociated at desire condition reversibly [16]. Very often polymeric materials have been played a vital role in the preparation of such depots. The polymeric materials are environment friendly and cost-effective. Thus there are huge benefits to using supramolecular assemblies for designing drug delivery system.

In this review, a number of these strategies and their use in the drug delivery will be highlighted. There are large amount of publication appears in each year during the past few decades regarding the various self-assembled noncovalent supramolecular systems, like cyclodextrins, crown ethers, cucurbit, niosomes and so on [17-23]. Therefore we decided to discuss some of the most important carrier for the application in biomedical applications. In this review we discuss three major macrocyclic host molecules: block copolymeric self-assembles, niosome, and cucurbit[n]urils (CBs).

A. Supramolecular Assemblies Based on Block Copolymers

Block-polymeric micelle is a special class of micelles that are formed by the block copolymers comprising of hydrophilic as well as hydrophobic segments [19, 24, 25]. In the self-assembly process the disordered building blocks form an ordered structure through a spontaneous organization governed by specific inter-blocks interaction. The primary requirement for the formation of self-assembled structure is to attain a minimum energy configuration in order to achieve a favorable spontaneous organization toward the equilibrium state of the system [26]. Block copolymers are made up of blocks of different polymerized monomers. The high-molecular-weight nonionic ABA type triblock copolymers consist of polypropylene oxide (PPO) groups as the central block unit and polyethylene oxide (PEO) groups as the outer blocks [18, 27]. A wide range of reports involving Pluronic block copolymers as drug delivery systems for clinical use or trials are published in literature [28,29]. It is reported that the central PPO block becomes more hydrophobic with increasing temperature, while the PEO blocks remain hydrophilic [30]. Owing to this amphiphilic na-

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ture, self-aggregation of Pluronic molecules in aqueous solutions leads to the formation of spherical micelles above a critical temperature and concentration, having hydrophobic PPO cores surrounded by hydrophilic PEO coronas [31]. Pluronics F127 and P123 are widely studied triblock copolymer as drug carrier due to its high stability, bio-adhesive characteristics, thermo-reversible gelling ability at room temperature and non-toxic properties, which make it a suitable vehicle for drug formulations [32, 33]. The block-copolymer micelles are efficient in intracellular drug delivery due to the presence of polyethylene oxide (PEO) groups in its corona which inhibit aggregation and protein adsorption along with this the hydrophobic PPO groups that efficiently incorporates hydrophobic drugs [34]. They efficiently deliver hydrophobic anticancer drugs across the blood, brain, and intestinal barriers [34, 35] and are also used in the treatment of multidrug-resistant tumors. Triblock copolymers interact with both anionic and cationic surfactants (e.g. sodium dodecyl sulfate (SDS), cetyltrimethyl ammonium bromide and so on) in aqueous media and resulting in to the formation of either mixed-micelles or various types of mixed aggregates of ionic surfactant-block copolymer mixed system [36, 19]. SDS binds to the block-copolymer micelles and form block copolymer/SDS mixed micellar complexes and by doing so the drug loading efficiency can be enhanced [19, 37]. In mixed-micelle formation process, block copolymer micelles dissociate into smaller mixed aggregates and thus the aggregation number of the copolymer reduces gradually with increasing concentration of SDS thereby lowering the CMC [36, 37]. Tirrell and co-workers have synthesized hydrogels by functionalizing triblock copolymers poly[(allylglycidyl ether)-b-(ethylene oxide)-b-(allylglycidyl ether)] with either guanidinium or sulfonate functional group and the cross-links triblock co-polymer has applicability in drug delivery systems [38]. Recently Zhao et al. showed that by the conjugation of light-emitting segments polyfluorene (PF) into the triblock copolymer forms a self-assemble fluorescent tracking nanocarriers which can be used for cancer therapy the drug delivery in cancer cells [39]. The block copolymer can also be used to synthesize hybrid nanocarrier by the formation of core-shell structure using Au nanoclusters as core and amphiphilic block copolymer as shell [40, 41]. Amphiphilic block copolymer increases the stability of the nanocarriers and also enhances the drug loading ability. The hybrid nanocarriers can offer high specificity towards cancer cell due to the presence of Au; therefore it can be promising candidate for controlled release of anticancer drugs to the specific to targeted cells [40, 41]. Du at al. has synthesized pH-sensitive block copolymer for the targeted delivery of the drugs by the dissociations of the aggregate trigger by pH [42]. Also Surnar et al. deign the block copolymer for the control intracellular release of the anticancer drugs in cells controlled by enzyme [43].

II. NIOSOMES

Niosomes are a non-ionic surfactant multilamellar vesicular system and these classes of vesicles were introduced by Handjani-Vila et al [44]. Niosomes are structurally similar with liposomes which are lipid-bilayer vesicles mimicking the eukaryotic bilayers. Therefore they improve cellular uptake by encapsulating drugs inside the self-closed spherical nanostructures thus protecting from the degradation and transfer them through the hydrophobic membranes of the cells [17]. Niosomes are nanoscopic lamellar structures and generally the sizes of niosomes are ranging between 10 to 1000 nm [45, 46]. In general, vesicles are made of natural or synthetic neutral or charged phospholipids whereas the niosomes are composed of biodegradable biocompatible non-ionic surfactants and cholesterol [45, 46]. The hydrophilic-lipophilic balance (HLB) value of a surfactant has a significant role in controlling drug encapsulation of the vesicle it forms [47, 48]. A surfactant with a HLB value ranging from 14 to 17 is not suitable to produce niosomes whereas surfactant with a HLB value of about 8.6 gives niosomes with the highest entrapment drug efficiency [47, 48]. Cholesterol influences the physical properties and structure of niosomes probably due to its interaction with the non-ionic surfactants [48]. The amount of cholesterol to be added also depends on the HLB value of the surfactants [45, 46]. As the HLB value increases, it is necessary to increase the minimum amount of cholesterol to be added in order to compensate for the larger head groups [45, 46, 49]. Niosomes are promising vehicles for drug delivery and as non-ionic in nature thus less toxic and improves the therapeutic index of drug by restricting its action to target cells [50, 51]. Niosomes can be easily prepared in the laboratory and the preparation methods must be selected according to its use, since they influence the number of bilayers, size distribution and drug encapsulation efficiency and the membrane permeability [52]. In comparison to liposomes, niosomes have some advantages, such as less toxicity owing to non-ionic nature, greater chemical stability, low cost due to the availability of starting materials; also have high compatibility with biological systems [50, 51]. These advantages along with the ampiphillic nature of these niosomes, allow them to encapsulate both the hydrophilic and hydrophobic drugs within the bilayer and it can deliver drugs through the deeper layers of the skin [53]. This renders them as become potential drug delivery vehicles.

Recently therere several reports have been published regarding the niosomal delivery [54-56]. Moghassemi et al. reported bovine serum albumin (BSA) load and release behavior in niosome synthesized by non-ionic sorbitanmonostearate (Span 60) and cholesterol [57]. The niosome can permeable to oxygen; therefore it also can be used for the carrier of hemoglobin for the patients [58].

III. CUCURBIT[N]URILS IN DRUG DELIVERY

In supramolecular systems cucurbit[n]urils (CB[n], n is the number of glycoluril units) are the important class of drug delivery vehicle. Cucurbiturils, their name came from the pumpkin family (Cucurbitaceae) due to the barrel-shaped structure and it was first synthesized by Robert Behrend in 1905 [59]. Depending on the number of glycoluril subunits (n = 5, 6, 7, 8 or 10) the cavity size of cucurbiturils can be vary [60, 61]. In drug delivery CB[6], CB[7] and CB[8] are the most commonly used vehicles to accommodates large number of drug molecule into its cavity [62]. The drug molecules encapsulate to the cucurbituril portal and form host-guest complexes through hydrophobic interaction and further stabilized by hydrogen bonding or ion-dipole interactions [63]. By the formation of host-guest complex it enhanced the chemical and physical stability by protecting the drug molecules from the environment and control release to the targeted area [63, 64]. Such host (drug)-guest(CB[n]) inclusion complex has comparatively high stability, providing reliable and robust connection for the fabrication of supramolecular systems. It is reported that the binding constant for cyclodextrin based host-guest complexes can reach upto104 M1 whereas that of CB based host-guest complexes can be upto 1015 M1 [65, 66]. Due to reasonable biocompatibility and comparatively strong affinities toward guest molecules, CBs have been received an increasing attention and exploited to host a large number of drug molecules for the purpose of enhanced drug delivery. The stability of pyrazinamide (pyrazine-2-carboxamide) and isoniazid (isonicotinohydrazide) drugs which are used for the treatment of tuberculosis, have been reported to be increased by the enclosure into the nanocavity of CB[7] [67]. Koner and coworkers have shown the relocation of guest molecules from a macrocyclic nanocontainer (CB[7]), used as a drug-delivery vehicle, to circulatory proteins (Bovine and human serum albumin) cavity [68]. Collins et al. used CB[6], CB[7], and CB[8] to form complex with albendazole and shown the enhancement of its aqueous solubility by 2000-fold [69]. They also used CB[7] to entrapment of the anti-cancer drug dinuclear platinum complex and explore its reaction rate, cytotoxicity, and interaction with DNA [70-72]. Wei et al. have improved the solubility of gefitinib which has low solubility in neutral pH, an inhibitor toward epidermal growth factor receptor(EGFR) for lung cancer treatment, by the host-guest complexation with CBs [73]. Wheate and co-workers also explored CBs to increase the aqueous solubility of some platinum complexes used for cancer cells treatment [72].

IV. SUMMARY AND OUTLOOK

Designing drug delivery vehicles, the ultimate challenge is the enhanced efficacy and safety. Compared to other nano-carrier, self-assembled supramolecular systems are one of the most promising classes of biomaterials containing high efficiency and controllable releasing to the targeted cells which reduces side effects. Due to the tunable size of the macromolecules they are easily accommodates large range of the drug molecules and easily eliminated from the body which reduces toxicity. Supramolecular systems carry the drugs by attaching with noncovalent interactions; therefore the release of the drug is easy due to the reversible nature. These advantages make the supramolecular system as a promising and long-term potential candidate for the developments of drug delivery system and researchers are more interest to modify them. For the treatment of cancer several side-effects often occurs and the normal cells affects during the treatment of chemotherapy and the drug use of the treatments are poorly water soluble. Therefore the developments in the research in supramolecular systems could help to overcome this challenge. This review has highlighted the synthesis of different supramolecular based systems that can provide new light in in-vivo control drug release. Nevertheless, many problems are still exist to reach the ultimate goal to achieve targeted delivery without any side effects which is the biggest challenge in cancer therapy and researchers are trying to develop by modifying this exciting class of materials for optimal biomedical applications in the future.

[1] Supramolecular drug delivery platforms in photodynamic therapy T.G. St Denis, M.R. Hamblin, in Applications of Nanoscience in Photomedicine, 2015

[2] J. Sunamoto Advanced Biomaterials in Biomedical Engineering and Drug Delivery Systems (1996) 76

[3] J. Webber and R. Langer,Chem. Soc. Rev., 46, 6600 (2017)

[4] R. Freeman, J.Boekhoven, M.B. Dickerson, R.R. Naik and S.I. Stupp, MRS Bull., 40, 1089 (2015).

[5] M.J. Webber, E.A. Appel, E.W. Meijer and R. Langer, Nat. Mater., 15, 13 (2016).

[6] J.A Hubbell and A. Chilkoti, Science,337, 303 (2012).

[7] M.W. Tibbitt, J.E. Dahlman and R. Langer, J. Am. Chem. Soc., 138, 704 (2016).

[8] A.C. Anselmo and S.Mitragotri, Bioeng. Transl. Med., 1, 10 (2016).

[9] O.C. Farokhzad and R. Langer, ACS Nano, 3, 16 (2009).

[10] H. Maeda, J. Wu, T. Sawa, Y. Matsumura and K. Hori, J. Control.Release, 65, 271 (2000).

[11] A.K. Iyer, G. Khaled, J. Fang and H. Maeda, Drug Discovery Today, 11, 812 (2006).

[12] R. Langer and J. Folkman, Nature, 263, 797 (1976).

[13] N.A. Peppas and A.R. Khare, Adv. Drug Deliv.Rev., 11, 1 (1993).

[14] K.E. Uhrich, S.M. Cannizzaro, R.S. Langer and K.M. Shakesheff, Chem. Rev.,99, 3181 (1999).

[15] J.R. Weiser and W.M. Saltzman, J. Control.Release,190, 664 (2014).
[16] K.Liu, Y.Kang, Z.Wang, and X. Zhang, Adv. Mater.,25, 5530 (2013).
[17] M.D.Daniell, and J.S. Hill, (1991) A history of photodynamic therapy.Aust N Z J Surg, 61: 3408.
[18] R. Kumar, M.-H. Chen, V. S. Parmar, L.A. Samuelson, J. Kumar, R.Nicolosi, S.Yoganathan, and C.A.Watterson, J. Am. Chem. Soc. 126, 10640 (2004).
[19] R.Mondal, N. Ghosh and S.Mukherjee,J. Phys. Chem. B,120, 2968 (2016).
[20] B.K. Paul, N. Ghosh, R.Mondal, and S. Mukherjee,J. Phys. Chem. B, 120, 4091 (2016).
[21] S.Biswal, P.N.Murthy, J. Sahu, P.Sahoo andF. Amir, Int. J. Pharm. Sci. Nanotechnol., 1, 1 (2008).
[22] S.de.M. Barros, S.K. Whitaker, P. Sukthankar, L. A. Avila, S. Gudlur, M. Warner, E.I.C. Beltro and J.M. Tomich,Arch BiochemBiophys.,596, 22 (2016).
[23] Drug Design, Development and Therapy Intranasal niosomes of nefopam with improved bioavailability: preparation, optimization, and in-vivo evaluation 2018:12 3501.
[24] U. Anand andS. Mukherjee, Langmuir,30, 1012 (2014).
[25] G. Wanka, H. Hoffmann, W. Ulbricht, Macromolecules,27, 4145 (1994).
[26] J. N. Israelachvili, Intermolecular and Surface Forces, Academic Press, New York, NY, USA, 2nd edition, 1992.
[27] M. Kumbhakar, T. Goel, S. Nath, T. Mukherjee, H. Pal, J. Phys. Chem. B, 110, 25646 (2006).
[28] B. Jeong, Y.H.Bae, D.S. Lee and S.W. Kim, Nature, 388, 860 (1997).
[29] A. Rsler, G.W.M.Vandermeulen and H.A. Klok, Adv. Drug Deliv. Rev. 64, 270 (2012).
[30] P. Alexandridis, T. Nivaggioli, and T.A. Hatton, Langmuir,11, 1468 (1995).
[31] P.Alexandridis and M.Tsianou,Eur. Polym. J.,47, 569 (2011).
[32] G. Dumortier, J.L.Grossiord, F. Agnely and J.C. Chaumeil, Pharm. Res.,23, 2709(2006).
[33] J. EscobarChvez, M.LpezCervantes, A.Naik, Y.Kalia, D.QuintanarGuerrero and A.J.GanemQuintanar, J. Pharm. Pharmaceut. Sci.,9, 339 (2006).
[34] W. Zhang, Y. Shi, Y. Chen, J. Ye, X. Sha and X. Fang, Biomaterials,32, 2894 (2011).
[35] E.V. Batrakova andA.V. Kabanov, J. Control.Release,130, 98 (2008).
[36] R. Ganguly, V.K.Aswal, P.A.Hassan, I.K. Gopalakrishnan andS.K. Kulshreshtha, J. Phys. Chem. B,110, 9843 (2006).
[37] Y. Li, R. Xu,S. Couderc, D.M. Bloor, E.Wyn-Jones andJ.F. Holzwarth, Langmuir, 17, 183 (2001).
[38] D. V. Krogstad, N. A. Lynd, S-H.Choi, J.M. Spruell, C.J. Hawker, E.J. Kramer and M.V. Tirrell, Macromolecules, 46, 1512 (2013).
[39] X. Zhao, K. Deng, F. Liu, X. Zhang, H. Yang, J. Peng, Z. Liu, L. Ma, B. Wang and H. Wei. ACS Biomater. Sci. Eng., 4, 566 (2018).
[40] T. Chen, S. Xu, T. Zhao, L. Zhu, D. Wei, Y. Li, H. Zhang and C. Zhao. ACS Appl. Mater. Interfaces,4, 5766 (2012).
[41] M.Romio, G.Morgese, L.Trachsel, S.Babity, C.Paradisi, D.Brambilla and E.M. Benetti,Biomacromolecules,19, 103 (2018). v D. Jianzhong,F. Lang and L. Qiuming, Macromolecules 45, 8275 (2012).
[42] B.Surnar and M.Jayakannan, ACS Biomater. Sci. Eng., 2, 1926 (2016).
[43] R. M.Handjani-Vila, A.Ribier, B.Rondot and G. Vanlerberghe, Int. J. Cosmetic Sci.,1, 303 (1979).
[44] I.F.Uchegbu and S. P. Vyas, Int. J. Pharm.,172, 33 (1998).
[45] I.F.Uchegbu andA.T. Florence, Adv. Colloid. Interface. Sci.,58, 1 (1995).
[46] M.J.Lawrence, S.Chauhan, S.M.Lawrence and D. J. Barlow, Pharm. Sci.,1, 49 (1996).
[47] A.Shahiwala and A. Misra, J. Pharm. Pharm. Sci.,5, 220(2002).
[48] S. Moghassemia andA.Hadjizadeh, J. Control. Release,185, 22 (2014).
[49] J. Jiao, Adv. Drug. Deliv.Rev.,60, 1663(2008).
[50] M. Shick, Nonionic Surfactants; Surfactant Science Series; Physical Chemistry: New York, 1987; Vol. 23.
[51] T.Liu and R.Guo, Langmuir, 21, 11034 (2005).
[52] R.Kakr, R.Rao, A.Goswami, S.Nanda and K.Saroha, Der Pharmacia Lettre.,2, 227 (2010).
[53] E. Moazeni, K. Gilani, F. Sotoudegan, A. Pardakhty, A.R. Najafabadi, R.Ghalandari,M.R.Fazeli and H.Jamalifar,27, 618 (2010).
[54] G. Shilakari Asthana, P.K. Sharma and A. Asthana, Scientifica, vol. 2016, Article ID 6492953, 10 pages, 2016.
[55] A.R. Mullaicharam and R. S. R. Murthy,J. Drug Deliv.Sci. Tech., 14, 99 (2004).
[56] S. Moghassemi, A. Hadjizadehand K.Omidfar, AAPS PharmSciTech.,1, 27 (2017).
[57] G.V. Radha, T.S. Rani and B. Sarvani, J. Basic and Clin.Pharm.,4, 42(2013).
[58] R.Behrend, E. Meyer and F.Rusche, Justus Liebig's Annalen der Chemie.,339, 1 (1905).
[59] A. Day, A.P. Arnold, R.J. Blanch and B. Snushall, J. Org. Chem., 66, 8094(2001).
[60] J. Kim, I.-S. Jung, S.-Y.Kim, E. Lee, J.-K.Kang, S. Sakamoto, K. Yamaguchi and K. Kim, J. Am. Chem. Soc. 2000, 122, 540 541;
[61] S. Walker, R.Oun, F.J. McInnes and N.J. Wheate, Isr. J. Chem., 51, 616 (2011)
[62] R. Warmuth, J. Incl. Phenom. Macro.,37, 1(2000).
[63] F. Chandra, K. Pal and A.L. KonerChemistrySelect,1, 6156 (2016).
[64] X. Ma and Y. Zhao,Chem. Rev.,15, 7794 (2015).
[65] X.J. Loh, Mater. Horiz.1, 185 (2014).
[66] N. Wheate, V. Vora, N. Anthony and F.J.McInnes, Incl. Phenom. Mol. Recognit. Chem.,68, 359 (2010).
[67] F. Chandra, K. Pal, S. Lathwala and A.L. Koner,Mol. BioSyst., 12, 2859 (2016).
[68] Y. Zhao, D.P. Buck, D.L. Morris, M.H. Pourgholami, A.I. Day and J. G. Collins, Org. Biomol. Chem. 6, 4509 (2008).
[69] N.J.Wheate, D.P. Buck, A.I. Day and J. G. Collins, Dalton Trans. 451, (2006).
[70] A.I. Day, R.J. Blanch, A.P. Arnold,C. Cullinane andJ. G. Collins, Chem. Commun. 1424, (2004).
[71] N. J. Wheate, J. Inorg. Biochem.,102, 2060 (2008).
[72] Y.Huang, Q.-H.Hu, G.-X.Song, Z.Tao, S.-F.Xue, Q.-J.Zhu, Q.-d.Zhou and G. Wei, RSC Adv., 4, 3348 (2014).