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Recent trends on hydrogels based drug delivery systems for infectious diseases

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Abstract

For centuries, the rapid spread and cure of infectious diseases have been a major concern to the progress and survival of humans. These diseases are the global burden and the prominent cause for the worldwide deaths and disability. Nanomedicine has emerged as the most excellent tool to eradicate and halt their spread. Various nanoformulations (NFs) using advanced nanotechnology are in demand. Recently, hydrogel and nanogel based drug delivery devices poses new prospects to simulate the natural intelligence of various biological systems. Owing to their unique porous interpenetrating network design, hydrophobic drug incorporation and stimulus sensitivity hydrogels owe excellent potential as targeted drug delivery system.

Present review is an attempt to highlight the recent trends of hydrogel based drug delivery systems for the delivery of therapeutic agents and diagnostics for the major infectious diseases including Acquired immune deficiency syndrome (AIDS), Malaria, Tuberculosis, Influenza and Ebola. Future prospective and challenges are also briefed.

Keywords

Nanomedicine; Drug delivery; Hydrogels; Infectious diseases; Ebola; Sensors

1. Introduction

From last few centuries, humans are handicapped to the sudden epidemics and emerging infectious diseases that makes them curious to seek growth in the development of new vaccines, antimicrobials and thus presently devoted towards nanomedicine and nanotechnology based therapeutics. Emerging infections (EIs) are basically defined as the

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infections arousing in a population, which existed previously and is continuously spreading in that geographic range.[1, 2] Infectious diseases are considered as the third leading cause of deaths in US.[3, 4] In early 1980's human immunodeficiency virus (HIV) was initially accepted and had infected an estimated of 3 million people world-wide (UNAIDS Epidemic update, 2008) leading to AIDS. Despite the new advancements in the field of anti-infectious agents in recent years, the treatment for the variety of bacterial and fungal infections as well as parasitic and viral diseases upholds a great challenge.

To have a basic understanding of the infectious diseases it can be described as a disorder occurring from the presence of pathogenic agent, which includes virus, bacterium, fungus. The infectious diseases come in the category of communicable diseases as they can be transferred from one person to the other that include dengue, malaria and tuberculosis whereas when the transfer occurs from one species to other, flu or influenza occurs.[5] These disease can be broadly classified firstly as diseases, which firmly persist like malaria, tuberculosis secondly earlier unknown diseases like severe acute respiratory syndrome and lastly to the diseases, which threaten to enhance in the near future (e.g., avian influenza). The developing countries are the major sufferers and half of the deaths are happening due to these infectious diseases.[6] For a better understanding, we need to gather our knowledge about the bacterial pathogens, which are classified as extracellular and intracellular pathogens on the basis of the *in vivo* life and pathogenicity. The main target in the localized diseases such as inflammation and infection are the overexpressed epitopes or receptors. The initialization of the use of antibiotics with the penicillin in late 1940s was a great success and further advancements for the stronger antibiotics begun.[7] Though the resistance to the antimicrobial drugs was a threat to the hospitals and community and the number of effective drugs to control infection by the old bacteria decreased. [8, 9] Thus the invention of the nano carrier systems offered antibiotics to be delivered selectively to phagocytic cells and to increase their cellular penetration and the treatment of the intracellular infections.[10] The factors behind these infections include number of aspects owing to the change in the environment, which increases the frequency of the contact with the host carrying an infection and thus increase the chance of encountering the microorganisms formerly unfamiliar to beings.

Tuberculosis (TB) is one of the most feared diseases until the discovery of antibiotics in 1940s that caused large scale human deaths.[11, 12] Over the last 20 years researchers are in the urge of discovering nanotechnology based drug carriers such as smart materials "nano/micro gels" inside which the cargos can be encapsulated and gives a sustained release of drugs rather than the conventional free drug delivery.[13] In the present article one of the section deals with the brief overview of the disease and the various benefits of hydrogel based drug delivery systems (DDS) for TB.

Nanomedicine actively target locations by the use of various NFs[14] as a DDS which include nanoparticles,[8] polymeric micelles,[15, 16] nanorods,[17, 18] nanospheres,[19, 20] solid lipid nanoparticles,[21, 22] nanoliposomes,[23, 24] dendrimers,[25, 26] metal nanoparticles[27, 28], fullerenes and quantum dots.[29, 30] These NFs have been useful in the development of the various different routes like systemic, oral, pulmonary, transdermal and have been helpful for the drug targeting and On-demand drug delivery techniques.[31] The technologies of

encapsulating various cargos inside these NFs have been the main attention owing to their numerous benefits like low toxicity, effective therapeutic dosages. Among all these nanoforms hydrogels especially nanogels have gained lot of attention and have emerged as an innovative and promising therapeutic interventions.[32–35] Moreover the clinical applications of these NFs are being upgraded yet the implementations of few strategies require more advanced therapies.[36, 37] The present article focusses on hydrogel based drug delivery systems and clinical applications of these systems to treat major infectious diseases. The other infectious diseases, which have caused destruction to human health care world-wide include the AIDS, tuberculosis, malaria, Influenza A, Ebola that have been discussed in the present review.

2. Hydrogel based systems for HIV

2.1. HIV Pathogenesis

Briefly, HIV is known to be a retrovirus due to its reverse mechanism than that used by human cells.[38] The retrovirus stores the genetic information as RNA rather as DNA as seen commonly in other living things.[39,40] The HIV obliterate the CD+4 lymphocytes and the infected people become more prone to the other infectious organisms, which is the worst aftermath of the virus as it is known that the death of the person is generally due to the other infections rather than directly from HIV. [41, 42] In simpler terms, the mechanism can be understood in terms of the fact that as soon as the virus enters the body attachment of numerous white blood cells occurs. Most importantly the helper T lymphocytes activate and coordinate with the other activated cells of the immune system. The surface receptor CD4 helps the HIV to attach to T lymphocytes represented as CD4+. The occurrence of the errors i.e., the mutations by the enzyme the reverse transcriptase during the process of making a copy of RNA to DNA increases, which thereby increases the HIV and eventually enhances the replication process. In a very short interval of time, i.e., within few days the infected persons genital fluids as well as blood get infected simultaneously reducing the numbers of CD4+. The most initial step in the infection cycle of HIV is the union of viral cover with a target cell and followed by the release of its genome into cell. Studies also reveal that HIV enters into cell via endocytosis at the cell membrane.[43]

2.2. HIV Diagnosis

The awareness about the occurrence of HIV infection is still very low among rural populations. The efforts by the National disease control plans for effective and comprehensive health education campaigns to increase this awareness.[44] The HIV test comprise the detection of the presence of HIV that causes acquired immunodeficiency syndrome (AIDS) in serum, saliva, or urine by detecting antibodies, antigens, or RNA. The common methods for the diagnosis used initially for the HIV-testing is enzyme-linked immunosorbent assay (ELISA) to detect antibodies to HIV-1. The other confirmatory test include Western Blot or an immunofluorescence assay (IFA). The specimens are confirmed HIV positive only when the specimens show repeatedly reactivity by ELISA and positive by IFA or reactive by Western blot. Immunoglobulin assays are also employed for detecting human immunodeficiency virus type 1 (HIV-1) infection. [45] Other testing methods not commonly available is nucleic acid testing.[46]

2.3. Therapeutics for HIV

Till 1987 the invention of antiretroviral drugs and the treatment consisted of treating complications from opportunistic infections and malignancies. The first effective therapy against HIV was the nucleoside reverse transcriptase inhibitor (NRTI) zidovudine (AZT). The invention of combinations of NRTIs was also not that successful to supress the virus for long periods. Thus highly active anti-retroviral therapy (HAART) was introduced instead of early anti-retroviral therapy (ART). Though it is a well-known fact that the NRTI are the major component of drug cocktails and are known to develop a varying degree of myopathy, lipodistrophy, or peripheral or central nervous system (CNS) neuropathy. These side effects are associated with mitochondrial toxicity of NRTIs. All these side effects are usually associated with mitochondrial toxicity of NRTIs that inhibit DNA polymerase γ and cause mtDNA dysfunction.[47] The reduction in the dosage and targeted drug delivery to the infected cells are the most demanding way to reduce the adverse toxic effects. The advancement in nanotechnology have come up with the development of NFs for encapsulation of the antiviral drugs that are more efficient and known for long term therapy. Moreover the DNA vaccines known for generating long-term humoral and cellular immune responses for protective immunity are accompanied by many major drawbacks such as low immunogenicity in clinical tests and early degradation caused by DNAases and lysosomes.[48] The injected naked DNA plasmids exhibit poor distribution and are inefficiently expressed. Thus nanocarriers as drug delivery systems are efficient carrier of DNA into mammalian cells and increases their stability and protects it from degradation.

Interestingly, the Central nervous system (CNS) is the most loved target for HIV, which gets infected at very initial stages of infection.[49] The hallmarks for HIV in CNS are the asymptomatic neurocongnitive impairment, mild neurocongnitive disorder (MND), HIV-associated dementia (HAD),[50] other disease on later stages of the infections include cryptococcal meningitis and primary CNS lymphonoma. In past few years, researchers have confronted various neurotoxic effects of present antiviral therapy contributing to the low efficiency for the eradication of HIV. Various conventional strategies for the safe delivery of different drugs to CNS include liposomes[51–53] nanoparticles,[54–56] colloidal drug carriers,[57] intranasal[58, 59] and olfactory route of administrations[60] etc. Antiviral treatments are often accompanied by accumulation of antiviral drugs in CNS due to poor permeability, occurrence of associated encephalitis and neurodegenerations in the CNS. As soon as the nucleoside reverse transcriptase inhibitors (NRTI) enters the neurons and cause inhibition of mDNA i.e., mitochondrial DNA directly affects ATP production and results in insufficient energy for cellular homeostatis maintenance. The entire permeability of the mitochondrial membrane depends entirely upon the charge and hydrophobicity. From these facts, it is inferred that hydrophilic and negatively charged compounds are less permeable. Thus cationic nanogels, which neutralizes the NTP (Active 5´- triphosphatases) and increase the cellular penetration are emerging candidates. Mitochondrial toxicity of NRTI has been greatly reduced by the combination of nanogel/NTP nanodrugs. Nanogel, based drug delivery systems are in demand and are now being explored for HIV.[43] Emphasis is given on the exploration of physiological accumulation of the nanogel in the brain, which plays an important role in pathogenesis of neuronal diseases. Nanogels are being modified using hydrophobic moieties or many such compounds, which have the capability to enhance the

permeability of BBB by crossing the tight junctions between the endothelial cells.[61] Though various limitations are associated and need to be taken care of such as the decrease in physical restrictiveness of endothelial tight junctions and overcrowding of molecules inside the brain and can cause the flooding and restrict the supply of essential nutrients. Owing to the biodegradability and biocompatibility the bio-polymeric nanogels[62] they are the most demanding delivery systems for the therapeutics interventions for CNS.[63] Nanotechnology based delivery systems including nanogels have found useful to overcome the challenge of the BBB integrity as by using these nanoforms. There is a great enhancement of permeability of the pharmaceutical excipients and thus can target the active site. Surface charge and hydrophobicity of the nanogels have a great influence on the adsorption of the plasma proteins and thus affect the uptake by transcytosis.[64] Polysorbate [80], a non-ionic surfactant have been exploited by NFs for brain delivery.[65] The endogenous protein widely used by antiretroviral drug delivery systems is transferrin and have proven to be very useful in targeting the BBB. The targeting mechanism may be passive or active. Other than these most importantly cell penetrating peptides i.e., HIV-1 Tat peptides are widely used for enhancing the brain delivery of anti-HIV drugs. Recently, a novel approach demonstrated by Kaushik et al. 2016 showed magnetically guided non-invasive delivery of a drug-nanocarrier to the central nervous system. This method is safe and exhibited improve navigation to the BBB.[66] NFs including nanogels target monocytes/ macrophages due to their significant role in HIV infection of the CNS. These possess various receptors like mannose residues and help them in the recognition and endocytosis of the nanocargos. The hydrogel nanoparticles are also termed as “nanogels” [67] are actively been used as DDS for both the hydrophilic and hydrophobic drugs with polymeric matrices and particles having high water absorption capacity. Efforts are being made to functionalize and modify the hydrogel based NFs for the brain delivery to eradicate neuro-AIDS.

A recent study by Tian et al [68] showed peptide based nanofibrous hydrogel (where, Nap represents naphthalene acetic acid, G represents glycine, F represents phenylalanine, Y represents tyrosine) Nap-GFFY-NMe act as a nanovector , a matrix of short peptide to form gelators of nanofibrous hydrogels and have the capability to condense DNA and have the potential of strong response against HIV (Figure 1). The study provided safe and effective platform for HIV DNA vaccine. It provides optimized cellular and humoral immune response in animals (mice) study and for multiple administration routes. It opened up the doors for peptide based nanofibrous hydrogels for HIV DNA vaccines and also delivering other vaccines and drugs.

Till date the clinical trials have shown no major success in anti-HIV based gels on conventional polymers or lipid emulsions, which suggest the need for novel molecular design of anti HIV gels. Supramolecular hydrogels are in high demand for the therapeutics.[69] In a recent report of conversion of anti-HIV prodrugs into self-delivery supramolecular hydrogelators show a great potential in sustained release of anti HIV therapeutics.[70] Li et al.[70] reported the development and characterization of supramolecular hydrogelators that may lead to potential anti-inflammatory and anti-HIV gels for the sustained release of reverse transcriptase inhibitors (e.g., lamivudine (3TC) and zidovudine (AZT)) against human immunodeficiency virus (HIV). This work demonstrated a novel approach of designing hydrogels that hold the potential of a multifunctional sustained drug

release for anti-HIV drugs. The self-assembled hydrogels are biocompatible in nature and are able to release the inhibitors and also show wide application in therapeutics under physiological conditions.[71] Figure 2 depicts the molecular design of the hydrogelator having anti-HIV and anti-inflammatory drugs and a phosphate group. The introduction of this phosphate group helps in hydrogelation at the certain physiological pH and also allow PAP to increase the viscoelasticity of the hydrogels.

The potential of cationic nanogel in HIV has been recently explored by many research groups.[72, 73] One of the important works led to the innovative development of biodegradable cationic cholesterol–ε-polylysine (CEPL) nanogel carriers for delivery of triphosphorylated NRTIs (nucleoside reverse transcriptase inhibitors). NRTIs are known to be the first-line drugs in AIDS treatment and components of the multi-drug cocktails of the HAART. The study presented a platform for low neurotoxicity and high anti-HIV activity eliminating many side effects for systemic administrations. This study demonstrated the advantages of a nanogel based delivery systems owing to small d~ 20nm nanocarriers prepared by the self-assembling spherical cationic CEPL polymer network.[43] Other functional modification by which nanogels are being modified for brain delivery is PEGylation of the cationic nanocarriers.[74] These smart carriers showed great potential to pass through the BBB. PEGylated cationic nanocarriers, loaded with negatively charged drugs, demonstrated longer blood circulation and better chances to penetrate the BBB.[75]

It is well reported that the use of NRTIs in antiviral therapy is neurotoxic and it is very difficult to eradicate neuro AIDS by using it. A very innovative and novel study by Greson et al. [73] demonstrated the use of nanogels based formulation as safer alternative to the current antiviral therapy. A low neurotoxicity and excellent antiviral activity of nano-NRTIs was reported (Figure. 3). The nanogels was synthesized using PEG and PEI using crosslinkers.[76] The synthesized nanogels were then modified with MAL-PEG-NHS (M.w. 5,000, 33% wt) linker molecules. Nanogel NG2 was synthesized using carbodiimide-activated carboxylated PAMAM dendrimer (Generation 5) with an excess of branched PEI (M.w. 1,200) to obtain a PAMAM-PEI core conjugate. The study suggested the great potential of nano-NRTIs in efficient CNS delivery.

A successful application of a product by the nanotechnology was the use of the VivaGel™ (SPL7013 Gel) used as a microbicides. These are the compounds, which are generally applied vaginally or rectally for the protection against the sexually transmitted infections. The active ingredient is SPL7013, a dendrimer exhibited antiviral activity for HIV and herpes simplex virus (HSV) virus in vitro and animal models. This gel passed the Phase I clinical trial in humans and give a future prospects for the expansion of phase II trials to evaluate the efficacy of these gels in the prevention of HIV and HSV-2 genital infections in women.[2, 77] The special attention to the treatment and control of HIV inside the central nervous system is due to the fact that the anti HIV drugs have a major limitation associated with them that they do not cross the Blood brain barriers and their movement is restricted by the powerful enzymes and numerous transporters and including members of the ATP binding cassette (ABC) and solute carrier (SLC) superfamilies which makes the brain a viral reservation site and results in the viral resistance and also lead to HIV associated dementia.

3. Hydrogel based systems for Malaria

3.1. Malaria Pathogenesis

Malaria is the most known fatal disease with very common occurrence in Africa, affects almost 100 countries worldwide and has become a high concern for public health. The infection is transmitted by the bite of female Anopheles mosquito.[78] The main reason for malaria proliferation is the increased number of drug resistant parasites. The WHO report (2014) estimates 3.3 billion people are at risk of malaria, among 1.2 billion are at high risk. In high-risk areas, more than one malaria case occurs per 1000 population.[79] Briefly, the pathogenesis of malaria can be best understood by the understanding the mechanisms including parasite invasion, parasite biology, and host defence.[80] The disease in humans occurs by the transmission of *Plasmodium* sporozoites by a bite from an infected anopheline. The pathway sporozoites take is via salivary glands of the mosquito through bloodstream of the host to the liver and attack the hepatocytes. There occurs a 1000-fold division till the formation of mature schizonts having thousands of daughter merozoites.[81] One of the causes of the morbidity and mortality of malaria is anemia and occurs after the massive erythrocytes lysis due to elevate parasitemia or immune haemolysis.

3.2. Malaria Diagnosis

For an effective disease management prompt and efficient diagnosis is essential. The very common symptoms of malaria include fever, body aches, nausea and vomiting, which are also seen in other common diseases. Thus laboratory examinations of the peripheral blood by microscopy, antigen detection and polymerase chain reaction (PCR) is the accurate test to confirm malaria. Light microscopy is one of the gold standards used for detection of malarial infection. This technique is accompanied by the quantification of the density of the parasite infection.

The present focus is on the betterment of the techniques used for the diagnosis, screening and successful detection of malarial diseases. Nanomedicine and diagnostics are playing an significant role in the bloodless detection of the low level of the malarial parasites.[82]

Prevention of the spread of infectious pathogens requires rapid and accurate identification of the infectious agents for proper treatment. Recently, developed fluorescent nanoparticles are so sensitive that even a single nanoparticle is capable of emitting a strong enough signal to be captured, thus enabling early identification of infections. Proper and effective treatment not only saves the patient, but also prevents the spread of the pathogens. Specific NFs developed to encapsulate the therapeutic agents, genes and deliver them to a target site and hence represents a promising strategy to boost immune responses for vaccination and boost the efficacy of drugs for the treatment.

Paul Ehrlich introduced the concept of Magic bullet according to which the main focus should be on “specifically targeting the causative agent”.[83] This concept triggered the minds of the scientists working in the field of drug discovery and delivery of drugs for malarial infections. The National Science Foundation of USA, found that nanotechnology plays a crucial role in redesigning and controlling the material dimension at nanoscale i.e., 1–100 nm. The technology uses the top down or bottom up processes, which makes the

nanomaterials superior in the surface as well as quantum properties. The intracellular and strewn location of parasites prompted the use of nanoparticulate systems for the treatment, imaging vector control and early diagnosis of the infection. Particular attention was given on the overcoming of pharmacokinetic mismatch associated with therapeutic molecules. Present section give an insight on the recent developments on hydrogels based delivery systems for malarial infection.

3.3. Therapeutics for Malaria

Literature reveals that the nanoparticles are being explored for drug delivery of antimalarial drugs which include pheroids,[84] liposomes,[85] solid lipid nanoparticles,[86] polymer-lipid nanoparticles,[87] dendrimers,[88] polymeric nanoparticles,[89] self-emulsifying drug delivery systems[90] for antimalarial drugs. In recent years, hydrogels based systems for antimalarial drugs are also being explored which have shown decent results. Curcumin has been described to be effective, either alone or in combination with artemisinin and its derivatives, in mice infected with various Plasmodium strains such as *P. falciparum*, *P. berghei*, *P. chabaudi*, etc. probably due to its immunomodulatory action, its inhibition of histone acetylation and generation of reactive oxygen species, or its action on PfATP6 protein which has reported implications in malarial infections.[91 92, 93] Nanoparticles of curcumin, both polymeric[94] and lipidic[95] are among the many novel approaches being explored by researchers to surmount these problems. The small size of these systems provides longer circulation time to the encapsulated drugs due to enhanced organ penetration and retention. Biodegradable nanoparticles have been developed for intracellular drug delivery. Moreover the emphasis is given on the stimuli responsive delivery systems due to their inherent characteristics like specificity to endogenous stimuli like lowering of the intestinal pH increased concentration of glutathione concentration or an increased level of enzymes like matrix metalloproteinases. These factors are influential at the cellular level such as the sensitivity towards varying pH directly influences the release of the cargo into the late endosomes or lysosomes to the cell cytoplasm. Moreover if at the tissue level it is seen we can further explore the specific microenviornmental changes occurring in the neoplastic diseases as well as inflammatory diseases or pathological states like ischemia. or infections.[96]

The parasitic infection “malaria” has been the major global health concern in tropical countries like India. Artemisinin and their derivative are the known effective treatments for antimalarial therapy. Though the therapy is restricted due to its high cost and availability and artemisinin combination therapies are in demand (ACT), [91, 97] which further have certain limitations like pharmacokinetic incompatibilities between artemisinin and the combination drugs. Novel strategies are being explored for the improvement of the functional performance of the curcumin to encapsulate it in variety of delivery systems like nanoparticles, hydrogel beads, liposomes, emulsions and biopolymer complexes. Dandekar et al [98] demonstrated the use of nanogels of curcumin in particle form using a combination of hydroxyl propyl methyl cellulose (HPMC) and polyvinyl pyrrolidone (PVP). The study showed that the *in vivo* antimalarial action when compared with the curcumin control the hydrogel nanoparticles can be used as an effective adjuvant therapy and prevent the recurrence and/or reduce the dose of the regular anti-malarial drugs. The study demonstrated

the extent of DNA damage in the individual cell by using an assay also known as single-cell gel electrophoresis (SCGE), a sensitive indicator of DNA damage. This technique showed fluorescent staining visualized as a “Comet” like structure with a circular head and a tail extending toward the anode due to the overall negative charge of damaged DNA. The length and intensity of the tail are indicative of the amount of DNA damage. The fluorescent intensities of the head and the tail are measured by the Comet software for computing the TL, TM, TMO, and percent DNA damage in animals treated with cyclophosphamide indicating its clastogenic potential. The results showed no Comet formation was observed in the treatment groups in animals of either sex, as well as for the control group. [98]

Thus the genetoxicity assays are helpful in confirmation of the nongenotoxicity and cellular safety of the developed HPMC nanoparticles of curcumin.

Recent literature reveals that the functionalization of the biodegradable polymeric hydrogels with the help of aromatic dipeptides have proven to be potential candidate for controlled and targeted delivery of therapeutics. They have been exemplified to effectively entrap vitamins like ascorbic acid, riboflavin, and vitamin B12, antibiotics like ampicillin and chloramphenicol, antimalarial drugs such as amodiaquin, anticancer drugs like fludarabine and mitoxantrone. An important study by Panda et al [99] demonstrated the self-assembly of a proteolysis resistant aromatic dipeptide containing a conformational constraining residue (ΔPhe) into a stable hydrogel. This dipeptide has free -N and -C termini. The hydrogel showed characteristics of being self-supportive, fractaline in nature, and possessed high mechanical strength. Their responsiveness towards environmental conditions like pH, temperature, and ionic strength was also revealed (Fig. 4). The gel matrix could encapsulate and release bioactive molecules in a sustained manner. The developed hydrogel showed no cytotoxicity to the HeLa and L929 cell lines in culture. These type of synthesis confirmed that on modulation of the functionality and synthesis procedures the hydrogels can be designed to entrap all the structurally different drug molecule and suggest that the entrapment process is mostly physical and unrelated to the chemical nature.

Recent trends in hydrogel technology suggest the great potential of hydrogels in drug delivery and diagnostics. Hydrogels have been explored as a simple, lab-on-chip PCR diagnostic for malaria that overcomes the challenges imposed by the molecular diagnostics, which faces the barriers in technology, reagent storage, cost effectiveness and knowledge which subsequently have hindered the introduction of these methods in developing countries. Simple Microscopy is the gold standard for malaria diagnosis but in local health centers with restricted resources, malaria is diagnosed presumptively in patients with fever.[100] Other new technologies include Immunochromatographic rapid diagnostic tests (RDTs) that provide an alternative to microscopy at the point of care though carries certain limitation like decreased sensitivity at lower levels of Parasitaemia inhibition at high levels of parasitaemia (prozone effect), inability to quantitate or distinguish malaria species in mixed infections, and failure to detect parasites with mutations in the genes encoding certain target antigens.[101–103] Thus the need to improvise the RDT performance, the diagnostics based on nucleic acid, PCR and isothermal amplification provide superior sensitivity.[104, 105] Hydrogels were recently explored as disposable plastic chip (Fig. 5) having a desiccated hydrogel with all the required reagents for Plasmodium specific PCR.[106]

These chip have numerous advantages like low-cost, room temperature storage and can be used on demand by rehydrating gels with unprocessed blood, moreover its performance exceeds the sensitivity by ten to fifty-fold from currently available diagnostics. This gel based chips were capable of detecting all the plasmodium species with a limit of detection for the plasmodium falciparum of 2 parasites/μL of blood. Thus this study contributes to the front-line malaria diagnosis, eradication programs and other preclinical trials. Thus it is predicted that hydrogels are novel candidate to be used in molecular diagnostics platform in developing countries. [106]

4. Hydrogels for Tuberculosis

4.1. Tuberculosis Pathogenesis

Of all the numerous prevalent forms of diseases Tuberculosis (TB) is one of the extreme vibrant cause of morbidity and mortality. It is one of the highly infectious diseases and known to be primarily spread by inhalation of aerosol droplets expelled by infected hosts. The first stage of tuberculosis occurs till 3 to 8 weeks and the aerosols get implanted in alveoli, the bacteria are disseminated by the lymphatic circulation to regional lymph nodes in the lung forming primary or Ghon complex.[107] The beginning of the second stage is of at least 3 months and is characterized by the hematogenous circulation of bacteria to lungs and other organs. This stage is accompanied by the fatal diseases like tuberculosis meningitis or miliary tuberculosis. The third stage occurs for 3 to 7 months and can be delayed to 2 years followed by acute pain in chest and inflammation of the pleural surfaces. [107]

4.2. Diagnostics of Tuberculosis

Of all the numerous prevalent forms of diseases Tuberculosis (TB) is one of the extreme vibrant cause of morbidity and mortality. In surge of the considerate attention needed to biology of the bacteria *Mycobacterium tuberculosis (*Mtb) infection, nanomedicine have come up with new delivery systems. The high multidrug resistance have limited the use of combination of antibiotics, which are widely accepted from last many years.[108] The WHO reported that about 9 million people developed active tuberculosis in 2013 and 1.5 million deaths. The two major types of tuberculosis namely Multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis are spreading at high rate with an estimated 480, 000 new cases in 2013.[109]

4.3. Therapeutics Tuberculosis

Therapeutic interventions are now being explored to actively cure TB as an adjunct to chemotherapy. Recombination technology have come up with viable BCG vaccines or by double deletion mutants of Mtb. The major front-line drugs by which TB can be effectively treated with a combination are Rifampicin **(**RIF), Isoniazid (INH), pyrazinamide (PZA) and ethambutol (ETB). Though the main limitations exhibited by these cargos in the treatment of the TB is the long time duration of therapy required to completely cure the patient, which give rise to patient non-compliance, decrease the attempts for a successful treatment and give rise to drug resistant strains.[108] It is well known fact that the use of these traditional anti TB drugs the *M. tuberculosis* achieve a non-replicating state in the host. Especially RIF, INH and ETB (excluding PZA) required the bacterial replication for their action and it is

predicted that the non-replicating state is believed to reduce *M. tuberculosis* phenotypically resistant to other bactericidal antibiotics.[110, 111] The introduction of drug resistance phenomena was followed up by the introduction of streptomycin for curing TB by Selman Waksman. Now the call for the worry is the emergence of the extensively drug resistant strain (XDR). The *M. tuberculosis* strains that are resistant to at least one of the second-line, injectable drug like capreomycin, kanamycin and to any fluoroquinolone drugs like ciprofloxacin, levofloxacin, moxifloxacin or ofloxacin). Owing to their high cost, toxicity and low efficacy high dosage is suggested as well as for a longer time interval i.e., 24 months. Moreover the use of second line anti tubular drugs also provide improved spectrum of antibiotics. Still we can say that there is a strong demand to develop such DDS using the current anti-tuberculosis drugs for their effective delivery. Nanomedicine is on impulse of developing delivery vehicles for more effective and improved treatments for TB. Here we provide the current overview of the development in nanomedicine for TB highlighting the use of hydrogels based DDS. [112, 113]

Regardless of prompt advancement over the last decade, hydrogel technologies have not yet been interconnected in the area of active clinical TB research. Intensive development of nanogels to provide effective delivery pathways with sustained and on demand drug delivery stand-in end-points for novel strategies in nanomedicine. An important investigation demonstrated that the inhalation delivery of poly(lactic-co-glycolic) acid (PLGA) microspheres (MS) when loaded with the anti-tuberculosis agent rifampicin (RFP–PLGA MS) to alveolar macrophage (Mϕ) cells could be an valuable drug delivery system for the management of tuberculosis Fig. 6. [114]

Recent trends suggest that Intravenous (IV) administration of microparticles (MPs) which have dimensions larger than the diameter of a capillary poses a great potential for passive drug targeting to the pulmonary circulation.[115] It is known that the capillary beds of organs such as the lung, act as mechanical filters that competently entrap MPs following IV administration.[116] The necessity to traverse the mucus/ surfactant and cell/ mucosal layers encountered from the ventilation gives the opportunity for the passive lung targeting by IV administration. In addition to the cell/mucosal barrier, it is well known that mucus represents a significant diffusional barrier to micron-sized particles.

Many reports on the bio distribution and use in the pulmonary delivery on the injected particles of chitosan, [117] Polyethylene glycol (PEG)[118], poly (lactic-co-glycolic acid) (PLGA), [119, 120] polystyrene,[121] albumin and macroaggregated albumin (MAA).[122] One of the important study by Deshmukh et al. [123] demonstrated the use a new stabilized aggregated nanogel particle (SANP) drug delivery system for targeting the lung. Biodistribution studies in male Sprague–Dawley rats were carried out with help of ex vivo imaging by covalently labeling with HiLyte Fluor™ 750 (DYE-SANPs).

It was observed that the free dye was frequently eliminated by renal filtration, whereas DYE-SNAP was accumulated inside the lung within 30 mins and was retained for 18 hours. The fluorescent signal was seen in the course of the study in 48 hour in kidney and was not observed in lungs at that point of time. Non toxicity was also evaluated by histopathological studies using H & E staining and broncho alveolar lavage (BAL) (Fig. 7). These

investigations suggested that the nanogels can serve as the potential alternatives for the treatment of various pulmonary diseases such as asthma, pneumonia, tuberculosis and disseminated lung cancer. [123]

One of the other major known forms of the tuberculosis is the infection to the colon, which give rise to intestinal tuberculosis. Intestinal tuberculosis is a colon infection caused by MTB that is usually treated just like the pulmonary form of the disease.[124] The restriction posed by the recent therapeutics is the long path of antibiotics to eradicate the infection, which requires, isoniazid (INH, 300 mg) and rifampin (RMP, 600mg) taken daily for 18 to 24 months which have a likelihood that the bacteria will develop to the treatment. Though various side effects are associated with both the drugs like effects of INH (rash, abnormal liver function tests, hepatitis, side roblastic anemia, high anion gap metabolic acidosis, and peripheral neuropathy) and RMP (hepatitis, liver failure, breathlessness, pruritus, nausea, vomiting, and flu-like symptoms) these side effects pushes the patient to discontinue the treatment and thus develop acquired drug-resistant TB during the course of therapy[125, 126] This drug-resistant TB is more severe public health issue in many developing countries due to the high cost of treatment and more medication requirements for a longer time interval. Nano medicine emerged with nanocarriers having characteristics to increase the patient compliance with very less side effects. These nano carriers have increased effects and the drugs can be entrapped into it for the sustained delivery.[127, 128] One of the recent study by Chen et al [129] a poly(methacrylic acid) (PMAA) nanogel was developed as a carrier of INH and RMP by a two-step approach as illustrated in Fig. 8. The nanogels showed a uniform spherical morphology (572 ± 23 nm). The LC of INH and RMP was 74.1 μg/mg and 39.3 μg/mg, respectively. The LE of INH and RMP was 62.5% and 33.7%, respectively. These gels demonstrated that the PMAA have a sustained release behavior in a medium simulating the gastrointestinal tract, and a case III mechanism. These nanogels demonstrated a potential as a more useful formulation than INH and RMP and is a step forward in the field of treatment against multidrug- resistant intestinal MTB.

5. Hydrogels for Influenza

5.1. Influenza Pathogenesis

Influenza A viruses have its place in the family *Orthomyxoviridae* and own 8 negative-sense RNA segments encrypting 11 known proteins. Out of these the 2 viral surface glycoproteins, hemagglutinin (HA) and neuraminidase (NA), form the root of the various serologically dissimilar virus subtypes.[130] Moreover the new subtypes have also been identified as 16 HA and 9 NA subtypes in wild water birds, which is considered as the natural host as well as the reservoir for the emergence of the all influenza A viruses. This is the major cause to infect the domestic poultry and mammals[131]. To start with the factors and source that transmit this infection to humans are the domesticated birds, which serve as an intermediate hosts for the transmission of wild bird influenza viruses. Recent trends show that the human infections with swine influenza virus A (H1N1) are on the rise on multiple continents. The World Health Organization (WHO) reports April 2009, the infections by the influenza virus subtype H1N1 were established in 7 countries. Also the highest number of subtypes H1N1 cases were reported in Mexico and 7 deaths. It is well known fact that the humans have no

immunity against this virus and is efficiently transmitted among humans very easily giving rise to pandemic. The latest data reported by the WHO for the National Influenza Centres (NICs) and other national influenza laboratories from 76 countries, areas or territories reported data to FluNet for the time period from 30 November 2015 to 13 December 2015* (data as of 2015–12-28 10:25:12 UTC).

5.2. Diagnosis of Influenza

The emphasis for the betterment to limit the spread and an early diagnosis for a prompt laboratory test for the diagnosis of H5N1 infection was made by (MacKay et al., 2008) [132]. Many research groups had constantly worked on the new laboratory methods for influenza detection, which included the virus detection by conventional virus culture monitored by the serological differentiation [133, 134] and also by the use of RT-PCR [135, 136]. Though these methods own limitations such as their high cost and efficient biosafety facilities. Efforts are made to replace the long-time taking methods like ELISA which is time consuming as well as rapid influenza antigen test[137, 138] by the QCM biosensor based technology detection. [139–141] The use of aptamers in diagnostics have also been highlighted in comparison to antibodies due to their ability to get chemically modified and easy labelling and stability. Basically aptamers are generally known to be artificial nucleic acid ligands used for specifically targeting against certain targets, such as amino acids, drugs and other bioactives.[142] Herein, we discuss the use of hydrogels for sensitive detection of the AIV H5N1. Moreover the use of DNA and aptamer based hydrogel systems for the biosensing applications have been highlighted.[143] The characteristic properties of DNA of folding into unique secondary and tertiary structures and its inherent biocompatibility and easy synthesis make it a perfect candidate to engineer hydrogel based systems for application in nanomedicine and biosensing.[144, 145] Hydrogel have the superiority to preserve the biological activity of the sensing material as well as diversity of substrates embedded within the hydrogel matrix. Owing to the high loading capability, relatively small amount of hydrogel could be employed and the patterning inside the surface modified microfluidic channels would provide a stable system. A high impact study carried out by Wang et al 2013[146] demonstrated the use of hydrogel based QCM aptasensor for AIV detection. This group developed an aptamer-ssDNA crosslinked polymeric hydrogel as a sensor coating material. The use of the hydrogel coating material made by the use of (acrylamide-co-aptamer) H5N1 with the titres of 6, 64, 6.4, 1.28 and 0.128 HAU was detected by the use of QCM biosensor. Figure 9 shows a decrease in resonance frequency shift for the detection of the target H5N1 with titres of 64, 6.4 and HAU and the corresponding resonance frequency was −200, −52, −22 Hz respectively. [146] The result showed that noticeable signal was obtained for H5N1 with a titre 0.128 HAU as shown by the typical detection curve. It is also observed that the hydrogels possess swelling on the sensor surface.

5.3. Therapeutics of Influenza

The operations of the influenza virus as a bioterrorism agent have prompted the recent research to develop novel vaccines and strategies to handle this pandemic. The toughest part to achieve a complete protection level against the increasing spread of the deadly virus is in the current vaccine strategies, which require more time to generate billion monovalent doses that have optimum immunization dose for 500 million individuals with that of the two doses

of the killed vaccines required for the defence. The two main recognised vaccines for this deadly virus are known as killed virus vaccine given as intramuscular injection and the other is a reduced live vaccine particular as a nasal spray. Though the emerging strains of virus which expresses variant antigenic epitopes urges the need for new vaccine development. Moreover the antigenic drift and shift causes the loss of effectiveness of the current influenza virus vaccines that show antiviral CD8+ T cell responses may evade the major drawback of the commercially available vaccines. Thus vaccines that have the capacity to generate the CD8+ T cell response s against the viral molecules and conserved among the various serotypes of influenza virus and can serve as "universal vaccines".[147] The major concern is that yet there is no such CD8+ T cell inducing vaccine against influenza virus. As these cells require replication and the protein immunization is ineffective an interesting study by the Boesteanu et al [148] developed a biopolymer encapsulated live influenza virus to vaccinate C57Bl/6J mice using a subcutaneous route of administration. The infection was induced by the exposure of the respiratory tract to virus. It is well known that from last many years' large doses of influenza virus intraperitoneally (IP) to prime animals for secondary responses[149–151] with reports of no infection. IP injection of 3×106 TCID50 PR8 influenza strain induces no inflammatory cytokines in tissues and no viral replication or weight loss in animals.[152] It was established that the subcutaneous route of administration of live virus did not source overt disease and mice neither lose weight, nor appeared sick. It was demonstrated that the subcutaneous vaccination of mice with live influenza virus was found to be safe immunodeficient Rag−/−γc−/− mice that received live influenza virus were healthy and had no viral replication in tissues.

The use of alginate biopolymer to encapsulate the live virus was an initiative to provide an additional layer of protection by aerosols containing the live virus (Fig. 10). This led to a strong CD8+ T cell mediated immune response upon rechallenge of vaccinated mice with a heterosubtypic H3N2 strain of influenza virus, and further this immune response was dedicated on a conserved epitope of influenza nucleoprotein (NP366–374). This novel vaccination approach provided heterosubtypic protection of mice against the extremely virulent influenza H7N7 strain.

Another interesting work contributed in the field of intranasal vaccine delivery for H5N1 influenza immunization involved the use of thermal sensitive hydrogel developed using N-[(2-hydroxy-3-trimethylammonium) propyl] chitosan chloride (HTCC) and a, b-glycerophosphate (a, b-GP). This system was an injectable form of hydrogels that have the tendency to gelate at body temperature enabling prolonged residence time of the H5N1 split antigen in nasal cavity. [153, 154]

It was also demonstrated that the system enhanced the transepithelial transport via the paracellular routes due to the disorganization of ZO-1 protein in nasal epithelial tissue. Superior antigen-specific systemic immune responses and mucosal IgA immunity without adjuvants was achieved in comparison to the naked H5N1 split antigen and MF59 adjuvant antigen. Figure 11 demonstrate the potential of the of HTCC hydrogels using non-invasive fluorescence imaging. It was well observed that no signal source from the fluorescence labeled antigen was detected after 1 h when mice were treated with PBS/antigen. Detection of strong fluorescence intensity after 1 h once hydrogel/antigen was directed, and the

residence time was for at least 2 h in the nasal cavity. It also shows the quantitative measurement of nasal fluorescence intensity and more than 54% antigen was in the nasal tissue after the co-delivery with hydrogel over 2 h. In comparison, a sharp decrease was observed in PBS/ antigen group, and only 12% of antigen retained in nasal cavity. Thus this system also supported the fact that hydrogels possess an enhanced delivery effect and suggested that the HTCC hydrogels are a perfect candidate to act as an adjuvant –free vaccine delivery systems for intranasal H5N1 split antigen vaccination.

6. Nanomedicine for Ebola

Ebola virus earlier known as Zaire ebola virus is one of the five viruses within the genus ebolavirus.[155] The major concern for the outbreak of this deadly diseases for public health is the shortage of approved vaccines and post exposure treatment. There is partial success in the development of the therapeutics and prompt diagnostics.[156] The upsurge for the post exposure therapeutics is in demand due to the localized and sporadic nature of ebola infection. The extent of survival of the non- human primates is typically 6–9 days once infected. This poses a great challenge on the treatment for reduction in virus replication till the immune response expands for effective control of the infection (Figure 12). Presently, the post therapeutics are to be given in an hour to completely protect the experimentally infected animals.[157, 158] The strong immunity against the adenovirus significantly hinders its development as antigen vectors. Nanomedicine is emerging as cutting edge in clinical medicine and provides a synergistic approach for design and diagnostics of NFs. The invent of mucosal vaccination over conventional intramuscular (IM) or subcutaneous immunization suggest an effective system and mucosal immune response.[159] Recently a research group showed that mucosal delivery of adenovirus-based vaccines could efficiently evade the pre-existing immunity. Ad-GPZ antigen co-delivered with QD- 60 and QD-79.5 hydrogels encouraged high systemic response as well as the respiratory mucosal immune responses thus exhibiting a magnified humoral immunity.[160]

Recent advancements show the use of Nanotechnology based electrochemical immunosensors based miniaturized devices which have the ability to target the analytes (pM level). Researchers suggest the use of miniaturized electrochemical ebola sensing systems for early detection of EBOV level.[161] The emphasis on the developments of hydrogel based sensors based on the dissociation and displacement of protein binding partners. In this context, the hydrogel technology can surely come up with market opportunities for personalised nanomedicine.

7. Future prospective and challenges

Though the dynamic research and development worldwide have controlled the intensification of the infectious disease yet the social factors contributing to these infections such as lack of adequate human and child health care, high international travel and the demographic as well as environmental factors which include urbanization, overgrowing population, cleanliness are the major challenges that need to be considered to limit the spread of the deadly diseases in 21st century.[162] In comparison to other therapeutic area, bacteria and viruses develop resistance to drugs. The frequent use of antibiotics has saved

millions of lives of humans though create newer resistant strains and encourage their spread. The major challenge lies with this increasing multi-drug résistance. This increased crises proportions in US and world- wide has urged the researchers to design new formulations and approaches for treatment of infectious diseases.

The prevention and cure of the deadly infections discussed so far caused by the bacteria and viruses presents a number of challenges. These bacteria produce a silent infection inside the cells and avoid the bactericidal mechanisms. The resistance to the antimicrobial drugs was a threat and thrust was on the innovative technologies for the development of novel invention of diagnostics and delivery approaches using nanotechnology for bacterial destruction. The need for efficient delivery for a better therapeutic index by improved therapeutic efficacy of drugs was met by the design of NFs. The important parameters which are needed to be taken care of are the toxicity profiles of the NFs, drug stability, effectiveness, pharmacokinetics and degradability. The significant challenges in the field of hydrogel based delivery systems for infectious diseases are the practical clinical applications of the designed NFs. Multifunctional systems to carry the therapeutic interventions are required. These systems should possess the talent to switch on and switch off which is basically “on demand drug delivery”. The biocompatibility and toxicity profiles in terms of the safe use of the NFs for human health care are the utmost parameter for considerable concern.

Hydrogel based nasal spray are in demand as they possess better route of drug delivery due to enhanced blood circulation and increased surface area for adsorption.[160] Moreover the stimuli responsive hydrogels based systems still remain a challenge for drug delivery as there is yet lot to explore for the simultaneous existence of pH gradient and an oxidative environment in certain pathological conditions. The interactions of the cell and genes and the hydrogels and the underlying mechanism at the nanoscale level has to be understood for a successful translation from lab to market applications in nanomedicine. As we are towards the beginning of the new millennium new NFs and diagnostic technologies would allow rapid disease cure and diagnosis and make things easier for clinicians to detect the organism causing the specific disease and existence of antimicrobial resistance genes. A long term commitment is required to fight against these infectious diseases. Prospective to exploit the nanotechnology based systems specifically hydrogels is due to their ability to transform the specificity and efficacy of the present existing drugs as well as improve their clinical applications. There is still a need to pursue the effective health infrastructures for the complete eradication of the epidemics and pandemics world-wide. These systems will act as catalyst for individual infectious diseases like malaria, slow down the spread of the deadly Ebola crisis and also the destruction triggered by the HIV/AIDS. Presently, there is an urgent need to outbreak the competences of nanotechnology and boost up the pathogen detection for deadly Ebola virus.[161] The quick detection of Ebola virus is the most important factor in lowering down the circulation rate of the virus inside the patient’s body. The detectable virus level is attained in at least 3 days after the symptoms appear. Thus funding agencies like the US National Institutes of Health (NIH) supports on the research and development for novel diagnostics for Ebola and Lassa fever, an acute viral hemorrhagic fever first known 1969 in Nigeria. The research group at Boston University College of Engineering and School of Medicine in collaboration with the company NextGen Assays, generated a device that

detects the disease by means of a single drop of blood from the patient, by shining light on viral nanoparticles attached to a silicon chip. [163, 164]

Classically several drugs which are used to cure infectious diseases face an important limitation known as drug resistance. The medical community including the pharmacists and chemist are in the urge of finding a simple regimen of medications for all the severe infectious diseases. Treatment of tuberculosis is one of the major example, which come up with the emergence of multi-drug-resistant TB (MDR-TB) known as a strain of TB susceptible to few first line medications and extensively drug resistant tuberculosis (XDR-TB) that is regarded as untreatable. The goal of eradicating the drug resistance for TB has been initiated by various organization such as World Health Organization's DOTS program (Direct Observed Therapy, short course) but are not completely successful to stop the cases of DR-TB. The innovation in development of NFs for infectious disease is by introducing such systems, which could shorten the drug regimen duration, lower the frequency of dosages, improved patience compliance and improve completion rates. Thus the NFs hold great potential in the reduction of drug resistance for many infectious diseases. The versatility in the forms of hydrogels that have been manufactured such as particle form (nanogels),[165] inhalable form,[166] liquid injectable form (intravenous and subcutaneous),[167] as a patch for scaffolds[168] and in oral dosages form[169] make them perfect candidate to be exploited for chemotherapy and drug resistance in infectious diseases. For tuberculosis the nanotechnology based systems allows the increased transcytosis in the gut lumen's M cells which enhance the intracellular uptake in the lining epithelium, and improved uptake in the Peyer's patch. This process reduces the loss of the active anti TB chemical in the bowels prior of entering the bloodstream and radically improve the bioavailability of the drug.[170, 171] The significant features of hydrogels such as particle size and surface can be modulated to avoid the rapid clearance by the phagocytic cells and thus promotes the active and passive targeting of the drug. The design of hydrogels in the form of controlled and sustained release systems improve the therapeutic efficacy and significantly reduce the side effects of the drug. The major advantages of using hydrogel based systems of the NFs to cure infectious diseases is their ability to reach the smallest capillary vessels owing to their tiny volume, porous structure that allow them to penetrate across the tissue by paracellular and transcellular pathways. It is noteworthy that the use of biodegradable polymers like chitosan, cellulose, Polylactic acid, PLGA etc for the synthesis of hydrogels make the NFs backbone completely degradable into compatible monomers which are non –toxic. These polymers owe the feature to be functionalized and have the ability to self-assemble into well-defined particles. Moreover, the nanogels formulations have been reported to show the efficient loading of payloads which is not achieved by the conventional nanotechnology based carriers.[172] NFs have also shown to functions as adjuvants to enhance the immunostimulatory properties of the old vaccines and can increase the immunogenicity of vaccines by activating immune inflammatory reactions which induces memory responses.

8. Conclusions

This review explored the salient features of hydrogels with their competence and potentials to cure infectious diseases. Owing to the tunable structural and functional characteristics of hydrogels obtained by modulating synthesis approach they find great potential as

nanocarriers to achieve site-specific drug delivery and release. Recently hydrogels have proven their potentials to develop future personalized nanomedicine to cure infectious diseases. In-spite of significant proven applications of hydrogels to manage infectious diseases, significant efforts should be made to design and develop smart hydrogels in nano-domain with improved characteristics and easy processing needed to develop therapeutics against target diseases. The emphasis to develop injectable hydrogels, nasal sprays and drops should be made for patient compliance. This review is a call to increase such significant efforts to develop hydrogel based therapeutic cargos-specific to target diseases, to be tested using animal model to promote as translational medicine.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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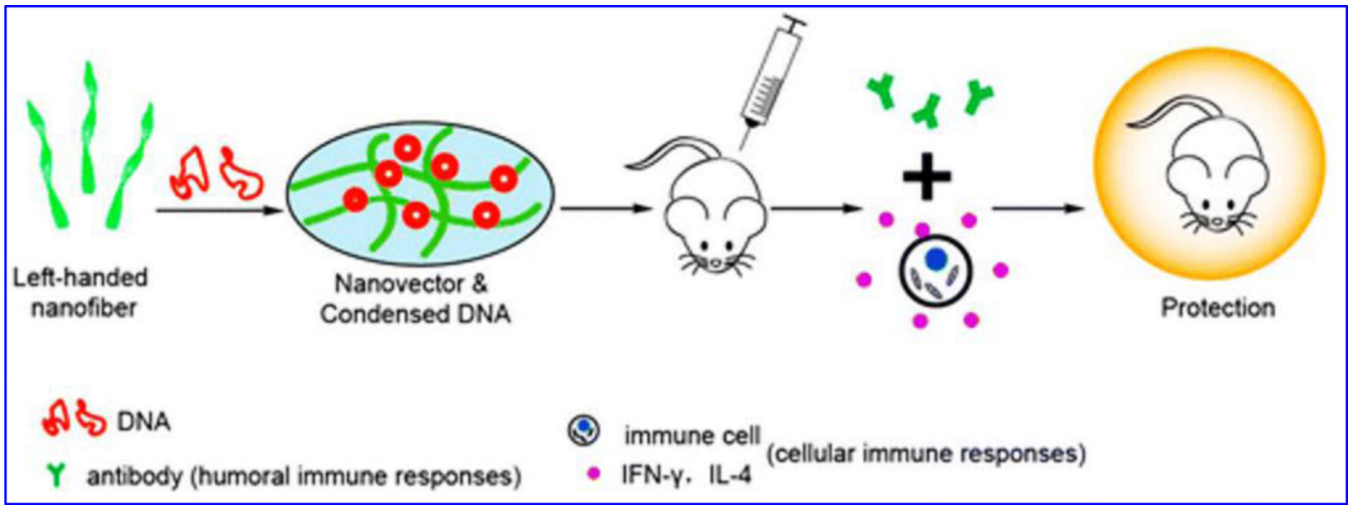

Figure 1.

Peptide based nanogels for HIV DNA vaccines. Reprinted with permission from Reference [68] with permission from Copyright (2014) American Chemical Society."

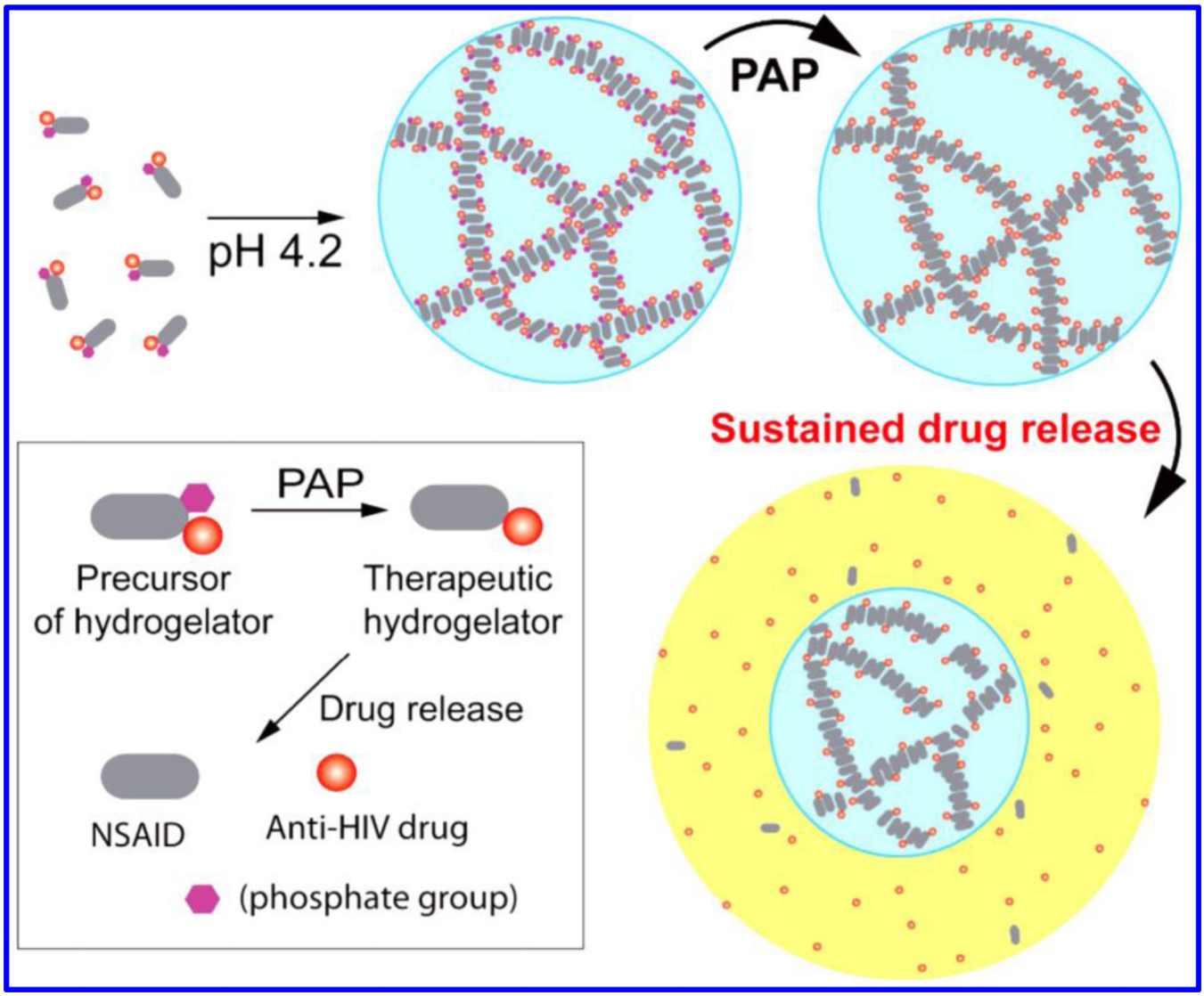

Figure 2.

The concept of enzyme responsive anti-HIV hydrogels for sustained release of anti-HIV drugs. Reprinted from reference [70] with permission from Copyright © 2013 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

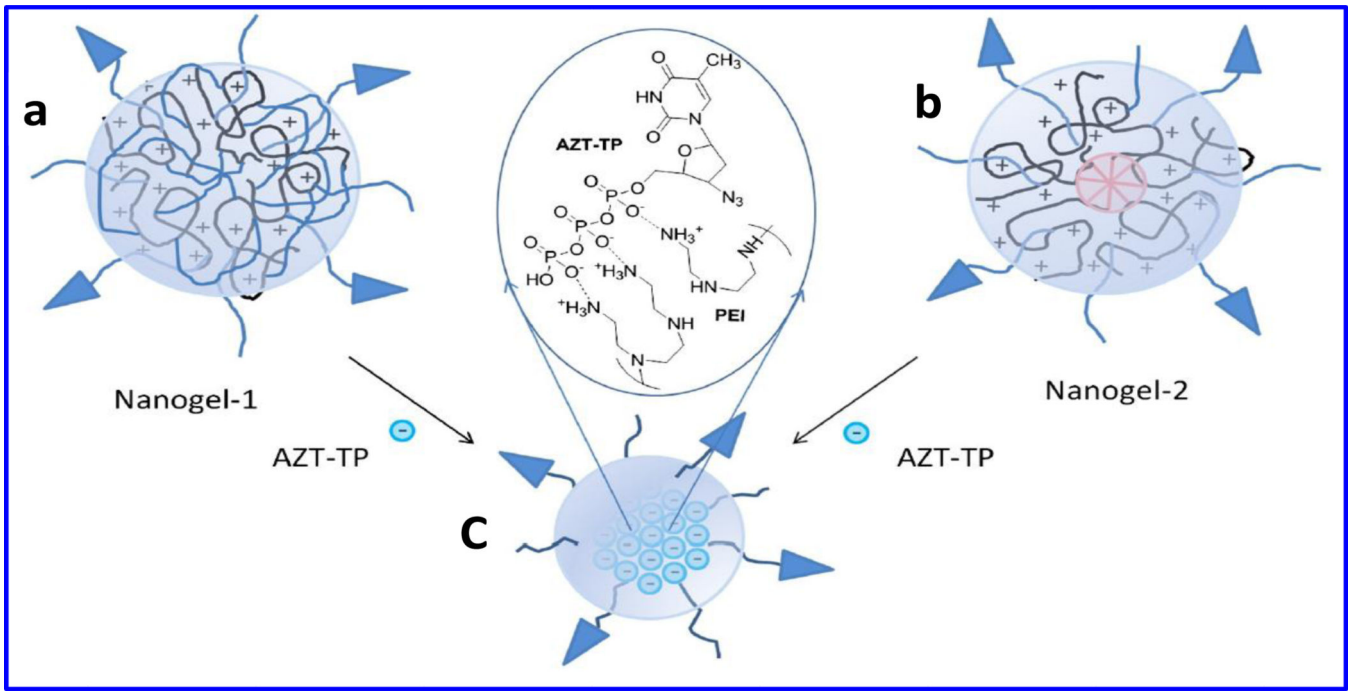

Figure 3.

Structures of nanogels (**A**) AP-NG1, (**B**) AP-NG2 and (**C**) preparation of AP-nano-AZT formulation. The insert shows polyionic complex between charged phosphate groups of AZT-TP and amino groups of PEI. Reprinted from Reference[73] Copyright (2014), with permission from Elsevier.

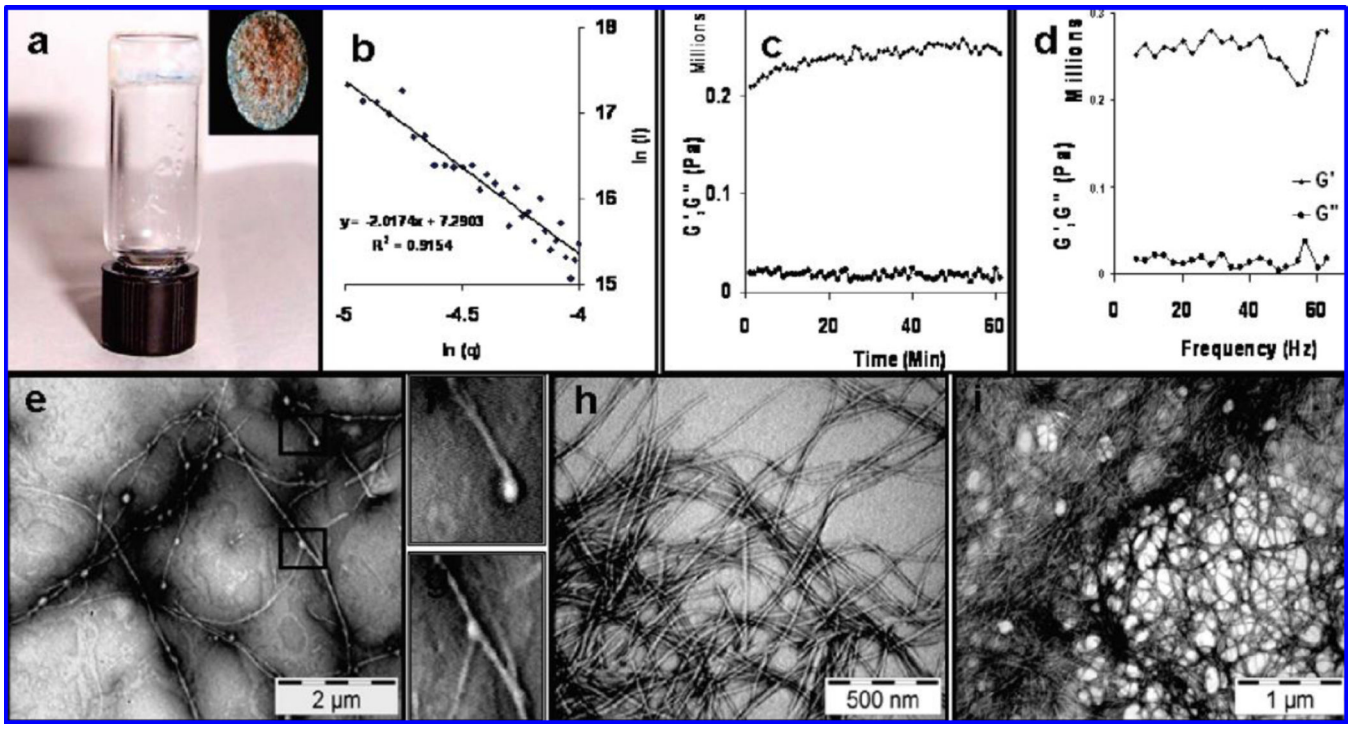

Figure 4.

(a) Self-supportive Phe-ΔPhe gel, inset shows birefringent nature of Phe-ΔPhe gel stained with congo red; (b) Fractal dimension of 0.25% Phe-ΔPhe gel; (C) Time sweep data comparing storage modulus (*G*') with loss modulus (*G*") of 1% Phe-ΔPhe gel prepared in 0.8 M sodium acetate buffer; (d) Frequency ramp of same gel; (e) Electron micrograph of 0.2% gel just after cooling; (f) Magnified electron micrograph of same sample showing fibers with vesicular nodes; (g) Branching of gel forming fibers at the nodes. Electron micrographs of the same gel (h) 15 min and (i) 30 min after cooling. Adapted from Reference.[99] from Copyright (2008) American Chemical Society

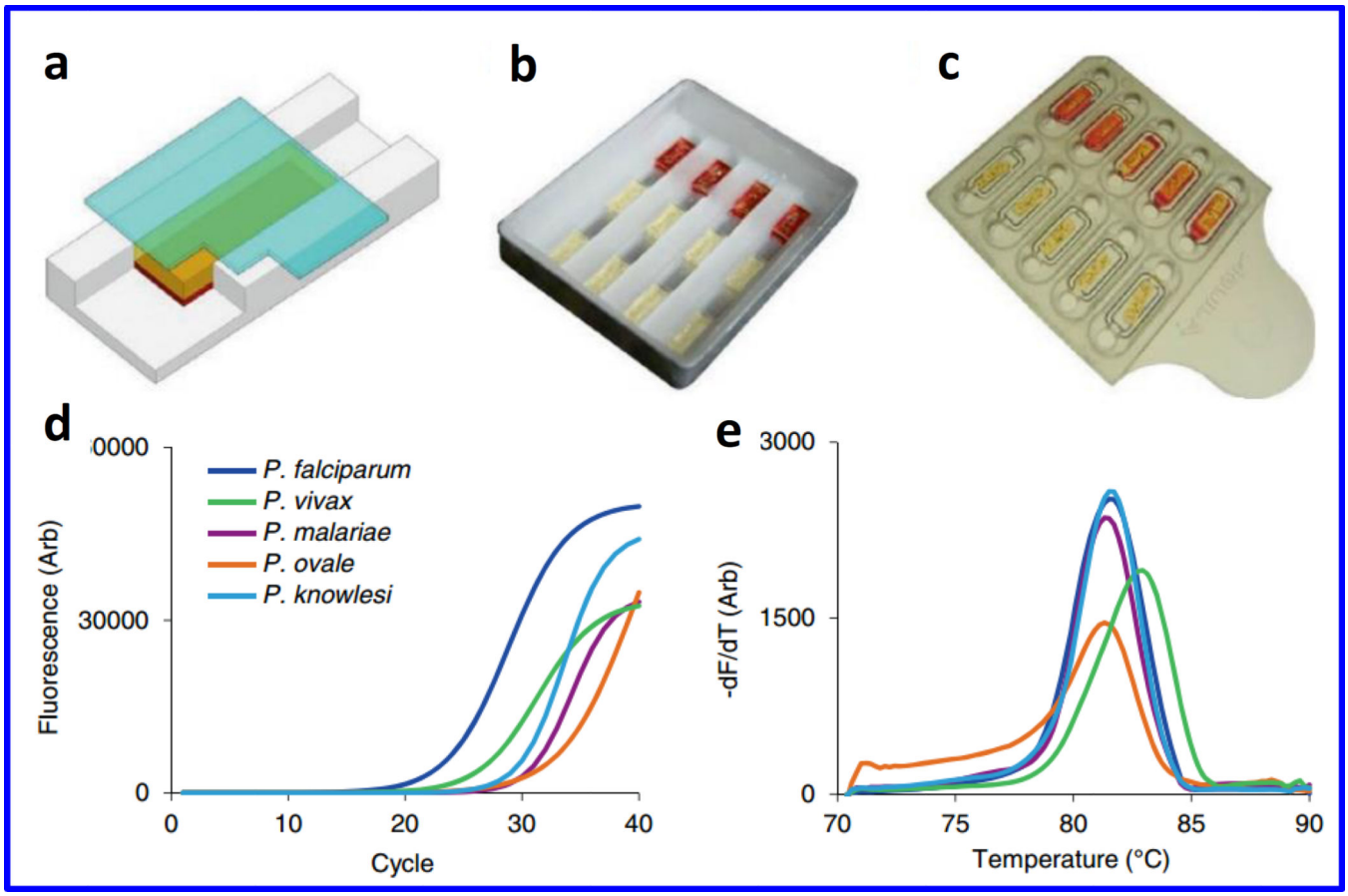

Figure 5.

A lab-on-chip for malaria diagnosis and surveillance. Reprinted from Reference [106] with permission Copyright © 2014 Taylor et al.

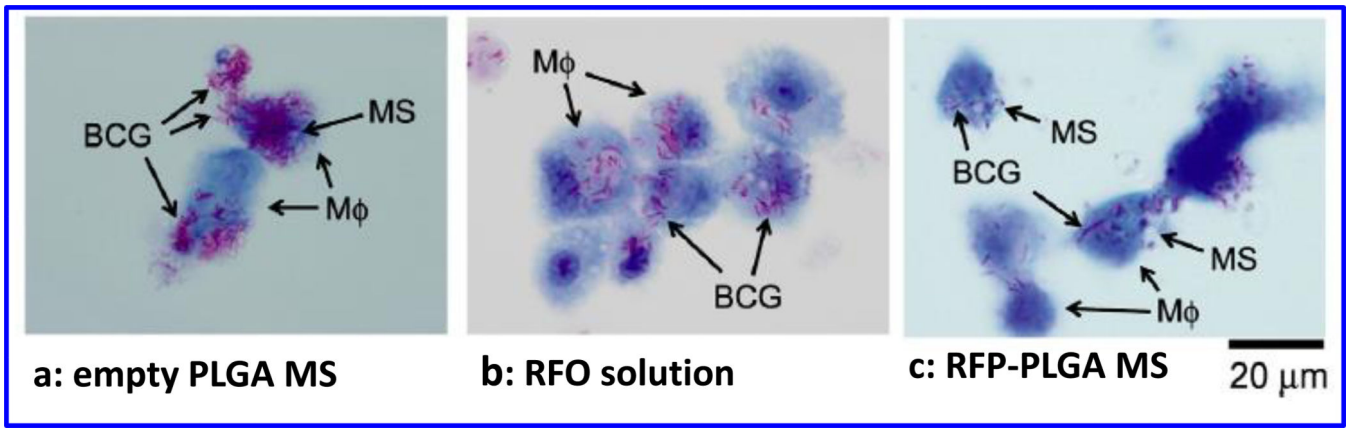

Figure 6.

Microscopic observation of BCG-infected NR8383 cells after treatment with RFP–PLGA MS or RFP solution. After treatment of BCG-infected NR8383 cells with either empty PLGA MS (A), RFP solution at 5.00 μg/mL (B), or RFP–PLGA MS containing 2.50 μg/mL of RFP (C) for 7 days at 37 °C, the BCG and Mϕ cells were stained with Ziehl–Neelsen carbol-fuchsin stain solution and Loeffler's methylene blue solution, respectively; and the Mϕ cells were observed under a light microscope at magnification ×1000. Reprinted from Reference[114] Copyright (2010), with permission from Elsevier.

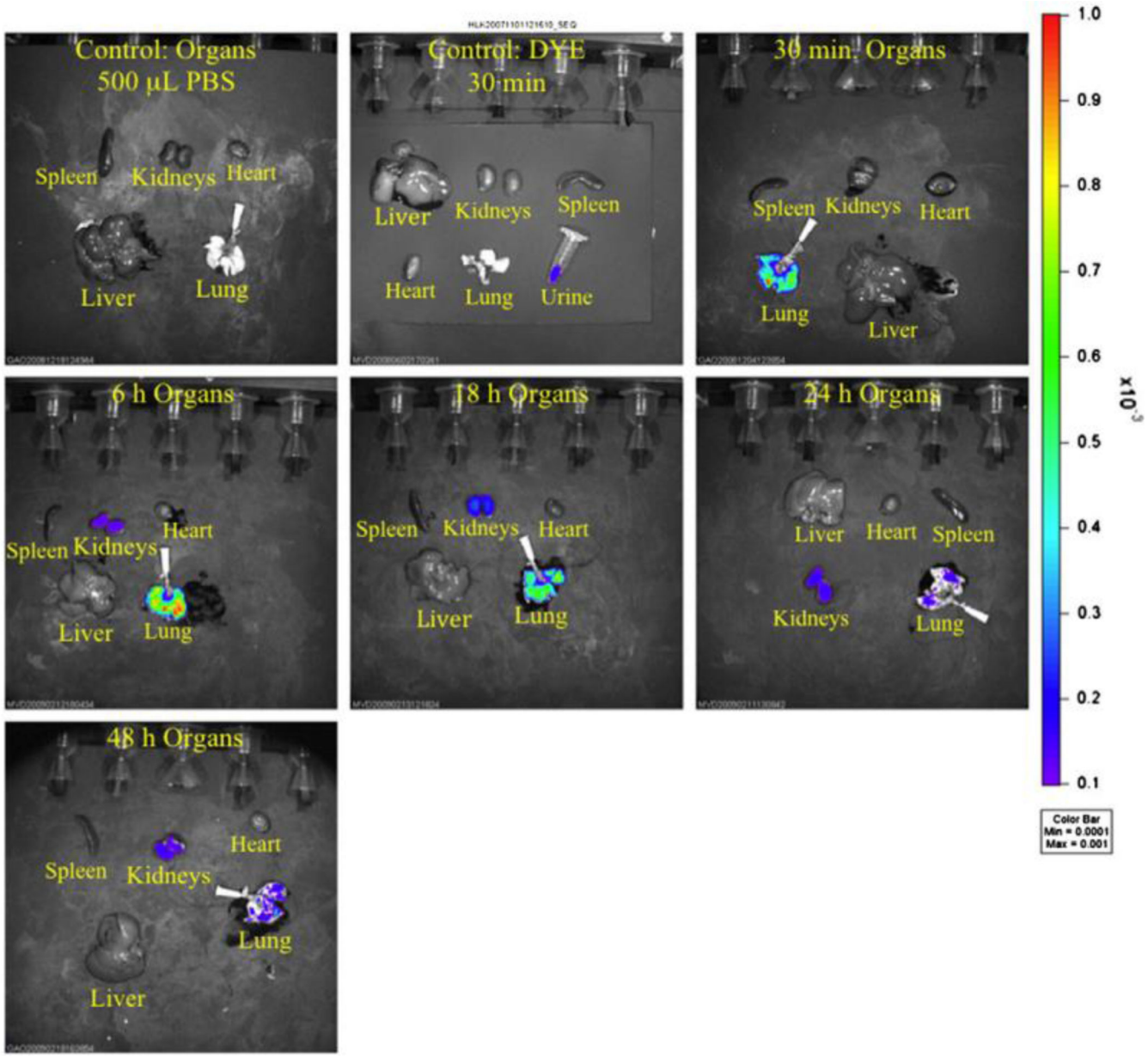

Figure 7.

Bio-distribution of DYE-SANPs following IV administration. Rats (n=3) were administered DYE-SANPs (30 μm) through a tail vein catheter. Animals were euthanized by intraperitoneal injection of pentobarbital (250 mg/kg), 0.5, 6, 18, 24, and 48 h later. The heart, lung, liver, spleen, and kidneys were removed and imaged intact using the IVIS®100 imaging system. Reprinted from Reference [123] Copyright (2012), with permission from Elsevier.

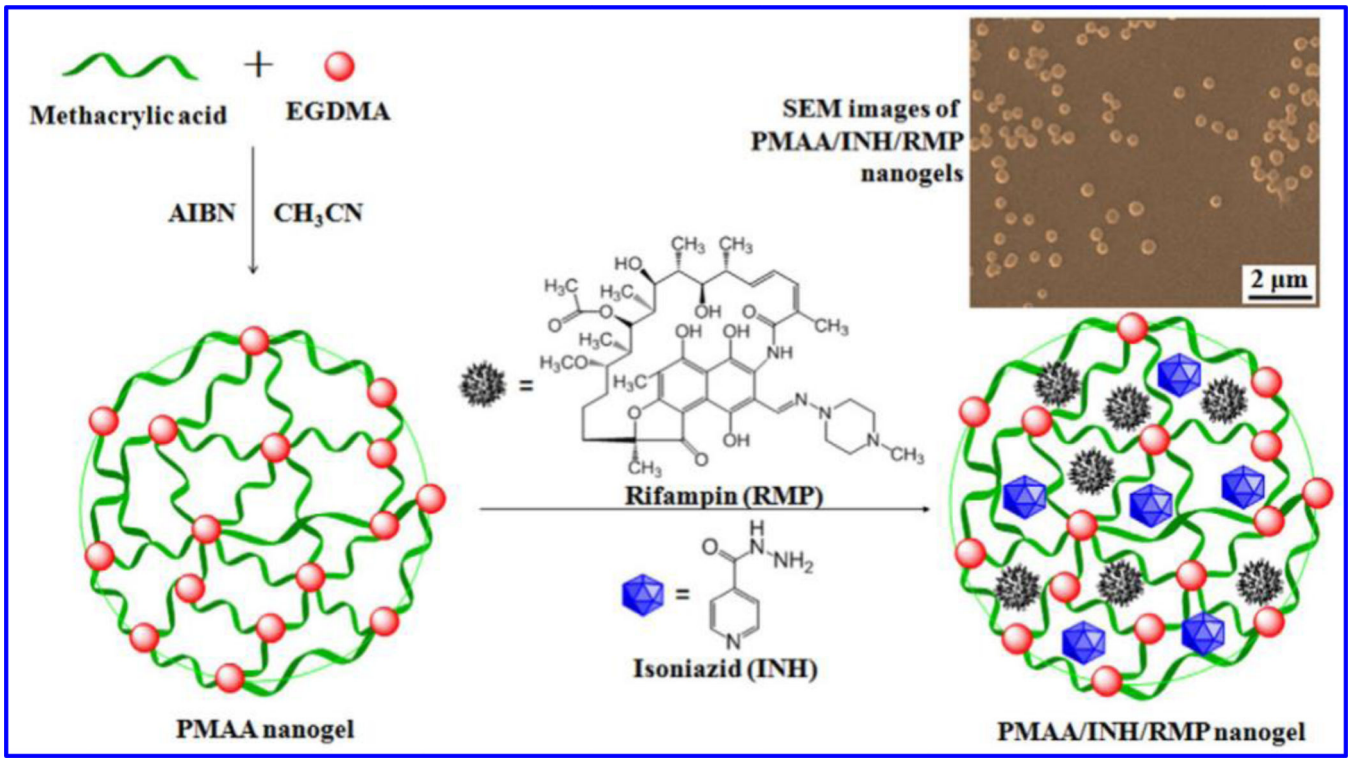

Figure 8.

Preparation of the PMAA/INH/RMP nanogel: Step 1, Methacrylic acid, EGDMA, and AIBN were added into CH3CN to obtain a PMAA nanogel; Step 2, Isoniazid (INH) and Rifampin (RMP) were loaded into the PMAA nanogel to produce the PMAA/INH/RMP nanogel. (Inset: SEM images of the obtained PMAA/INH/RMP nanogels.) Reprinted with permission from Reference[129] Copyright (2016), with permission from Elsevier.

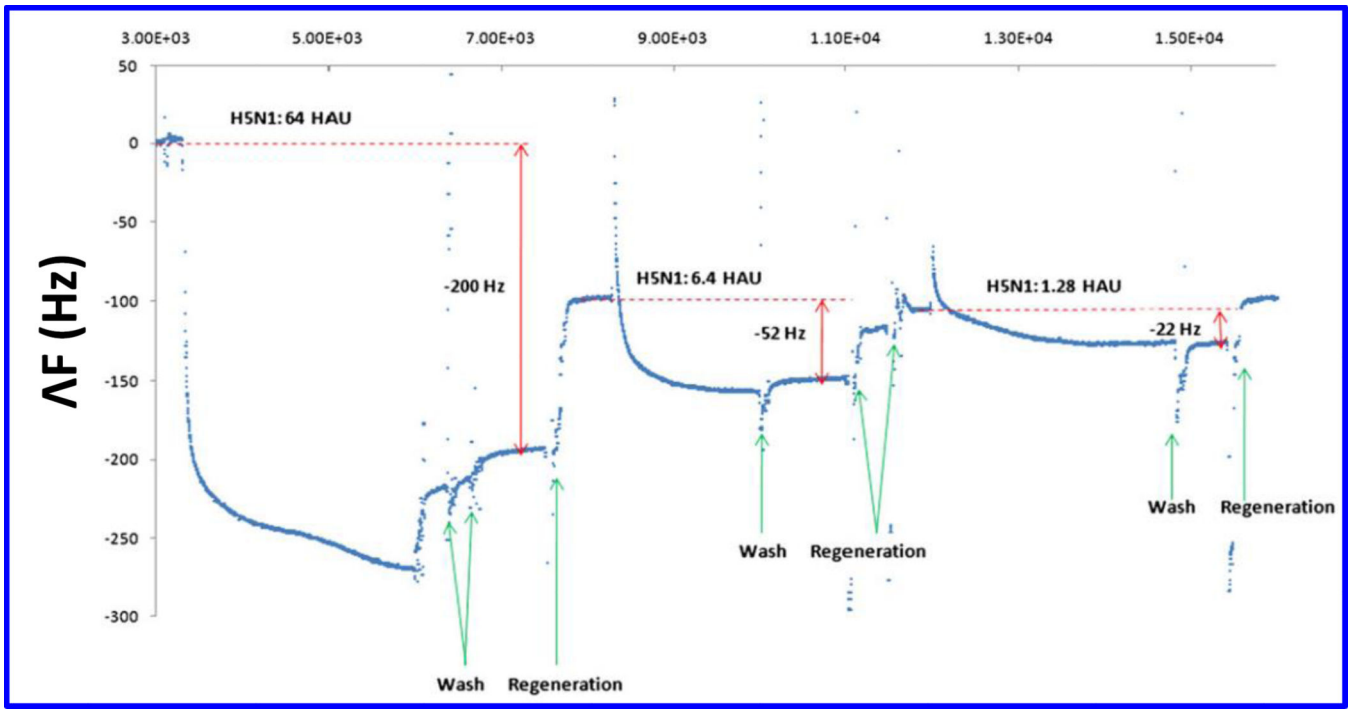

Figure 9.

Frequency shifts (DF) corresponding to different titres of AIVH5N1 (64, 6.4 and 1.28 HAU, respectively) for aptamer hydrogel I coated QCM sensor. Reprinted from Reference [146] Copyright (2016), with permission from Elsevier.

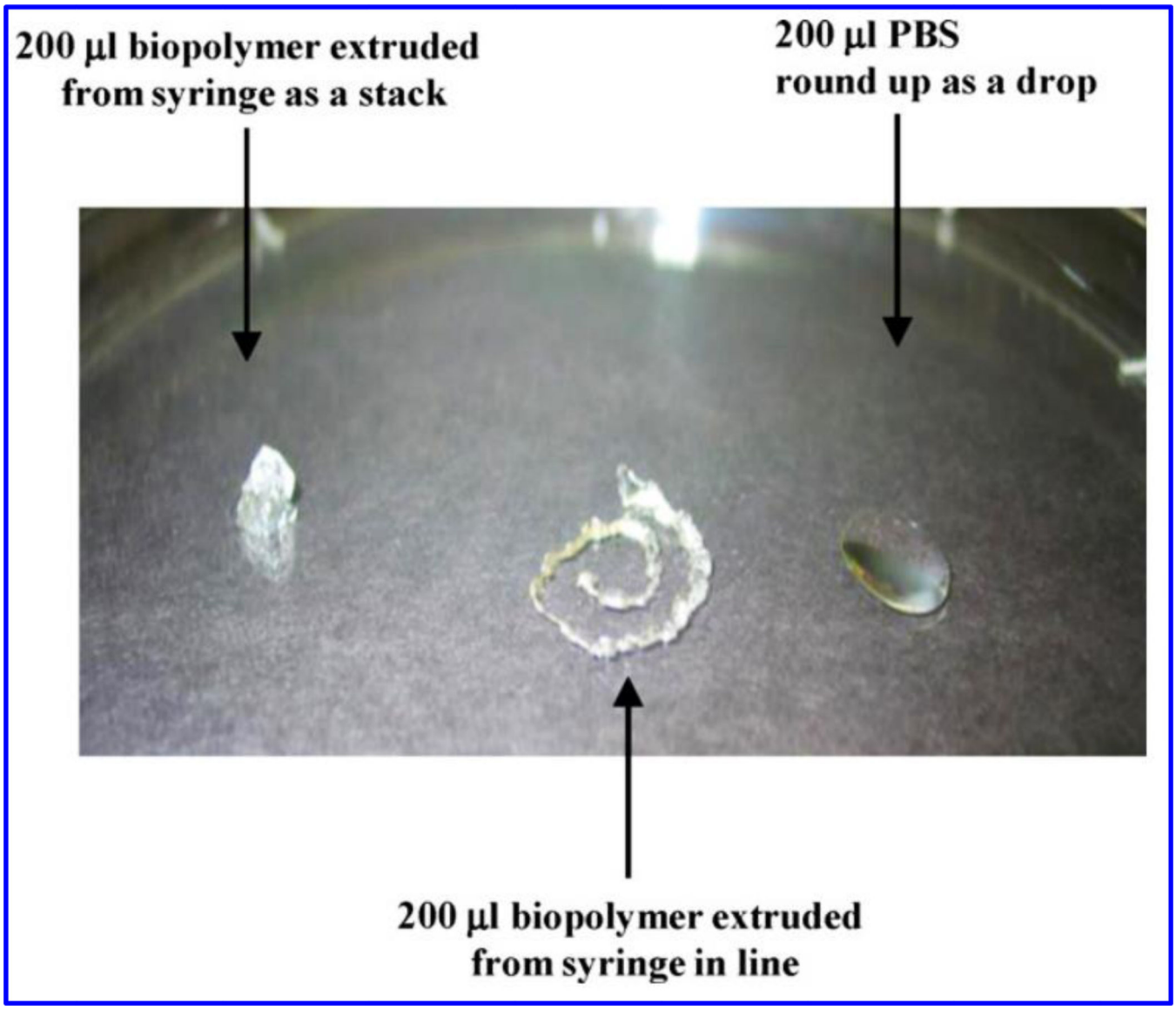

Figure 10.

Biopolymer releases no fluid when extruded through a 26G needle. The alginate based biopolymer used to encapsulate live influenza virus for SQ immunizations of mice can be easily extruded from a syringe with a 26G needle, without phase separation. When extruded through the needle of a syringe, either as a stack (left) or in line (middle), there is no release of liquid from the biopolymer. For comparison, a drop of PBS is shown (right). Reprinted from reference[148] Copyright (2016), with permission from Elsevier.

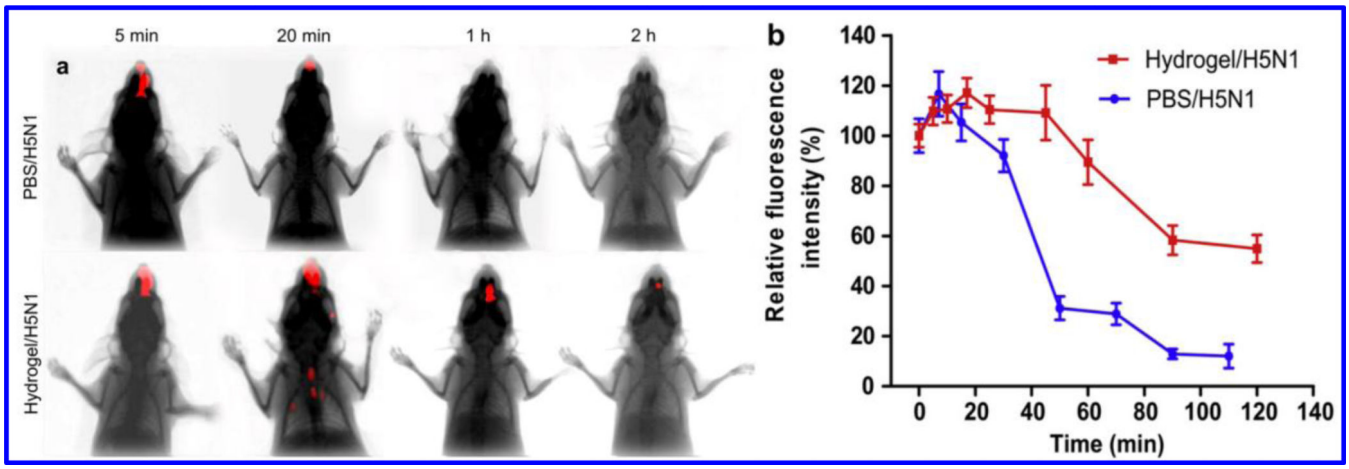

Figure 11.

Fluorescence intensity detected after intranasal administration of NHS-Cy5 labeled H5N1 in PBS or hydrogel at different time intervals (a). Relative fluorescence intensity in the nasal cavity over time was displayed in (b). Relative fluorescence intensity was calculated from absolute fluorescence (% of the initial fluorescence in the nasal cavity). n ¼ 4 mice for each group and error bars indicate the standard error of the mean. Reprinted with permission from reference [153] Copyright (2012), with permission from Elsevier.

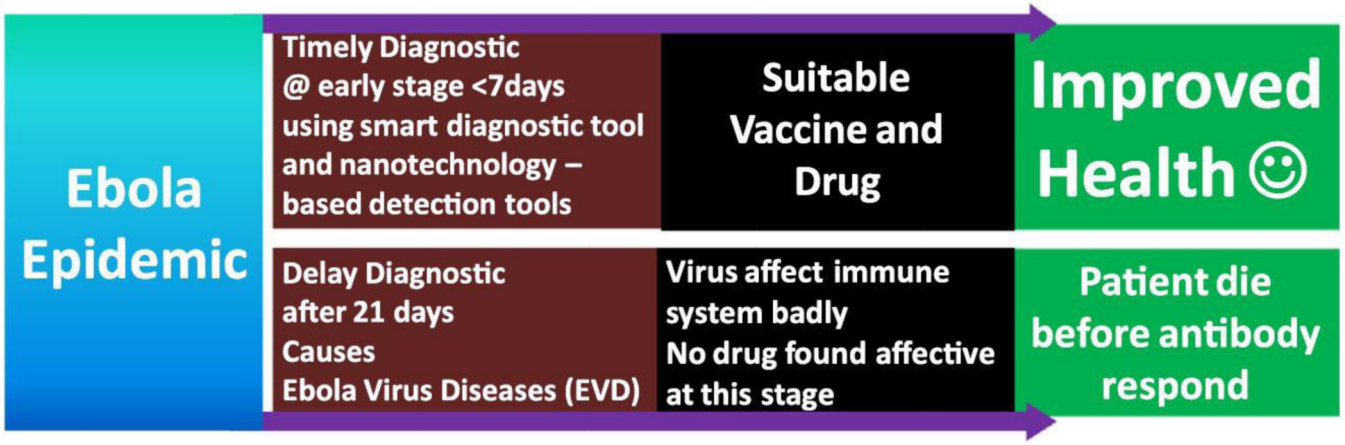

Figure 12.

Schematic illustration of possible future prospects of miniaturized nano-enabling electrochemical Ebola sensor for POC application. Reprinted from reference [161] Copyright (2012), with permission from Elsevier.