ISSN 2348 – 8034
Impact Factor- 5.070

GLOBAL JOURNAL OF ENGINEERING SCIENCE AND RESEARCHES

Solubility Enhancement of Piperine

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ABSTRACT

The objectives of this research were to construct and characterise a piperine's solubility and rate of dissolution improved as a result of the multicomponent crystal formation. Powder X-ray diraction (XRD), differential scanning calorimetry (DSC), and Fourier transform-infrared (FT-IR) spectroscopy were used to characterise the unique multicomponent crystal's solid state. In distilled water, the profiles of solubility and dissolution rate were assessed. Under conditions of high relative humidity (75 and 100 RH), the physical stability was assessed. The co-crystalline phase of piperine was identified in this unique multicomponent crystal by the analysis of the single crystal X-ray diraction structure. The thermogram of the dierential scanning calorimetry, cocrystal displayed a single, distinct endothermic peak. The cocrystal caused piperine to dissolve more quickly and with better solubility than intact piperine. The development of a channel structure within the cocrystal was the cause of this enhancement. The cocrystal remained stable in a humid environment as well.

Keywords: *Piperine; Curcumin; liposomes; microspheres; nanoparticles, transferosomes, ethosomes,*

I. INTRODUCTION

Piperine along with its isomer chavicine is an organic compound that either belongs to the lipid family that consists of either fat or fatlike substances or alkaloids that comprises nitrogenous compounds with specific physiological properties (Panahi et al. 2014). This is one of the sharp-tasting elements in fruits like black pepper (*Piper nigrum*) and long pepper (*Piper longum*) (Mazzanti et al. 2016). The isomer chavicine, which has the same chemical formula but a different molecular structure from that of piperine, is what gives peppers their intense flavour. The loss of pungency in peppers, when preserved for a long time is due to the slow conversion of chavicine into piperine. In black and white pepper, piperine content varies from 5-9%. Piperine is insoluble in water and due to this reason; it is typically extracted from pepper by using dichloromethane and other substituent organic solvents (Quijia et al. 2022). Piperine can also be artificially prepared by treating concentrated alcoholic extract of pepper with an alcoholic solution of potassium hydroxide. This step is initiated to remove resin that actually contains chavicine which is a monomer of piperine (Doucette et al. 2013). Then this solution is separated from its insoluble residue and is left to stand overnight. This step is done so that the alkaloids present in the solution start to crystallize to form piperine. Piperine is a major component alkaloid/amide present in the fruit of black pepper (Piper nigrum) and long pepper *(Piper longum)* (Kannappan et al. 2011). The piperine is used not only for the dietaries as the spices, but also as a useful drug with great potential for medicine. The piperine is one of the most well-known components because of its high medicinal properties In Indian medicine (Dahmani et al. 2010). Piperine is a bioactive alkaloidal phytomedicine/nutrient that is present in the fruits and roots of Piper nigrum and Piper longum (Shao et al. 2015). PPN is a potent bioactive compound, which has been reported to have several therapeutic activities including “anti-metastatic (Vasavirama et al. 2014).Piperine is a major secondary metabolite isolated from plants of the Piperaceae family, especially from *Piper nigrum L.,* which is known as the king of spices. These species are cultivated in tropical regions, such as Indonesia, Brazil, and India (Pradeep et al. 2002).This plant has been widely used as both a household spice and a traditional medicine (Gorgani et al. 2017). In addition, piperine has been used to improve cognitive function and as a protective agent against neural degeneration and memory impairment (Johri et al. 1992). Furthermore, piperine has been used as a bioenhancer when coadministered with some active pharmaceutical ingredients, such as rapamycin, curcumin, domperidone, and anti-tuberculosis drugs (Katiyar et al. 2016). The production of a multicomponent crystal phase has become a common technique to change physicochemical

characteristics, such as solubility and dissolution rate. Due to its crystalline form, a multicomponent crystal containing a tiny organic molecule is probably quite stable. The low molecular weight of the coformer contributes to the low final dosage. Therefore, compared to other complicated forms, multicomponent crystals containing tiny organic molecules have substantial benefits. As a result, we concentrated on the creation of piperine's multicomponent crystals in our work. A salt, cocrystal, hydrate, and solvate are often components of a multicomponent crystal phase (Zarai et al. 2013). Numerous studies have shown that forming a multicomponent crystal phase of API with an appropriate excipient could improve its physicochemical characteristics, including permeability, bioavailability, physical stability, compressibility, and pharmacological efficacy. (Vioglio et al. 2017; Zaini et al. 2019). As far as we are aware, there have only been two research on the multicomponent crystal phase of piperine: one using a co crystal with resveratrol and the other using a salt with a halide (Putra et al. 2018; Kennedy et al. 2018).A solubility investigation of piperine (H) was therefore omitted in order to focus on the co crystal of resveratrol and piperine, which was examined to increase resveratrol's solubility. Although the Piperine's crystal structure (He et al. 2017). Despite reports of salt, its solubility was not investigated. Consequently, no research has been done on the solubility enhancement brought about by multicomponent crystals. Piperine has three crystal forms (form I, II, and III). These crystal forms show remarkable differences in their physicochemical properties, such as melting point and solubility. Form I is the most stable polymorph and has a lower intrinsic dissolution rate than forms II and III; the melting point of form I is 131.38 ◦C (Pfund et al. 2015). Piperine or 1-peperoyl piperidine is a solid having the molecular formula C17H19O3 N, melting point 128° C and is optically inactive, sparingly soluble in water with cis-trans isomerism . It shows high lipophilicity, is weakly basic, and exhibits non-saturable passive absorption kinetics. A natural phytomedicine/nutrient called piperine (PPN) has solubility properties in solutions of water and ethanol and water and surfactants & the super critical carbon dioxide (CO_2) and near critical CO_2 at different temperatures has also been reported (Raman et al.2002; Kumoro et al. 2009). Piperine does not only add a pinch of flavour to food but also to alcohol, for example, brandy, which is known for having a small amount of it. While piperine may sound like a pleasant spice, it can also be a strong repellent. It can be found in most insecticides, particularly those that kill the common housefly (Govindarajan et al. 1977). Exploring the broad-spectrum bioactivities of piperine has been demonstrated over a decade that can be harnessed in agriculture as pesticide and medicinal use. Te insecticidal properties of piperine have been first observed in 1924(Han et al. 2019). Piperine is also known to increase the bioavailability and in vivo efficacies of nutrients and medications by inhibiting enzymes (cytochrome P450, UDP-glucoronyltransferase) (Kozukue et al. 2007). Piperine is poorly water soluble, which limits its oral absorption. Only 7–12% of the absorbed piperine from investigations using the everted sac model could be identified in the serosal medium (Suresh et al. 2007). Conventional extraction methods available for piperine extraction from pepper do not improve aqueous solubility. On an industrial scale, pepper is comminuted into flakes or ground into coarse powder and then extracted repeatedly with an organic solvent such as acetone, ethanol or chlorinated hydrocarbons.(Marion et al. 1960) In Asian countries, pepper is broadly used as a medicinal herb for treating gastrointestinal diseases (Mehmood et al. 2010) in which piperine might act as the major active component. Therefore, piperine appears to be a potential immunomodulator for therapeutic usage against inflammatory diseases as well as bacterial infection. However, the relationship between the metabolic and pharmacologic effects of piperine is unclear; particularly, the underlying action mechanism of piperine in the setting of bacterial infection is largely unknown. Considering that pepper acts as a seasoning in improving digestion and appetite, aimed to investigate the effects of its main component piperine on several cellular signalling pathways,One of these pathways is the mTOR signaling. mTOR is a highly conservative molecule in eukaryotic evolution, which is necessary for maintaining metabolic homeostasis, cell proliferation, survival, and promoting protein synthesis (Fingar et al. 2004; Thoreen et al. 2012).

Isolation and extraction of piperine from piper species-

Piperine was discovered in 1819 by Hans Christian oersted, who isolated it from the fruits *of Piper nigrum, the source plant of both black and white pepper* (Patel et al. 2022; Stecher et al. 1960). It can be isolated from the fruits of *P. nigrum* or *P. longum*. The powdered fruits of the plant are extracted with dichloromethane at room temperature with stirring for 12 hours. The extract is filtered, concentrated in vacuum, and then the residue is purified on an alumina column. Pure piperine can also be obtained by crystallization from ethanol, which may be required for food and/or medicinal usages. Piperine is obtained directly from the crude residue in lesser amounts by extraction in

alcohol, filtration and successive crystallization. Piperine can be synthesized from the interaction of piperyl chloride (formed from piperic acid and phosphorus pentachloride) and piperidine. (35)

Physical and chemical properties of piperine –

Piperine is a nitrogenous pungent substance (Raffaele et al. 2002). The chemical structure of piperine places it in the group of cinnamamides (Balsamo et al. 1975). The congeners of cinnamamides possess sedative, hypnotic, anticonvulsant, antidepressant, and skeletal muscle relaxing properties. Light yellow or white crystalline powder in the shape of needles or short rods is highly pure piperine. Only with powerful acids can it produce salts. The flavour of piperine with alcohol is similar to pepper (Balsamo et al. 1977). The molecular formula of piperine is $C_{17}H_{19}NO_3$ and IUPAC name 1-[5-(1,3-Benzodioxol-5yl)-1-oxo-2,4- pentadienyl] piperidine. Molecular mass of piperine is 285.34 gm mol-1 and Taste is firstly Tasteless but burning after taste. The Melting point of Piperine is 130 °C & Solubility Insoluble in water but soluble in benzene, acetic acid, Stereoisomer isopiperine, isochavicine and chavicine (Majeed et al. 2000; Tabuneng et al. 1983; Shankaracharya et al. 1979).

S.N 0	COMPOUND NAME	POLYMER NAME	MECHANISM	Time increase bioavailability and solubility / solubility high /low	REF.
1-	Curcumin and piperine	Zein and chitosan	Their co-administered piperine with curcumin to increase the bioavailability of curcumin (2 gm of curcumin with 20 mg of piperine increase the curcumin bioavailability	The highest incapsulation efficiency of curcumin 92% and piperine 87% were observed	(Baspinar et al. 2018)
2-	Piperine	PVP-K25 , HPMC K-100 , low substitution hydroxypro pylcellulose (LS-HPC) and carboxymethyl starch sodium (CMS-Na)	co-solvency of phospholipids which lead to enhanced wettability and dispersibility of the drug powder Further exchange the dissution rate of drug	drug release and enhance oral bioavailability of poorly water-soluble drugs. Meantime, the novel multi-particulate tablets could be used as a promising dosage form for Pipreine in the clinic which provides a new approach for personalized dose regimen and long term therapeutic efficacy	(Zhu et al. 2020)
3-	Piperine	-	Piperine-PNL affects both Phase I and Phase II metabolism, and in order to establish this mechanism of action, we must choose a model molecule that only goes through Phase II, so highlighting (and isolating) the formulation's impact on this metabolic route.	It demonstrates that the medications are fully dissolved in their dissolved state and that adding weakly water-soluble	(Cherniakov et al. 2017)

				molecules to the PNL boosts the perceived solubility of the drugs.	
4-	food grade piperine	Ethyl lactate, Polysorbate 20 (Tween® 20), Sorbitane monooleate 80 (Span® 80), food grade piperine, cannabigerol	**P-glycoprotein** (**P-gp**), an **efflux** membrane **transporter** (phase I, and phase II enzymes).	Single oral administration of Tetrahydrocannabinol and Cannabidiol in SNEDDS in male Wistar rats resulted in a 6-fold and 4-fold increase in AUC, respectively. Incorporation of piperine led to an additional increase in AUC of 1.5- fold for THC and 2-fold for. The piperine compound itself has relatively poor water solubility, the SNEDDS formulation dissolves the piperine and increases solubility in an aqueous environment via thermodynamically stable nano particles	(Izgelov et al. 2020)
5-	Piperine	_	Due to piperine's lipophilic nature and PGP inhibitory effects, increased micelle formation, hyperemia, and epithelial cell wall modification, or an increase in the bioenergetics processes of the gastrointestinal epithelium as a result of piperine's thermogenic properties, bioavailability may be enhanced.	Comparing CDSSDP female and male groups to CDSSD female and male groups, a mean of 58 and 68% increases in serum candesartan AUC were seen.	(Zulal et al. 2015)
6-	Piperine	β-Cyclodextrin	Due to the solid-state interaction of βCD molecule with the aromatic ring of PP molecule which was confirmed by Raman spectra, solubility of PP was enhanced dramatically.	The solubility of PP was increased as a result of inclusion in βCD/ Owing to an	(Ezawa et al. 2016)

				improved solubility of the GM (PP/βCD = 1/1)	
7-	Polysorbate piperine	Phospholipids / chitosan	drug release from lipid nanoformulations in combination with intracellular P-gp inhibition ensured a higher anticancer drug concentration inside the cancer cells	it was confirmed that optimum concentration of polysorbate 80 required for maximum solubilization of piperine was 5.5% w/v	(Kumari et al. 2020)
8-	yellow crystalline piperine	polyethylene glycolpolylactide-co-glycolide nanopartical	Loading of piperine onto starch nanoparticles has resulted in enhanced solubility of piperine in aqueous solution due to the highly hydrophilic nature, small-sized and large surface areas of the starch nanoparticles. The high surface area to volume ratio of starch nanoparticles also increased the interactions of piperine molecules with the aqueous solution,	its low water solubility (40 mg l–1 at 18°C), poor bioavailability and cytotoxicity at high concentrations. These shortcomings have prompted research efforts to encapsulate piperine onto various nano-carriers in order to improve its water solubility and bioavailability	(Chong et al. 2020)
9-	Piperine	α-, β-, and γ-cyclodextrins	the inclusion complexes inhibit muscarinic M3 receptor-mediated competition. Also, cAMP-induced protein kinase A activation and Inositol trisphosphate-induced Ca2+ emission control are expected.	Preparing the inclusion complex of PP with each CD by different methods may lead to an understanding of the chemical properties and inclusion complex formation that improves the poor water solubility of PP.	(51)
10-	Polyphenol-curcumin , piperine	Cu-Pi nanoparticles	Loading of piperine onto starch nanoparticles has resulted in enhanced solubility of piperine in aqueous solution due to the highly hydrophilic nature, small-sized and large surface areas of the starch nanoparticles. The	The solubility of organic solvents in water was an important parameter affecting the mean	(Moorthi et al. 2012)

			high surface area to volume ratio of starch nanoparticles also increased the interactions of piperine molecules with the aqueous solution,	size of nanoparticles	
11-	quercetin, genistein, naringin, sinomenine, piperine, glycyrrhizin and nitrile glycoside	trimethylated chitosan	that piperine modifies the rate of glucuronidation by lowering the endogenous UDPglucuronic acid content and also by inhibiting the transferase activity Piperine inhibits human P-glycoprotein and cytochrome P450 3A4 (CYP3A4)[32]. Both the proteins contribute to a major extent to first-pass elimination of many drugs.	Piperine, the active principal present in P. longum was isolated and its bioavailability enhancing action was established. Further research on several classes of drugs including antitubercular, leprosy, antibiotics, non-steroidal antiinflammatory drugs, CVS and CNS drugs showed similar results. Piperine was found to increase bioavailability of different drugs ranging from 30% to 200%. Subsequent research has shown that it increases curcumin bioavailability by almost ten-fold	(Kesarwani et al. 2013)
12-	Piperine powder	chitosan (CS) and pentylentetrazol (PTZ)	Piperine raises GABA levels in the brain and inhibits sodium and calcium channels. In a mouse model of epilepsy caused by PTZ. piperine activates TRPV1 receptors to have an anticonvulsant effect. Additionally, it was discovered in a different study that piperine, either by itself or in combination with sodium valproate, reduces PTZ-induced seizures by enhancing GABAergic neurotransmission.	piperine solubility was improved by encapsulation with CS-STPP NPs.	(Anissian et al. 2018)
13-	Black pepper and piperine.	Phosphatidylcholine, Sodium	its capacity to decrease the absorption of cholesterol by differentiated Caco-2	Except for a 1 mg/mL	(Duangjai et al. 2013)

		taurocholate	cells. Since piperine, a key component of black pepper, was similarly found to lower total plasma cholesterol, LDL, and VLDL in rats given a high-fat diet, it is believed to play a significant role in these effects.	concentration of black pepper extract, lipid micelle micellar cholesterol solubility was unaltered.	
14-	Piperine	1,3-benzodioxole	Its effectiveness against many diseases and chronic conditions appears to be a result of its capacity to influence a wide variety of signalling pathways. One of the few explanatory findings in the range of its bioenhancer capabilities is the augmentation of bioavailability by delaying the glucuronidation events, affecting certain proteins and enzymes, and enhancing the absorption of nutrients from the stomach.	Despite having several biological functions, piperine has limited water solubility and low bioavailability; as a result, it is delivered via a modified drug delivery method and in the wrong dosages.	(Tripathi et al. 2022)
15-	Curcumin and piperine	Poloxamer 407, Helix pomatia,	the presence of piperine improved the recovery of curcumin by affecting the rapid metabolism of this compound in the cell	piperine incorporated in the oil phase of all emulsion samples. Poloxamer 407 (4%) were used in the stabilization of emulsions	(Gülseren et al. 2014)
16-	piperine	Monoolein/ poloxamer	Piperine has the potential to interact with co-administered drugs (ie, drug–herb interaction) through inhibition of metabolism of the drug mediated by cytochrome P450 enzymes. When the rats were treated with PPD-cubosome loaded with piperine, the cumulative absorption of PPD into the general circulation was adequately increased	Although PPD-cubosome loaded with piperine may increase the absorption of PPD by about 64%, the efflux ratio of PPD-cubosome loaded with piperine was not significantly different from that of the PPD-cubosome. This may be because of fewer metabolic enzymes in the Caco-2 cell monolayer than in the human body; thus, piperine may not have a significant impact	(Jin et al. 2013)

				on the efflux ratio	
17-	Curcumin, piperine	glyceryl tripalmitate, 1,2-dipalmitoyl-rac-glycero-3-phosphocholine	studied the interaction of piperine with curcumin on combined quantum chemical and molecular docking techniques and concluded that piperinepiperine (i) forms an intercalation complex with curcumin, which further aids in transport of curcumin, and (ii) inhibits certain cytochrome P450 family of monoamine oxidase enzymes such as CYP3A4, UDPglucuronosyltransferase (UGT) and UDP-glucose dehydrogenase (UDP-GDH) that are responsible with glucuronosylation of curcumin (i.e., elimination from the body), thereby enhancing the bioavailability as well as biological activity of curcumin	The release solubility indicated release of nearly 40% curcumin and 7.5% piperine	(Bolat et al. 2020)
18-	Piperidine and Piperine	Cyclodextrin	Piperine and piperidine suppress a number of cancer forms.	This could be caused by piperine's poor water solubility and low bioavailability.	(Mitra et al. 2022)
19-	Piperine, curcumin	2-hydroxypropyl-b-cyclodextrin	In order to fight infections, piperine and curcumin can diminish antibiotic resistance by complexation, decrease cell-to-cell communication (quorum sensing), and inhibit pore-forming toxins.	Higher biological efficiency of the nutraceutical system in vivo is suggested by a rise in the solubility of curcumin and piperine as well as permeability through membranes that mimic gastrointestinal walls and the blood-brain barrier.	(Stasiłowicz et al. 2020)
20-	Piperine	Poloxamer 407	The first to demonstrate that apoptosis and inflammation suppression are additional potential mechanisms underlying the demonstrated neuroprotective effect of PIP in the colchicine-induced SDAT model.	low water solubility. Furthermore, the drug suffers extensive first-pass metabolism and the absolute oral bioavailability in	(Elnaggar et al. 2015)

				Wistar rats is 24%.10 The drug also has pH-mediated metabolism to piperidine and photoisomerizatio n	
21-	Hesperetin and piperine	Cocrystal	The process and potential chemical components of aged citrus peel (chenpi) in preventing lung cancer development from chronic obstructive pulmonary disease.	These cocrystals are connected by hydrogen bonds between hesperitin and Piperine with a 1:1 stoichiometric ratio. In addition, the routine physical and chemical properties of the cocrystal were systematically characterized, and the cocrystal's solubility and bioavailability were evaluated	(Liu et al. 2022)
22-	Piper nigrum	Sn-hexane, methylene chloride, ethyl acetate	In vitro studies have shown that piperine possesses antioxidant properties that quench or reduce free radicals, hydroxyl radicals, and ROS.22 Additionally, piperine was discovered to have an antioxidative impact against oxidative stress brought on by cadmium in a recent study employing cultured human peripheral blood cells.	Due to low solubility of the pipeline and low bioavalibility of hisperidin to 64%	(Park et al. 2019)
23-	Piperne	-	Because leucine is a large, neutral (aliphatic) amino acid that requires specialised transporters to enter cells, it seems unthinkable that it could pass through a cell membrane in an unintended manner. By increasing the quantity of SLC7A5/SLC3A2, the system L1 amino acid transporter for Leu and other large neutral amino acids, to the cell membrane, our research showed that piperine enhanced mTORC1 activation.	It has long been established that piperine increases bioavailability of clinical drugs.	(Pan et al. 2015)
24-	Piper longum	Hydrophilic lipids G44 and G50	indicated piperine to be a weak base, existing in unionized form in the intestinal milieu and as an ionized	piperine reached a maximum of 74% in sacs incubated	(Khajuria et al. 1998)

			moiety in stomach. It therefore, may be getting absorbed predominantly through intestine.	with piperine in physiological buffer, presence of cycloheximide as well as in sacs depleted with Na ions	
25-	curcumin and piperine	sodium carboxymethyl cellulose	More thorough research on the effects of piperine on liver protection is required, and it may offer fresh perspectives on the prevention and treatment of fatty livers. It's interesting that co-administration of curcumin and piperine doesn't seem to benefit the effects of curcumin on anti-diabetic and antioxidant properties.	-	(Li et al. 2015)

Table No.1 Brief description about compounds

Techniques for Solubility Enhancement of Piperine -

1. Nano particles-

Curcumin as the active compound of turmeric has antioxidative, antiinflammatory, antimicrobial and anticancer properties among others. However, its disadvantageous properties like low solubility, poor bioavailability and rapid degradation under neutral or alkaline pH conditions or when exposed to light limit its clinical application. These problems can be solved by a smart combination of using a natural enhancer like piperine and preparing nanoparticles by a proper method like electrospray. Due to these facts it was aimed in this study to develop curcumin and piperine loaded zein-chitosan nanoparticles step by step. For that purpose various formulation parameters like the concentrations of zein, curcumin, piperine and chitosan and the preparation parameters like the applied voltage and the nozzle diameter were investigated step by step. The nanoparticles were characterised by investigating their shapes, morphologies, particle sizes with help of SEM images and the cytotoxicity on neuroblastoma cells. It was succeeded to prepare curcumin and piperine loaded zein-chitosan nanoparticles having a mean particle size of approximately 500 nm and high encapsulation efficencies for curcumin (89%) and piperine (87%). Using a curcumin concentration of 10–25 mg/ml resulted in reduction of the viability of approximately 50% of the neuroblastoma cells. The here developed nanoparticle formulation consisting of solely natural compounds showed good cytotoxic effects and is a promising approach with appropriate properties for final consumption (Baspinar et al. 2018).

The purpose of this work was to investigate the potential use of starch nanoparticles as piperine nanocarriers. As nanocarriers for the encapsulation of piperine, starch nanoparticles with mean particle diameters ranging from 50 nm to 200 nm have been created. Using in-situ nanoprecipitation, piperine has been effectively loaded onto starch nanoparticles. The synthesis circumstances, such as the kinds and concentrations of surfactants, as well as the initial piperine concentrations, had an impact on the loading capacity of piperine. The largest amount of piperine that could be loaded onto starch nanoparticles under ideal circumstances was 4.74 mg mg-1. Over the course of 168 hours and at a physiological pH, piperine was seen to slowly and steadily release from starch nanoparticles (Chong et al. 2020).

Curcumin Identify a suitable method for the preparation of curcumin–piperine (Cu-Pi) nanoparticles to overcome oral bioavailability and cancer cell targeting limitations in the treatment of cancer. Cu-Pi nanoparticles were created using several different techniques, including the Fessi, emulsion vpolymerization, solid dispersion, and thin film hydration methods. To investigate the impact of various manufacturing parameters on the Cu-Pi nanoparticles, optimisation was conducted. The Fessi method generated particles with a minimum average size of 85.43 nm, a

ISSN 2348 – 8034
Impact Factor- 5.070

polydispersity index of 0.183, and a zeta potential of 29.7 mV. Cu-Pi nanoparticles were unaffected by the change in organic solvent (acetone or ethanol). The use of a 1:10:10 ratio of drug, polymer, and surfactant, as well as the use of anionic surfactants or combinations of anionic surfactants and cationic polymers or non-ionic surfactants and cationic polymers, had a significant impact on Cu-Pi nanoparticles. Cu-Pi nanoparticles coated with PEG-containing copolymer using the Fessi method had the smallest average particle size, the best polydispersity index, and the best zeta potential, all of which are within the study's allowable bounds. In order to overcome the limits of oral bioavailability and cancer cell targeting, this dual nanoparticulate drug delivery technology appears to be promising (Moorthi et al. 2012).

According to recent data, the field of nanomedicine is expanded by encapsulating hydrophobic medicines in biodegradable polymers. Black pepper's primary alkaloid, piperine, has strong anticonvulsant properties. However, piperine's restricted therapeutic use is a result of its low water solubility. This work used a pentylentetrazol (PTZ)-induced kindling model to examine the effects of piperine nanoparticles on seizure behaviour and astrocyte activation. Piperine was loaded onto chitosan-sodium tripolyphosphate nanoparticles (CS-STPP NPs). Ten days prior to PTZ treatments, animals were given daily intraperitoneal (i.p.) injections of free piperine or piperine NPs at doses of 5 or 10 mg/kg. This treatment was continued until the last PTZ injection. Nissl staining and immunostaining against NeuN were used to assess the neuroprotective effects of piperine NPs. GFAP immunostaining was used to investigate the activation of astrocytes. When compared to free piperine groups, behavioural data indicated that piperine NPs had prevented the development of seizure parameters. Additionally, piperine NPs groups had lower levels of cell loss and astrocyte activation. These findings imply that piperine NPs improve astrocyte activation and boost neuroprotection in the chemical kindling model of epilepsy. This might offer a successful therapeutic approach for the management of epilepsy disease (Anissian et al. 2018).

Piperine may be the mechanism through which black pepper (*Piper nigrum L.*) reduces blood lipids *in vivo* and prevents cholesterol uptake in vitro. In order to test this, the current study compared the effects of black pepper extract and piperine on cholesterol uptake and efflux in Caco-2 cells, distribution of cholesterol transport proteins in the membrane and cytoplasm of these cells, and physicochemical characteristics of cholesterol micelles. Similar reductions in cholesterol uptake into Caco-2 cells were seen in response to piperine or black pepper extract, both of which contained the same quantity of piperine. Both treatments decreased the amounts of the proteins NPC1L1 and SR-BI in the membrane, but not their cellular expression as a whole. With the exception of black pepper extract at a dosage of 1 mg/mL, lipid micelle micellar cholesterol solubility was unchanged. These findings imply that the active ingredient in black pepper, piperine, inhibits cholesterol absorption by internalising the cholesterol transporter proteins (Duangjai et al. 2013).

It is frequently suggested that lipid particle encapsulation can increase curcumin bioavailability. This bioactive molecule is poorly soluble in water and breaks down quickly when consumed. To ascertain the impact of interfacial composition on absorption, the uptake of curcumin from oil in water emulsions made with two distinct emulsifiers, Tween 20 and Poloxamer 407, was examined in the current work. Because piperine is known to suppress b-glucuronidase activity, it was added to the curcumin to reduce the amount that might be broken down. In order to simulate intestinal uptake, the emulsions were given to Caco-2 cell cultures, and the amount of curcumin recovered was assessed (Gülseren et al. 2014).

The factors prevent PPD from being used to treat human diseases. Methods: To increase the oral bioavailability of PPD, its absorption, and to prevent its metabolism, we employed cubic nanoparticles containing piperine in this study. By fragmenting bulk glyceryl monoolein (GMO)/poloxamer 407 cubic gel, PPD and piperine-loaded cubic nanoparticles were created, which were then tested using transmission electron microscopy and differential scanning calorimetry. The bioavailability and metabolism of PPD and its nanoparticles in vivo were next investigated. First, we assessed the in vitro release of PPD from these nanoparticles and their absorption across the Caco-2 cell monolayer model (Jin et al. 2013).

ISSN 2348 – 8034
Impact Factor- 5.070

Piperine-containing cubic nanoparticles were utilised to increase the oral bioavailability of PPD, its absorption, and to prevent its metabolism. By fragmenting bulk glyceryl monoolein (GMO)/poloxamer 407 cubic gel, PPD and piperine-loaded cubic nanoparticles were created, which were then tested using transmission electron microscopy and differential scanning calorimetry. The bioavailability and metabolism of PPD and its nanoparticles in vivo were next investigated. First, we assessed the in vitro release of PPD from these nanoparticles and their absorption across the Caco-2 cell monolayer model (Bolat et al. 2020).

The two main alkaloids taken from black pepper (Piper nigrum) are piperine and piperidine. Piperidine is a heterocyclic component with the chemical formula (CH2)5NH. These two chemicals have been found to have a variety of medicinal qualities, including the ability to fight cancer. Breast, ovarian, gastric, glioma, lung, oral squamous, chronic pancreatitis, prostate, rectal, cervical, and leukaemia cancers are just a few of the malignancies that piperine has the ability to treat. Whereas, when used alone or in combination with other cutting-edge medications, piperidine functions as a possible clinical agent against cancers like breast, prostate, colon, lung, and ovarian cancer. Numerous important signalling pathways, including STAT-3, NF-B, PI3k/At, JNK/p38-MAPK, TGF-ß/SMAD, Smac/DIABLO, and p-IB malignancies, are required for the development of cancers. by these two phytochemicals, are controlled. Both of these phytochemicals help in cell cycle arrest and cell migration inhibition to reduce the ability of cancer cells to survive. The current review emphasises the therapeutic value of piperine and piperidine against various malignancies (Mitra et al. 2022).

The kneading method was used to create the curcumin-piperine in 2-hydroxypropyl-b-cyclodextrin nutraceutical system. X-ray powder diffraction (XRPD), differential scanning calorimetry (DSC), infrared spectroscopy (FT-IR), and nuclear magnetic resonance (NMR) were used to describe interactions between the system's components. The solubility of the curcumin-piperine system, its permeability through biological membranes (gastrointestinal tract, blood-brain barrier), and its antioxidant, antimicrobial, and enzyme inhibitory activities against acetylcholinesterase and butyrylcholinesterase were all improved by the use of hydroxypropyl-b-cyclodextrin as a carrier-solubiliser (Elnaggar et al. 2015).

2. **solid dispersion**

The various functions of piperine (Pip), including its antidepressant and anti-epileptic properties, have received much research. However, Pip's applicability in the therapeutic setting may ultimately be hampered by its limited water solubility and low bioavailability. In this work, a formulation technique was put forth to overcome Pip's low bioavailability and dose splitting problems on its own. To obtain an enhanced and sustained release profile in vitro, matrix pellets (Pip-SR-pellets) made of Pip solid dispersion (Pip-SD) and hydroxyl-propyl-methyl cellulose-K100 were developed with a mixture of excipients that included lactose, MCC, LS-HPC, and CMS-Na, the Pip-SR-pellets were compressed into fast dissolving tablets (FDTs). XRD and a study of the Pip-SD's solubility were used to describe it. Scanning electron microscopy analysis of the cross-sectional morphology of the Pip-FDTs demonstrated that Pip-SR-pellets maintained their structural integrity during compression and were dispersed uniformly within the Pip-FDTs. The Pip-SR-pellets' release profile was very similar to that of the Pip-FDTs. The relative bioavailability of Pip-SR-pellets was shown to be 1.62 times more than that of Pip-SD and 2.70 times higher than that of the pure medication, according to an in vivo pharmacokinetics investigation (Zhu et al. 2020). Different solid dispersion (SD) techniques were used to increase medication solubility. The medication to carrier ratios were as follows for urea, polyethylene glycol 6000 (PEG), and mannitol: 1:2, 1:4, and 1:6 for each substance. As bioavailability boosters, piperine and quercetin (natural P-glycoprotein inhibitors) were utilised. The SDs were prepared in a suspension form and delivered orally during bioavailability studies in a rat model.

Depending on the drug to carrier ratio, all carriers increased drug solubility in water by a factor of 2 to 4. Mannitol-made solid dispersions' release kinetics revealed zero-order drug release. First order drug release kinetics were demonstrated by urea and PEG 6000-based solid dispersions. The change of CDS into an amorphous form in mannitol solid dispersion was confirmed by FTIR analyses, which were supported by release kinetic experiments. When quercetine and piperine were added, the drug's bioavailability in the animals increased by 27 and 68%, respectively (Zulal et al. 2015). The kneading method was used to create the curcumin-piperine in 2-hydroxypropyl-

b-cyclodextrin nutraceutical system. X-ray powder diffraction (XRPD), differential scanning calorimetry (DSC), infrared spectroscopy (FT-IR), and nuclear magnetic resonance (NMR) were used to describe interactions between the system's components. The solubility of the curcumin-piperine system, its permeability through biological membranes (gastrointestinal tract, blood-brain barrier), and its antioxidant, antimicrobial, and enzyme inhibitory activities against acetylcholinesterase and butyrylcholinesterase were all improved by the use of hydroxypropyl-b-cyclodextrin as a carrier-solubiliser (Stasiłowicz et al. 2020).

3-NanoLipospheres-
Cannabidiol (CBD) and 9-tetrahydrocannabinol (THC), two lipophilic phytocannabinoids, are effective treatments for a variety of illnesses. Both compounds only have a 9% oral bioavailability due to their poor water solubility and substantial first pass metabolism in the gastrointestinal system. The Advanced ProNanoLiposphere (PNL) pre-concentrate is a cutting-edge lipid-based Self-Emulsifying Drug Delivery System that we have created. The PNL is made up of emulsifying excipients with GRAS status that are known to decrease Phase I metabolism of lipophilic active substances and boost solubility. Advanced PNLs are PNLs that have a natural enhancer for absorption built in. Natural alkaloids and phenolic compounds, which are these molecules, have been shown to block some phase I and phase II metabolic activities. . Here, we create th0e Advanced-PNL formulations using piperine, curcumin, and resveratrol. We have therefore investigated the impact of these Advanced-PNLs on the oral bioavailability of CBD and THC. The most efficient of the evaluated formulations, CBDpiperine-PNL increased AUC six times more after oral treatment as compared to CBD solution. The same pattern was observed in THC-piperine-PNL pharmacokinetic studies, which led to a 9.3-fold rise in AUC compared to THC solution. For the synchronised delivery of piperine and CBD or THC to the enterocyte site, our Piperine-PNL can be utilised as a platform. This co-localization increases the bioavailability of CBD and THC by influencing the pre-enterocyte and enterocyte stages of the absorption process. The additional increase in CBD and THC absorption caused by piperine's incorporation into PNL is ascribed to piperine's inhibition of Phase I and Phase II metabolism in addition to PNL's inhibition of P-gp and Phase I metabolism. These groundbreaking findings open the door to using the piperine-PNL delivery system for other poorly soluble, highly metabolizable substances that can't currently be given orally (Cherniakov et al. 2017).

4- Nano dispersion
Black pepper contains the naturally occurring alkaloid piperine, which has a wide range of pharmacological properties. The most extensive use of piperine is for improving medication absorption, with evidence to support this claim that it can decrease first pass effect mechanisms. However, papers claiming an apparent action of a metabolic inducer undercut the role of piperine as an absorption enhancer alongside these findings. The purpose of this research is to evaluate the oral absorption of cannabidiol (CBD) following acute piperine dose to that following repeated administration of piperine in a lipid-based formulation. The freely moving rat model was used to assess the preclinical effects of piperine on CBD absorption. The findings of this study showed that the effects of piperine when administered continuously or in a single dosage regimen did not differ significantly. In comparison to the control group without piperine, the oral bioavailability of CBD increased almost 2.5 times in both groups (Izgelov et al. 2020).

5- Inclusion Complexes
The black pepper contains a bitter substance called piperine (PP), which has beneficial biological properties but is almost insoluble in water. The current study's objective was to generate a coground mixture (GM) comprising PP and -cyclodextrin (CD) (molar ratio of PP/CD = 1/1) and then assess the GM's physicochemical composition and solubility of PP. The GM's DSC thermal behaviour indicated that piperine's melting peak was absent. The GM's PXRD profile showed a halo pattern and lacked the expected peaks from PP and CD. The PP/CD combination in solution exhibited a stoichiometric ratio of 1/1 according to Job's plot. The benzene ring (C=C), the methylene groups (CH2), and the ether groups (C-O-C) of PP all had scattering peaks in the GM that were broadened and moved to lower frequencies. In contrast to pure PP and pure CD particles, the GM particles were agglomerated and had a rough surface, according to SEM micrographs. After 15 minutes of dissolution tests, the amount of PP that was dissolved in the GM was significantly higher (approximately 16 times) than it was for pure PP. Moreover, 1 H-1

ISSN 2348 – 8034
Impact Factor- 5.070

H NMR nuclear Overhauser effect spectroscopy was used to determine the interaction between the PP and CD cavities. spectra of NMR (Ezawa et al. 2016).

6- Nano micelles formulation

The primary objectives of this work were to create polysorbate-phospholipid micelles of piperine loaded with azithromycin, investigate the factors that increase piperine's oral bioavailability, and stop bacterial growth. Polysorbate and phospholipid were optimised for the creation of polysorbate-phospholipidpiperine mixed micelles that were drug-loaded. According to these research, the optimal concentration of polysorbate 80 needed for the highest solubilization of piperine was 5.5% w/v. This concentration showed the maximum solubility of piperine and was very similar to the 5.0% w/v CMC value. The highest CMCs of polysorbate 80 and phospholipid, 62.4414 and 83.1122, respectively, were discovered in batch F3. Three final batches were chosen as the best batches, i.e., F2, F3, and F4 (1:10:4, 1:15:4, and 1:20:4, respectively) for final formulation, based on the optimisation of phospholipid and polysorbate 80. The formulation's maximum solubility, or 11.3057 mg/ml in batch F3, was discovered. Using a zeta analyzer, the size of the nanoformulations was discovered to be 0.3396 r.nm. In 0.1 N HCl, the drug release was assessed after 5, 10, 15, 30, and 60 minutes. Phosphate with a 7.4 pH was also added, and the release was assessed after 30, 60, 120, 180, and 240 minutes. The highest drug content was observed in formulation F3, while the highest entrapment efficiency was discovered in formulation F1. The formulation F3 had the greatest medication release. The method of employing azithromycin-loaded phospholipid nanoformulations demonstrated antibacterial activity in the nutrient agar plate. These compositions stop bacteria from growing visibly. It was demonstrated that the concentration of 100 mg/ml produced the largest zone of inhibition. The MIC endpoint was discovered to be 50 mg/ml, which is the formulation concentration at which there is the least amount of visible growth around the dice (Kumari et al. 2020).

The solubility of piperine (PP) in biorelevant media was examined, as well as the effects of its ground mixtures (GMs) and coprecipitates (CPs) on intestinal contractions when formulated in inclusion complexes with -, -, and -cyclodextrins (CDs). Both the CP (PP/CD) and CP (PP/CD) readings from differential scanning calorimetry (DSC) and powder X-ray diffraction (PXRD) indicate the production of inclusion complexes. The integrated intensity ratios of CP (PP/CD) and CP (PP/CD) protons were revealed by nuclear Magnetic Resonance (NMR) analysis to be 1/2 and 1/1, respectively, matching the corresponding molar ratios in the corresponding GM inclusion complexes. The intestinal contraction test demonstrated that the rate of carbachol (CCh) intestinal contraction in the presence of 2.0 105 M PP was equivalent to that in the absence of PP. In contrast, inclusion complexes produced by CP (PP/CD), GM (PP/CD = 1/2), and GM (PP/CD = 1/1) dramatically reduced intestinal contractility at PP 1.0 108 M. There were no discernible differences between CP and GM. The PP/CD inclusion complex was 6–7 times more soluble in the fasted-state-simulated intestinal fluid (FaSSIF, pH 6.5) than was the PP alone. PP formed an inclusion complex that had the effect of reducing intestinal contraction. This finding suggests that PP/CD will work well as an antidiarrheal (Ezawa et al. 2021).

Piperine uses and health benefits-

*Piperine is widely used in modern herbal medicine. It also has a long history of use in primitive medical practices. These are very good sources of relief for chronic diseases like cough, nausea, headache and indigestion. It also has inflammatory properties. Piperine is considered to be very useful in health supplements as it helps in enhancing the bioavailability of some vitamins and minerals (*Derosa et al. 2016*). Piperine is also used to inhibit p-glycoprotein and CYP3A4 enzymes in the human body that helps in metabolism and transport various metabolics throughout the body.it is also used to support a healthy breathing pattern, joint pains and ulcer in the stomach (88).*

Some of the Health Benefits of Piperine Can be Elaborated as Follows:-

*Stress Management: Enzymes such as adrenaline and catecholamines are produced in the body in order to manage stress level in our mind. It has been observed that intake of piperine combined with vitamin C increases the release of these hormones and helps in managing stress level in a much better way (*Park et al. 2020*).*

Weight Management: Studies show that piperine also possesses some thermogenic properties that help increase the basal metabolic rate in the human body and thus helps in weight reduction by cutting down excess fatty cells.

ISSN 2348 – 8034
Impact Factor- 5.070

*Increase Bioavailability: Piperine has a unique property that helps in the assimilation of key nutrients in the human body that includes amino acids, beta carotene, Vitamin B6 and selenium (*Garg et al. 2001*).*

CONCLUSION

The use of herbal medicines has lately been more widespread worldwide due to its therapeutic advantages and absence of side effects when compared to modern drugs. However, despite their amazing in vitro results, many herbal drugs and herbal extracts show decreased or no in vivo efficacy due to their low lipid solubility or improper molecular size, which causes poor absorption and hence poor bioavailability. Innovative drug delivery methods that boost the bioavailability of herbal medication administration systems have been made available by modern technology. Over the past 10 years, various herbal medicines have been successfully adapted for delivery utilising a range of cutting-edge carriers, including liposomes, microspheres, nanoparticles, transferosomes, ethosomes, lipid-based systems, etc. Many herbal compounds, including quercetin, genistein, naringin, sinomenine, piperine, glycyrrhizin, and nitrile glycoside, have been demonstrated to improve bioavailability. The purpose of this study is to present a summary of the several novel drug delivery methods that have been developed to administer drugs (herbal ones) and enhance therapeutic response. Along with studies on enhancing bioavailability and their alleged mechanisms of action, a profile of herbal bioavailability enhancers has also been attempted.

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