Review Article

Smart Drug Delivery Systems as Game Changers in Therapeutics

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ABSTRACT

Smart Drug Delivery Systems (SDDS) have emerged as panacea for many clinically useful drugs weighed down with toxicity. The discovery of Amphotericin B as a liposome has raised hopes and directed mammoth efforts in SDDS. The concept of manipulation of toxicity has given rise to additional significant approaches like targeting and use of physico-chemical approaches. Currently the spectrum of SDDS comprises of targeting liposomes, drug loaded biodegradable microspheres, stimuli responsive drug polymer conjugates, smart hydrogels, polymeric micellar particles, intelligent lipoprotein carriers, and nano carriers. There is a wealth of knowledge accumulated worldwide in the area of SDDS, which can be extremely beneficial to industry as well as practitioners of health care. In this article an overview of developments are reviewed.

Introduction

Smart drug delivery systems

Conventionally, the systemic administration of a drug can be best described as drug being exposed to the entire body, which can be called as "Random Walk" to meet its target. During its course of travel in the system, it is likely to interact with nontargets and targets as well, to initiate intended drug action. This can be best described as throwing plenty of stones so that at least one of them will succeed in striking a target in the tree. The abundant hits on nontargets are likely to be injurious and harmful for the system. This has been the universal practice of the systemic administration of all therapeutic classes of medicines. One of the major drawbacks of administering the drug to the whole of the body is unnecessary exposure of the drug throughout the body with increasing risk of toxicity and adverse drug reactions (ADRs). The best way to circumvent is to make magic bullets, which can precisely act on predetermined targets. This will result in minimizing the drug administered and circumventing unnecessary exposure of the drugs to nontargets resulting in improved safety and therapeutic benefits. With recent advances in polymer sciences and nanotechnology, designing intelligent smart drug delivery systems (SDDS), with targeted actions has now become a reality.

Drug toxicity is caused due to long-term treatment protocols of chronic disease like diabetes, hypertension, cancer, and acquired immunodeficiency syndrome (AIDS). Drug safety is a critical factor in long-term treatment wherein careful evaluation of risk: Benefit ratio handicaps the therapeutics. The active pharmaceutical ingredient (API) invariably carrying a burden of drug safety issues extending beyond generations is a major concern of modern medicines. Prediction and risk minimization of drug safety issues, various efforts and alterations in chemical features although attempted has resulted with limited success. The advancement in basic sciences, along with applied therapeutics with convergence of molecular biology has made the landscape clearer with rational application of suitable physico-chemical models. Application of this approach mandates precise identification and characterization of the target in disease conditions.

The next logical approach is to deliver the drug to the specific target without interacting with other tissues and biomolecules, while it is having a random walk across the body to reach the target. The challenge is to render the API inert, while it is administered and transported. After reaching the vicinity of the target, the API should be transformed from inert to active state. Many attempts were made to address this issue using prodrug approach, which was successful with few drugs and could not be applied universally to all medicines in general. Advances in polymer

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science have been much rewarding as it offers novel polymers, which can be used for making novel drug delivery systems. The polymers are also imbibed with properties like sensitivity to various physicochemical and biological stimuli. The current approach for SDDS uses extensively novel polymers, sensitive to a variety of biological and physicochemical stimuli, a few of such examples are mentioned in Table 1.

An anti-inflammatory drug can be enveloped in a polymer capsule, which is designed to be sensitive to inflammatory mediators like cytokine or leukotriene. These nano/microencapsulated anti-inflammatory SDDS when administered in the organism are distributed across the body. However, the SDDS is programmed to release the API in case it comes across the inflammatory mediators, thereby providing targeted delivery to the inflamed tissue with minimum to negligible toxic/adverse effects.

Advances in SDDS

SDDS refers to intelligent approaches in formulations technologies, focused on transporting an API from its dosage form to the target site as per the drug safety norms to achieve its intended therapeutic action in the body.[1] By taking into consideration both quantity and span of drug residency, it tries to provide logical site-targeting within the system along with facilitation of systemic pharmacokinetics. Conventional drug delivery, in contrast, is not only approached with API chemical modification, such as prodrug, but it also encompasses medical devices or drug-device combination products. These conventional drug delivery systems have been facing failures in precise and effective therapeutic delivery of dosage form with suitable route of administration.[2]

Table 1: Application of smart polymeric materials in drug delivery systems

Smart polymeric material	Stimuli	Induced transitions	Applications in drug delivery systems	References
Poly (*N*-isopropyl acrylamide)	Temperature	Water soluble coils to water-insoluble globules followed by subsequent collapse of polymer or precipitation from solution or adsorption/desorption	Intelligent carriers in a diverse range of applications including thermosensitive doxorubicin magnetic nanoparticles and in separations.	Piskin (2004) Gutowska *et al.* (1992)
Hydroxy propyl cellulose		Hydrated swollen state to dehydrated shrunken state	Size-exclusion chromatography	Adrados *et al.* (2001)
Poly (acrylic acid) Poly (N, N′- dimethyl amino ethyl methacrylate)	pH	Compact unionized state to swollen ionized state	Colon specific drug delivery. Specifically for delivery of anticancer drugs for treating colon cancer. Drug delivery in the stomach for treatment of peptic ulcers, stomach cancer, etc.	Qiu and Park (2001)
Poly (*N*-isopropyl acrylamide) hydrogels containing ferromagnetic material, Ethylene-co-vinyl acetate (EVAc)	Magnetic field	Reversible collapsing of the hydrogel under the influence of magnetic field	Polymer used in the treatment of intercellular hyperthermia. For insulin delivery	Takahashi, Sakai, and Mizutani (1997), Creque *et al.* (1980)
Polythiophene gel, Poly (2-hydroxyethyl methacrylate) (PHEMA)	Electric field	Swelling and deswelling induced by electric field	Potential use as small-scale actuators and valves in microsystems application. Administration of propranolol hydrochloride	Irvin, Goods, and Whinnery (2001)
Dodecyl isocyanate Poly (ethylene glycol) grafted poly(2-Hydroxy ethyl methacrylate)	Ultrasound	Disrupt the orderly chains on the surface of the drug-containing polymer	Controlled drug delivery in various chronic diseases	Kwok, Mourad, Crum, and Ratner (2001)
Poly (*N*-isopropyl acrylamide) with tri sodium salt of copper chlorophyllin	Light	Reversible collapse of gel	Potential use as a photo-responsive artificial muscle or switch	Suzuki and Tanaka (1990)
Poly (acrylic acid) and poly (oxy propylene - co-oxy ethylene) glycol	Inflammation	Mucoadhesive liquid composition that undergoes sol–gel transformation at body temperature can be tailored for stimuli-responsive drug delivery.	Used for development of ophthalmic, buccal, nasal, vaginal, transdermal, injectable, implantable, and nonaerosol pulmonary drug delivery systems	http://www. Medlogic. com
Ethylene-co-vinyl acetate (EVAc), Polypyrrole	Glucose	Detection of high glucose levels in the body by amperometric or potentiometric technique using glucose oxidase enzyme for substrate polymer crosslinking.	Insulin release due to high glucose concentration, i.e., in hyperglycemia as glucose biosensors	Brown *et al.* (1996), Gerard *et al.*
Methyl vinyl ether-co-maleic anhydride	Morphine	Reversible collapsing of the hydrogel	Naltrexone	Roskos *et al.* (1992)
Poly (ethylene-co-vinyl acetate)	Antibody	Reversible collapsing of the hydrogel	Naltrexone, ethinyl estradiol drug delivery	Pitt *et al.*(1985)
Polypyrrole	Urea	Amperometry, Potentiometry, Conductometry, Capacitance Measurement are the detection techniques in high urea levels using urease enzyme for substrate polymer crosslinking.	In treatment of Hyperuremia as urea biosensors	Gerard *et al.*
Polyaniline, Polypyrrole, Polyacetylene	Metal	Conducting polymers	Biosensors	Gerard *et al.*

The modification of the drug release profile, absorption, distribution, and elimination by the drug delivery technologies helps in facilitating not only the product safety and effectiveness but in turn also leads to patient suitability and compliance. The drug release from these systems mainly takes place by diffusion, degradation, swelling, and affinity-based mechanisms.[3] The noninvasive per oral, topical, transmucosal (nasal, buccal/sublingual, vaginal, ocular, and rectal) and inhalation routes are the most preferred routes of administration utilized by SDDS.[4] There are in general, many medications such as peptide and protein, antibody, vaccine, and gene-based drugs that cannot be delivered using these routes because of the drug's vulnerability to enzymatic degradation and low bioavailability problems due to molecular size and charge disputes. Therefore many protein and peptide drugs have to be administered by injection or a nano needle array. For example, many immunizations are based on the delivery of protein drugs and are often done by injection.

Current efforts in the spectrum of drug delivery involve the upgradation of targeted delivery, which delivers the drug only to the target area of the body (e.g., in cancerous tissues) and to provide sustained or controlled release of drug from the formulations over a period of time to provide effective therapy in patients. In order to achieve proficient targeted delivery, the designed system must be capable of escaping the host's defense mechanisms and reach its anticipated site of action.[5] Some of such effective sustained release formulations as SDDS include targeting liposomes, drug loaded biodegradable microspheres, stimuli responsive drug polymer conjugates, smart hydrogels, polymeric micellar particles, intelligent lipoprotein carriers, and nano carriers.

SDDS is dedicated to deliver the prescribed medicament to a patient in a manner that increases the concentration of the medication in the recognized vicinity of target sparing its release near nontargets. The objective of a SDDS is to confine the drug to the target, provide specific drug interaction with the diseased tissue and provide controlled release of the drug in the target site exclusively. In a conventional drug delivery system, API follows absorption distribution metabolism excretion (ADME) cycle, which begins with the absorption across a biological membrane, whereas in SDDS the API enclosed in polymer escapes this cycle. One of the advantages of SDDS is the declining frequency of dosage administration as it can be designed for control or sustained release. This can be beneficial in achieving the finest patient compliance with a consistent outcome of the drug effects, minimization of ADR, with reduced fluctuation in systemic drug levels. The SDDS are not popular as they are expensive in contrast to the conventional dosage forms. However, with evidence of pharmaco economics, the patient reported outcomes and health technology assessments, the justification for changing over the conventional dosage forms to SDDS can be furnished. The intention of SDDS is mainly to deliver a certain effective dose of a therapeutic agent for a prolonged period of time to a targeted diseased area within the body in order to maintain the required tissue and plasma drug levels in the body and evading any damage to the healthy tissue via the drug. For instance, the tissue-specific toxicity to the liver and spleen can be prevented by SDDS since it circumvents the host's defense mechanisms and prevents unnecessary buildup of the API in these organs. During the formulation of an effective SDDS, few design criteria must be taken into account such as the drug properties, ADRs, the route of administration, the delivery of the drug to a targeted site, and the disease.

Drug delivery approaches

There are various innovative drug delivery approaches tried so far, some of which include liposomes, polymeric micelles, lipoprotein-based carriers, nano-based carriers, and dendrimers. The major requirements of an ideal drug delivery approach are nonhazardous, biocompatible, biodegradable, and nonimmunogenic. The liposomes were the first to appear in the market as a SDDS in resolving the issue of Amphotericin B toxicity in combating systemic fungal infections. It was discovered that the manipulation of toxicity without compromise on efficacy is possible by SDDS. This above success has earned the niche position for liposomes as a popular and premier approach in resolving issue of drug delivery. They are simple to prepare, experiment, and utilize. Liposomes are not only nonhazardous, nonhemolytic, and nonimmunogenic but also biocompatible and biodegradable as well. They can be designed to avoid self-regulated body clearance mechanisms or enzymatic inactivation. The challenge faced by liposome is its poor shelf life due to its rapid washout from plasma by reticuloendothelial clearance, which brings down the duration of action. The intention of formulating the SDDS was mainly to treat the conditions, such as AIDS and cancer, in which the toxicity of the drug was limiting factor for application. For example, disease management of cancerous tumors in which the objective of the therapy is to discriminate between cancerous and the normal tissues. Due to numerous efforts across the world, on these lines of thought, the spectrum of approaches surfaced out utilizing innovative techniques and materials, with a specialized field collectively popular as SDDS.

Models of smart drug delivery

A complex chain of responses needs to be undergone by the smart drug polymeric system for their *in vivo* survival so that they can deliver and release the drug into the target cells. Compared with various approaches used to enhance the efficacy of chemotherapy, the use of stimuli responsive carrier systems that release the drug in response to changes in pH, glutathione concentration, or the presence of specific enzymes of cell organelles have proven to be the most effective approach. Nanoparticles and nanocapsules, which are stimuli responsive, have evoked great interest because of their high prospect for *in vivo* survival. These nanosized capsules on internalization are competent in shielding various drugs, storing and releasing them inside the cells.

In case of polyelectrolyte micelles, in response to added salt, the electrostatic forces keep these particle assemblies together. The cores of these weak polyelectrolytes micelles, laden with drugs and enzymes, comprise of pH-dependent particles, which become unsteady and release the drugs on changes in pH.[6]

Stimuli-responsive nanogels have become the recent promising drug delivery systems. The receptor-mediated endocytic pathways internalize pH sensitive nanogels to the target site. These nanogels possess an attribute of viruses to migrate from one cell to another, leaving remnants behind thereby possessing virus mimetic properties. These virus mimicking nanogels consist of a drug-loaded core bordered by a polyethylene oxide (PEO)–bovine serum albumin double shell that is ornamented with folate groups able to bind to the precise cell receptors. The nanoparticles swell and release drugs sequestered in the particle core in the acidic endosome. The virus-mimetic nanogels, on internalization, enter the endosomes where they experience a pH-triggered volume expansion and simultaneous

release of the drug. However, the nanogels on swelling escape from the endosome after disrupting the endosomal membranes. The nanogels shrink back to their initial size when exposed to acidic pH and migrate to another cell similar to virus.

A considerable progress made in the field of smart drug-delivery systems has thereby been depicted by these models. After a considerable study in this regard, it has been found that, capsules and vesicles have higher stability than micelles and nanogels. This helps the former to show a much greater drug-loading capacity than the latter. The crosslinking of the polymers helps to regulate both mechanical and chemical stability.

Strategic advantages of smart polymers as intelligent drug delivery systems as improved drug delivery

The wastage of API as a result of various mechanisms like firstpass effect is a major concern, which can be as high as 70-80% because of its metabolism. The drug metabolisms can also take place in lungs, intestine, and kidney. All cells are capable of metabolizing the molecules it comes across. In fact, only a fraction of administered drug is utilized for therapeutic action. As it is difficult to identify the target and release the API just sufficient to act, it is administered in such a large proportion after overlooking for the metabolic losses. The improved drug delivery is a hope to address the above issue by making a drug envelope and monitoring its release properties in the vicinity of the target. It will also help in saving the cost in case of very expensive APIs.

For example, Amphotericin B, when administered as a bare drug, needs to be given in high concentration and patients are subjected to toxicity. This is easily resolved by making an improved drug delivery system called liposomes.

Thermo sensitive targeted liposomes

The widespread applications of liposomes in drug delivery have been limited by its incompetent drug release, as a result of which thermo sensitive liposomes are designed so that the drug can be induced to release from the liposomes by mild hyperthermia. The thermo sensitive liposomes release the drug once exposed to temperature of 42°C. With this technology maximum drug accumulation in the tumor tissues is achieved to show targeted action and its rapid release can be triggered at the threshold temperature.[7]

Thermo magnetic targeted drug delivery systems

The drug can be released from the thermo magnetic liposomes by triggering the threshold magnetic hyperthermia. One such liposome is folate receptor targeted liposome, which gets triggered by threshold magnetic hyperthermia for the drug release. These formulated magneto liposomes demonstrate thermo sensitivity and tough responsiveness to magnetic fields, which helps to destroy the tumor cells exclusively in contrast to both commercially available preparation and nonmagnetic folate-targeted liposomes. Thermomagnetic liposomes of methotrexate shows improved and effective magnetic targeting and drug release when it gets triggered by threshold magnetic hyperthermia.[8]

Smart polymers have been found to have widespread applications in the biomedical field [Figure 1] such as delivery systems of therapeutic agents, tissue engineering scaffolds, cell culture supports, and bio separation devices. The flexibility and untapped potential of smart polymeric materials makes them one of the most remarkable ingredients in drug delivery formulations.

Magnetic field responsive nanoparticles have been extensively been used in the targeted drug delivery such as the usage of contrast agents in magnetic resonance imaging (MRI). These magnetic nanoparticles have successfully been used in the treatment of intercellular hyperthermia since they selectively destroy the tumor tissue under the influence of high-frequency magnetic fields.[8]

Magnetic polymer beads used in targeted drug delivery

The researchers have found magnetic polymer beads to be a unique asset in SDDS. The beads being highly susceptible to external magnetic field can be easily separated from other components of the mixture with the help of magnets. This forms the basis of various separation applications and thus validates its use in targeted drug delivery systems. The specific functional groups bind to the shell of beads, which makes the separation highly selective and specific. The beads can be concentrated exactly at the given site by applying an external field, which can be utilized specially in targeted delivery of anticancer drugs in treatment of cancerous tumors. The polymer beads can also be administered in hyperthermia therapy since they are responsive to high-frequency magnetic field. Magnetic field responsive nanoparticles have been extensively been used in the targeted drug delivery such as the usage of contrast agents in MRI. These magnetic nanoparticles have successfully been used in the treatment of intercellular hyperthermia since they selectively destroy the tumor tissue under the influence of high-frequency magnetic fields.[8]

Smart polymers in gene delivery system

Smart polymers show improved gene delivery to the myocardium and skeletal muscle cells. For example, the pluronic and di-(ethylene glycol) divinyl ether multiblock copolymers have been designed for sustained delivery of plasmid deoxyribonucleic acid (DNA) in *in vitro* as well as *in vivo*. The other benefits of smart polymers in gene delivery system include biodegradability and site specificity.[8]

Another innovative SDDS used in gene transfer is thermo responsive hydrogels. The DNA release into the surrounding muscle tissue is controlled by the three dimensional structure of hydrogel. The duration of gene expression is thereby enhanced by this controlled release of therapeutic gene. The hydrogel for gene transfer in the heart locally showing biodegradable and thermo responsive properties had recently been synthesized. A fourfold increment of this gene expression has been found compared with that of naked plasmid.[8]

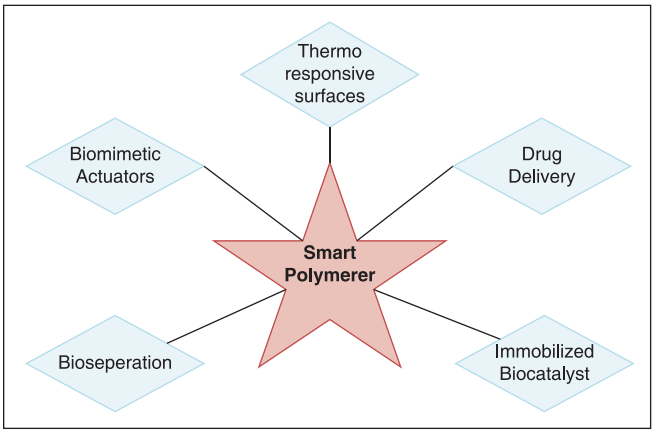

Figure 1: Use of smart polymers in biotechnology and medicine

Immobilized biocatalysts

Enzyme activity and substrate access to the enzyme molecule are significantly affected by the drastic variations in the polymer conformation caused by environmental changes in a solution or hydrogel comprising of covalently coupled enzyme and smart polymer. Immobilized biocatalysts utilize the idea of reversible transition between the soluble and insoluble states of smart polymers. An enzymatic reaction is catalyzed by biocatalyst in its solubilized state, which enables its application for insoluble or poorly soluble substrates hence proving advantageous. On completion of the reaction, the products are separated and the conditions are altered to precipitate the catalyst so that it can in turn be separated and reutilized in the next cycle, after redissolution.

Application of smart polymers in biomimetic actuators

Numerous attempts have been made for effective conversion of chemical energy into mechanical energy in living organisms.[9] Biomimetic actuators made from smart polymers are also capable of transforming chemical energy directly into mechanical work as seen in living organisms. The biomimetic actuators could be applied in future 'soft' machines that require more biological than mechanical principles. In contrast to biological systems, biomimetic actuators have an advantage of withstanding very unfriendly environments.

Hydrogel beads as smart drug delivery [Figure 2]

In immobilized enzyme containing smart hydrogels, the products of the enzymatic reaction between the substrate and the immobilized enzyme activates the gel's phase transition. This helps to translate the chemical signal such as presence of the substrate, into the environmental signal like pH change and then on into the mechanical signal, specifically shrinking or swelling of the smart gel. This idea can be utilized in drug-delivery systems where drug is liberated in response to a chemical signal. For example, insulin can be induced to release in response to increasing glucose concentration. In response to small changes in pH or temperature, the swelling or shrinking of smart hydrogel beads can be used successfully to control drug release, since the diffusion of the drug from the beads depends on the gel state.[10,11] On attachment of smart polymer onto a microcapsule wall[12] or a liposomal lipid bilayer,[13] there are conformational transitions of the polymer, which affects the integrity of the microcapsule or liposome and hence results in the regulated release of the drugs from the drug loaded microcapsule or liposome.

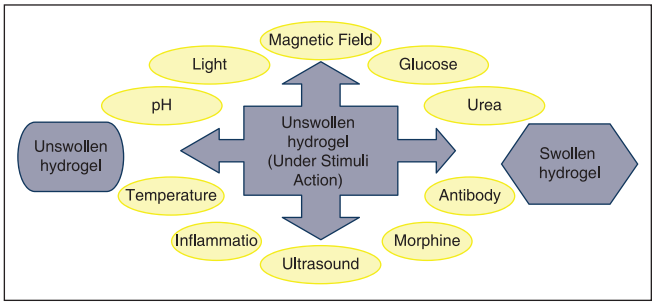

Figure 2: Response of a smart polymer to different stimuli that triggers drug delivery (Gupta *et al.*, 2002)

Smart polymer grafted membranes in drug delivery

Modification of the membrane's pores by grafting smart polymers onto them helps to control the membrane's permeability. A thermo responsive polymer grafted onto the surfaces endows the surface with considerable thermo responsive properties like being hydrophilic below the critical temperature of the polymer transition and being hydrophobic above it. For example, contact-angle measurements[14] and water absorbency[15] demonstrate that grafting the surface with poly (*N*-isopropyl acrylamide) results in changes in hydrophobicity. Successful HPLC separation of steroids[16,17] and drugs[18] was possible with thermo responsive hydrophobic–hydrophilic surfaces.

Bio separation strategy of smart polymers in drug delivery

The three stages of all bio separation processes are first, the target substance and impurities between two phases are preferentially partitioned; second, the separation of the stationary and mobile phase in a chromatographic column are being mechanically separated and finally, the target substance is being recovered from the enriched phase.[19,20]

Other advantages of smart polymers as intelligent drug delivery systems

Ease of manufacture and characterization

Smart polymers used in SDDS are easy to manufacture and characterize and less expensive. They are strong, resilient, flexible, biocompatible, biodegradable, nonthrombogenic, easy shaping, and coloring. They have the capacity to maintain the drug stability of the drug delivery systems. They are good nutrient carriers as well.

Management of toxicity

One of the major drawbacks of administering the drug to the whole of the body is unnecessary exposure of the drug throughout the body with increasing risk of its toxicity and ADRs. The best way to circumvent is to make magic bullets, which can go and act on predetermined targets. With advances in polymer sciences and nanotechnology, designing intelligent SDDS, with objectives of targeted actions and thereby reduced toxicity has now become a reality.

By providing targeted action, this SDDS will ensure complete or nearly complete drug release to the predetermined diseased/affected target site. This intention will thereby prevent the unnecessary drug release to other parts of the body thereby leading to negligible toxic effects as well as ADRs. Other advantages of using SDDS is that only a small dose of the drug will serve the purpose effectively thereby reducing dosage frequency, improving patient compliance, and minimizing the expenditure in case of expensive APIs.

For example, Amphotericin B, when administered as a bare drug needs to be given in high concentration and patients are subjected to toxicity. This is easily resolved by incorporating it in SDDS. These SDDS will release the drug completely to the affected area thereby relieving the patient of the disease symptoms with invariably less dosage frequency and reduced cost.

Biodegradable smart polymers as drug delivery systems

Smart polymers have a very good advantage of being biodegradable. Once it enters into the system after releasing the drug to which

it is bound at the target site it degrades and gets eliminated from the body without causing any harmful or toxic effects. This biodegradable quality of smart polymer renders its usage safe and desirable as a drug delivery system. Its biodegradable nature also prevents intervention to remove it from the body once the drug's targeted release is achieved. This helps in ensuring patient compliance as well as is a cost effective innovative approach of drug delivery system.

Conclusion

The technology forecasts have indicated failure of new drug discovery in all fronts of therapeutic area. The mega drug discovery programs are becoming extremely counterproductive due to uncertainty of success and huge capital losses. In contrast, the advances in life sciences have indicated the paradigm shift in the morbidity and mortality of new diseases and conditions. The demand for the safe drugs is more important than efficacy. The hope to meet the challenge springs out by the concepts and technology development of rendering currently available drugs into safe and useful drugs. The reduction in costs can also be achieved due to minimization of doses in SDDS, hence rendering the medicines universally affordable.

References

1. Available from: http://www.reference.md/files/D016/mD016503.html [Last cited on 2014 Jan 6].
2. Available from: http://medical-dictionary.thefreedictionary.com/drug+delivery [Last cited on 2014 Jan 6].
3. Wang NX, von Recum HA. Affinity-based drug delivery. Macromol Biosci 2011;11:321-32.
4. Available from: http://en.wikipedia.org/wiki/Drug_delivery [Last cited on 2014 Jan 6].
5. Bertrand N, Leroux JC. The journey of a drug carrier in the body: An anatomo-physiological perspective. J Control Release 2011;161:152-63.
6. Kakizawa Y, Kataoka K. Block copolymer micelles for delivery of gene and related compounds. Adv Drug Deliv Rev 2002;54:203-22.
7. Li L, ten Hagen TL, Schipper D, Wijnberg TM, van Rhoon GC, Eggermont AM, *et al*. Triggered content release from optimized stealth thermosensitive liposomes using mild hyperthermia. J Control Release 2010;143:274-9.
8. Zhu L, Huo Z, Wang L, Tong X, Xiao Y, Ni K. Targeted delivery of methotrexate to skeletal muscular tissue by thermosensitive magnetoliposomes. Int J Pharm 2009;370:136-43.
9. Urry DW. Molecular machines: How motion and other functions of living organisms can result from reversible chemical changes. Angew Chem Int Ed Engl 1993;32:819-41.
10. Cooper SL, Bamford CH, Surata TT. Polymer Biomaterials in Solutions, as Interfaces and as Solids. J Biomed Mater Res 1996;30:171. VSP publishers, Inc., Utrecht, The Netherlands.
11. Kim YH, Kwon IC, Bae YH, Kim SW. Saccharide effect on the lower critical solution temperature of thermosensitive polymers. Macromolecules 1995;28:939-44.
12. Kidchob T, Kimura S, Imanishi Y. Thermoresponsive release from poly (L-lactic acid) microcapsules containing poly (N- isopropyl acrylamide) gel. J Chem Soc Perkin 1 1997;2:2195-9.
13. Meyer O, Papahadjopoulos D, Leroux JC. Copolymers of N-isopropylacrylamide can trigger pH sensitivity to stable liposomes. FEBS Lett 1998;421:61-4.
14. Takei Y.G, Aoki T, Sanui K, Ogata N, Sakurai Y, Okano T, *et al*. Dynamic contact angle measurement of temperature-responsive surface properties for poly (N-isopropylacrylamide) grafted surfaces. Macromolecules 1994;27:6163-6.
15. Kondo T, Koyama M, Kubota H, Katakai RJ. Characteristics of acrylic acid and N-isopropylacrylamide binary monomers–grafted polyethylene film synthesized by photografting. Appl Polym Sci 1998;67:2057-64.
16. Kanazawa H, Kashiwase Y, Yamamoto K, Matsushima Y, Kikuchi A, Sakurai Y, *et al*. Temperature-Responsive liquid chromatography. 2. Effects of hydrophobic groups in N-isopropylacrylamide copolymer-modified solica. Anal Chem 1997;69:823-30.
17. Kanazawa H, Kashiwase Y, Yamamoto K, Matsushima Y, Kikuchi A, Sakurai Y, Okano T, *et al*. Temperature-responsive chromatography using PNIPAAm-modified silica. Anal Chem 1996;68:100-5.
18. Hosoya K, Kimata K, Araki T, Tanaka N. Temperature controlled high- performance liquid chromatography using a uniformly sized temperature- responsive polymer- based packing material. Anal Chem 1995;67:1907-11.
19. Hoffman AS. Applications of thermally reversible polymers and hydrogels in therapeutics and diagnostics. J Control Release 1987;6:297-305.
20. Gehrke SH, Andrews GP, Cussler EL. Chemical aspects of gel extraction. Chem Eng Sci 1986;41:2153-60.

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