Available online on 15.01.2019 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

Open Access Review Article

Chitosan-based transdermal drug delivery systems to overcome skin barrier functions

Syam S. Nair *

Department of Chemistry, School of Physical and Mathematical Sciences, University of Kerala, Kariavattom, Trivandrum-695 581, India

ABSTRACT

Transdermal drug delivery system has been developed or being developed to vanquish the downsides associated with conventional strategies as it avoids first pass hepatic metabolism, improved patient compliances, easy termination of therapy, possibility of self-administration etc. The main challenge in designing transdermal patch is to overcome the low permeability of skin. Several strategies have been developed to overcome the barrier properties and to enhance the transportation of drug molecules across the skin. In the last decades numerous transdermal patches fabricated from polysaccharides have been reported. There has been a growing interest in using chitosan in transdermal formulations thanks to their biocompatibility, non-toxicity, film forming ability, non- skin irritancy etc. This article highlights the application of chitosan in the development of transdermal drug delivery systems such as microneedles, films etc.

Keywords: Transdermal drug delivery, first pass hepatic metabolism, low permeability, microneedles

Article Info: Received 10 Nov 2018; Review Completed 28 Dec 2018; Accepted 01 Jan 2019; Available online 15 Jan 2019

Cite this article as:

Nair SS, Chitosan-based transdermal drug delivery systems to overcome skin barrier functions, Journal of Drug Delivery and Therapeutics. 2019; 9(1):266-270 http://dx.doi.org/10.22270/jddt.v9i1.2180

***Address for Correspondence:**

Syam S. Nair, Department of Chemistry, School of Physical and Mathematical Sciences, University of Kerala, Kariavattom, Trivandrum-695 581, India

INTRODUCTION

Conventional route of drug delivery while commonly employed have several drawbacks that may be effectively overcome by non-conventional routes. These approaches may appear fascinating relative to the expense and duration for the development of new drug molecules. Among several non-conventional approaches that have been tried with varying level of success transdermal route is attractive. For several years substantial research has been devoted to transdermal drug delivery system. The main benefits of transdermal route include prevents first pass liver effect, easy termination of therapy, possibility of painless therapy, prevents the intervention of intestinal and gastric fluids etc [1]. However the protective barrier properties of the skin remarkably reduce the permeation of drugs molecules across the skin [2]. For transdermal therapy to be potential, the drug molecules have to reach the vasculature in desired amounts to generate a therapeutic effect. In the recent decade's substantial research have been conducted to develop potential transdermal device which can effectively transport drug molecules across the skin. The present article detailed the application of chitosan in the fabrication of effective transdermal drug delivery system.

Among several polysaccharides, chitosan is one of the chief commercially significant biodegradable polymer from a pharmaceutical point of view. Chitosan is a distinct cationic polysaccharide and is different from other polysaccharides in the perspective that cationic character is absent in other polysaccharides. The polycation polymer contains glucosamine and N-acetyl glucosamine units linked together through β-(1-4) glycosidic bonds. The structure of chitosan is displayed in Figure.1. Chitosan is obtained by the alkaline deacetylation of N-acetyl glucosamine polymer, chitin which is the major building constituent of shrimp and crab shell [3]. The application of chitosan is restricted as it is insoluble in water. However it is soluble in dilute acids including formic acid, acetic acid, lactic acid etc. The presence of remarkable nitrogen content makes chitosan a commercially fascinating polymer as it can act as a chelating agent [4].

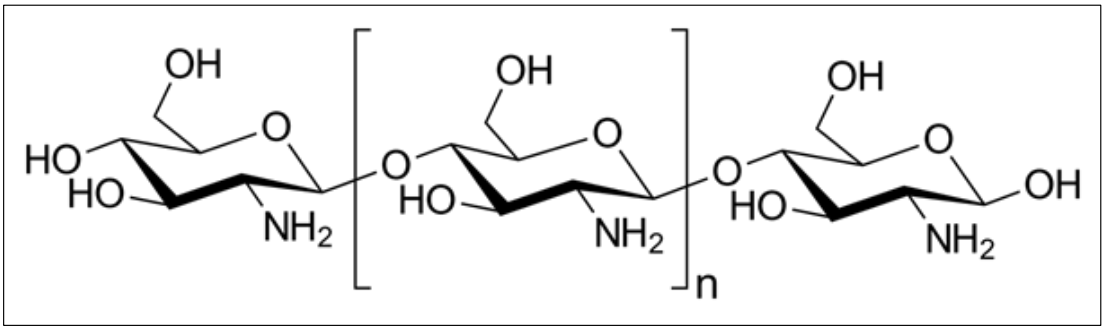

Figure 1: Structure of chitosan [5]

Currently graft polymerization approach is employed on pristine chitosan to enhance the existing properties and to incorporate required features for specific applications [3]. Chitosan displays several biological activities including cholesterol lowering, antihypertension and immune response activity. The enhanced attention of chitosan especially in the biomedical field is because of its exceptional properties including non-cytotoxicity, biocompatibility, capacity to interact with certain organic compounds, biodegradability, susceptibility to enzymatic hydrolysis and non-allergenic behavior [6]. These behaviors are mainly beneficial to several biological applications such as wound healing, tissue engineering and drug delivery. In addition to the detailed properties, the excellent film forming ability and non-skin irritatancy encouraged several research groups to explore CS in TD drug delivery system. Although several research group utilized CS as a TD drug delivery platform, there are many opportunities which required to be investigated.

TRANSDERMAL PATCHES FROM CHITOSAN

Allena et al fabricated a transdermal patch composed of chitosan and hydroxypropyl methyl cellulose for the delivery of metformin hydrochloride across the skin [7]. Dibutyl phthalate was incorporated as plasticizer. The device displayed better tensile strength and folding endurance. The release of metformin hydrochloride from the device followed zero order kinetics and non-fickian diffusion mechanism. The investigation revealed that the device with hydroxypropyl methyl cellulose : chitosan in the ratio 1:5 together with dibutylphthalate was efficient to transport metformin hydrochloride.

Ali et al developed a transdermal device by adding glibenclamide nanocrystal and microcrystal into chitosan solution [8]. The patch showed satisfactory physicochemical properties without significant agglomeration of glibenclamide particles during the processing steps. After 24 hours, glibenclamide nanosystem and microsystem, respectively released 85 ± 3.1 and 61 ± 3.9 % glibenclamide. Furthermore glibenclamide nanosystem and microsystem showed 498 ± 33.35 and 362 ± 25.5 µg/cm^2 cumulative permeation, respectively in 24 hours. In addition, cumulative flux of 23.14 and 13.64 µg/cm^2/h was shown by nanosystem and microsystem, respectively. *In vivo* test undoubtedly displayed the superior capacity of the nanosystem to decrease glucose level of blood. The article firmly stated that the glibenclamide nanosystem have the potential to maintain greater concentration of drug for long time.

Balamurugal and Agrawal prepared chitosan based transdermal patch for the skin transportation of lisinopril by solvent evaporation strategy without adding permeation enhancers [9]. The lisinopril-polymer incompatibility was confirmed using DSC and FTIR mapping. *In vitro* skin penetration tests were carried out on rat skin and cadaver skin, which revealed that the patch followed Higuchi kinetics with diffusion mediated lisinopril release. The safety of the patch was studied using *in vivo* skin irritation assays which displayed no sign of irritability.

Behin et al developed a transdermal patch for the delivery of glipizide which is commonly used for type 2 diabetes treatments [10]. They first prepared an inclusion complex of glipizide and β cyclodextrin and the complex was incorporated into chitosan matrix. The patch containing 1.5 % w/v chitosan displayed the highest glipizide content of 97.65 %. After 24 hour 96 % of glipizide was released from the patch. The thickness and folding endurance of the formulation increased with increase in chitosan concentration. The glipizide release followed Higuchi plot with diffusion controlled pattern. Skin irritation assay showed the non-toxicity of the patch. The *ex-vivo* test showed constant glipizide permeation for long periods.

Can et al fabricated transdermal device of ondansetron using chitosan as matrix and 2-(2-ethoxy-ethoxy)ethanol (Transcutol) as plasticizer [11]. They studied the effect of terpenes such as nerolidol, eucalyptol and limonene on the skin permeation of drug molecules. FTIR mapping was carried out to study the impact of chitosan membrane formulation on the *in vitro* conformational order of lipid layers. The outcomes revealed that the patch composed of transcutol and terpenes could be employed to fabricate ondansetron transdermal patches. Compared to other terpenes eucalyptol displayed the highest skin permeation enhancing effect.

Sarkar et al prepared novel transdermal patch composed of cellulose nanofibrils and chitosan to transport ketorolac tromethamine efficiently across the skin [12]. The cellulose nanofibrils were prepared from jute fibres. FTIR mapping confirmed the efficient loading of drug molecules in the matrix. The XRD profile revealed the crystalline nature of the prepared transdermal membranes. The drug release pattern from the device suggested that the release rate of ketorolac tromethamine was sustained after the addition of cellulose nanofibrils.

Cui et al reported about transdermal patch from chitosan and polyvinyl alcohol by elctrospinning strategy [13]. Glutaraldehyde was used as crosslinker for the developed composite nanofibres. They reported that no destruction in the morphology of the nanofibre was observed after crosslinking. The thermomechanical properties of the material were remarkably improved after crosslinking ascribed to the formation of network structure. Drug release tests proved that crosslinked device displayed no burst release profile and followed Fickian diffusion mechanism.

Another research group developed chitosan-gelatin composite membrane and examined its potential for the transdermal delivery of theophylline [14]. SEM images revealed that the drug molecules were homogeneously distributed in the matrix. FTIR and DSC analysis confirmed that there existed only weak interaction between drug and polymer. *In vitro* skin permeation test proved that up to around 6 hour, only moderate changes on theophylline release pattern was observed with increased concentration of gelatin in the device. However the release rate of theophylline was improved at higher release time with increased gelatin content, ascribed to the enhanced swellability of the membrane. The theophylline release followed non-Fickian mechanism.

Hemant and Shivakumar fabricated chitosan acetate membrane to transport propranolol hydrochloride across the skin [15]. They modified chitosan acetate with acetaldehyde and the content was loaded with propranolol hydrochloride. Drug content in the patch was about 0.9 to 1.4 mg/cm^2. The release of propranolol hydrochloride was significantly higher in chitosan acetate compared to pristine chitosan. The permeability coefficient for chitosan and chitosan acetate was respectively, 0.97 x 10^4 and 6.12 x 10^{-4} gcm^2/day. They reported that FTIR and DSC analysis showed the absence of drug-polymer interaction. Kashinatha et al prepared valsartan loaded modified chitosan for the transdermal drug delivery. They modified chitosan with acetaldehyde and glycerin was added as plasticizer [16]. They reported that valsartan permeation was increased with increase in glycerin content, especially at chitosan concentration of 20 to 30 % w/w. However further addition of plasticizer did not remarkably enhanced drug permeation. Stability assay suggested that the devices were stable.

Kim et al developed silver hybridized chitosan device to deliver drug molecules across the skin [17]. They reported that the patch prepared from 3 % silver nitrate, 1 % chitosan and 0.003 % sodium borohydride showed enhanced tensile strength and drug delivery potential. The release of drug molecules was enhanced due to the increase in silver content. Compared to pure chitosan, the developed device could transport drug molecules 1.5 times faster. Kim et al prepared another transdermal device based on chitosan and poly(L-3,4-dihydroxyphenyl alanine) [18]. Drug molecules were quickly released from the developed poly(L-3,4-dihydroxyphenyl alanine) filled chitosan device when compared with pristine chitosan.

Maji et al fabricated maleic anhydride cross-linked polyvinyl alcohol-chitosan device for the transdermal delivery of alprazolam [19]. The absence of drug-polymer interaction was confirmed using FTIR. The drug permeability was remarkably enhanced with increase in polyvinyl alcohol content. The alprazolam release followed Higuchi kinetics. Furthermore the diffusion coefficient was found to be around 0.5 suggesting Fickian diffusion. Skin irritation test showed that the patches were non-toxic. Ramesh and Sireesha dispersed chitosan nanoparticles in carbopol gel and evaluated its potential to transport ramipril across the skin [20]. FTIR and DSC analysis confirmed the absence of interaction between drug and polymer. The drug release followed first order kinetics with diffusion controlled mechanism.

Sadasival et al prepared transdermal device of insulin based on chitosan and tripolyphosphate based ionotropic gelation strategy [21]. The developed nanoparticles displayed size range of 465 and 661 nm with enhanced drug encapsulation efficiency. Controlled release transdermal devices were prepared by the combination of chitosan with hydroxypropyl methylcellulose, polyvinyl pyrrolidone K30 and polyethylene glycol 400. The drug release improved with the increase in content of hydrophilic polymers.

Shinde et al fabricated transdermal devices using hydroxypropyl methylcellulose, chitosan and eudragit RL-100 [22]. To improve the permeability an inclusion complex with hydroxypropyl-β-cyclodextrin was also prepared. They studied the effect of oleic acid and propylene glycol on transdermal drug delivery. Device containing eudragit showed the highest folding endurance. Furthermore, the tensile strength was enhanced with increase in eudragit content. Drug release studies showed that the release of drug was sustained with increasing the content of eudragit in the device. The device incorporated with inclusion complex of drug displayed enhanced permeation when compared with device incorporated with plain drug. Finally they reported that hydroxypropyl-β-cyclodextrin in conjugation with chemical penetration enhancers such as oleic acid and propylene glycol displayed a higher permeation flux.

Siddaramaiah et al prepared chitosan and hydroxypropyl methylcellulose blends in different composition [23]. Glycerine was used as plasticizer. The mechanical properties increased with increasing composition of hydroxypropyl methylcellulose. The device possessed improved transparency. The drug molecules were homogeneously dispersed in the matrix. They evaluated the potential of the device to transport propranolol hydrochloride. Thakur et al fabricated chitosan and montmorillonite composite membranes for the transdermal drug delivery [24]. Swelling ratios and water uptake of the device was reduced with increase in montmorillonite content. The addition of montmorillonite increased the tensile strength and decreased the extensibility, ascribed to the creation of intercalated structure and reduction in mobility of polymer chain segments. They reported that the prepared device could efficiently deliver curcumin across the skin.

Varshosaz et al prepared lidocaine loaded device with different molecular weight and concentration of chitosan [25]. Lecithin was employed as permeation enhancer. The bioadhesion of the device was reduced with increasing concentration of chitosan. The drug release rate was enhanced with increasing the molecular weight and concentration of chitosan ascribed to the improvement on lidocaine-chitosan repulsion. The lidocaine flux was higher for 3 % high molecular weight chitosan gel compared to standard gel. Venugopal et al prepared insulin encapsulated chitosan nanoparticles for transdermal delivery [26]. The developed device efficiently transported insulin across the skin as revealed by the remarkable reduction in plasma glucose level.

MICRONEEDLES FROM CHITOSAN

Chen et al in an article stated that it is necessary to reduce the dosage needed for vaccination especially in the case of epidemic emergencies [27]. They examined the capacity of microneedles fabricated from chitosan for low-dose immunization. The device was composed of antigen loaded chitosan microneedles and polyvinyl alcohol/polyvinyl pyrrolidone supporting array patch. Polyvinyl alcohol and polyvinyl pyrrolidone furnished additional strength to attain superior microneedle insertion into the skin. The insertion of the device permitted a sustained antigen (ovalbumin) release for up to 28 days. They observed that rats applied with devices with low-dose antigen had persistently high antibody levels for 18 weeks, superior to intramuscular injection. Furthermore ovalbumin embedded chitosan microneedle had higher immunogenicity compared to

ovalbumin added chitosan solution. The investigation revealed that the developed device could efficiently deliver antigens across the skin.

Chen and coworkers developed another microneedle device based on chitosan for the transportation of macromolecules [28] They reported that the device possessed excellent tensile properties to be applied on rat skin. It pierces porcine skin and rat skin of depth around 250 and 200 µm, respectively. They employed bovine serum albumin as model macromolecule to evaluate the capacity of developed patch. *In vitro* drug release test displayed that the patch could furnish a sustained release of molecules for 8 days. Confocal studies revealed that the macromolecules could diffuse across the skin through the punctured areas produced by the microneedle. Furthermore the incorporation of bovine serum albumin in the patch did not change its secondary structure.

The same research group used chitosan for the fabrication of microneedle which could be used for vaccination [29]. They also incorporated poly(L-lactide-D,L-lactide) in the device for supporting as it furnished excellent tensile properties. The device pierce skin to around 600 µm depth which is necessary for the delivery of antigens to antigen presenting cells. Ovalbumin was employed as model antigen. They reported that the application of ovalbumin loaded microneedle in rat skin produced remarkably higher ovalbumin-specific antibody response which continued for around 6 weeks.

Marin et al prepared microneedles from carboxymethycellulose and chitosan [30]. The fabrication was performed under condition that helped the formation of polyelectrolyte complex based on the electrostatic interaction by oppositively charged carboxymethycellulose and chitosan. They reported that the device showed decreased hydration. Protein release test displayed that chitosan coating remarkably affected the release profile. Justin et al fabricated microneedle patch based on chitosan and grapheme quantum dots [31]. The developed chitosan-grapheme quantum dots nanocomposite displayed low cytotoxicity. Further, fluoresce blue in the presence of UV light, permitted the tracking of drug molecules attached on grapheme quantum dots by fluorescent imaging. They reported that the addition of 0.25-2.0 wt% of graphene quantum dots in the device remarkably enhanced the electrical conductivity. The device incorporated with 1 % grapheme quantum dots possessed enough mechanical strength to pierce across the skin. The device showed improved drug release profile compared to microneedle prepared from chitosan alone. Furthermore the device could deliver drugs with high molecular weight through iontophoresis.

CONCLUSION

In this article we investigated the applicability of chitosan in formulating transdermal drug delivery systems. The study clearly indicated that it is feasible to transport therapeutically effective amount of drug molecules across the skin using transdermal devices prepared from chitosan. Chitosan is efficient to transport both small and large molecular weight therapeutics. At the same time more investigation are to be required to further improve the potential of chitosan based devices.

REFERENCES

1. Pegoraro C, MacNeil S, Battaglia G. Transdermal drug delivery: from micro to nano. Nanoscale. 2012; 4:1881–1894.
2. Tahara Y, Honda S, Kamiya N, Piao H, Hirata A, Hayakawa E, Fujii T, Goto M. A solid-in-oil nanodispersion for transcutaneous protein delivery. Journal of Controlled Release. 2008; 131:14–18.
3. Thakur VK, Thakur MK, Recent Advances in Graft Copolymerization and Applications of Chitosan: A Review, ACS Sustainable Chemistry & Engineering, 2014, 2:2637-2652.
4. Rabea EI, Badawy MET., Stevens CV, Smagghe G, Steurbaut W, Chitosan as Antimicrobial Agent: Applications and Mode of Action, Biomacromolecules, 2003, 4:1457-1465.
5. Mahapatro A, Singh DK, Biodegradable nanoparticles are excellent vehicle for site directed in-vivo delivery of drugs and vaccines, Journal of Nanobiotechnology, 2011, 9:1-11.
6. Elgadir MA, Uddin MS, Ferdosh S, Adam A, Chowdhury AJ K, Sarker MZI, Impact of chitosan composites and chitosan nanoparticle composites on various drug delivery systems: A review, Journal of Food and Drug Analysis, 2015, 23:619-629.
7. Allena RT, Yadav HKS, Sandina S, Sarat Chandra Prasad M, Preparation and evaluation of transdermal patches of metformin hydrochloride using natural polymer for sustained release, International Journal of Pharmacy and Pharmaceutical Sciences 2012, 4.
8. Ali HSM, Hanafy AF, Glibenclamide Nanocrystals in a Biodegradable Chitosan Patch for Transdermal Delivery: Engineering, Formulation, and Evaluation, Journal of Pharmaceutical Sciences 2017, 106:402-410.
9. Balamurugan M, Agrawal SS, Formulation and evaluation of chitosan based bioadhesive transdermal drug delivery systems of lisinopril for prolonged drug delivery, Der Pharmacia Sinica, 2013, 4:1-7.
10. Behin SR, Punitha IS, Saju F, Development of matrix dispersion transdermal therapeutic system containing glipizide, Der Pharmacia Lettre, 2013, 5:278-286.
11. Can AS, Erdal MS, Gungor S, Ozsoy Y, Optimization and characterization of chitosan films for transdermal delivery of ondansetron, Molecules (Basel, Switzerland), 2013, 18:5455-5471.
12. Sarkar G, Orasugh JT, Saha NR, Roy I, Bhattacharyya A, Chattopadhyay AK, Rana D, Chattopadhyay D, Cellulose nanofibrils/chitosan based transdermal drug delivery vehicle for controlled release of ketorolac tromethamine, New Journal of Chemistry, 2017, 41:15312-15319.
13. Cui Z, Zheng Z, Lin L, Si J, Wang Q, Peng X, Chen W, Electrospinning and crosslinking of polyvinyl alcohol/chitosan composite nanofiber for transdermal drug delivery, Advances in Polymer Technology, 2018, 37:1917-1928.
14. Vediappan V, Subramanian K, Fabrication and evaluation of chitosan-gelatin composite film as a drug carrier for in vitro transdermal delivery, International Journal of Pharmaceutical Sciences and Research 5: 438-447
15. Hemant K, Shivakumar H, Development of Chitosan Acetate Films for Transdermal Delivery of Propranolol Hydrochloride, Tropical Journal of Pharmaceutical Research, 2010, 9:197-203
16. Kashinatha BP, Shivakumar S, Devprakash, Prashant S, Design and evaluation of transdermal film of valsartan by using modified polymer, Journal of Pharmacy Research, 2012, 5:2823-2829
17. Kim JH, Kim S, Kwon IB, Hyun Kim M, Lim J, Simple fabrication of silver hybridized porous chitosan-based patch for transdermal drug-delivery system, Materials Letters, 2013, 95:48-51.
18. Kim JH, Lim JI, Park HK, Porous chitosan-based adhesive patch filled with poly(l-3,4-dihydroxyphenylalanine) as a transdermal

drug-delivery system, Journal of Porous Materials, 2013, 20:177-182.

19. Maji P, Gandhi A, Hana S, Maji N, Preparation and Characterization of Maleic Anhydride Cross-Linked Chitosan-Polyvinyl Alcohol Hydrogel Matrix Transdermal Patch, Journal of PharmaSciTechi, 2013, 2:62-67.
20. Ramesh Y, Sireesha V, Transdermal patch of ramipril loaded chitosan nanoparticles dispersed in carbopol gel, Journal of Drug Delivery & Therapeutics, 2017, 7(6):56-65
21. Sadhasivam L, Transdermal patches of chitosan nanoparticles for insulin delivery, International Journal of Pharmacy and Pharmaceutical Sciences, 2015, 7:84-88
22. Shinde A, Shinde A, More H, Design and evaluation transdermal drug delivery system of gliclazide, Asian Journal of Pharmaceutics, 2010, 4:121-129
23. Siddaramaiah, Kumar P, Divya KH, Mhemavathi BT, Manjula DS, Chitosan/HPMC Polymer Blends for Developing Transdermal Drug Delivery Systems, Journal of Macromolecular Science, Part A, 2006, 43:601-607.
24. Thakur G, Singh A, Singh I, Formulation and evaluation of transdermal composite films of chitosan-montmorillonite for the delivery of curcumin, International journal of pharmaceutical investigation, 2016, 6:23-31.
25. Varshosaz J, Jaffari F, Karimzadeh S, Development of bioadhesive chitosan gels for topical delivery of lidocaine, Scientia Pharmaceutica, 2006, 74:209.
26. Venugopal V, Jayachandran, Transdermal delivery of insulin by biodegradable chitosan nanoparticles: Exvivo and in vivo studies, Iranian Journal of Pharmaceutical Sciences, 8: 315-321
27. Chen MC, Lai KY, Ling MH, Lin CW, Enhancing immunogenicity of antigens through sustained intradermal delivery using chitosan microneedles with a patch-dissolvable design, Acta Biomaterialia, 2018, 65:66-75.
28. Chen MC, Ling MH, Lai KY, Pramudityo E, Chitosan Microneedle Patches for Sustained Transdermal Delivery of Macromolecules, Biomacromolecules, 2012, 13:4022-4031.
29. Chen MC, Huang SF, Lai KY, Ling MH, Fully embeddable chitosan microneedles as a sustained release depot for intradermal vaccination, Biomaterials, 2013, 34:3077-3086.
30. Marin A, Andrianov AK, Carboxymethylcellulose–Chitosan-coated microneedles with modulated hydration properties, Journal of Applied Polymer Science, 2011, 121:395-401.
31. Justin R, Román S, Chen D, Tao K, Geng X, Grant RT, MacNeil S, Sun K, Chen B, Biodegradable and conductive chitosan–graphene quantum dot nanocomposite microneedles for delivery of both small and large molecular weight therapeutics, RSC Advances, 2015, 5:51934-51946.