Nanoparticles Delivery For Skin Cancer

Nanoparticulate Strategies:

Due to advancement in technology and investigations carried out to understand the cellular and molecular basis of skin and skin cancer, development of new strategies for treatment are evolving at a rapid rate. Conventional therapies available for treatment of skin cancer such as surgery, chemotherapy, radiation therapy have several disadvantages like efflux by transporters, toxicity issue, uncontrolled and non-selective drug release. As symptoms and severity of skin cancer varies widely, development of therapies is a challenging task. Novel nanotechnological strategies developed for treatment of skin cancer includes liposomes, transfersomes, ethosomes, lipid nanoparticles, carbon nanotubes, dendrimers, polymeric nanospheres, nanosuspension, nanocapsules, nanoemulsion. These nanocarriers have several advantages, enhanced penetration across stratum corneum being the most important. They show improved targeting to neoplastic cells due to enhanced permeability and retention effect. They improve solubility of poorly soluble drugs, reduce dose, side effects and modify pharmacokinetics. These carriers have shown promising results in enhancing effectiveness, quality of life, survival rates and decreasing unwanted side effects. Fate of the drug administered topically is mainly determined by characteriscs of its carrier, which should exert localized effect. We have discussed various nanocarriers, their advantages, mechanism and examples of drugs loaded in nanocarriers that have proved increased effectiveness over the existing therapies for treatment of melanoma, basal cell carcinoma and squamous cell carcinoma.

Liposomes:

They have proved as more effective delivery for treatment of skin cancers. Liposomes are fatty bodies consisting of bilayer of lipids formed due to hydrophobic interactions with hydrophilic part facing the aqueous core. Hydrophobic as well as hydrophilic drugs can be delivered with the help of liposomes. they were developed to enhance penetration across the stratum corneum and deliver drug in deeper tissues. Mechanism of drug release is based on structural similarity between liposomes and stratum corneum. Liposomes undergo fusion with outermost layer of stratum corneum, disrupting its structure and increasing fluidity of bilayer. Interaction leads to formation of intercellular lipid lamella which enhances the mobility lipophilic molecules in SC. This enhances drug penetration in the subsequent skin layers.

A. Mohan et al successfully developed PEGylated nanoliposomes of resveratrol and 5-fluorouracil to improve chemotherapeutic efficacy for treatment of head and neck squamous cell carcinoma. It reduced the threshold concentration necessary to achieve synergestic effect. Bax and caspase 3 were upregulated whereas bcl-2, cyclin D1 and akt were downregulated, resulting in apoptosis. S. Singh developed liposomal formulation of doxorubicin and celecoxib for the treatment of skin cancers. Liposomes were reported to increase the permeation across SC and combination of drugs inhibited the cancer cell viability by greater than 99%. AKT and COX-2 pathways were reported to be inhibited. A study performed by A. Hussain reported5- FU liposomes show slow and sustained drug release pattern. Skin deposition and permeation was also reported to be enhanced. Recently, gene cancer therapy has been evolved which delivers

siRNA liposomes responsible for silencing the gene involved in cancer growth.

Transfersomes :

Transfersomes use as delivery vehicles for skin cancer treatment is evolving because of their instinctive ability to cross the skin. They exhibit enhanced penetration across stratum corneum due to their deformable nature. These are modifications of liposomes in which the bilayer is composed of edge activator ie. surfactant such as tween 20, Span 60, sodium cholate and phospholipids. The edge activator destabilizes the bilayer by decreasing interfacial tension and leads to formation of metastable membrane, thereby enhancing the deformability. A pyrimidine analogue, 5-fluorouracil is a well known anticancer agent which acts by inhibiting thymidylate synthase. This prevents DNA replication as synthesis of the nucleotide thymidine is dependent on thymidylate synthase. However, topical delivery of 5-fluorouracil in conventional formulations exhibits poor percutaneous permeation. Formulation of 5-fluorouracil into transfersomal gel increased its penetration, cytotoxic effect and showed two fold increase in drug release.

Transfersomes cross the stratum corneum intact and reach the epidermis. Osmotic gradient that is the difference in water content across the stratum corneum layers is sufficient to force these vesicles intact across the stratum corneum. The hydrophilic nature of phospholipid avoids dry conditions and are attracted towards the hydrophilic areas. For these vesicles to remain maximally swollen are attracted to areas of high water content and penetrates deeper into the skin. Two mechanisms are proposed by which transfersomes enter the stratum corneum. The first mechanism proposed by cevc and blume takes advantage of difference in water content across the layers of stratum corneum. On reaching the pore the edge activators accumulate in the stress induced area due to their increased natural tendency towards the curved structures ie. the pores. Also stressful conditions enable the destabilized and stabilized molecules to redistribute making them deformable. Induction of stress occurs when the vesicles get dry. Vesicle will not be able to penetrate through the last layer of stratum corneum as it has very less amount of water. Finally, partitioning of the vesicle in acceptor phase ensures drug release into the epidermal layers. Non-occlusive procedure of transfersome application is followed, otherwise it will disrupt the osmotic gradient and hinder its penetration.

In second mechanism the intercellular lipid lamellae is modified by vesicle bilayers which enter SC by acting as penetration enhancers. The physicochemical properties of the drug decides the mechanism that will be taken up by the vesicles. El Maghraby et al reported that the vesicles partitioning in the acceptor phase is limited. According to El Maghraby et al. method of preparation, vesicle composition, charge, membrane lamellarity, size, membrane fluidity and elasticity were the major attributes that contribute to variable results observed.

As reported by ashif khan et al 5-fluorouracil formulation in carbopol based transfersomal gel increased skin permeation and deposition. They also compared the effect of tween-80 and span-80 as edge activators. It was found that tween-80 is superior to span-80 in relation to vesicle size and entrapment efficiency. Eun kyung oh studied the topical delivery of 5-ALA by using cationic transfersomes as vehicles for photodynamic therapy. The results indicated good storage stability and physicochemical properties in terms of entrapment efficiency and particle size. They also reported increased permeation of 5-ALA across skin, enhanced accumulation and induction of PpIX photosensitizer inside body.

A major disadvantage of these vehicles is the delivery of hydrophobic drugs.

Lipid Nanoparticles: SLN and NLC

In recent years, development of lipid nanoparticles for treatment of skin malignancies has evolved to some extent. They came into picture as liposomes posed stability problems, enhanced cutaneous absorption and drug targeting. SLN consists of solid lipids and surfactants providing stability whereas in NLC solid lipids are replaced by liquid lipids. SLN exhibited less loading capacity and drug expulsion. Hence, NLC's were developed.

On application, these formulations form a thin film on the surface of skin resulting in occlusion due to hydrophobic nature of film. This prevents evaporation of water from the skin surface, thereby increasing hydration of stratum corneum from 10-20% to 50%. This leads to swelling of corneocytes and increase in the water content in intercellular lipids. Gaps between the corneocytes are increased allowing the drug molecules to penetrate deeper. Occlusion also prevents evaporation of volatile compound and exerts reservoir effect on drug. Initially, drug penetrates at faster rate under occlusion. Removal of the occlusive film leads to dehydration of stratum corneum, reducing the movement of drug. This results in stratum corneum acting as reservoir of drug.

Nanoparticle's increased surface area resulted in 15 times more occlusiveness as compared to microparticles due to enhanced contact with stratum corneum. SLN matrix has solid lipids which undergo beta modification on storage forming perfect crystals, thereby resulting in drug expulsion. NLC matrix is composed of mixture of solid and liquid matrix that do not form perfect crystals, thus preventing expulsion of drug. Iboth of them increased penetration of non-polar compounds and had very less effect on polar compounds.

Rituraj bharadwaj et al formulated paclitaxel for treatment of skin cancer by ultrasonication and high speed homogenization technique. SLN's were dispersed in topical gel and were found to exhibit sustained release. This gel exhibited quite high efficiency as compared to normal paclitaxel topical gel. Rasha A. Khallaf et al reported enhanced diffusion and release rate of 5-FU SLN formulated in sodium CMC gel , proving it to be promising drug delivery. A study conducted by T. geetha et al reported that anticancer agent sesamol's formulation in SLN increased its bioavailability by enhancing its retention on skin and exerted desired anticancer effect. Doxorubicin permeability was found to be enhanced by formulating them in SLN, as reported by Ailar Tupal et al. RS Paruvathanahalli formulated 5-FU NLC hydrogel by high pressure homogenization technique in which LBS was used as liquid lipid, PRE as solid lipid and polyoxyl-15-hydroxystearate as surfactant. He reported that retention and permeation were enhanced while skin irritation was reduced. 5-ALA NLC were developed by AS. Qidwai which showed increased concentration in target skin layers, enhanced cytotoxicityand penetration. This enhanced the efficiency of PDT as it directly affected the accumulation of PpIX photosensitizer.

Carbon Nanotubes:

Coaxial sheets of graphite folded into cylinder are known as carbon nanotubes containing carbon allotropes. They were developed to overcome the poor stability, scale up hurdles and low encapsulation efficacy of previously developed nanocarriers. They may consist of single

graphite sheet known as single walled carbon nanotubes or several sheets of graphite known as multi walled carbon nanotubes.

The mechanism by which these nanotubes release drug is either by application of electric current induced by applied potential across the application area or polymer degradation . Application of voltage across the applied area causes the electrons to flow in a specified direction, repelling the anionic drug from carbon nanotubes and forcing them to cross stratum corneum. The potential required to force the drug across stratum corneum is determined to be 1.1 volt. Carbon is used as it is good conductor and induces electron flow on application of voltage. Several advancements in carbon nanotubes has been made such as CNT polymer drug loaded microneedle which offers significant strength. The needle forces the drug across the skin layers and promotes drug penetration in deeper layers of skin. Loading hydrogels with carbon nanotubes delivers the drug on providing electrical stimuli. Yun et al explained the release of drug from hydrogels loaded with Multi walled carbon nanotubes. On applying voltage, the ionization of functional groups in polymer was altered, governing release of drug from formulation.

KS siu et al. successfully formulated siRNA in single walled carbon nanotube for treatment of melanoma. siRNA silences the gene responsible for development of cancer and exerts anticancer effect. However, delivery of siRNA in vivo is quite difficult. Formulating it into carbon nanotubes enhanced its entry in cell and protected it. By silencing gene it reduced the tumor growth within 25 days. The fullerenes have intrinsic ability of generation of reactive oxygen species or singlet oxygen. This fact has been utilized in enhancing the efficacy of photodynamic therapy. A. Karunya et al reported that formulation of photosensitizers in carbon nanotubes enhanced biocompatibility, selective targeting, stability and increased generation of reactive oxygen species. Camptothecin multi walled carbon nanotubes were functionalized with polyvinyl alcohol for treatment of skin cancer. A study performed by PN Samanta et al compared the effects of 5- aminolevulinic acid boron nitride nanotubes and 5-ALA carbon nanotubes. The results indicated that boron nitride nanotubes are more favourable as compared to carbon nanotubes. A study performed by J. Shi et al compared the efficacy of hematoporphyrin monomethyl ether hyluronic acid carbon nanotubes by subjecting to PDT and PTT alone and combination of photodynamic therapy and photothermal therapy. Hyluronic acid CNT exhibited high aqueous solubility and tumor targeting. Hematoporphyrin monomethyl ether was then adsorbed on this hyluronic acid CNT. It was observed that combination of photodynamic therapy and photothermal therapy showed superior effect over individual therapies.