BIOENHANCERS: A BRIEF REVIEW

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ABSTRACT
Bio-enhancers are chemical entities which promote and augment the bioavailability of the drugs which are mixed with them and do not exhibit synergistic effect with the drug. The need for bioenhancers arises due to drugs which are poorly available, administered for long periods, toxic and expensive. Bio enhancers can be classified based on their natural origin as well as based on the various mechanisms elicited by them when in combination with drugs to improve their bioavailability. Therefore, the need of the hour is to carry out extensive research on these bioenhancers so that they could be utilized in the drug formulations.

Keywords: Bio availability, P-glycoprotein, bio-enhancers

INTRODUCTION

Definition:
“Bio-enhancers are substances which stimulate and enhance the bioavailability of the drugs, which are mixed with drugs and do not exhibit synergistic effect with the drug.”

Need for bioavailability enhancers:
Lipophilicity and size of molecule both are the most important preventive factors for molecules to pass the biological membrane and to be immersed systematically following administration through oral or topical route. Several plant extracts and phytoconstituents, despite having excellent bioactivity in vitro demonstrate less or no in vivo actions due to their poor lipid solubility or inappropriate size of molecule or both, resulting reduced absorption and poor bioavailability. It is often found that, when individual contents are extracted from the plant extract there is loss of specific bioactivity. Sometimes some constituent of the many constituents plant extract are damaged in gastric environment when taken orally. They reduce the dose, reduce the duration of treatment and therefore reduce problems of drug resistance. Due to dose economy, they make treatment cost-effective.

Herbal bio-enhancer is phyto-molecules that at low doses promote and augment the bioavailability or biological activity of drug. Bio-enhancers are such agents, which by themselves are not therapeutic entities but when combined with an active constituent proceed to the potentiating of the pharmacological effect of the drug. Such formulations have been found to increase the bioavailability or bio-efficacy of a number of drugs even when reduced doses of drugs are present in such formulations. Many synthetic and herbal drugs suffer from the problem of low bioavailability. Bioavailability is the extent and rate to
which a substance enters total systematic circulation and becomes available at the required site of action.\(^1\)

Evidence has been obtained for such classes of drugs which are:

a) Poorly bioavailable and/or efficacious,
b) Require prolonged therapy,
c) They are highly toxic and expensive.

These are phyto-molecules development of which is based on ancient knowledge of Ayurveda. They enhance the bioavailability of drugs when administered at low doses. Due to this dose is decreased, reduces duration of treatment thus drug-resistance problems also reduces. The treatment is made cheaper, reduce in drug toxicity and reduce in adverse reaction. When used in combination with number of drug classes such as antibiotics, ant tuberculosis, antiviral, antifungal and anticancer drugs they are quite effective. Oral absorption of vitamins, minerals, herbal extracts, amino acids and other nutrients are improved by them. They act through several mechanisms which may affect mainly absorption process, drug metabolism or action on drug-target.

Herbal medicine is a practice as old as mankind and during the last century chemical and pharmacological studies have been performed on a many extracts of plant to determine their chemical composition and to confirm the indications of traditional medicine.\(^2\)

Ayurveda has made a major contribution to the drug discovery process through reverse pharmacology, with new means of identifying active compounds and reduction of drug development cost. Recent developments of another Ayurveda-based technology, this time, enhancing bioavailability of drugs, have produced a revolutionary shift in the way medicines are administered. Phyto-chemical and phytopharmacological studies have long been established overall health boosting capacities of various plant products but there is a great interest and medical need for the improvement of bioavailability of a large number of herbal drug and plant extract which are poorly lipid soluble and so are less bio-available. Many herbal drugs and herbal extracts despite of their extraordinary potential in-vitro finding, demonstrate less or no in-vivo actions due to their poor lipid solubility or improper molecular size or both, ultimately resulting in poor bioavailability.

Various components of an extract may contribute to the synergistic action of the extract and treatment like purification and separation can lead to a partial loss of specific activity due to the removal of chemically related substances contributing to the activity of the main components. Very often the chemical complexity of the extract seems to be important for the bioavailability of the active components. Most of the plant constituents, specifically phenolic, are water soluble and so the major problem for less bioavailability is the inability to cross the lipid membranes of intestine. The bioavailability can be improved with the use of different novel delivery systems like liposomes, marinosomes, noisome and lipid based systems which can enhance the rate of release as well as the capacity to cross the lipid rich bio-membranes. Phospholipids based drug delivery systems have been
found to be promising for the effective and efficacious herbal drug delivery.²

Concept:

The concept of ‘bioavailability enhancers’ is derived from the old traditional system such as Ayurveda (which means science of life). In this traditional system, black pepper, long pepper and ginger are collectively known as “Trikatu”. In Sanskrit it means three acrid. The action of bio enhancers was first documented by Bose who defined the long pepper’s activity to leaves of Adhatoda vasika, which increased the anti asthamatic properties of Adhatoda vasika leaves.³

Background:

The term bioavailability enhance which are commonly known as bio enhancer was initially invented when Indian Scientists discovered and scientifically validated piperine as the world’s first bioavailability enhancer in 1979. C.K. the director of the institute analyzed a list of formulations of ancient Indian Ayurveda and designed the occupied theory that Trikatu enhances efficacy of formulation.

Trikatu has three ingredients:
1) black pepper (Piper nigrum)
2) long pepper (Piper longum)
3) ginger (Zingiber officinale).

Based upon this hypothesis, most significant component of Trikatu, ‘Piper longum’ was establish to increase the bioavailability of many drugs, therefore, it was confirmed that Trikatu contains piperine which is a bioenhancer.³

Criteria for selection:

The following criteria are the existing criteria use for the selection of essential medicines. They date from 2001, when the selection procedures were reviewed following extensive consultation with Member States and Organizations, and have been approved by The Executive Board of the World Health Assembly. The expert meeting is asked to review these criteria in relation to selection of essential medicines for children. The matter of appropriate dosage forms and strengths of medicines for children is covered currently in point

1. The Burden of disease in children may be different from that in adults but is still identified as a criterion.

   a) endorse these criteria for selection of essential medicines for children
   OR

   b) Propose modifications to be referred to the next meeting the Expert Committee on the Selection and Use of Essential Medicines.

2. The choice of essential medicines depends on several factors, including the disease burden and sound and adequate data on the efficacy, safety and comparative cost effectiveness of available treatments. Stability in various conditions, the need for special diagnostic or treatment facilities and pharmacokinetic properties are also considered if appropriate. When adequate Scientific evidence is not available on current treatment of a priority disease, the Expert Committee may either defer the issue until more evidence becomes available, or choose to make recommendations based on expert opinion and experience.
3. Most essential medicines should be formulated as single compounds. Fixed ratio combination products are selected only when the combination has a proven advantage in therapeutic effect, safety or compliance over single compounds administered separately. Examples of combination medicines that have met these criteria include new formulations for Tuberculosis and malaria.

4. In cost comparisons between medicines, the cost of the total treatment, and not only the unit cost of the medicine, is considered. Cost and cost effectiveness comparisons may be made among alternative treatments within the same therapeutic group. But will generally not be made across therapeutic categories (for example, between treatment of tuberculosis and treatment of malaria). The absolute cost of the Treatment will not constitute a reason to exclude a medicine from the Model List that other wise meets the stated Selected criteria. The Patent status of a medicine is not considered in selecting medicines for the Model List. Which treatment is recommended and which medicines are selected depend on many factors, such as the pattern of prevalent diseases, treatment facilities, the training and experience of available personnel, financial resources, and genetic, demographic and environmental factors. The following criteria are used by the WHO Expert Committee on the Selection and Use of Essential Medicines.

5. Only medicines for which sound and adequate evidence of efficacy and safety in a variety of setting is available should be selected.

6. Relative cost-effectiveness is a major consideration for choosing medicines within the same therapeutic category. In comparisons between medicines, the total cost of the treatment – not only the unit cost of the medicine – must be considered, and be compared with its efficacy.

7. In some cases, the choice may also be influenced by other factors such as pharmacokinetic properties or by local considerations such as the availability of facilities for manufacture or storage.

8. Each medicine selected must be available in a form in which adequate quality, including bioavailability, can be ensured; its stability under the anticipated conditions of storage and use must be determined.

9. Most essential medicines should be formulated as single compounds. Fixed dose combination products are selected only when the combination has a proven advantage in therapeutic effect, safety, adherence or in decreasing the emergence of drug resistance in malaria, tuberculosis and HIV/AIDS.4

Novel property of bio enhancers:

These bio enhancers have different property, but they have some special property which is required to give their bio enhancing activity and these novel properties are as follows:

1. Nontoxic to humans or animal.
2. Should be effective at a very low concentration in a combination.
3. Should be easy to formulate.
4. Enhance uptake or absorption.
5. Enhance activity of drug molecule.
Mechanism of action of bio enhancers:

There are different chief mechanisms via which the various bio-enhancers exert their properties of increasing bioavailability on the drug molecule.

1. By enhancing the absorption of orally administered drugs from GIT by enhancing the supply of blood.
2. By means of modulating the active transporters located in various locations. E.g. P-glycoprotein (P-gp) is pumps out drugs because it is efflux pump and avoid it from reaching the target site. Bio enhancers in such case act by inhibiting the P-gp.
3. Decreasing the elimination process thereby extending the sojourn of drug in the body.
4. Inhibiting the drug metabolizing enzyme like CYP3A4, CYP1A1, CYP1B2, CYP2E1, in the liver, gut, lungs and various other locations. This will facilitate to overcome the first pass effect administered drug.
5. Inhibiting the renal clearance by preventing glomerular filtration, active tubular secretion by inhibition P-gp and facilitating passive tubular re absorption. Few other postulated theories for herbal bio-enhancers are
6. Reduction in hydrochloric acid secretion and increase in gastrointestinal blood supply.
7. Inhibition of gastrointestinal transit, gastric emptying time and intestinal motility.
8. Cholagogoue effect.
10. Suppression of first pass metabolism and inhibition of drug metabolizing enzyme and stimulation of gamma glutamyl transpeptidase (GGT) activity which enhances uptake of amino acids.\(^4\,5\)

Hurdles in bio-enhancers:

1. One of the challenges is to improve on properties of drug formulations such as longer duration of circulation in blood, enhanced surface area, protection of incorporated drug from degradation, crossing of biological barriers and site specific targeting.
2. Other challenge is large scale production.
3. The challenges of scaling up involve small amount of Nano-materials, agglomeration and the chemistry process.
4. In bio enhancers the advances also bring different challenges for regulatory control.\(^4\)

Classification of bio enhancer

The bio enhancers are classified into two different classes on the different basis. There are two classes of bio enhancers which are as follows:

1] Bio enhancers based on origin (Table-1)
2] Bio enhancers based on mechanism of action (Table-2)

Drug absorption barriers:

The epithelial barriers of intestinal mucosa must be passed by different drug to transport it into systemic circulation from lumen of gut to show its biological activity. The different biological and anatomical barriers are available for the penetration of epithelial membrane by oral drug delivery system. The different structures are available in intestinal epithelium which acts as barriers for the transfer of drug from GIT to systemic circulation. The stagnant layer is aqueous in nature and due its hydrophilic nature is potential barrier to the absorption of drugs.
Table 1-Based on origin:

<table>
<thead>
<tr>
<th>Plant origin</th>
<th>Animal origin</th>
</tr>
</thead>
<tbody>
<tr>
<td>E.g. Capsaicin, Ginger, Aloe Vera, Curcumin, Stevia, Genistein, Naringin, Caraway, Turmeric, Pepper, Peppermint oil</td>
<td>E.g. Cow urine distillate (Kamdhenu ark).</td>
</tr>
</tbody>
</table>

Table 2-Based on mechanism of action:

<table>
<thead>
<tr>
<th>Inhibitors of P-gp efflux pump and other efflux pump</th>
<th>Suppressors of CYP-450 enzyme and its isoenzymes</th>
<th>Regulators of GIT function to facilitate better absorption</th>
</tr>
</thead>
<tbody>
<tr>
<td>E.g. Caraway, Genistein, Sinomenine, Black Cumin, Naringin, Quercetin</td>
<td>E.g. Naringin, Gallic acid and its ester, Quercetin.</td>
<td>E.g. Aloe Vera, Niaziridin, Ginger, Liquorice.</td>
</tr>
</tbody>
</table>

The membranes around cells are lipid bilayer containing proteins such as receptors and carrier molecules. Drugs require spending of energy to cross the lipid membrane by carrier mediated transport or passive diffusion. Within the proteins there are aqueous channels are available for the passage of small water soluble molecules such as ethanol. The molecules whose size is greater than 0.4 nm lead to problem in passing through these aqueous channels. Recent work shown that the P-gp which is efflux pump possess very important role in avoiding the appropriate entry of drug into systemic circulation. There is different type of ATPase such as P-gp which is energy dependent transport membrane drug efflux pump, which belongs to members of ABC transporters. The molecular weight of P-gp is ~170 kilo Dalton and has 1280 amino acid residues. Since P-gp is gaining importance in absorption improvement much work has still been made about its modulation due to its substrate selectivity and distribution at the site of drug absorption.

METHODS USED FOR ENHANCEMENT OF ABSORPTION OF ORALLY ADMINISTERED DRUGS:

There have been many approaches in use to enhance the intestinal absorption of poorly absorbed drugs [Fig-1]. These approaches are as follows
Figure 1-Methods of bio-enhancement of bio enhancer

Absorption enhancers:

There are many absorption enhancers such as salicylates, surfactants, fatty acids, chelating agents, bile salts and polymers are help to improve the intestinal absorption. Chitosan, particularly trimethylated chitosan, increases the drug absorption via Para-cellular route by redistribution of the cytoskeleton F-actin, causing the opening of the rigid junctions. Fatty acids, bile and bile salts are surface active agents which help in increase absorption of hydrophobic drugs by increasing solubility in aqueous layer or by enhancing fluidity of apical membrane and basolateral membrane. EGTA and EDTA are calcium chelators which enhances absorption by decreasing extracellular concentration of calcium, which causes disruption of cell-cell contacts.

Prodrug:

Chemical modification of drug to pro drug and more permeable analogues is done to increase drug absorption and to increase bioavailability has been widely studied as an important and useful approach. There are various Ampicillin derivatives which are known as most common example of agent which enhances lipophilicity, to enhance absorption of polar drug by pro drug phenomenon [Fig-2]. Due to hydrophilic nature of Ampicillin, only 30-40% of drug gets absorbed from GIT. The produgs of Ampicillin like Pivampicilline, Bacampicilln and Talampicillin are synthesized by etherification of carboxyl group of Ampicillin .The parent compound are less lipophilic than prodrug and these prodrug provide better oral administration and they
showed higher bioavailability in comparison with ampicillin.

![Chemical structure of Bacampicillin](image)

**Figure 2-** Mechanism of transfer of pro drug to drug

**Dosage form and other approaches:**

To improve the intestinal absorption of poorly absorbed drugs, utilization of permeability enhancing dosage form is one of the most important practical approaches. Liposomes and emulsions are dosage formulations which help to increase intestinal absorption of insoluble drugs. To maximize the drug absorption, particle size reduction methods like micronization, nanoparticulate carriers, complexation and liquid crystalline phase are used. 7, 8

**P-glycoprotein inhibitors:**

P-gp inhibitors are used to improve per-oral drug delivery which obtained special interest. To enhance oral bioavailability different studies has been established for the possible use of P-gp inhibitor that reverse the P-gp-mediated efflux in challenge to increase the efficiency of drug transport across the epithelia [fig-3]. In the process of modulating pharmacokinetics the absorption, distribution, metabolism and elimination of P-gp substrate is influenced by P-gp inhibitors. 8, 9

**MEDICINAL PLANTS AND THEIR COMPOUNDS USED AS BIOENHANCERS**

**Piperine:**

Piperine is a 1-piperoyl piperidine which is a pioneer alkaloidal component of Piper nigrum Linn or Piper longum Linn. Piperine or mixture of components containing piperine helps to enhance the bioavailability [Fig-4], to increase level of blood in the body and efficacy of many drugs. It helps to increase efficacy of many drugs such as drugs including components of leaves of vasaka, vasicine, sparteine, rifampicin, phenytoin, sulfadiazine and propranolol. 10
Cefadroxil (65%), Amoxycillin (90%) and Erythromycin (105%), Cephalexin (85%), use of it the bioavailability of many quantity of 10-30 mg/kg of body weight. By the effect like bio enhancer it is used in regulates the intestinal function. To show membrane. To facilitate absorption it responsible for effect like bio enhancers. The transcription inhibitory activity of Rifampicin is increased by Piperine, by several folds against Mycobacterium smegmatis. The transcription of DNA template inhibits by Rifampicin, exclusively by binding to the β-subunit of RNA polymerase. Piperine show no inhibitory effect for the growth of Mycobacterium smegmatis, when used alone even at higher concentration of 50 µg/ml, but it increases inhibitory activity of Rifampicin when given within ratio of 24:1, at the lower concentration of 0.125-0.5 µg/ml. The binding ability of Rifampicin to RNA polymerase is enhanced by Piperine. 12

**Drumstick pods:**
The bioactivity of commonly used antibiotics against gram-positive bacteria like mycobacterium smegmatis, Bacillus subtilis and gram-negative bacteria like Escherichia coli is enhanced by Niaaziridin a nitrile glycoside which is isolated from the pods of Moringa oleifera. The activity of Rifampicin, Ampicillin, and Nalidixic acid is enhanced by 1.2 - 19 folds against the gram- positive strain. The activity ofazole antifungal drugs such as clotrimazole against Candida albicans is also enhanced by 5 - 6 folds. The absorption of Vitamin B12 also enhanced. 13

**Liquorice:**
Glycyrrhizagalabra is source of liquorice. Glycyrrhizin is active component of liquorice due to which bio enhancing activity is observed [Fig-6]. The cell division inhibitory activity of anticancer drug ‘Taxol’ was enhanced by 5 folds
against the breast cancer cell lines development and multiplication. In presence of glycyrrhizin inhibition of cancerous cell development by taxol was higher than treatment with taxol alone. Glycyrrhizin enhances the transport of many antibiotics like Rifampicin, Tetracycline, Nalidixic acid, Ampicillin and Vitamins B1 and B12 across the gut membrane. Absorption enhancing activity obtained from the same concentration and simultaneous treatment of sodium deoxycholate and dipotassium-glycyrrhizin was higher than sodium deoxycholate alone in Caco-2 cell monolayers.\(^{14}\)

![Figure 6- Constituent found in Liquorice](image)

**Black cumin:**

Bioactive fraction of Cuminum cyminum enhances the bioavailability of Erythromycin, Cephalexin, Amoxycillin, Fluconazole, Ketoconazole, Zidovudine and 5-Fluorouracil. The doses responsible for the bioavailability enhancement activity ranged from 0.5 to 25 mg/kg body weight. It in itself is an effective gastric stimulant, carminative and anthelmintic, anti-diarrheal, galactagogue, diuretic and also beneficial in hoarseness of voice. Luteolin especially has been demonstrated to be a potent P-gp inhibitor in literature. Cumin OR Caraway (Carum carvi) seeds enhance the bioavailability of antibiotics, antifungal, antiviral and anticancer drugs [Fig-7]. The effective dose as bio enhancer is in the range of 1-55 mg/kg body weight. They have carminative, mild stomachic, aromatic and diuretic actions. It shows greater bio enhancing effect when used in combination with bio enhancer from Zingiber officinale and piperine.\(^{15}\)

![Figure 7- Constituent found in Black cumin](image)

**Garlic:**

In garlic Allicin is the active bio enhancer phyto-molecules [Fig-8] which enhances the antifungal activity of Amphotericin B against pathogenic fungi such as Candida albicans, Aspergillus fumigatus and yeast Saccharomyces cerevisiae.

![Figure 8- Constituent found in Garlic](image)
Antifungal activity of the Allicin enhanced against S. cerevie when given along with Amphotericin B.  

**Quercetin:**

The role of it is in enhancing bioavailability, increasing level of blood and increasing efficacy of a many drugs including Dilitazem, Digoxin and Epigallocatechin gallate. Enhancing absorption of epigallocatechin gallate from the intestine is due to increased amount of Quercetin [Fig-9] administered along with epigallocatechin gallate.

![Figure 9- Constituent found in Quercetin](image)

**Morning glory plant:**

Lysergol, a phytomolecules, is isolated from higher plants like Riveacorymbosa, Ipomoea violacea and Ipomoea muricata. The killing activities of many antibiotics on bacteria is enhanced and is a promising herbal bioenhancer.

![Figure 10- Constituent found in Aloe vera](image)

**Aloe vera:**

Whole leaf extract and inner filled gel are two different Aloe Vera preparation which result in indicate that the aloes improve the absorption of vitamin C and vitamin E. The absorption is slower and vitamins last longer in the plasma with aloes, it enhances the bioavailability of Vitamin C and E in human. It is a very promising future nutritional herbal bioenhancer [Fig-10].

![Figure 11- Constituent found in Genistein](image)

**Genistein:**

Genistein is reported to be able to inhibit P-gp, BCRP and MRP-22 efflux function. The intestinal absorption of paclitaxel was dramatically increased when co-administered with Genistein, a substrate for efflux transports such as P-gp and MRP2.

**Sinomenium acutum:**

The mechanism underlying the increase in bioavailability of paeoniflorin is explained as sinomenine could decrease the efflux transport of paeoniflorin by P-gp in the small intestine. There are various chemical
constituents [Fig-12] in this plant responsible for bio enhancing action are: isotertrandrine, curine, sinactine, sinomenine, magnoflorine.\(^{21}\)

**Figure 12-** Constituent found in Sinomenium acutum

**Naringin:**

The anti-oxidant, anti-ulcer, anti-allergic and blood lipid lowering are pharmacological actions exhibited by it. It is able to inhibit intestinal CYP3A4, CYP3A1, CYP3A2, P-gp and therefore acts as a bio enhancer. Pretreatment with oral ingestion of naringin at the 3.3mg/kg and 10mg/kg improves the AUC for intravenous paclitaxel (3 mg/kg) in a dose dependent manner. Naringin at 3.3-10 mg/kg body weight dose enhances the bioavailability of paclitaxel [Fig-13]. Other drugs bioenhanced are Diltiazem, verapamil, Sequinavir and cyclosporine A.\(^ {22}\)

**Figure 13-** Constituent found in Naringin

**HERBAL FORMULATIONS USED AS BIOENHANCERS DERIVED FROM VARIOUS PLANT PART**

There are various herbal formulations are available which are act as bio enhancers and they are present in plant source which show there bio enhancing action by different mechanism. The herbal formulations which are used as bio enhancers are as follows: Herbal liposomal formulation (Table 3), transferosome (Table 4), microsphere (Table 5), nanoparticles (Table 6), and lipid based herbal formulation (Table 7), recent patent on herbal controlled release formulations (Table 8).

**APPLICATIONS**

These techniques of bio enhancers is principally targeted the toxic drugs, expensive drugs, rare drugs, poorly bio-available drugs and the drugs which are used for longer duration. However it can also be used in any drugs influenced by bio enhancers. The innovation and explanation of bioavailability enhancers has lead to several patent applications. Piperine is marketed as mono-preparation bio enhancer and as a constituent of nutritional additive that contain different vitamins, curcumin resveratrol or coenzymes.

Since bio enhancers can reduce the dosage and cost of expensive medication while making treatment safer, in humans first time its application has been done in treating TB for which the existing drugs are toxic and expensive and they are administered for
longer period. Country like India where low treatment costs for health check care are essential, the drug Risorine is approved against tuberculosis. In addition the antibiotics Rifampicin and Isoniazid it contains piperine.\textsuperscript{23}

**Table 3-Herbal liposomal formulation**

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Active ingredient</th>
<th>Application</th>
<th>Method of preparation</th>
<th>% entrapment efficiency</th>
<th>Route of administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quercetin liposome</td>
<td>Quercetin</td>
<td>Lower dose, improved dispersion in BBB</td>
<td>Reverse evaporation technique</td>
<td>60%</td>
<td>Intranasal</td>
</tr>
<tr>
<td>Liposome encapsulated silymarin</td>
<td>Silymarin</td>
<td>get better bioavailability</td>
<td>Reverse evaporation technique</td>
<td>69.22%</td>
<td>Buccal</td>
</tr>
<tr>
<td>Liposome Artemisia arboresens</td>
<td>Artemisia arboresens</td>
<td>Targeting of essential oils to cells</td>
<td>Film method and sonication</td>
<td>60-74%</td>
<td>In-vitro</td>
</tr>
<tr>
<td>Ampelopsin liposome</td>
<td>Ampelopsin</td>
<td>Increase efficiency</td>
<td>Film ultrasound method</td>
<td>62.90%</td>
<td>In-vitro</td>
</tr>
<tr>
<td>Paclitaxel liposome</td>
<td>Paclitaxel</td>
<td>Efficiency of high entrapment</td>
<td>Thin film hydration method</td>
<td>94%</td>
<td>In vitro</td>
</tr>
<tr>
<td>Curcumin liposome</td>
<td>Curcumin</td>
<td>Long circulation with high trap efficiency</td>
<td>Ethanol injection method</td>
<td>88.27%</td>
<td>In-vitro</td>
</tr>
<tr>
<td>Garlicin liposome</td>
<td>Garlicin</td>
<td>Increase efficiency</td>
<td>Reverse phase evaporation</td>
<td>90.77%</td>
<td>In-vitro</td>
</tr>
</tbody>
</table>

**Table 4-Transferosomes:**

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Active ingredient</th>
<th>Application</th>
<th>Biological activity</th>
<th>Droplet size</th>
<th>Route of administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capsaicin transferosomes</td>
<td>Capsaicin</td>
<td>Increase skin penetration</td>
<td>Analgesic</td>
<td>150.6 nm</td>
<td>Topical</td>
</tr>
<tr>
<td>Colchicine transferosomes</td>
<td>Colchicine</td>
<td>Increase skin penetration</td>
<td>Antigout</td>
<td>-</td>
<td>In-vitro</td>
</tr>
<tr>
<td>Vincristine transferosomes</td>
<td>Vincristine</td>
<td>Increase entrapment efficiency and skin penetration</td>
<td>Anticancer</td>
<td>120 nm</td>
<td>In-vitro</td>
</tr>
</tbody>
</table>
### Table 5-Microspheres

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Active ingredient</th>
<th>Application</th>
<th>Biological activity</th>
<th>Method of preparation</th>
<th>Size in mm</th>
<th>Route of administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rutin-alginate chitosan microspheres</td>
<td>Rutin</td>
<td>Targeting into cardiovascular &amp; cerebrovascular system</td>
<td>Cardiovascular and cerebrovascular</td>
<td>Complex coacervation method</td>
<td>165-195</td>
<td>In-vitro</td>
</tr>
<tr>
<td>Zedoary oil microspheres</td>
<td>Zedoary</td>
<td>Sustained release and higher bioavailability</td>
<td>Hepatoprotective</td>
<td>Quasi emulsion solvent diffusion method</td>
<td>100-600</td>
<td>Oral</td>
</tr>
<tr>
<td>CPT loaded microspheres</td>
<td>Camptothecin</td>
<td>Prolonged release of camptothecin</td>
<td>Anticancer</td>
<td>Oil in water evaporation method</td>
<td>10</td>
<td>Intraperitoneal or intravenously</td>
</tr>
<tr>
<td>Quercetin microspheres</td>
<td>Quercetin</td>
<td>Significantly decreases the dose size</td>
<td>Anticancer</td>
<td>Solvent evaporation</td>
<td>6</td>
<td>In-vitro</td>
</tr>
</tbody>
</table>

### Table 6-Nanoparticles:

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Active ingredient</th>
<th>Application</th>
<th>Biological activity</th>
<th>Method of preparation</th>
<th>% entrapment efficiency</th>
<th>Route of administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triptolide nanoparticles</td>
<td>Triptolide</td>
<td>Enhance the penetration of drug</td>
<td>Antiinflammatory</td>
<td>Emulsification ultrasound</td>
<td>-</td>
<td>Topical</td>
</tr>
<tr>
<td>Nanoparticle of cascuta chinensis</td>
<td>Flavonoid and lignans</td>
<td>Improve water solubility</td>
<td>Hepatoprotective and antioxidant activity</td>
<td>Nano suspension method</td>
<td>90</td>
<td>Oral</td>
</tr>
<tr>
<td>Artemisinin nanocapsules</td>
<td>Arteminin</td>
<td>Sustained drug release</td>
<td>Anticancer</td>
<td>Self-assembly procedure</td>
<td>90-93</td>
<td>In-vitro</td>
</tr>
<tr>
<td>Radix salvia miltiorrhiza nanoparticles</td>
<td>Radix salvia</td>
<td>Better bioavailability</td>
<td>angina pectoris, Coronary heart diseases, myocardial infraction</td>
<td>Spray drying technique</td>
<td>96.68</td>
<td>In-vitro</td>
</tr>
<tr>
<td>Taxol loaded nanoparticles</td>
<td>Taxol</td>
<td>develop bioavailability</td>
<td>Anticancer</td>
<td>Emulsion solvent evaporation</td>
<td>99.44</td>
<td>In-vitro</td>
</tr>
</tbody>
</table>
Berberine loaded nanoparticles | Berberine | Sustained drug release | Anticancer | Ionic gelatin method | 65.40 | In-vitro

### Table 7-Lipid based herbal formulation:

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Active ingredient</th>
<th>Application</th>
<th>Biological activity</th>
<th>Method of preparation</th>
<th>Dose</th>
<th>Route of administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ginkgo biloba lipid based systems</td>
<td>Flavonoids</td>
<td>Stabilizes ROS</td>
<td>Cardio protective and antioxidant activity</td>
<td>Phospholipid complexation</td>
<td>100mg</td>
<td>Subcutaneous</td>
</tr>
<tr>
<td>Silybin lipid based systems</td>
<td>Flavonoids</td>
<td>Inhibit lipid peroxidation</td>
<td>Hepatoprotective and antioxidant</td>
<td>Phospholipid complexation</td>
<td>120mg</td>
<td>Oral</td>
</tr>
<tr>
<td>Ginseng lipid based systems</td>
<td>Flavonoids</td>
<td>Increases absorption</td>
<td>Nutraceutical immune modulator</td>
<td>Phospholipid complexation</td>
<td>150mg</td>
<td>Oral</td>
</tr>
<tr>
<td>Green tea lipid based systems</td>
<td>Ginsenoside</td>
<td>Increases absorption</td>
<td>Nutraceutical</td>
<td>Phospholipid complexation</td>
<td>50-100mg</td>
<td>Oral</td>
</tr>
<tr>
<td>Grape seed lipid based systems</td>
<td>Epigallocatechin</td>
<td>Increases absorption</td>
<td>Systemic antioxidant</td>
<td>Phospholipid complexation</td>
<td>50-100mg</td>
<td>Oral</td>
</tr>
<tr>
<td>Hawthorn lipid based systems</td>
<td>Procynidins</td>
<td>The blood TRAPn significantly elevated</td>
<td>Cardio-protective, anti-hypertensive</td>
<td>Phospholipid complexation</td>
<td>100mg</td>
<td>Oral</td>
</tr>
<tr>
<td>Quercetin lipid based systems</td>
<td>Flavonoids</td>
<td>Exerted better therapeutic efficacy</td>
<td>Antioxidant and anticancer</td>
<td>Quercetin Phospholipid complexation</td>
<td>50-100mg</td>
<td>Oral</td>
</tr>
</tbody>
</table>
Table 8-Recent patents on herbal controlled release formulations:

<table>
<thead>
<tr>
<th>US patent number</th>
<th>Active ingredient</th>
<th>Novel system incorporate</th>
</tr>
</thead>
<tbody>
<tr>
<td>US 5948414</td>
<td>Opioid analgesic and aloe</td>
<td>Nasal spray</td>
</tr>
<tr>
<td>US 6340478 B1</td>
<td>Ginsenosides</td>
<td>Microencapsulated and controlled release formulation</td>
</tr>
<tr>
<td>US 6890561 B1</td>
<td>Isoflavones</td>
<td>Microencapsulated formulation</td>
</tr>
<tr>
<td>US 6896898 B1</td>
<td>Alkaloids of aconitum species</td>
<td>Transdermal delivery system</td>
</tr>
<tr>
<td>US patent 2005/0142232 A</td>
<td>Oleaginous oil of Sesamum indicum and alcoholic extract of Centella asiatica</td>
<td>Brain tonic</td>
</tr>
<tr>
<td>US patent 2007/0042062 A1</td>
<td>Glycine max containing 7s globulin protein extract, curcumin, Zingiber officinalis</td>
<td>Herbal tablet dosage form</td>
</tr>
<tr>
<td>US patent 2007/0077284</td>
<td>Opioids analgesics (phenanthrene gp)</td>
<td>Transdermal patch</td>
</tr>
<tr>
<td>US patent 7569236132</td>
<td>Flavonoids and terpenes</td>
<td>Microgranules</td>
</tr>
</tbody>
</table>

APPLICATIONS

These techniques of bio enhancers is principally targeted the toxic drugs, expensive drugs, rare drugs, poorly bio-available drugs and the drugs which are used for longer duration. However it can also be used in any drugs influenced by bio enhancers. The innovation and explanation of bioavailability enhancers has lead to several patent applications. Piperine is marketed as mono-preparation bio enhancer and as a constituent of nutritional additive that contain different vitamins, curcumin resveratrol or coenzymes.

Since bio enhancers can reduce the dosage and cost of expensive medication while making treatment safer, in humans first time its application has been done in treating TB for which the existing drugs are toxic and expensive and they are administered for longer period. Country like India where low treatment costs for health check care are essential, the drug Risorine is approved against tuberculosis. In addition the antibiotics Rifampicin and Isoniazid it contains piperine.

CONCLUSION

There are many herbal drugs which are used as bio enhancers, which can increase activity of active drug when give in combination with active drug. New chemical substances with new modes of action are what modern pharmaceutical research is all about. Drug discovery process is highly aided by different system such as ayurveda through reverse pharmacology with new means of identifying active compounds and development cost also reduced. The research is now aimed at use of bio enhancers along with active drugs so as to increase their bioavailability in the systemic circulation. Bio enhancers being cheaper in cost are easily available to larger section of society.

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CONFLICT OF INTERESTS

Declared None

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7) Patil Umesh K, Singh Amrit, Chakraborty Anup K. International J of Recent Advances in Pharmaceutical Research. People’s Institute of Pharmacy & Research Centre, People’s University, Bhanpur, Bhopal-462037 (M.P.), India. October 2011; section-4: 16-23.


