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Review on Recent Approaches for Bioavailability and Bioenhancer

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Abstract :-

High therapeutic potential is associated with the discovery of numerous novel chemical entities, however many of these substances have undesirable pharmacokinetic qualities because of poor solubility and/or poor membrane penetration characteristics. The latter is primarily brought about by the lipid-like barrier that epithelial mucosal layers impose and which drug molecules must get through in order to have a therapeutic impact. Pre-systemic metabolic breakdown of drug compounds, primarily by cytochrome P450 enzymes found in the liver hepatocytes and intestine enterocytes, is another barrier. Although the first-pass impact is avoided by the nasal, buccal, and pulmonary modes of administration, they still rely on drug molecules being absorbed across the mucosal surfaces to transport medication throughout the body. By modifying membrane permeability and/or pre-systemic metabolism, bioenhancers (drug absorption enhancers of natural origin) can increase the amount of unaltered medication that enters the systemic blood circulation. An overview of natural bioenhancers and their primary modes of action for the nasal, buccal, pulmonary, and oral routes of drug administration is the goal of this study. Poorly bioavailable medications, such as big, hydrophilic therapies, are frequently injected. By enabling systemic administration of these poorly bioavailable medications via different routes of administration (such as oral, nasal, buccal, or pulmonary routes of administration), bioenhancers may be used to benefit patients. They may also be used to decrease dosages of small-molecule medications, which would lower treatment costs.

- **Keywords:-** bioenhancer, cytochrome P450, drug absorption enhancer, efflux, metabolism, P-glycoprotein, pharmacokinetic interaction, tight junction.

Introduction :-

The percentage of a medicine that is delivered that enters the systemic circulation is known as its bioavailability, which is a subtype of absorption. A medication's bioavailability is 100% when given intravenously, by definition. However, because to intestinal endothelial absorption and first-pass metabolism, a medication's bioavailability is typically[TH] lower when delivered by routes other than intravenous than it is when supplied intravenously. In this way, extravascular formulation's area under the plasma drug concentration curve versus time (AUC) is compared to intravascular formulation's AUC to determine bioavailability numerically. Because AUC is inversely correlated with the dose that has reached the systemic circulation, it is employed.

A drug's bioavailability is measured on average; to allow for population variability, the deviation range is displayed as The lowest value of the deviation range is used to represent true bioavailability and to determine the drug dose required for the drug taker to obtain systemic concentrations similar to the intravenous formulation. This ensures that the drug taker who has poor absorption is dosed appropriately. The bottom value of the deviation range is used to dose without knowledge of the drug taker's absorption rate in order to ensure the intended efficacy, unless the medication has a constrained therapeutic window.

Bioenhancer –

After the discovery of the first bioenhancer ever discovered, piperine, a new branch of medical science known as "bioenhancers," "biopotentiators," or "bioavailability enhancers" was first formally formed in 1979. With this drug technology, less medication is destroyed, wasted, and eliminated from the body after being taken orally.

Without possessing any pharmacological action of their own at the dose used, bioenhancers are described as compounds that increase the bioavailability leading to an increase in the bioefficacy of active drugs with which they are mixed. Depending on their mode of action, they may increase the bioavailability of toxins, vitamins, and allopathic medications. For instance, piperine boosts the bioavailability of a number of minerals and medications, including beta-carotene, vitamin A, vitamin B6, vitamin B6, coenzyme Q10, and aflatoxin B1.

Increased Increased drug levels in the bloodstream that are available for drug activity are referred to as bioavailability. Increased bioefficacy refers to the drug's improved effectiveness as a result of improved bioavailability or other processes.

Bioavailability and Biopharmaceutic:-

Classification Systems (BCS)

A medicine must be accessible as an aqueous solution at the absorption site in order for it to be absorbed. This suggests that a drug's water solubility and dissolution rate are crucial factors that affect its oral bioavailability [1]. It is believed that roughly 70% of all novel chemical entities (NCE) have low water solubility and fail to have commercial viability due to their restricted bioavailability [2]. This is a significant difficulty in the creation of formulations of poorly water-soluble medications. To enter the systemic circulation, medication molecules must cross a biological membrane at the absorption site. . In order to determine the pace and extent of medication absorption as well as its bioavailability, it is important to consider the drug's gastrointestinal permeability [3]. By including them into the Biopharmaceutic Classification Systems, solubility and permeability have been shown to be crucial in regulating bioavailability (BCS). In order to anticipate the absorption profile of pharmacological products, BCS, a scientific framework for classifying therapeutic substances based on their solubility and intestinal permeability, has been demonstrated to be useful [4-6]. When determining the appropriate course of action to take to increase a drug's bioavailability, it is crucial to take the BCS class of the drug material into account. A pharmacological substance is deemed very soluble by the United States Food and Drug Administration (USFDA) BCS guidance when the highest dose strength is soluble in 250 mL or less of aqueous media over the pH range of 1- 6.8 at 37 1°C [7]. The degree of intestinal medication absorption in humans can be used to directly estimate a drug's permeability.

Bioavailability with Bioenhancers :-

The BCS shows that the classes III and IV medications have low intestinal permeability; hence, methods that can raise the permeability of these compounds will probably increase their bioavailability. It is possible to view the usage of bioenhancers as a novel idea. When supplied in conjunction with a medicine at low doses, bioenhancers increase the bioavailability of that drug. A good bioenhancer should be affordable, accessible, safe, and efficient. It should also be rapid-acting, have predictable and reproducible activity, not induce its own pharmacological effects at the dose employed, and be compatible with other APIs. When used wisely, bioenhancers can reduce therapeutic dosages because of improved bioavailability, which lowers the expense, toxicity, and adverse effect profiles of drug treatment. From a historical perspective, Bose claimed that the use of a condiment, long pepper, to boost the antiasthmatic activity of the leaf of the Adhatodavasica species was the precursor to bio-enhancement. 1.3 Herbal medicines and bioavailability Since the dawn of time, phytomedicine has played a significant part in pharmacotherapy. Today, about 50% of beneficial medications come from natural sources. According to a number of publications, significant populations in developing nations frequently use herbal medicine products (HMPs) as a kind of complementary and alternative therapy. Additionally, studies reveal that over the past 20 years, there has been an increase in the prevalence of the use of HMPs in industrialised countries, where complementary and alternative medicine is currently becoming more and more popular. A number of causes, including the belief that herbal products are safer because they are natural in origin, have been attributed to the resurgence of interest in HMPs. Other factors include the affordability of herbal medications and the notion that they might be useful in treating specific conditions where conventional therapy have failed. There are many instances of herbal products with outstanding in vitro activities but with dismally low in vivo efficacy, despite their large therapeutic effects and low adverse effect profiles. Animal and human clinical trial investigations on HMPs have discovered these, demonstrating the low bioavailability of herbal medications. Because of their inadequate molecular size, poor aqueous solubility, and/or poor intestinal permeability, numerous plant extracts and phytoconstituents exhibit diminished in vivo activities, which leads to decreased absorption and ultimately poor bioavailability. . For instance, an extract of the plant Azadirachta indica, which is commonly used in native medicine to treat malaria, showed high in vitro activity against different strains of Plasmodium falciparum, but it required extremely high doses (e.g. 800 mg/kg body weight) to show meaningful in vivo activity. Similar to milk thistle, Silybum marianum has Silymarin as the primary bioactive ingredient derived from its seed. Silymarin has a wide range of uses, including oral therapy for chronic liver disorders. However, because to its weak aqueous solubility, low bioavailability as a result. It has been proven that adding a herbal bioenhancer to the formulation of HMPs with low in vivo activity can increase their efficacy, in addition to existing methods used to increase the solubility and bioavailability of APIs. When the intestinal permeability of the bioactive ingredients is restricted, the need for bioenhancers is particularly relevant. In essence, creating a formulation with the best bioavailability will be aided by a better understanding of the physicochemical properties of the bioactive components of HMPs.

- In pharmacology, bioavailability is a subcategory of absorption and is the fraction (%) of an administered drug that reaches the systemic circulation.[1]
- By definition, when a medication is administered intravenously, its bioavailability is 100%.[2][3] However, when a medication is administered via routes other than intravenous, its bioavailability is generally[TH] lower than that of intravenous due to intestinal endothelium absorption and first-pass metabolism. Thereby, mathematically, bioavailability equals the ratio of comparing the area under the plasma drug concentration curve versus time (AUC) for the extravascular formulation to the AUC for the intravascular formulation.[4] AUC is used because AUC is proportional to the dose that has entered the systemic circulation.[5]
- Bioavailability of a drug is an average value; to take population variability into account, deviation range is shown as ±.[4] To ensure that the drug taker who has poor absorption is dosed appropriately, the bottom value of the deviation range is employed to represent real bioavailability and to calculate the drug dose needed for the drug taker to achieve systemic concentrations similar to the intravenous formulation.[4] To dose without knowing the drug taker's absorption rate, the bottom value of the deviation range is used in order to ensure the intended efficacy,

unless the drug is associated with a narrow therapeutic window.[4] For dietary supplements, herbs and other nutrients in which the route of administration is nearly always oral, bioavailability generally designates simply the quantity or fraction of the ingested dose that is absorbed.

- In pharmacology, relative bioavailability measures the bioavailability (estimated as the AUC) of a formulation (A) of a certain drug when compared with another formulation (B) of the same drug, usually an established standard, or through administration via a different route. When the standard consists of intravenously administered drug, this is known as absolute bioavailability (see above).

- reductions in drug cost, toxicity, and other adverse effects. Present day research on expensive, toxic and scarce drugs or drugs that exhibit poor bioavailability demands the use of an ideal bioenhancer which should be safe, effective, economical, easily procured,non-addictive etc [2]

Bioequality And Bioenhancer :-

- Relative bioavailability is one of the measures used to assess bioequivalence (*BE*) between two drug products. For FDA approval, a generic manufacturer must demonstrate that the 90% confidence interval for the ratio of the mean responses (usually of *AUC* and the maximum concentration, C_{max}) of its product to that of the "brand name drug"[OB] is within the limits of 80% to 125%. Where *AUC* refers to the concentration of the drug in the blood over time $t = 0$ to $t = \infty$, C_{max} refers to the maximum concentration of the drug in the blood. When T_{max} is given, it refers to the time it takes for a drug to reach C_{max}.

- While the mechanisms by which a formulation affects bioavailability and bioequivalence have been extensively studied in drugs, formulation factors that influence bioavailability and bioequivalence in nutritional supplements are largely unknown. As a result, in nutritional sciences, relative bioavailability or bioequivalence is the most common measure of bioavailability, comparing the bioavailability of one formulation of the same dietary ingredient to another.

Bioenhancer -

After the discovery of the first bioenhancer in the world, piperine, a new branch of medical science known as "bioenhancers," "biopotentiators," or "bioavailability enhancers" was first formed scientifically in 1979. [2] With this drug technology, less medication is destroyed, wasted, and eliminated from the body after being taken orally. Bioenhancers are compounds without any pharmacological action of their own at the dose employed that increase the bioavailability leading to an increase in the bioefficacy of the active drugs with which they are mixed. [1] Depending on their mode of action, they may increase the bioavailability of toxins, vitamins, and other nutrients. For instance, piperine enhances the bioavailability of a number of nutrients and medications, including phenytoin, theophylline, propanolol, and aflatoxin B1. These include betacarotene, vitamin A, vitamin B6, vitamin B6, coenzyme Q10, and other vitamins and minerals. [8]

Increased Increased drug levels in the bloodstream that are available for drug activity are referred to as bioavailability. Increased The term "bioefficacy" refers to a drug's increased effectiveness as a result of improved bioavailability or other processes.

• Drug Bioavailability Enhancing Agents of Natural Origin (Bioenhancers) that Modulate Drug Membrane Permeation and PreSystemic Metabolism

High therapeutic potential is associated with the discovery of numerous novel chemical entities, however many of these substances have undesirable pharmacokinetic qualities because of poor solubility and/or poor membrane penetration characteristics. The latter is primarily brought about by the lipid-like barrier that epithelial mucosal layers impose and which drug molecules must get through in order to have a therapeutic impact. Pre-systemic metabolic breakdown of drug compounds, primarily by cytochrome P450 enzymes found in the liver hepatocytes and intestine enterocytes, is another barrier. Although the first-pass impact is avoided by the nasal, buccal, and pulmonary modes of administration, they still rely on drug molecules being absorbed across the mucosal surfaces to transport medication throughout the body. By modifying membrane permeability and/or pre-systemic metabolism, bioenhancers (drug absorption enhancers of natural origin) can increase the amount of unaltered medication that enters the systemic blood circulation. An overview of natural bioenhancers and their primary modes of action for the nasal, buccal, pulmonary, and oral routes of drug administration is the goal of this study. Drugs with poor bioavailability, such as large, hydrophilic therapeutics, are frequently injected. By enabling systemic administration of these poorly bioavailable medications via different routes of administration (such as oral, nasal, buccal, or pulmonary routes of administration), bioenhancers may be used to benefit patients. They may also be used to decrease dosages of small-molecule medications, which would lower treatment costs.

Chitosan and Derivatives :-

It has been demonstrated that chitosan can improve buccal mucosal tissue absorption of the big bioactive peptide transforming growth factor (TGF-). In a diluted lactic acid solution, 2% chitosan-H (MW: 1 400,000; degree of deacetylation: 80%) was used to create a gel. The chitosan gel included I125-labeled TGF-b (MW: 25 Kda), same like the PBS control solution. The permeability of TGF- through porcine buccal mucosa dermatomed to a thickness

of roughly 700 m was investigated using continuous-flow perfusion chambers. The location of TGF- within the buccal mucos was also determined by horizontal sectioning and counting. Results showed that chitosan increased the permeability of the bioactive form of TGF. Results demonstrated that chitosan enhanced the permeability of the TGF-β bioactive peptide in buccal mucosa six- to seven-fold, even though oral mucosa is relatively impermeable to TGF-β due to its large size.

Furthermore, compared to the control PBS solution, an increased amount of TGF-β was found in the superficial layers of the epitheliu. Enhanced penetration of

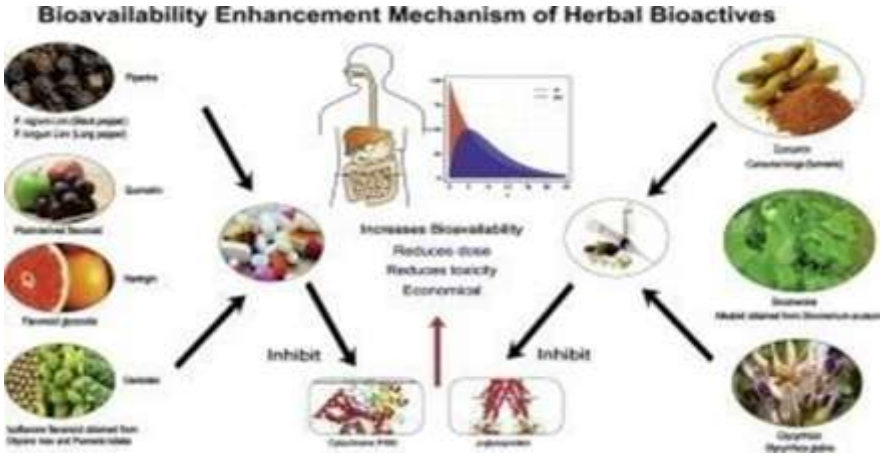

Fig no. 1

Due to chitosan's mucoadhesive properties, greater drug retention at the application site may be the cause of TGF- entering the buccal mucosa. Interference with lipid structure in the intercellular areas of the epithelium is another possible mechanism by which chitosan increased drug transport across the buccal epithelium.

When chitosan was utilised as a bioenhancer for peptide and protein absorption, another in vitro investigation showed lower trans-epithelial electrical resistance (TEER) of the buccal epithelial TR146 cell culture type. In this study, chitosan glutamate concentrations of 20 g/mL and higher demonstrated enhanced transport of large hydrophilic compounds, 3H-mannitol and fluorescein isothiocyanate labelled dextrans (FITC-dextrans), at pH 6. 3H-mannitol showed the highest cellular permeability, and decreasing permeability was observed for FITC-dextran with molecular weights (MW) of 4000 Da Except for FD20, all of the test substances' increased permeability brought on by chitosan was statistically significant. The TEER of the TR146 cell culture model was significantly decreased to 30% in the presence of chitosan glutamate at concentrations of 20 g/mL and higher in comparison to untreated cells. The buccal mucosal intercellular barrier is not based on tight junctions, unlike the nasal and intestinal mucosal membranes, so tight junction modulation cannot be the mechanism by which permeability enhancement occurred. Therefore, it was proposed that disruption of lipid organisation in the buccal mucosa was to blame.

Classification

Bioenhancers can be classified according to their source of origin, either plant based or animal based or else according to their site of action. Bioenhancers so far almost exclusively discovered in plants, increase the bioavailability of other substances in different ways:

- Increase of absorption in the intestine
- Inhibition of degradation in the intestine and the liver by inhibition of drug metabolising enzymes (inhibiting first pass mechanism of destruction of drugs).
- Inhibition of elimination in the drug in gut and through bile by inhibition of efflux pumps.
- Increase of drug permeability of pathogens.
- Inhibition of defense mechanisms of pathogens or tumor tissue (such as efflux of drugs)
- Increasing binding possibilities on binding sites (such as DNA and proteins) of the pathogen • Improving overcoming of the blood-brain barrier

• Applications of recent research

- The bioenhancer technology is particularly focused at dangerous pharmaceuticals, pricey drugs, hard-to-find drugs, drugs with low bioavailability, or drugs that need to be administered for extended periods of time. It can, however, also be utilised in any medication affected by bioenhancers. Several patent applications have been made as a result of the discovery and characterisation of bioenhancers. Piperine is sold

as a bioenhancer in single-ingredient preparations and as part of dietary supplements that also include Coenzyme Q10, curcumin, or other vitamins.

- Why Bioenhancers have been used for the first time in people to treat tuberculosis because the current treatments are toxic and expensive and require long-term administration. This is because bioenhancers can reduce dosage and expense of pricey medications while improving treatment safety. Risorine is a tuberculosis medicine that is licenced in India, where affordable medical care is crucial. It also contains piperine in addition to the antibiotics rifampicin and isoniazid. A pharmaceutical compound that is taken orally can be bioenhanced using bioenhancers, which also results in better formulation. Bioenhancers are an innovative idea that are based on a conventional system of Indian medicine and when used properly can lead to research.

1. Concept of bioavailability enhancers

The traditional, centuries-old Ayurvedic medical system is where the idea of "bioavailability enhancers" originated (science of life). Black pepper, long pepper, and ginger are collectively referred to as "Trikatu" in Ayurveda. "Trikatu" signifies three acrids in Sanskrit.

Bose (1929) was the first to describe how long pepper increased the antiasthmatic properties of Adhatoda vasika leaves, which is how the action of bioenhancers was first discovered.

1. Definition and history of bioavailability enhancers

"Bioavailability enhancers" are drug facilitators; they are molecules that, when used alone, do not exhibit typical drug activity. However, when combined with other molecules, they can potentiate the drug molecule through conformational interaction, increase the drug's bioavailability across the membrane, act as receptors for the drug, and increase the drug's receptivity in target cells. A "bioenhancer" is a substance that, at the amount employed, can increase the bioavailability and bioefficacy of the medicine with which it is coupled without exhibiting any usual pharmacological activity of its own.

These are functional excipients that are added to formulations to enhance the absorption of a drug that is pharmacologically active and are also known as "absorption enhancers." Piperine was discovered and scientifically verified as the first bioavailability enhancer in the world in 1979[9] by Indian researchers at the Regional Research Laboratory, Jammu (RRL, currently known as Indian Institute of Integrative Medicine, Jammu).

The institute's director, C.K. Atal, carefully examined a list of traditional Ayurvedic medicines from ancient India that were once used to cure a variety of illnesses. He noticed that, out of the 370 Ayurvedic formulations examined, 210 contained either Trikatu or one of its ingredients, Piper longum (P. longum), which is used to treat a wide range of diseases. He came up with the working theory that Trikatu made formulations more effective. *Trikatu* has three ingredients: black pepper (*Piper nigrum*), long pepper (*P. longum*) and ginger (*Zingiber officinale*). Based on this hypothesis, these ingredients were studied, which found that one of the ingredients, '*P. longum*', 'Piper' increased the bioavailability of many drugs[10].

The active ingredient in P. longum, piperine, was isolated, and its role in increasing bioavailability was confirmed. Similar findings were supported by additional study on a number of pharmacological classes, including antitubercular, leprosy, antibiotic, non-steroidal anti-inflammatory, CVS, and CNS medications. Piperine was discovered to boost the bioavailability of many medications by 30% to 200%. It enhances curcumin bioavailability by almost ten times, according to later study.

However, it was also noted that not all medications had their bioavailability increased by piperine, and that the effect varied depending on the drug.

3. Drug absorption barriers

Piperine, the active component of P. longum, was isolated, and its contribution to improved bioavailability was validated. Additional research on other pharmaceutical classes, including antitubercular, leprosy, antibiotic, non-steroidal anti-inflammatory, CVS, and CNS drugs, supported similar findings.[11] It has been found that piperine increases the bioavailability of many drugs by 30% to 200%. According to a later study, it increases curcumin bioavailability by almost ten times.[11]

It was also noted that piperine did not increase the bioavailability of all medications, and that the effect varied depending on the drug.[12]

Recent research has demonstrated that P-glycoprotein and other drug efflux pumps play a critical role in preventing effective medication entry into the systemic circulation[13].

P-glycoprotein, an energy-dependent transmembrane drug efflux pump and ATPase, is a member of the ABC transporter family. It contains 1 280 amino acid residues and has a molecular weight of -170 kDa[14].

4. Methods for enhancement of bioavailability of orally administered drug

4.1. Absorption enhancers

Many absorption enhancers, including bile salts, surfactants, fatty acids, chelating compounds, salicylates, and polymers[15],[16], are successful in enhancing intestinal absorption. Trimethylated chitosan, in particular, improves drug absorption via the paracellular pathway by redistributing the cytoskeletal F-actin and causing the tight junctions to open. Bile, bile salts, and fatty acids are surfactants that improve absorption by either making hydrophobic medicines more soluble in the aqueous layer or by making the apical and basolateral membranes more fluid. The extracellular calcium concentration is decreased by calcium chelators such ethylene glycol tetraacetic acid (EGTA) and ethylene diamine tetraacetic acid (EDTA), which disrupts cell-cell connections and increases absorption[17].

4.2. Prodrugs

One of the well-known instances of increasing the lipophilicity of substances to improve the absorption of a polar medication using prodrug strategy[18] is the many ampicillin derivatives.

Due to the hydrophilic nature of ampicillin, only 30%–40% of it is absorbed from the digestive system (GIT). The production of ampicillin derivatives like pivampicilline, bacampicilln, and talampicillin involved esterifying the carboxyl group of the antibiotic.

4.3. Dosage form and other pharmaceutical approaches

The intestinal absorption of insoluble drugs was improved by different dosage formulations like liposomes and emulsions[19],[20]. Drug absorption is also increased by particle size reduction techniques like micronization, nanoparticular carriers, complexation, and liquid crystalline phases[21],[22].

4.4. P-glycoprotein inhibitors

P-glycoprotein inhibitors try to increase the effectiveness of drug transport across the epithelial membrane by reversing P-glycoprotein-mediated efflux. In the process of modulating pharmacokinetics, P-glycoprotein inhibitors affect the metabolism, absorption, distribution, and elimination of P-glycoprotein substrates[23].

6. Mechanism of action of bioenhancers of herbal origin

Herbal bioenhancers function through a variety of methods. The mechanisms of action of various herbal bioenhancers may be the same or different. Nutritional bioenhancers work on the gastrointestinal tract to improve absorption. Drug metabolism mechanisms are the main targets of antimicrobial bioenhancers.

Several different mechanisms of action for herbal bioenhancers have been proposed, including (a) a decrease in hydrochloric acid secretion and an increase in gastrointestinal blood supply[24], (b) an inhibition of gastrointestinal transit, gastric emptying time, and intestinal motility[25], [26], (c) changes in GIT epithelial cell membrane permeability[27], [28], (d) a cholagogic effect[27], (e) bioenergetics.

6.1. Mechanism of action of piperine

Piperine's bioenhancer effect has been attributed to a variety of processes, including DNA receptor binding, cell signal transduction modification, and drug efflux pump inhibition[31].

In general, it blocks the enzymes that break down drugs, promotes absorption by activating gut amino acid transporters, blocks the cell pump that removes drugs from cells, and blocks intestine glucuronic acid synthesis.

When a drug passes through the liver after being absorbed from the GIT, it may inhibit enzymes involved in drug metabolism or increase GIT absorption of the drug. The hepatic activities of UDP-glucuronyltransferase and arylhydrocarbon hydroxylase were severely inhibited by piperine when administered orally to rats[32].

Another study found that piperine alters the rate of glucuronidation by decreasing the amount of endogenous UDP-glucuronic acid and by suppressing the activity of the transferase[33].

Cytochrome P450 3A4 (CYP3A4) and human P-glycoprotein are both inhibited by piperine[34]. Both proteins play a significant role in the first-pass removal of many medications.

The metabolising enzymes CYP1A1, CYP1B1, CYP1B2, CYP2E1, CYP3A4, and others are among those that piperine inhibits or stimulates. Therefore, bioenhancers will have an impact on the majority of drugs that are metabolised by these enzymes.

Other proposed mechanisms include increasing the responsiveness of target receptors to drugs, acting as receptors for drug molecules, dilating the GIT vasculature to increase drug absorption, and modifying the dynamics of cell membranes to increase drug transport across cell membranes[35].

7. Need for bioavailability enhancers

The primary barriers to chemicals passing the cellular membrane and being systemically absorbed after oral or topical administration are lipid solubility and molecular size.

Numerous plant extracts and phytoconstituents exhibit poor absorption and bioavailability despite having excellent bioactivity in vitro because of their poor lipid solubility, improper molecular size, or both. It is frequently observed that specific bio-activity is lost when individual constituents from the plant extract are isolated. When taken orally, some of the multi-constituent plant extract's constituents may occasionally be destroyed in the gastric environment. They reduce the dose, shorten the treatment period and thus reduce drug resistance problems. Due to dose economy, they make treatment cost-effective, minimize drug toxicity and adverse reactions.

8. Problems/disadvantages/hurdles with bioenhancers

Despite the success of bio-enhancers in medication delivery, not all methods have been equally effective. There are problems that need to be fixed with the new bio-enhancers that are being produced. The physicochemical properties of the nanomaterials can be changed, however, to enhance properties like prolonged blood circulation, increased functional surface area, protection of the drug's incorporation from degradation, passage through biological barriers, and site-specific targeting.

The manufacture of herbal bio-enhancers on a big scale is another difficulty for research and development. For eventual commercialization, laboratory or pilot technologies must always be scaled up. Low concentration of nanoparticles, agglomeration, and the chemical process are obstacles to scaling up; it is simpler to change nanomaterials at the laboratory scale than at the industrial scale[36]. Another difficulty is maintaining the size and makeup of nanoparticles that improve bioavailability on a broad scale.

The development of herbal bio-enhancers presents new difficulties for regulatory control. Regulations that take into account the physicochemical and pharmacokinetic characteristics of nano drug products, which differ from traditional drug products, are becoming more and more necessary. The European Medicines Evaluation Agency and the Food and Drug Administration of the United States have taken the initiative to identify some potential scientific and regulatory challenges[36].

9. Future prospects

Scaling-up is hampered by low nanoparticle concentration, agglomeration, and chemical reactions; it is easier to alter nanomaterials at the laboratory scale than at the industrial scale[36]. Maintaining the size and composition of nanoparticles that enhance bioavailability on a large scale is another challenge.

For regulatory control, the development of herbal bio-enhancers poses new challenges. Regulations that consider how nano drug products differ from conventional drug products in terms of their physicochemical and pharmacokinetic properties are becoming more and more essential. The Food and Drug Administration of the United States and the European Medicines Evaluation Agency have made an attempt to highlight some potential scientific and regulatory challenges[36].

10. Role of natural compounds from medicinal plants as drug bioavailability enhancers

10.1. Quercetin

(2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxy-4Hchromen-4-one) is a flavonoid, an aglycone form of a number of other flavonoid glycosides found in citrus fruits.

Quercetin has exhibited a wide range of beneficial biological activities including antioxidant, radical scavenging, anti-inflammatory, anti-atherosclerotic, anti-tumoral and anti-viral effects[37]. Quercetin has been shown to increase bioavailability, blood levels and efficacy of a number of drugs including diltiazem, digoxin and epigallocatechin gallaate[38]–[41].

The plasma concentrations, the area under the plasma concentration-time curve (AUC) and peak concentration [C(max)] of diltiazem in the rabbits pretreated with quercetin were significantly higher than those obtained from untreated group. It was reported that diltiazem is metabolized by CYP3A4 both in the liver and small intestine[42],[43]. The absorption of diltiazem in the intestinal mucosa was inhibited by P-glycoprotein efflux pump[44],[45]. The increased AUCs and C(max) of diltiazem by pretreatment of quercetin might have been resulted from the inhibition of the P-glycoprotein efflux pump and the metabolizing enzyme, CYP3A4 in the intestinal mucosa[46],[47]and restraint of the metabolizing enzyme, CYP3A4[48].

The absorption of epigallocatechin gallate was also reported to be enhanced with red onion supplementation, abundant source of quercetin. The AUC of epigallocatechin gallate determined over a period of 6 h increased from 1 323 to 1 814 ngh/mL, when co-administered with quercetin. It was demonstrated

that increased amount of quercetin administered along with epigallocatechin gallate could increase absorption of epigallocatechin gallate from the intestine[41].

11. Recent advances of bioenhancers

Ketoprofen-loaded solid lipid nanoparticles (SLNs) made from beeswax and carnauba wax were prepared and characterised by Kheradmandnia et al. They discovered that the mean particle size of the drug-loaded SLNs decreased upon mixing with Tween 80 and egg lecithin as well as upon increasing total surfactant concentration. The capacity of SLNs to absorb a weakly water-soluble medication like ketoprofen was demonstrated by their high drug entrapment efficiency of 97%. After 45 days of storage, differential scanning calorimetry thermograms and high-performance liquid chromatographic analysis showed that nanoparticles were stable with barely detectable drug leakage. Additionally, it was discovered that when compared to nanoparticles with more carnauba wax in their structure, those with more beeswax in their core displayed faster drug release. In order to determine the amount of camptothecin in animal organs after it has been administered in SLNs, Martins et al. developed and validated a straightforward reversed-phase HPLC method. They came to the conclusion that the method is accurate, precise, and reliable and can be used to determine the amount of CPT in rat organ samples following i.v. administration of camptothecin in suspension, in physical mixture with SLN, and incorporated in SLN[49

In their formulation and characterization of curcuminoids-loaded SLNs, Tiyaboonchai et al. discovered that, under ideal processing conditions, lyophilized curcuminoids-loaded SLNs displayed spherical particles with a mean particle size of 450 nm and a polydispersity index of 0.4, up to 70% (w/w).

Wang et al. assessed the emodin-loaded solid lipid nanoparticles' synthesis, characterisation, and anticancer activity tests (E-SLNs). Particle size analysis, zeta potential measurement, drug entrapment efficiency (EE), stability, and in vitro drug release behaviour were used to look into the physicochemical features of the E-SLNs. After being kept for 4 months in storage, the E-SLNs demonstrated stable particle size at (28.63.1) nm, ideal drug EE, and comparatively long-term physical stability. E-SLNs were a promising vehicle for oral drug delivery because their sustained profile of drug release could last for up to 72 hours. The delivery of emodin as lipid nanoparticles may also be a promising strategy for the treatment of cancer, according to these findings[51].

By employing sodium lauryl sulphate, an anionic surfactant, as a stabiliser, Kwon et al. created silk fibroin coated SLNs that were then electrostatically coated with the substance when the SLN was in an acidic environment. Being positively charged, the silk fibroin covering of the nanoparticles would interact significantly with negatively charged skins, increasing skin permeability[52].

Conclusion:-

An novel idea known as "bioenhancers" was developed based on an ancient Indian medical method (as mentioned by Charaka, Sushruta and other apothecaries in traditional system of medicine). The idea would be helpful in lowering medicine costs, toxicity, and other negative consequences, and might ultimately have a favourable impact on the national economy of our/country one's (as sought by WHO). It meets all requirements to be regarded as an excellent drug. It has a significant impact on many different drug classes and is non-addictive, inexpensive, easy to obtain, and safe. The economics of drug development are an issue for new drug development technology**.**

An important predictor of drug absorption is bioavailability. It stands for the administered dose fraction that, when given orally or through another extravascular dosing route, successfully reaches the systemic circulation.

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