Chapter

A Review on the Various Drug Delivery Systems of Andrographolide

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Abstract

Herbal plants have a broad spectrum of therapeutic activity which results in growing interest to carry out research on plants for their efficacy. Andrographolide, one such effective bioactive entity derived from the plant Andrographis paniculata Nees. Leaves and roots of this plant have been used over centuries because of its medicinal properties and help in promoting health. According to Indian Herbal Pharmacopoeia and WHO, Monographs plant is used for malaria, colitis, poisonous snake bites, tuberculosis, ulcer, dysentery caused by bacterial infection and carbuncles. Countries in Southeast Asia are using this plant for the treatment of diabetes, commonly for fever and common cold. Overall pharmacological properties include analgesic, antipyretic, antiviral activity, hepato-protective activity, upper respiratory tract infections, anticancer activity, anti-diabetic activity, antimicrobial activity, anti-inflammatory, anti oxidant resistance, cardioprotective, hypoglycaemic, anti-tumor and immuno-stimulatory activities. Andrographolide belongs to class II drug of Biopharmaceutical classification system, as it poorly soluble and highly permeable. This article reviews various drug delivery systems that are tried out in andrographolide includes liposomes, niosomes, microemulsions, solid lipid nanoparticles, polymer entrapment, complexation with acyclodextrin, and microspheres.

Introduction

Pharmaceuticals of plant origin have a wide range of interest nowadays as it is safe over synthetic chemical entities. Herbal plants have a broad spectrum of therapeutic activity which results in growing interest to carry out research in plants for their efficacy. Researchers believe that the efficacy is because of the bioactive constituent present in the plant, so they are trying to prove it by correlating the phytochemical component with its pharmacological activity.For example the plant derived products containing bioactive molecules are Aspirin, Vincristine, Vinblastine, Colchicum, Colchicine, Docetaxel and Paclitaxel.

Andrographolide, one such effective bioactive entity derived from the plant Andrographis paniculata Nees. Leaves and roots of this plant have been used over centuries because of its medicinal properties and help in promoting health. Indian Pharmacopoeia reports that, a minimum of 24 formulations in ayurveda contains Andrographis paniculata as a major component. On account of its medicinal importance it is included in WHO monograph (2002). According to India Herbal Pharmacopoeia and WHO, Monographs plant is used for malaria, colitis, poisonous snake bites, tuberculosis, ulcer, dysentery caused by bacterial infection and carbuncles. Countries in Southeast Asia are using this plant for the treatment of diabetes, commonly for fever and common cold [1]. Overall pharmacological properties include analgesic, antipyretic, antiviral activity, hepato-protective activity, upper respiratory tract infections, anticancer activity, anti-diabetic activity, antimicrobial activity, anti-inflammatory, antioxidant resistance, cardioprotective, hypoglycaemic, anti-tumor and immuno-stimulatory activities [2,3]. A.paniculata is studied for its phytoconstituents and so far more than 80 compounds have been reported. Flavonoids, Quinic acids, Xanthones and Noriridoids are isolated from this plant. Despite these compounds the particular compound that is responsible for the bitter taste is due to diterpene lactones [4]. Among the diterpene lactones, abundant andrographolide compound is responsible for the pharmacological activities.

Phytoconstituents

Andrographis paniculata contains flavonoids and diterpene lactones. It also contains alkanes, ketones and aldehydes in the leaves and stem [4,5]. Flavonoids are isolated mainly from roots and leaves also containa minimum amount of it. Various diterpene lactones are extracted and isolated, where Andrographolide is considered to be the reason for the biological activity as well as the bitter taste of the leaves. Various diterpene lactones are: Andrographolide, Bisandrographolide-A, Neoandrographolide, Andrograpanin, 14-Deoxyandrographolide, Andrographiside, Isoandrographolide, Andrographolactone, 14-Deoxy-11-oxo-Andrographolide, Deoxyandrographiside,

3-O-β-D-glucopyranosylandrographolide, Andropanoside, Andropanolide, 14-Deoxy-12-methoxyandrographolide, Andrographic acid, Bisandrographolide ether, Andrographatoside, etc.,

The major phytoconsituent of A.paniculata is andrographolide and a main source for its medicinal property.Its IUPAC name is 3-[2-[Decahydro-6-hydroxy-5-(hydroxymethyl)-5,8a-dimethyl-2-methylene-1-napthalenyl]ethylidene]dihydro-4-hydroxy-2(3H)-furanone. Its molecular formula $C_{20}H_{30}O_5$.

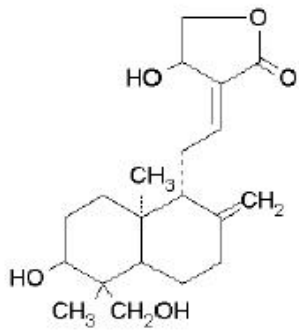

Figure: Molecular structure of Andrographolide.

It is bitter, colourless, neutral crystalline substance. It is soluble in ether, chloroform, acetone, methanol. In water it is sparingly soluble. Chemical constituents are isolated, extracted and quantified by using suitable methods. Various extraction methods includes cold maceration, supercritical CO_2 extraction, ultrasonic extraction, Soxhlet extraction, column chromatography technique and liquid-solid extraction. Other methods are solid phase extraction, microwave or ultrasound assisted extraction, supercritical fluid extraction and enzymatic extraction. Analytical methods are used to quantify and qualify the bioactive component. Different chromatographic techniques are used to quantify the active constituents such as micellar electrokinetic chromatography, gas chromatography, high performance liquid chromatography, capillary electrophoresis and thin layer chromatography. Other modern techniques include GC-MS, HPLC-MS [4].

Dosage forms of Andrographolide

Andrographolide belongs to class II drug of Biopharmaceutical classification system, as it poorly soluble and highly permeable. This diterpene is having an α,β- unsaturated γ- lactone ring connected by means of decalin ring system through an unsaturated C_2 moiety. It has poor aqueous solubility, bitter taste, it is unstable in the gastrointestinal tract because of its extremely acidic or alkaline conditions. Its oral absorption is poor, also fast and extensive metabolism results in low bioavailability. So to design the dosage form for andrographolide one should consider the above properties. Andrographis plant extracted tablets are prepared as per Chinese pharmacopeia and used for the indications mentioned in the same. Whereas the plant's bioactive component andrographolide is developed into a pill. The injection dosage form is also commericially available which is prepared by chemically modifying andrographolide with the addition of sodium bisulfate. The resulted andrographolide sodium bisulfate have enhanced solubility which is used as the antipyretic agent. However, it shows some allergic and toxic effects in human. In some cases administering large IV doses within a short time leads to nephrotoxicity [12]. So before designing the dosage form, various parameters are to be considered in such a way to obtain a better dosage form.By investigating the problems related to the drug's efficacy, various dosage forms are formulated to overcome the difficulties. Various drug delivery systems that are tried out in andrographolide includes liposomes, niosomes, microemulsions, solid lipid nanoparticles, polymer entrapment, complexation with a cyclodextrin, and microspheres.

Microspheres

Andrographolide loaded microsphere formulation with PLGA (poly (D,L-lactide-co-glycolide)) as a carrier of drug was studied by Yunxia Jiang et al. They prepared the sustained release microspheres for potential cancer chemotheraphy. Andrographolide shows a potent anti cancer activity as it acts both directly or indirectly over cancer cells. It inhibits proliferation, anti- angiogenic, induce cell cycle arrest and apoptosis, chemoprotective activity and immuno stimulating

property. Solvent evaporation method used to prepare an s/o/w emulsion was utilized for the formulation preparation. The experimental data were analysed using Response surface methodology which helped in designing and optimizing the formulation. Results concluded that the prepared microspheres were found to be having spherical shape with smooth surface, the average particle size of 53.18± 2.11µm, entrapment efficacy of 75.79±3.02%, and drug loading was 47.06± 2.18%. Invitro drug release showed initially a low burst release ~14% within the first eight hours and a sustained release upto nine days. The release was found to be Korsmeyer-Peppas model with non- fickian diffusion kinetics. So the drug release mechanism was because of diffusion of the drug from the polymer and erosion of the polymer over micropheres. Invivo studies showed the bioavailability of 67.51% when given by i.m., administration. Additionally *Invitro-Invivo* correlation study showed the good linear relationship between each other [6].

However removal of organic solvents in the microsphere preparation is difficult, this will cause high tissue toxicity which considered to be the disadvantage in formulation development in industrial level.

Microemulsion

Hong du et al.attempted to improve the solubility of andrographolide in the aqueous solution using microemulsion technique. The prepared O/W microemulsion using isopropyl myristate of 2.5%w/w as the oil phase, a surfactant- Tween 80 of 25%w/w, and co-surfactant- alcohol of 50%w/w. The obtained microemulsion had the particle size of 15.9nm. The resulted formulation was having a high capacity of solubilization and stable, also showed better anti-inflammatory effects comparing with that of tablets. It was proved that the andrographolide loaded microemulsion indicated a low oral toxicity in mice [7].

Although acute oral toxicity is noted, the given suggestion is that patients with alcohol intolerance should be careful with the formulation. Alcohol is considered to be the notable obstacle in the further

formulation development. Phase separation is noted, may be due to alcohol evaporation eventhough it is at a high temperature of 80°C, the temperature may affect the alcohol content which has an effect on the formulation.

Liposomes

Leishmaniasis, an intracellular protozoan parasitic disease was treated with liposomal andrographolide which was investigated by Jayanta Sinha et al. As drugs like pentavalent antimonial shows high toxicity, even the substitutional drugs like pentamidine and amphotericin B were also ineffective so it became essential to design a dosage form having therapeutic action with less toxicity. Andrographolide was considered for the study because of its usage over years for its therapeutic action and importantly its inherent toxicity was less because of its plant origin. In this study mannose grafted liposome with intercalated drugs could be directed particularly to the reticulo-endothelial systems through identification of mannosyl- fucosyl receptors on the macrophage surface. Invivo antileishmanial activity of mannose- grafted liposome with intercalated andrographolide showed 86% of splenic burden was reduced, also 8- dose treatment showed reducing splenic burden upto 94%. Incase of toxicity it was non toxic to host macrophages.The notified changes in histologic studies were positive in animals treating with mannose grafted liposome intercalated drug, the appearance was normal and healthy in red pulp and white pulp region. There appears no monocyte migration and confirms the reduction of the infection [8].

Despite the fact that andrographolide may have a better clinical application, it found to be changed in presence of some reductase and oxidase. Because of chemical reduction andrographolide gets converted into deoxyandrographolide. Similarly in case of oxidation CH_2OH on C_4 of andrographolide gets converted into carboxylic acid groups. These changes are due to the ester bond's hydrolysis or unsaturated acyl chains of lipid's oxidation. Likewise drug leakage from

vesicles or formation of a larger particle because of aggregation of fusion of vesicles results out in physical instability. These problems may affect the self life of the final liposome formulation.

Niosomes

Anti- hepatocellular carcinomic activity of andrographolide niosomes was examined by Tu et al. Niosomes are the novel drug delivery systems used for targeted drug delivery. Andrographolide containing niosomes were targeted HepG2 cell lines and its anti hepatocellular carcinomic activity was studied. Niosomes were prepared by thin film hydration method with ultrasound sonication to get good optimum particle size, encapsulation efficiency and drug loading ratio. As the particle size of the prepared liposomes were of 206nm which was possible to target the liver, as the particle size of liver targeting drug should be 200nm. Encapsulation efficacy was 72.36% and drug loading ratio was 5.90%. From DSC thermograms andrographolide niosomes shows the endothermic melting peaks at 60.23°C and 116.77°C, this might be due to the vesicle bilayer and interaction of andrographolide with vesicle bilayer. These results showed the preformed andrographolide niosomes. Using LC-MS method andrographolide in kidney, blood, spleen, heart, liver, lungs, were analysed after IV administration. Results showed that drugs affinity was mainly towards liver, spleen, lungs and kidney except for the heart. Organ distribution ability was better and its slow tissue clearance might be because of its ability to slow release. Niosomes increased the liver targeting efficency of andrographolide [9,10]. However the drug loading efficacy is low. Route of administration have to be verified in specific, as giving of andrographolide through intravenous administration is not advisible in most cases.

Solid Lipid Nanoparticles

Modified solvent injection method was used for the preparation of Andrographolide SLN using cetyl alcohol, Tween 80, PVA, ethyl al-

cohol respectively as lipid carrier, surfactant, stabilizer and an organic solvent. Here the attempt was to increase the oral bioavailability of the drug and targeting cancer cells to determine the anticancer activity of Andrographolide SLNs. Invitro dissolution study shows the drug release in a sustained manner but however, there appears a suspicion about the incorporation of the drug at the surface of solid lipid nanoparticles. Because there showed an accumulated drug release and reduce the release of drug at latter stage. All these might be due to solubilized or dispersed andrographolide released slowly by dissolution and diffusion from the lipid matrices. Entrapment efficacy and drug loading of andrographolide SLNs were 91.4±0.4% and 18.60±0.15% and percentage yield was found to be 95.716±1.83, [11] everything appears to be fine. But andrographolide SLNs seems to have stability issues related to an increase in particle size during storage. Unpredictable gelation tendency may also occur. Unexpected polymeric transitions should be considered while designing solid lipid nanoparticles.

Complexation with Cyclodextrin

Enhancing solubility of andrographolide by forming inclusion complexes with cyclodextrin was explored by Lai Wai Ping. Complexation of andrographolide with β-cyclodextrin, γ-cyclodextrin and 2-hydroxypropyl-β-cyclodextrin were prepared by the spray drying method and investigated for its complexation efficiency, drug-CD molar ratio, influence of polymer and the operational condition of the spray dryer. The study showed that complexation was influenced by the type of cyclodextrin, drug-cyclodextrin molar ratio, temperature and feed rate of the spray dryer. These were important for complexation, dissolution property and stability of the formulation. This study concluded that andrographolide- β-cyclodextrin of molar ratio 1:2 with a feed rate of 5ml/min at an inlet temperature of 150°C was considered as the suitable condition. Furthermore, this complex had a better solubility in the whole gastro intestinal tract and having highest stability in all pHs as well as enhanced self life in the GI tract. The fast releasing fraction was appeared in andrographolide- β-cyclodextrin

complex [12]. The study report encourages pharmaceutical product development from the obtained information. A shortcoming of this method is reproducibility of physicochemical characteristics, difficulty in incorporating into the formulation of dosage forms and small dose of drugs are complex.

Apart from the above drug delivery system there are some other delivery systems too that includes Phytosome, patches, implants, micropellets, gel matrix, floating drug delivery systems, etc,- Among these, studies are carried out in some cases while others need to be investigated.

Conclusion

Eventhough various drug delivery systems are analysed yet there prevails a hindrance in developing a fully efficient dosage form without any issues. Scale up of the techniques and feasibility of commercialization are the major limitations, as some can be formulated in a laboratory level while considering industrial productions there occurs a problem. Just incase of solid lipid nanoparticles the drawbacks are particle size variation during storage, unpredictable polymeric transitions, and unexpected gelation tendency. These can be rectified with intensive research using analytical tools. Considering Liposomes and niosomes which are already available in the market in dosage forms containing herbal extracts and bioactive constituents. Cosmetochem company marketed the liposomal preparation in the name of Herbasec which are the herbal constituents like extracts of white hibiscus, green tea, white tea, guarana and aloe vera. These products are used for the cosmetic purpose as it has the anti oxidant effect which prevents aging. Another company Indena patented Phytosomes technology. It commercializes the plant extract or constituents of Centella asiatica (triterpenes), Ginkgo biloba (ginkgoflavonglucosides, ginkgolides, bilobalide), grape seed (polyphenols), etc [13]. So issues in andrographolide liposome can be overcome by carrying out an advanced study regarding its physical and chemical instability. Incase of

andrographolide niosomal preparation route of administration has to be analysed, as it is a powerful tool in targeted drug delivery.Considering disease and organ specificity may help to decide further drug design. Cyclodextrin complexed drugs are already accessible in the market either in solid form or solution form. It is considered to be one of the promising drug delivery systems. By scrutinizing the complications related to dosage forms of andrographolide resulted out in better formulation development. Using different types of novel drug delivery system for phytopharmaceuticals will broaden the research area as well as encouraging the drug development process using herbal drugs.

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