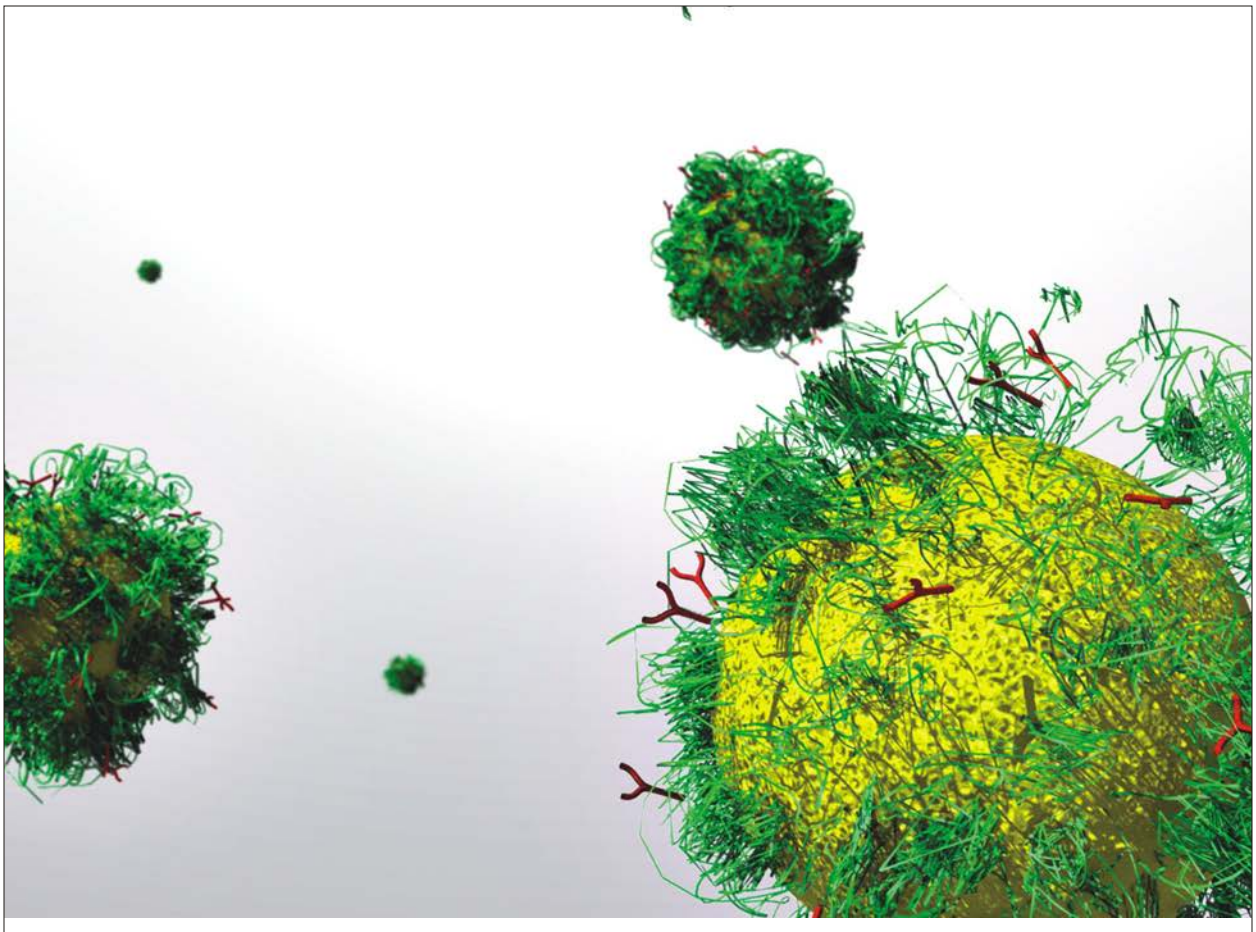

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Nanotechnologies for Boswellic Acids

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ABSTRACT

Boswellic Acids (BAs) are the main ingredients of *Boswellia serrata* (Family: Burseraceae) gum resin extract for the treatment of a variety of inflammatory diseases besides acting as both internal and external stimulant, expectorant, diuretic and stomachic. Despite its multipurpose benefits, BAs have low oral bioavailability especially 11-keto-β-boswellic acid (KBA) and 3-acetyl-11-keto-β-boswellic acid (AKBA), (the most therapeutically potential BAs) because these BAs are lipophilic in nature and not solubilises into the intestinal fluid thus limiting its systemic availability. For decades, many attempts have been made to compensate for these disadvantages, with the development of improved delivery platforms as the feasible approaches. The past ten years has witnessed the encouraging progress in the use of nano scale drug delivery systems on BAs such as loading BAs into liposomes, solid lipid nanoparticles as well as the latest reported technologies such as niosomes, phytosomes and nanomicelles etc. This review summarizes the recent works on the design and development of nanoscale delivery systems of BAs, with the goal of harnessing the true difficulties of this multifunctional agent in the clinical arena.

Key words: Boswellic acids, nanotechnology, novel drug delivery system, proniosomes

INTRODUCTION

Boswellic Acids (BAs) are pentacyclic triterpenoids belonging to ursane group which are the major constituents of the gum derived from the plant *Boswellia serrata* Roxb. ex Colebr. (family Burseraceae, Syn. B. glabra), commonly known by the names Salai guggal, white guggal, Indian olibanum or dhup (Shah *et al*., 2009). *Boswellia serrata* gum resin is a complex mixture of terpenoids and sugars comprising more than 200 different species including essential oil (8-10%), polysaccharides (45-60%) and higher terpenoids (Upaganlawar and Ghule, 2009). The essential oils contain alpha thujene and p-cymene. The higher terpenoids constitute one of the major components of gum resin comprising mainly β-boswellic acid as the main triterpenic acid along with β-boswellic acid, 11-keto-β-boswellic acid (KBA) and corresponding acetates acetyl β-boswellic acids (ABA), acetyl-11-keto-β-boswellic acid (AKBA) and acetyl α-boswellic acid (Fig. 1). Boswellic acids (BAs) are pentacyclic triterpenoids (Poeckel and Werz, 2006). They are certainly involved in defence mechanism, have been reported to possess diverse biological activities that include immunomodulation, anti-inflammatory, anti-cancer and antiviral properties as shown in Table 1.

Bioavailability of boswellic acids: Among six most important derivatives of Boswellic acids, KBA and AKBA are the most potent inhibitors of 5-lipoxygenase (Safayhi *et al*., 1992; Sailer *et al*., 1996). Low water insolubility and extensive phase I metabolism are the main limiting factors, responsible for low metabolic stability of KBA and AKBA.

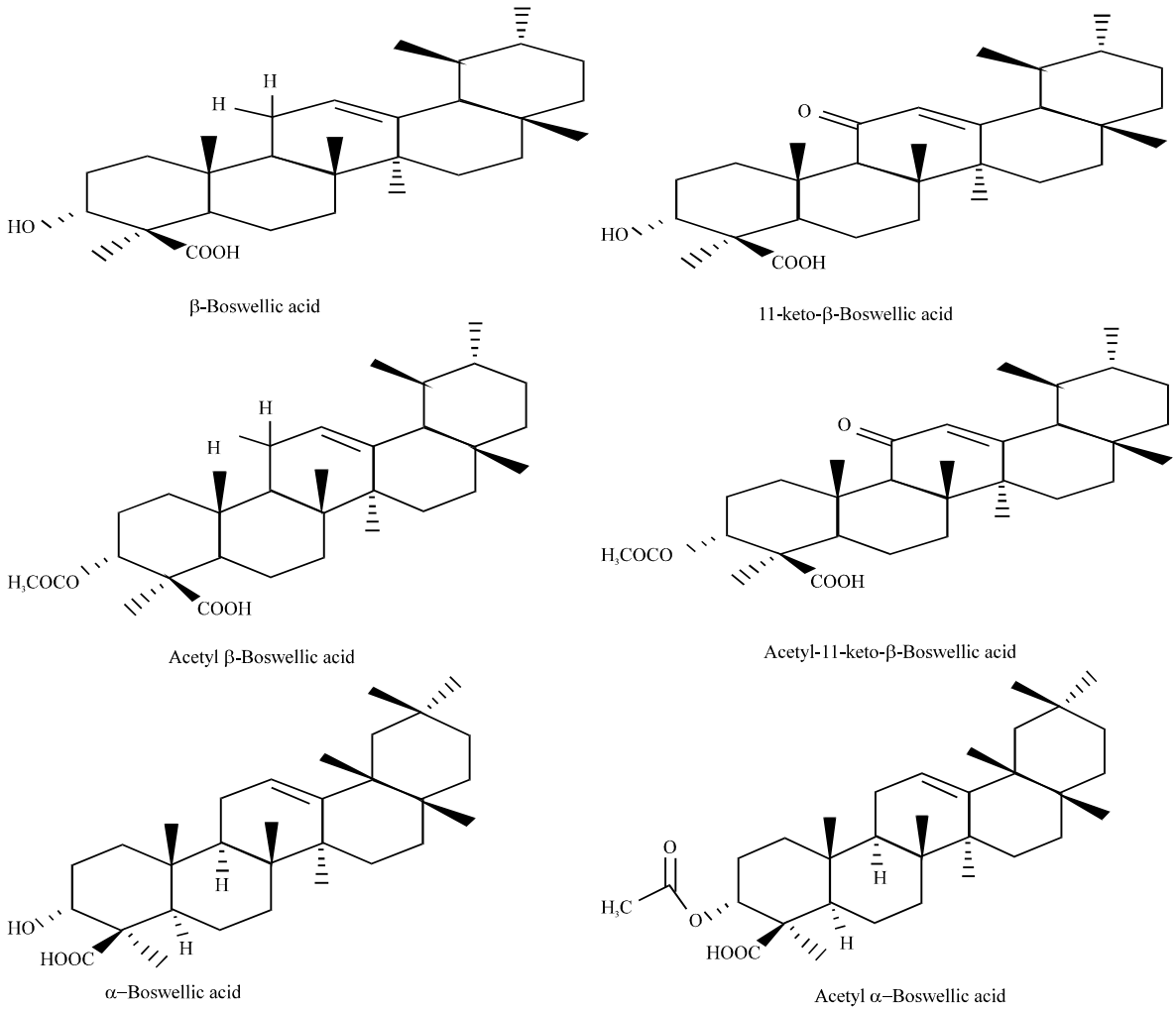

Fig. 1: Chemical structure of six major boswellic acids

Table 1: Pharmacology of *Boswellia serrata* and their scientific findings

Pharmacological activity	References	Key scientific findings
Arthritis	Sharma *et al*. (2010)	Boswellic acids significantly reduced inflammation markers and the population of leucocytes in bovine serum albumin-induced arthritis in rabbits
	Singh and Atal (1986)	Salai guggal extract caused marked suppression of carrageenan or dextran induced edema in rats or mice, thus exerting anti-arthritic activity
	Reddy and Dhar (1987)	Administration of boswellic acids/salai guggal increased the lysosomal stability and reduced á-glucornidase activity in adjuant arthritic animal
Anti-inflammatory	Singh *et al*. (1996)	Boswellic acids mixtures showed 25-46% inhibition of paw edema in rats and mice
	Ammon *et al*. (1991)	Studies on leukocytes migration showed marked inhibitory effect on both the volume and leukocyte population of pleural exudate
Anti-cancer	Hoernlein *et al*. (1999)	Boswellic acid derivatives induced apoptosis in human leukaemia cell lines. AKBA inhibited topoisomerase I from calf thymus

Table 1: Continue

Pharmacological activity	References	Key scientific findings
	Lu *et al.* (2008)	The apoptotic effects of AKBA on human prostate cancer cells were correlated with the activation of caspase-3 and caspase-8 as well as with polyribose polymerase cleavage
Immunomodulatory	Pungle *et al.* (2003)	*Boswellia serrata* extract inhibited passive paw anaphylaxis reaction in rats in dose dependent manner
	Altmann *et al.* (2004)	Boswellic acids induced Ca^{2+} mobilization and MAPK activation in human leucocytes
Hypolipidemic	Zutsi *et al.* (1986)	Water soluble fraction of *Boswellia serrata* extract decreased total cholesterol (38-48%) and increased HDL in rats fed on atherogenic diet, thus proving its hypolipidemic potential
Antimicrobial	Kasali *et al.* (2002)	Essential oil isolated from bark of *Boswellia serrata* exhibited significant inhibitory activity against *S. aureus*
Neuroprotective	Moussaieff *et al.* (2008)	Incensole acetate exerted a potent neuroprotective effect on mice following head trauma. This effect was concomitant with a significant anti-inflammatory effect of the compound on mice brains

Preliminary pharmacokinetic studies revealed very low conc. of KBA in human plasma after oral administration of *Boswellia serrata* extract (Sterk *et al.*, 2004). Further studies revealed that about 80% of initial conc. of KBA is metabolized after 15 min and less than 1% of starting conc. is remained after 120 min. But this was not observed in case of AKBA whose starting conc. still remained approximately same after 120 min (Kruger *et al.*, 2008). The above described metabolic behaviour of KBA and AKBA is due to extensive hepatic phase I metabolism (Buchele and Simmet, 2003; Reising *et al.*, 2005). A further reason for the lower plasma levels of AKBA compared with KBA might be greater volume of distribution of AKBA associated with its greater lipophilicity. (Reising *et al.*, 2005).

To overcome these limitations many approaches have been investigated including synthetic analogues, combined with other dietary components, using nanoscale drug delivery systems. Among these methods, nanoscale drug delivery systems have become main alternatives for many researchers as a potential area to develop new formulations of therapeutically bioactive components. Many successful attempts of combination of nanotechnology and traditional medicine have been made in the past using other targets.

Consequently, a good understanding of nanotechnologies is necessary for the advancement of BAs with higher efficacy. Till date many studies have focused on loading BAs into liposomes or nanoparticles, forming solid lipid nanoparticles and much progress has been made in the past ten years. The purpose of this review is to provide an updated summary of the applications of novel delivery systems of BAs, so that further strategy can be planned.

Lipid based drug delivery systems: Lipid based drug delivery is a promising approach to enhance bioavailability of poorly water-soluble compounds since it presents the drug to the gastrointestinal tract in a solubilized state. Lipids, such as natural oils and fats, have historically been used as convenient carriers for oral administration and topical application of drugs. Lipid-based drug delivery system is an attractive option for resolving drug delivery issues with poorly water soluble drugs. Complexing of the phospholipids, with the standardized botanical extracts, has provided dramatic bioavailability enhancement and faster and improved absorption in the intestinal tract (Bombardelli *et al.*, 1989; Xiao *et al.*, 2006; Maiti *et al.*, 2007; D`Mello and Rana, 2010; Sharma *et al.*, 2010).

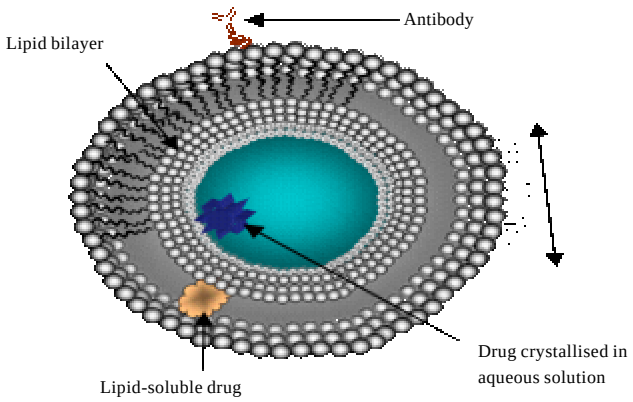

Fig. 2: Structure of liposome

Liposomes: Liposomes are micro-particulate or colloidal carriers, usually 0.05-5.0 μm in diameter which forms spontaneously when certain lipids are hydrated in aqueous media (Fig. 2). They are closed spherical vesicles consisting of a lipid bilayer that encapsulates an aqueous phase in which drugs can be stored (Malam *et al.*, 2009). Possessing the advantages of high biocompatibility, easy preparation, chemical versatility and simple modulation of their pharmacokinetic properties by changing the chemical composition of the bilayer components, liposomes as a drug delivery system have been used to improve the therapeutic activity and safety of drugs for many years (Terreno *et al.*, 2008). By the same token, liposomes have been found wide application in ameliorating BAs bioavailability and efficacy; indeed, various modifications of liposomal BAs have been developed such as polymeric conjugation on the liposome surface to acquire better clinical outcomes.

Phytosomes: Phytosomes results from the reaction of a stoichiometric amount of the phospholipid (phosphatidylcholine) with the standardized extract or polyphenolic constituents (like simple flavonoids) in an aprotic solvent (Bombardelli *et al.*, 1989). Phosphatidylcholine is a bifunctional compound, the phosphatidyl moiety being lipophilic and the choline moiety being hydrophilic in nature. Specifically the choline head of the phosphatidylcholine molecule binds to these compounds while the lipid soluble phosphatidyl portion comprising the body and tail which then envelopes the choline bound material. Hence, the phytomolecules produce a lipid soluble molecular complex with phospholipids, also called as phyto-phospholipid complex. Molecules are anchored through chemical bonds to the polar choline head of the phospholipids, as can be demonstrated by specific spectroscopic techniques (Bombardelli, 1991; Bombardelli and Spelta, 1991). Precise chemical analysis indicates the unit phytosome is usually a flavonoid molecule linked with at least one phosphatidylcholine molecule. The result is a little micro sphere or cell is produced. The term "phyto" means plant while "some" means cell-like. The phytosome technology produces a little cell, whereby the plant extract or its active constituent is protected from destruction by gastric secretions and gut bacteria owing to the gastro-protective property of phosphatidylcholine (Murray, 2008).

Difference between phytosomes and liposomes: Likewise phytosomes, a liposome is formed by mixing a water soluble substance with phosphatidylcholine in definite ratio under specific

conditions. Here, no chemical bond is formed; the phosphatidylcholine molecules surround the water soluble substance. There may be hundreds or even thousands of phosphatidylcholine molecules surrounding the water-soluble compound. In contrast, with the phytosome process the phosphatidylcholine and the plant components actually form a 1:1 or a 2:1 molecular complex depending on the substance (s) complexed, involving chemical bonds (hydrogen bonds). This difference results in phytosome being much better absorbed than liposomes showing better bioavailability. Phytosomes have also been found superior to liposomes in topical and skin care (cosmetic) products (Bhattacharya, 2009; Kidd, 2009).

Niosomes: Niosomes are lamellar structures that are microscopic in size (Fig. 3). They constitute of non-ionic surfactant of the alkyl of dialkyl polyglycerol ether class and cholesterol with subsequent hydration in aqueous media. The surfactant molecules tend to orient themselves in such a way that the hydrophilic ends of non-ionic surfactant point outwards while hydrophobic ends face each other to form the bilayer (Aungst, 1993; Rajera *et al*., 2011).

Compared with liposomes, niosomes offer higher osmotic stability with lower cost and greater availability of surfactants (Varshosaz *et al*., 2003; Junyaprasert *et al*., 2008). They improve the therapeutic performance of the drug molecules by delayed clearance from the circulation, protecting the drugs from biological environment and restricting effects to target cells (Attia *et al*., 2007).

Boswellic acids are known to have a significant anti-inflammatory effect but a higher dose is required to produce therapeutic effect. Sharma *et al*. (2010) prepared the complex of BAs to increase its bioavailability and hence to reduce dose size. Thus, the anti-inflammatory effect of boswellic acid-phosphatidylcholine (BA-PC) complex was compared with boswellic acid and also with phenylbutazone, in carrageenan-induced paw edema, in albino rats. The inhibition of inflammation was found to be better in the BA-PC complex-treated group, when compared with the standard phenylbutazone or boswellic acid-treated group. This increase in anti-inflammatory activity was due to increased absorption of the BA-PC complex than boswellic acid.

The complex was also converted into vesicles (phytosomes) and other vesicular systems (liposomes and niosomes) were also prepared for their topical anti-inflammatory effect against

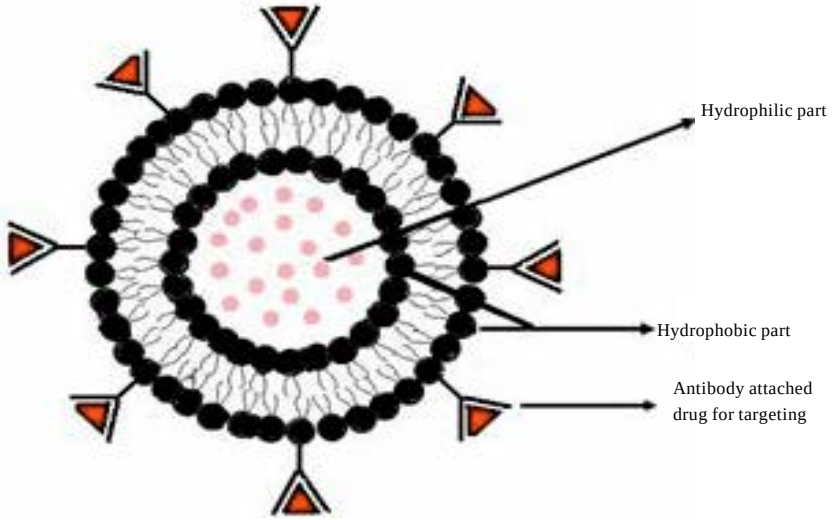

Fig. 3: Structure of niosome

carrageenan-induced paw edema in rats. In this study the phytosomes were found to be more effective than other vesicular systems and plain boswellic acid. The activity order was found to be as follows:

Phytosomes>Niosomes>Liposomes>Phenylbutazone>Boswellic acid

This increase in anti-inflammatory activity of phytosomes was due to their small size, when prepared as vesicles. Also compexation with PC greatly enhanced the absorption of the BA-PC complex through skin. Thus, the present study clearly indicates the superiority of the, BA-PC complex over plain boswellic acid, in terms of better absorption, enhanced bioavailability and improved pharmacokinetics (Sharma *et al.*, 2010).

Another study shown that lecithin formulation significantly improves the absorption of BAs and promotes their tissue penetration, demonstrating the achievement of tissue concentrations of these compounds in the range of their anti-inflammatory activity.

Nanoparticles: Nanoparticles (NPs) which are particles ranging in size from 1 to 100 nm, possess distinct physical and chemical properties that can be exploited for drug delivery (Malam *et al.*, 2009) Encapsulating drugs within NPs can improve the solubility and pharmacokinetics of drugs and sometimes enable targeting and slow release. Generally, nanoparticles' carrier materials can be divided into synthetic biodegradable high molecular polymers (polyvinyl alcohol, polylactic acid etc) and natural polymers (proteins, polysaccharides, etc) (Wang and Thanou, 2010). Among the various nano-drug systems solid lipid NPs and polymer micelles that are widely applied and intensively studied on BAs.

Nandan *et al.* (2013) prepared BAs nanoparticles using nanoprecipitation technique. The formulation was a milky white nanosuspension with particle size ranging from 150-190 nm which is optimum for drug delivery application. The result of an *in vitro* experiment demonstrated that BAs loaded nanoparticles enhanced cellular uptake and increased bioactivity in inducing apoptosis and suppressing proliferation of tumor cells. In another study the potential of enhancing the anticancer effect of BAs nanoparticles in prostate cancer cells was confirmed (Nandan *et al.*, 2013).

Solid Lipid Nanoparticles (SLNs): SLNs are made of natural or synthetic lipid or lipoid, such as lecithin and triglycerides which are solid at human physiological temperature (Zhu *et al.*, 2009). SLNs present many potential advantages. For example, they protect labile compounds from chemical degradation, provide sustained-release to improve the availability of the drug and target the effect to improve the efficiency of the drugs (Kakkar *et al.*, 2011). Shi *et al.* (2012) prepared frankincense and myrrh oil loaded solid lipid nanoparticles (FMO-SLNs), with an average particle size of 113.3±3.6 nm using the high pressure homogenization technique. Pharmacological studies demonstrated significant improvement in anti-tumor efficacy. Evaporation loss of active components in FMO could be reduced in SLNs (Shi *et al.*, 2012).

Polymeric micelles: Another feasible approach to figuring out a way to solve the poor solubility, stability and bioavailability of BAs is to encapsulate it within micelles (Sahu *et al.*, 2008). Recently, polymeric micelles have gained attention as an excellent delivery system for poorly water-soluble drugs due to their high drug-loading capacity, high water-solubility, low toxicity and appropriate size (<200 nm) for long circulation in the blood (Kwon and Teruo, 1996; Huh *et al.*, 2005).

Goel *et al.* (2010) developed polymeric nanomicelles of AKBA by radical polymerization method using N-isopropylacrylamide, vinylpyrollidone and acrylic acid. In-vitro skin permeation studies through excised abdominal skin indicated a threefold increase in skin permeability compared with AKBA gel containing the same amount of AKBA as AKBA polymeric nanomicelles gel. The AKBA polymeric nanomicelles gel showed significantly enhanced anti-inflammatory and anti-arthritic activity compared with the AKBA gel (Goel *et al.*, 2010).

Microspheres: When a pharmaceutical agent is encapsulated within or dispersed in polymer materials, drug safety and efficacy can be greatly improved and new therapies are possible. Given the protection and selective permeation properties and organ-targeted release feasibility, microspheres and microcapsules are broadly applied not only in the food-making and cosmetics industry but also in pharmaceutical fields such as drug delivery recently. Thus, a series of natural active ingredients such as zedoary oil, rutin and andrographolide have been made into microspheres or microcapsules (Li *et al.*, 2009).

Fartyal *et al.* (2011) have made attempt to deliver BAs by microspheres. They were prepared by the solvent evaporation method using polymers Hydroxyl Propyl Methylcellulose (HPMC) in fixed ratio and ethylcellulose in varient ratios. The prepared microspheres exhibited prolonged drug release (18 h) and remained buoyant for >12 h. The mean particle size increased and the drug release rate decreased at higher polymer concentration. *In vitro* studies demonstrated the diffusion controlled drug release from the microspheres (Fartyal *et al.*, 2011).

PROBLEMS NOW CONFRONTING

An ideal nanoscale agent enables drug arrivals and acts preferentially at the selected target, hence the therapeutic effect could be markedly improved. Undoubtedly BAs, an excellent representative derived from traditional medicine has been proven effective in long-term use and preclinical trials. Therefore it is of great significance to overcome the current limitations of BAs.

BAs liposome formulations are known to improve bioavailability and efficacy and reduce toxicity but no tissue specificity is associated with the liposomes. After entering the body, liposomes are rapidly taken up by the reticuloendothelial system in the liver and spleen, leading to a short circulation time. Sometimes phospholipids undergoes oxidation and hydrolysis leads to low physical and chemical stability. Therefore, developing effective modifications of liposomes such as polymeric conjugation on liposome surface becomes essential to acquire better clinical outcomes. Niosomes have some disadvantages like aggregation, fusion of vesicles and leaking or hydrolysis of encapsulated drugs. Furthermore, microemulsions also contain multiple surfactants which lead to inevitable toxicity. Thus the choice of the surfactants is critical for the formulation of microemulsions.

FUTURE PROSPECTS

To overcome the systemic side effects of BAs associated with their available lipid based formulations other novel drug delivery approaches has been introduced like proniosomes and Self-emulsifying Drug Delivery Systems (SEDDS) which can bypass the limitations of the BAs.

Proniosomes are dry formulation of water-soluble carrier particles that are coated with surfactant and can be measured out as needed and dehydrated to form niosomal dispersion immediately before use on brief agitation in hot aqueous media within minutes. The resulting niosomes are very similar to conventional niosomes and more uniform in size. The proniosome

approach minimizes the problems which are associated with niosomes like physical stability, shelf life etc., by using dry, free-flowing product which is more stable during sterilization and storage. Ease of transfer, distribution, measuring and storage make proniosomes a versatile delivery system with potential for use with a wide range of active compounds (Nasr, 2010; Yadav *et al*., 2010; Azmin *et al*., 1985). Priliminary studies indicate that niosomes may increase the absorption of drugs from the gastrointestinal tract following oral ingestion and prolong the existence of the drug in the systemic circulation due to the slow release of the encapsulated drug (Vora *et al*., 1998).

Self-emulsification is a phenomenon which has been exploited commercially for many years in formulations of emulsifiable concentrates of herbicides and pesticides. The most popular approach is the incorporation of the active lipophilic component into inert lipid vehicles surfactant dispersions self-emulsifying formulations emulsions and liposome with every formulation approach having its special advantages and limitations. SEDDS or self-emulsifying oil formulations (SEOF) are defined as isotropic mixtures of natural or synthetic oils, solid or liquid surfactants or, alternatively, one or more hydrophilic solvents and co-solvents/surfactants. There has been growing interest in the use of lipidic excipients in formulations and, in Self-emulsifying Lipid Formulations (SELFs) because of their ability to solubilize poorly water-soluble 'lipophilic' drugs and overcome the problem of poor drug absorption and bioavailability (Charman *et al*., 1992; Gursoy and Benita, 2004; MacGregor *et al*., 2004; Pouton and Porter, 2008; Singh *et al*., 2008; Patel and Sawant, 2009).

These formulations have shown to reduce the slow and incomplete dissolution of a drug, facilitate the formation of its solubilized phase, increase the extent of its transportation via intestinal lymphatic system and bypass the P-gp efflux thereby augmenting absorption from the GI tract (Humberstone and Charman, 1997; Porter and Charman, 2001).

CONCLUSION

Taken together, there is no doubt that development of novel delivery systems of BAs with better curative effects will be critical for future development of BAs as a therapeutic agent. We strongly believe that a desired preparation not only will load and keep the drug stable but will also exactly deliver the drug to candidate cells to enhance the therapeutic effect and reduce the toxicity to normal cells. This is an arduous and complex job only by multi-disciplinary cooperation we can bring this promising natural medicine to the forefront of therapeutic agents for inflammation, cancer and other diseases.

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