Budding Frontiers in delivery of drugs

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ABSTRACT

For managing and treating the diseases , medicine relies in drugs which are the active agents and are not effective inherently . The drug benefit relies in the manner via which drug is delivered or administered in the body. Delivery of drug affects the metabolism, distribution, absorption and pharmacokinetics , toxicity and excretion. As there is a wide development in the therapeutics and biologics , an urgent need is for improving materials and chemistry for the materials for delivering them to the required site at therapeutic concentration in the required time period. An overview on delivery of drug has been provided following the highlights of the delivery of drugs in the field of RNA and in localized therapy and also in biological system of drug delivery.

Keywords: Pharmacokinetics , Toxicity , Excretion Drug delivery, Biologics.

INTRODUCTION

For managing or reversing the disease course , medicine relies on the drugs or therapeutics i.e the agents those are pharmacologic-ally active. These agents are not effective inherently . Their benefit is directly proportional to the manner by the way in which these are administered. The phenomenon of absorption, excretion, toxicity therapeutic effect duration , drug pharmoacokinetics and metabolism (Bruton, B., et al, 2011). On the discovery of therapeutic models a need is felt for improved delivery modes and also a clear understanding of the process of adminstrating drug and its effect on the safety and efficacy needs to be monitored. Ideally, drugs which are applied in the in vivo conditions at therapeutic concentration precisely targets the cells that are responsible for causing of the disease. Controlling the drug delivery is not an easy task. The prediction of rates at which the drugs are released and targettibf the specific tissue and also to analyse which drugs are quite stable is a difficult job.

To overcome these limitations , the DDS system that is the drug delivery system has been designed via using great chemical strategies and a wide array of materials. The drug delivery systems are designed as technologies which have been designed in such a manner by which the specificity of the therapeutics is improved by stabilizing them in an in vivo method by controlling the release and also by lovcating there effect . A variety of therapeutics have been released for a long time period at the required locations withiun the body. The drugs physiochemical attributes tailors the properties of the drug delivery system and also the route of adminstration. This can be seen in given figure 1 , By the advancement in the material

science, synthetic chemistry , conjugate chemistry and medical chemistry the system of drug delivery has been propelled which are most commonly used in the clinic.

The medicine field is actively trans-formatting as a great emergence in the drugs conjugates , antibodies, proteins, nucleic acids have been observed. The therapeutic molecules which have large magnitude than those of the smaller ones are highly sensitive to the environment requires proper protection, specificity and bio availability . It resulted in the involvement of the drug delivery system. Drugs can be introduced into the body in different ways and their delivery requires different designing criteria. Systematic delivery involves the delivery of drug to avoid the clearance via following reticuloendothiol and thus enters the targeted tissue . The local delivery by drug delivery system avoids the damage to the surrounding tissue. The control release of the drug prevents the dumping of the dose. The orally involved delivery system overcomes the extreme change in the pH value and accommodate the changes occurring in the bio molecule concentration which vary with the food that we intake.

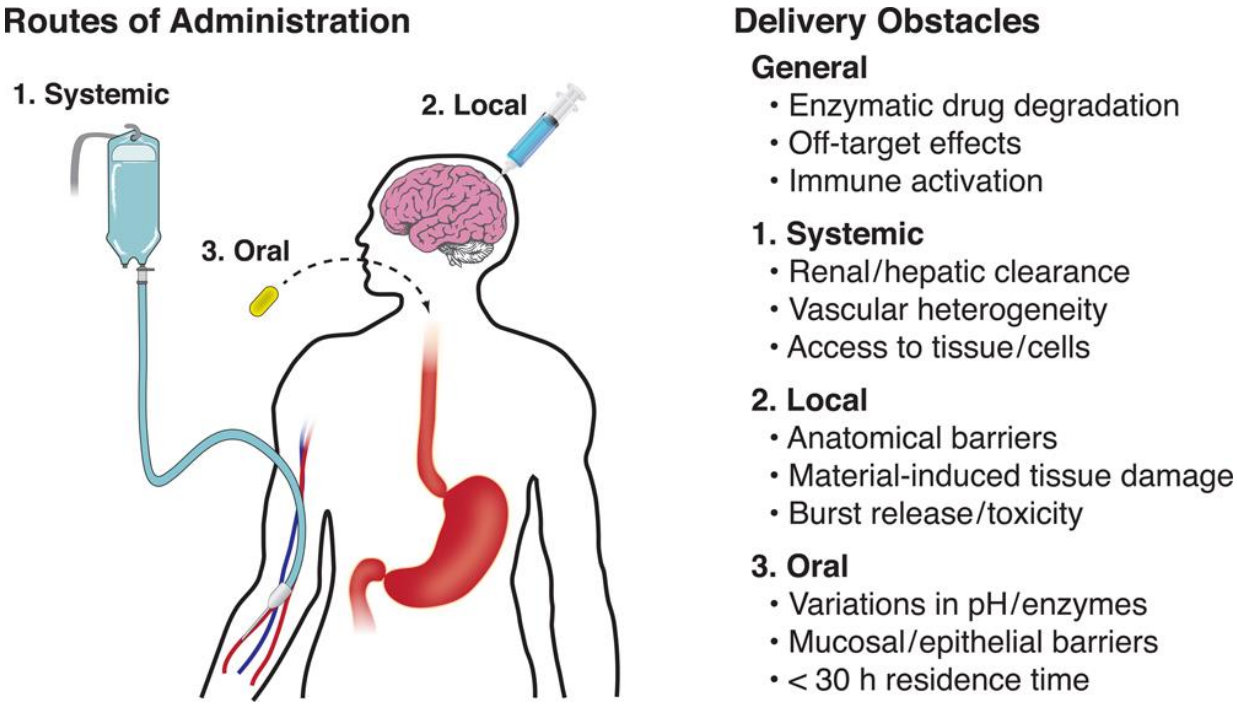

Figure 1 Administration of delivery of drug into the human system

CONTROLLED RELEASE BY THE DRUG DELIVERY SYSTEMS

CRS is one of the most important class of the drug delivery system. These are designed in a way to deliver drugs in a way that they can be delivered in a manner ranging from days to years with a predetermined profile. There are many advantages of an ideal CRS (Levy., 1973). In the standard adminstration , the peaks and valleys should be avoided for maintaing the concentration of the drug which lies within the drug window. For increasing the potency and limiting the side effects of the target the drug should be localized at the desired action site. CRS should also made the efforts in reducing the required number of doses. The delivery of drugs by an ideal CRS are degraded fastly when acquired in the body by their own. The field of CRS engineering is quite challenging .There is a requirement of the material that can hold sufficient therapeutic amount so that the drugs can be protected from the breakage during its

release and is able to release the course ranging from days to years. The designing of CRS should be in such a way that their potential drawbacks can be avoided (Langer., 1998) . It should be designed in such a manner that it can accurately account for the CRS materials potential toxicity and the degradation of its products . During the process and after the adminstration discomfort should be avoided by CRS.

Also the CRS design should mitigate the additional costing of the device. When these design constraints were given, it was quiet unknown whetеher these materials will be able to control the drug release in the body. In 1960 it was discovered that small hydrophobic , lipophilic molecules could easily diffuse through the tubing made up of silicone (Folkman J, 1990). By using the silicone rubbers , for controlled releasing of bioactive agents it inspired at using of histamine, atropine, steroid hormones, and antischistosomal and antimalerial drugs (Bass ,P. et al. 2010). it has been found that the release of materials via these molecules takes place ranging within the required course . it has been depicted by these observations that such controlled release of the bioactive agents leads to the development of norplant DDS , which is a contraceptive that can be implanted and is made up of capsules composed of silicon , and for five years levonorgestrel is released (Diaz et al., 1982).

Due to these early findings, a rapid evolvement has been observed in controlled release of drug delivery. Osmotic pumps has been used as oral CRS. Drugs which are loaded with the hydrogels have been used as opthalmic drug delivery system (witcherele et al., 1960). For sustained release of the drugs , microsphere encapsulation has been used . Mathematical models have been developed by researchers to quantify the release of drugs from CRS (Pepas et al., 1984).CRS has been commercialized by the corporation ALZA. An emergent requirement to for controlled release of these large drug molecules , the molecular biologists have improved the ability of generating and characterizing proteins. It was believed that the large molecules were not be able to entrapped and could be released from the polymeric material that has been implanted in controlled form. This percpective has changed the view that proteins are diffused from the implants which were of polymeric nature in a 100 day course. Hydrophobic polymers like poly EVA(ethylene-co-vinyl acetate) was mixed with protein which was lipophilized after being solbulised.

An interconnected network of pores was observed between the polymer matrix which was of impermiable nature before occuring the phase seperation between the polymer and protein. Macromolecules weighing within the range of millions found to diffuse via pores when the fluid which was aqueous entered and the narrow path slowed the release of protein whuch took several months to occur. This process has been used for releasing the angeogenesis inhibitors and angeogenic factors so that the vascular pruning and growth can be understood . In the following years many techniologies dealing with the controlled release of drugs have been developed like those dealing with the matrices and reservoirs osmotic pumps, hydrogels activated via solvents and also biodegradable materials.Furthur advances includes the introduction of the intelligent materials which releases drugs according to the enviornmental stimuli.Nanotechnology dealing with pharmaceutics has been established and expanded for including dendrimers, polymeric micromicelles, liposomes and polymeric nanospheres.microelectronics have also been incorporated into the controlled release technologies for engineering the remotely triggered therapeutic release.

Substantially, the field of drug delivery has grown. The biomedical engineers, chemical engineers are optimising the DDS system with great sophistication and high control. Presently many products dealing with drug delivery are in the market and there sale in the

year 2013 has been around $150 billion.There are few concepts that are cosidered to be fundamental for the DDS . Firstly the materials chemical structure is related to the efficacy of DDS. Small modifications can badly affect the materials targeting, safety and degradation. Secondly , the shape and size of the drug delivery system matters a lot, the properties of the material are affected and also the interactions with the immune system are affected. Thirdly DDS engages itself actively with the body even they are not designed to do so.

SYSTEMATIC DELIVERY OF RNA

The gene expression can be manipulated by RNA by various biological mechanisms.The production of protein can be inhibited by miRNS nad siRNA. The epigenetic signal can be affected by the long non coded RNA. Functional proteins are produced by mRNA.Permanent changes can be made to the genomic DNA by using Ca enzyme and sgRNA(cech et al., 2014) . The clearance should be avoided by the immune system and the exit should occur by the blood stream and the right cell should be accessed in the complex tissue and then the entry into the cytoplasm or nuclus should be made without ignoring the response of immune system which is not required much.

It has been found that delivery of modified siRNA does not alter the sequence of RNA and the vehicle which properly delivers the siRNA can also deliver the miRNA provided their chemical and physical properties should be similar. Earlier target was made on focusing siRNA to liver as DDS disfuction could pave to various diseases like metabolic disorder, cancer etc. Promising results have been observed when the delivery of drug is very low as from the blood lipids are naturally absorbed by the liver.

A lot of improvement has been seen in this field by using the chemistry of nanoparticles. Hundreds and thousand of ionizable, cationic, and well defined lipids which are like lipids can be sysnthesized and after that these are made into nanoparticles which are stable by making the use of polyethylene glycol (PEG), 1,2-dioleoyl-sn-glycerophosphoethanolamine (DOPE) etc. Or helper molecules. These helper molecules are found to be very important for their nanoparticle behaviour. Their presence, absence , molaer ratio can affect the efficacy largely. The behaviour of the particle also matters by the method via which it has been formulated. Example, materials which are formed by using the microfluidic devices are found to be best then those formed by using the extrusion method. The delivery of Hepatocyte siRNA has found to be improved by advancing our knowledge to understand the interaction of DDS with the body.

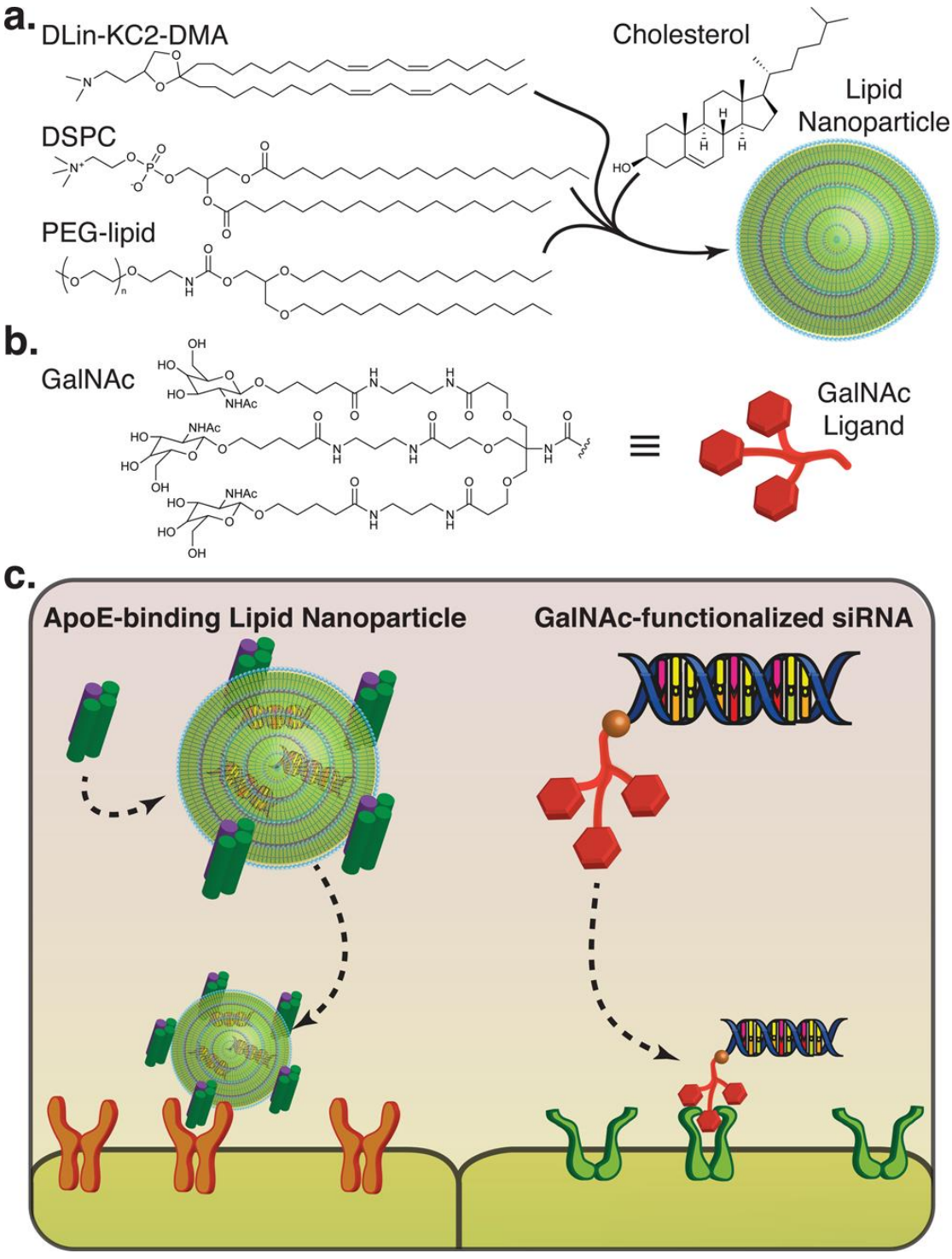

Figure 2:- biological interactions involving RNA delivery

It can be seen in the given figure 2, among the various examples, one is the example of the nanoparticle which is lipid (DLin-KM2-DMA), peg lipid, DSPC lipid has been found to deliver siRNA very effectively to the targetted hepatocytes in various animal models as shown in figure 2a and 2c. but it has been observed that these have not worked well in the genetically engineered mice in which the serum apoliprotein and lipoprotein has been found to be absent . in normal mice, nanoparticle has been found to bind with the ApoE serum, and hepatocytes naturally endocytose this serum. This is the manner by which the nanoparticles are targetted naturally to the hepatocytes without other targetting ligands aptamers or antibodies.

The same behaviour of Apoe was not found with the nanoparticles of lipid . The receptor Asialogycoprotein can bind to siRNA via conjugation and these has been expressed on the hepatocytes, this can be seen in figure 2b and 2c. By following the subcutaneous and intravenous adminstration , the conjugates of GalNAc endocytes via hepatocytes. It was observed that conjugates of GalNacs have been handeled quite well in mice , non human primates, and rats and for around hundred and forty days have silences the genes of human beings. AONs , that is antisense oligonucleotides have been successfully delivered to liver . AONs are found to be chemically similar to the siRNA and these bind via biological mechanisms. On mRNA , AONs gets easily binded during mRNA and thus the mRNA translation gets altered . In absence of conjugated DDS or nanoparticles, a targetted AON Apoliprotein B has been approved clinically. For increasing the delivery, the endocytic pathways could be easily manipulated and along the conjugates and nanoparticles the bioactive molecules can easily administered in the body .

Liver is mostly targetted during the delivery system of siRNA and thus many patients gets benefit via this efficient delivery to the targetted non liver tissues but this delivery is quite challenging and improvements are being continued . With increasing number of DDS pre - clinical data have been obtained . Low delivery of dose to the endothelial cell has been reported via nanoparticle and has delivered upto five siRNAs invivo and is used for studying the gene regulation during hypertension, metastasis. In hepatocytes , gene expressions are not reduced . Small RNA affects the signaling of the cancer and a large number of small therapies of RNA have been designed for targetting metastasis and primary tumors. Protein production are reduced by the occurance of naturally occuring miRNAs.

The molecules are of same size and charge similar to those of siRNA . Packaging of the same nanoparticles takes place for achieving therapy rational combination . mRNAs are the attractive drug molecules as these serves as the gene therapies which replaces the dysfunctional proteins . RNAs which are unmodified can be degraded and immunogenic. For improving stability, and altering the therapeutic duration specific nucleotide occurring on miRNAs, siRNAs should be altered chemically, but this is not found to be true in case of big RNA. Despite these so many hurdles for successful delivery , nanoparticles delivers mRNA and thus the gene expression is increased in hepatocytes and subcutaneous tumors.

Future of Drug delivery

The goal for the technologies involved in delivery of drugs relates with the maintainance and transportation of the drugs therapeutic concentration at the targeted site . it can be visualised that our future will be focussed on following,

A. Efficiency to be enhanced at both cellular and tissue level and also efforts to be made to increase the molecules delivery via barriers like the, vagina, lungs, skin, brain, intestine.
B. To achieve release of the preprogrammed pulsate over the required time period via generating the technologies that act in long run.
C. For the personalized therapies , development of technologies that are related with the delivery of drugs.
D. Merging the advances technologies like artificial intelligence (AI), soft and wireless technologies, and also the machine learning with the drug delivery.

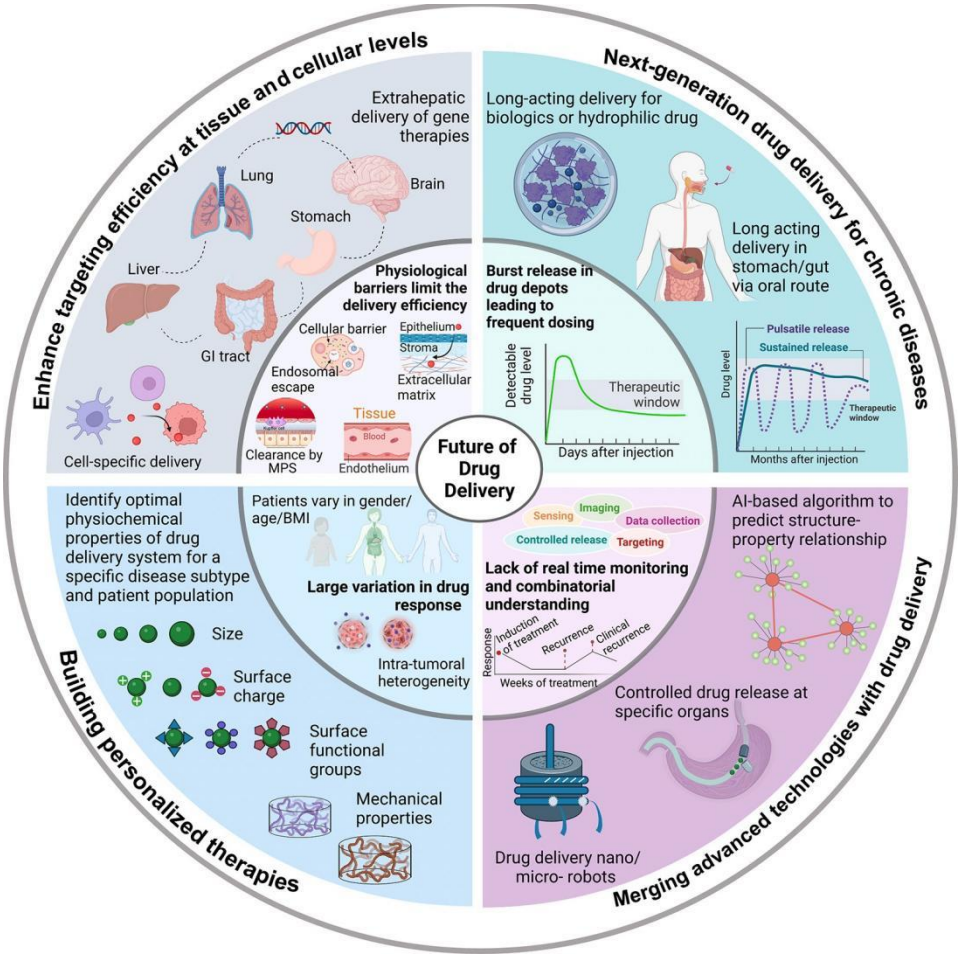

Figure 3: Future and challenges in drug delivery

For overcoming the biological barriers , achieving the desired delivery requires deep understanding at both the cellular and tissue level including how the material of drugs interact with the matrix which is extracellular , also with the cell types in the targeted tissue . the local administration provides the simple route for delivering drugs into the diseased tissue. Its limitation is that it is limited to only those organs that are easily approachable and still we are unable to overcome the anatomical and physiological barriers occurring in the tissues. The mucus which is present in lungs and the intestine is posessing a huge barrier which is having a great impact on the delivery of orally ingested or inhaled particles (Dong et al., 2020). The stroma and the extracellular matrix which is present in the microenviornment of tumor limits the penetration of the whole system and the efficacy also gets limited for best immunotherapies(Dai et al., 2018). These barriers can be overcommed by using the innovative approaches. The rate of absorption has been increased when the luminal mixing resulting topical deposition for payload dealing with drug , and this all is because of the robotic capsule which helps in drug delivery(Zan et al ., 2019).

As the nanaoparticles get cleared by the RES system that is reticuloendothelial thereby the targetting by the use of nanoparticles remains a challenging field. Another chgallenging field is the delivery of genes in the tissues which are extra hepatic. After the intravenous or subcutaneous adminstration in rats and mice across the barrier occuring in between the brain and blood has enhanced the penetration when conjugation between the hydrophobic moieties have been found to take place like among those of alpha tocopherol and cholestrol(Nagata et al., 2021) 41. the delivery of nucleic acids have been made possible into the stomach of swine via oral dose of the small injector capsules. Much efforts are required for developing the noble delivery techniques for targetting the genes delivery to the hepatic tissues like those present in vagina, lungs, intestine, brain .

DELIVERY OF DRUGS FOR CHRONIC DISEASES

One of the challenge in health care community of the pharmaceutical industry is the bad adherence to the drugs and which has resulted in approximately 125000 deaths per year (Peter et al., 2015) . The delivery methods which are quite long lasting are quite critical for the chronic diseases which requires years of treatments in patients whose setting of resources are quite low and have limited access in the field of health care . At present there are 63 drugs that are approved by FDA and are the long acting products of the drug found in the market. Among these 23 drugs, are formed via biodegradable formulations. The non biodegradable ones enables the release of drug in controlled manner for long period of time when compared with biodegradable implants and injectables but these require the surgical removal after being used and this poses challenge when resource setting is low.

The biodegradable formulations are the ideal ones and there burst release is very high and it can serve as issue for the drugs which possess small therapeutic window and can also shortens the life of the formulations. Due to the rapid release of the drugs, the long lasting formulations are not suitable for injecting . Focus lies in developing drugs which are injectable and whose burst release is also very minimum. Advancement has been made in field of long lasting druf delivery following the oral route. This has been demonstrated by developing an ingestible capsules relating with antiretroviral drugs and also developing a pill for risperidone ER or memantine.

Future delivery systems which will be long lasting will possess precise control over kinetics release at steady rate and these systems will have advantages for diseases like diabetes, asthma, and hypercholesterolemia which have rhythmic cycles and where the medication timings are critical and also the therapeutic outcomes are improved. Recently it has been reported that multiple vaccine doses can be provided with just a single injection and such kind of approaches are found to be quite useful for diseases like COVID - 19 or measles and have benefitted people who have frequent medical care access.

CONCLUSION

The drug delivery field has an exciting and a very bright future. The landscape of the current therapeutics shift from the molecules of small level to biologics where system of drug deliveries continues to evolve. Expectations are being made to have breakthrough in the technologies through which the enhancement can be seen in encapsulatiom of the biologics and there controoled release in a long time period and also delivering them across the physiological complex barriers. Future also relies on developing mateerials which are more effective and efficient in targetting specific programme which is responsive to the biological cues and can be easily integreted into the clinical translation. Global healthcare is the major area of concern which can become more accessible by increasing the efficacy and precxision and also making them easier and affordable to use.

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