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Review Article

Bionanocomposites: Technique towards Enhancement of Solubility, Drug Release and Bioavailability

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ABSTRACT
According to Biopharmaceutical classification system (BCS) of drugs are categorized on the basis of their solubility parameter and rate of dissolution of various drugs with their bioavailability in human body, and it was found that BCS class –II drug has poor aqueous solubility and affects its release, as the aqueous surroundings in GI tract greatly influences the drug release, particularly it affects the bioavailability of drug. The Bionanocomposite is the type of biohybrid materials or biopolymers fused in combination of two or more different compounds by using natural or bio carriers. Bionanocomposite widely used in drug design and development of innovation for various pharmaceutical drugs, new dosage forms and in clinical pharmacology. The present review mainly focusing on the simple and convenient method of preparation of bionanocomposite with the help of Microwave irradiation method by using natural/bio carriers such as acacia, gelatin, cassia and ghatti gum etc. to enhance the solubility of poorly water soluble BCS Class –II Drugs and improved its rate of dissolution for such drug entities which affects the bioavailability. Prepared bionanocomposite can be characterized by Scanning Electron Microscopy, Fourier transform infrared spectroscopy, Differential Scanning Calorimetry, X-Ray Diffraction Studies and transmission Electron Microscopy. Further, this review mainly highlights the application and future prospective use of Bionanocomposite, which will help in formulation of drug with improved bioavailability.

Keywords: Bionanocomposites, BCS Class-II drugs, enhancement of Solubility, optimized drug dissolution and drug release.

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INTRODUCTION
Orally administered drugs get absorbed through gastrointestinal (GI) Membrane by diffusion mechanism. The objective of drug dissolution enhancement is achieved by understanding the drug profile and aqueous nature of (GI) surroundings. It is well-known that one third of the drug population is water insoluble [1]. Sustained release drug delivery system significantly increase interest for researcher. The solid dispersions of Lovastatin formulated by using water soluble carriers and same has been evaluated to improve its solubility and dissolution characteristics, which minimize dosing frequency to improve its stability. The

method adopted for formulating uniform and stable lovastatin solid dispersions with enhanced surface area and dissolution rate by the solvent evaporation method. However, Solid dispersion technology implies to optimize the *in-vitro* and *in-vivo* dissolution properties of poorly water soluble drugs and to control its dissolution rate. Solid dispersion technique reported remarkably enhanced absorption of drugs and formulated in tablets for Sustained release drug delivery system for [2, 3].

An experimental study of drug solubility is not a single event but it provide multiple times along the drug discovery and development process, the assays and their focus varying with the phase. Thus, the physicochemical properties of compounds like pKa, solubility, permeability, stability and lipophilicity. Drugs with poor solubility with high failure risk during discovery and development. From the recent study 40% of new chemical compounds are hydrophobic in nature and solubility of active pharmaceutical ingredients (API) has always been a concern for formulator [4]. Moreover, pharmaceutical solid polymorphism for greater awareness of the effect that polymorphism may have on the bioavailability, manufacturability, and stability of the drug product, there has come regulatory recommendations with regard to polymorphism appearing in both new drug applications, Particularly for oral-solid dosage forms. Since, this provides a perspective of pharmaceutical solid polymorphism in drug development and in regulation [5]. Salt formation are employed for solubility enhancement technique where drug are modified accordingly their properties thus, drug having ionisable functional groups in order to overcome some undesirable characteristic of the parent drug. Around 50%of drug administered as salts. The therapeutic effect of the medicinal substances is often optimized by conversion into a salt form. It can be selected because of low cost of raw materials, ease of crystallization, and percent yield [6].

As in pharmaceutical product development bioavailability and bioequivalence play a central and vital role. The biopharmaceutics based on solubility and permeability utilized in new drug discovery and lead optimization due to the dependence of drug absorption and pharmacokinetics. Biopharmaceutical classification system (BCS) is based on solubility tests for various drugs; they correlate with their bioavailability in human body. It is widely applied in design and development of innovation drugs, new dosage forms (permeability amplifiers), in clinical pharmacology (drug-drug, drug-food interaction) and also by regulation agencies of several countries as the scientific approach, for testing of waiver on bioavailability [7]. Hence, the approach towards the enhancement of solubility, dissolution and bioavailability of such poorly water soluble or practically insoluble drugs can be achieved by converting them into bionanocomposite form by mixing drug entity with natural/ bio carriers and by using Microwave irradiation method.

During the drug development process, the importance is given to its bioavailability and bioequivalence which determines the internal drugabsorption provided by U. S. Food & Drug Administration [8]. BCS is scientifically describing with their three rate limiting steps in oral absorption.

Step 1: From dosage forms to drug release;

Step 2: Maintenance of dissolved state through Gastro-intestinal (GI) tract;

Step 3: Permeation through GI membrane into hepatic circulation.

Drugs administered orally depend on their solubility and tissue permeability can be investigated from its *in-vivo* drug release profile. The drug substance having solubility will not be a governing parameter if the absorption of the drug is permeation rate limited and hence in such cases the *in-vitro* dissolution study can be used to study the bioavailability or bioequivalence of the drugs through *in vitro - in vivo* correlation. The drug in the GI fluid passes freely through the biomembranes at a rate higher than it dissolves or released from the dosage form if the absorption of the drug is dissolution rate limited. The specifically designed *in-vivo* study will be required in such a case, to access the absorption rate, and hence its bioavailability and to demonstrate the bioequivalence ultimately. Such a drug substance is a good candidate for controlled delivery provided they qualify in terms of their pharmacokinetics and pharmacodynamics for controlled release development, also if a drug itself having low solubility and slow dissolution rate, the release will automatically get lower and the dosage form not required an inbuilt release retardation mechanism, rather the absorption will now be governed by the gastric emptying rate. The dosage form must be able to restrain within the absorption window for a sufficient time, so that absorption can take place. In such case, a hydrodynamically balanced (floating) system or a mucoadhesive dosage form will serve the purpose. Hence, the BCS can work as a guiding

tool for the development of various oral drug delivery technologies [9].

Biopharmaceutical classification system:

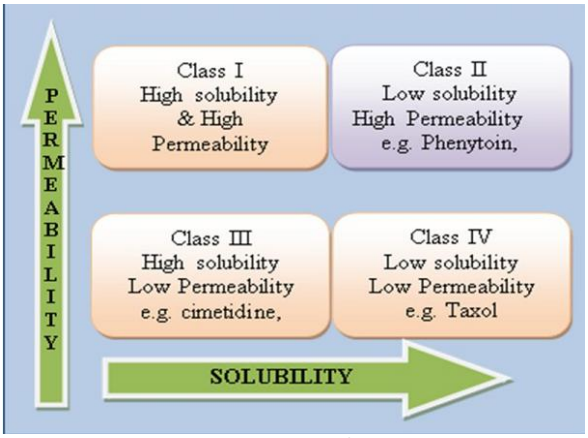

Figure 1: Biopharmaceutical classification system

Class-I drugs: These drugs exhibit a high absorption number and a high dissolution number. The rate limiting step is drug dissolution and if dissolutionis very rapid then gastric emptying rate becomes the rate determining step. e.g. Metoprolol, Verapamil and Propranolol.

Class-II drugs: These drugs have a high absorption number but a low dissolution number. *In- vivo* drug dissolution is then a rate limiting step for absorption except at a very high dose number. *In vitro- In vivo* correlation is usually accepted for class I and class II drugs. e.g. Phenytoin, Mefenamic acid, Danazol and Nifedipine.

Class- III drugs: It involves permeability is rate limiting step for the drug absorption process. These drugs exhibit a high variation in the rate and extent of drug absorption. Since the dissolution is rapid, the variation is attributable to alteration of physiology and membrane permeability rather than the dosage form factors. e.g. Cimetidine, Acyclovir(antiviral), Neomycin B and Captopril.

Class-IV drugs: This class of drug has number of overwhelm for effective in oral administration. These drugs rarely developed and reach to the market. e.g. Taxol

The above classification is based on drug dissolution and absorption model, which help to identify the key parameters controlling drug absorption as a set of dimensionless numbers. The solubility was called as "high" or "low" and the permeability was allotted as "low", "intermediate," or "high". This classification was developed based on the calculated surface area descriptors and on another hand solubility and permeability. Once the solubility and permeability characteristics of the drug are known it becomes an easy criterion for the research scientist to decide upon which drug delivery technology to follow or develop [10].

Thus, from the BCS, most of the drugs belong to class II shows poor solubility in aqueous medium with high membrane permeability. Since, the dissolution of drugs will be the rate-limiting step in drug absorption from the oral solid dosage forms of this class [11]. Due to poor solubility of drugs belongs to class-II category in aqueous medium is big challenge and this overwhelm can be solved by using various solubility enhancement techniques, one of the most formidable aspects of drug development. A significant description of the solubilisation and delivery of insoluble drugs can be found in Liu's monograph [12]. The Noyes–Whitney equation shows factors in dissolution rate with surface area [13]. The Ostwald–Freundlich and Kelvin equations demonstrate that this no longer applies below a particle diameter of approximately 1 mm, remarkably less than 0.1 mm, where the extreme curvature of the particles leads to an increase in dissolution pressure and hence solubility [14, 15]. A particle size reduction technique leads to an increase in surface area and dissolution rate. Nanonization has been used to get a particle size between 100 nm -1000 nm.

Techniques to enhance Solubility [16-18]:

Various Techniques are used to enhance the solubility.

1. Chemical Modifications like Salt Formation, Co-crystallization, Co-solvency, Hydrotropic, Solubilising agent, Nanotechnology.

2. Physical Modifications like Particle size reduction (micronisation, nanosuspension), Modification of the crystal habit, Complexation, Solubilization by surfactants, Drug dispersion in carriers.

The technology used to describe the term as 'solubility enhancing' can be misleading, since although the phenomenon of super-saturation is true, the techniques used do not increase the solubility of insoluble compounds. More accurately, they present the drug in a form which is optimal to its absorption, given its solubility limitations. It is also important to be aware that water solubility also requires the specification of temperature and pH; under certain physiological conditions many important drugs only show aqueous solubility, and reach to the site of absorption[12].

Process of solubilisation: The process of solubilisation involves distinct steps by breaking the inter-ionic or intermolecular bonds in the solute, the separation of the molecules of the

solvent to provide space in the solvent for the solute, interaction between the solvent and the solute molecule or ion[14].

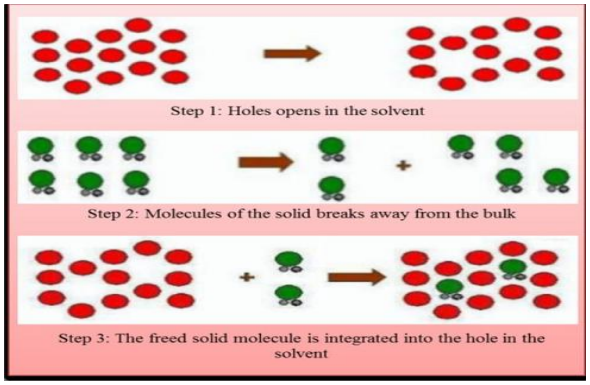

Figure 2: Process of solubilisation

Nanocomposite

A Nanocomposite is a combination of two or more different materials with different properties of each and that are fused, by an effort to blend the best properties of both. A composite consists of two materials of varying natures and combination of those shows improved in their properties greater than that of individual. A physical mixture of drug and Natural or bio carrier in the composite by nanotechnology and their evaluating parameters as drug release profile by *in-vivo* and *in -vitro* and bioavailability in biological system hence termed Bionanocomposite [19].

Nanocomposites majorly classified on the basis of microstructure into three types:

(a) Nanolayered composite
(b) Nanofilamentary composites
(c) Nanoparticulates composites

Classification of Nanocomposites: On the basis of structure nanocomposite can be classified as follows.

A) Non polymer based nanocomposite:

Metal/Metal Nanocomposite
Metal/Ceramic nanocomposites
Ceramic/Ceramic Nanocomposites

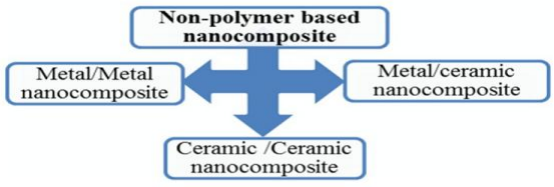

Figure 3: Non-polymer based Nanocomposites

B) Polymer based nanocomposite:

Polymer/ceramic nanocomposite
Inorganic/ Organic polymer nanocomposites
Polymer/ Layered silicate Nanocomposites
Polymer/polymer Nanocomposites
Biocomposites/bionanocomposite

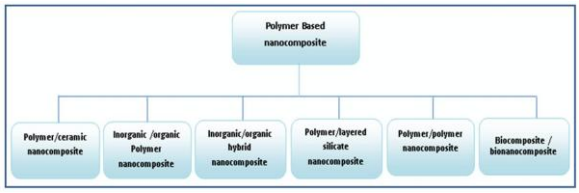

Figure 4: Polymer based Nanocomposite

A physical mixture of drug with natural carriers prepared by simple blending/conversion of drug with carrier in required ratios (drug: carriers) for 10 min. and microwave irradiation method used to prepare Bionanocomposites. This can be applied for various approaches like enhancement of solubility, dissolutions and bioavailability of drug candidates for poorly water soluble drugs.

A main prospective field of research in industries and academia is the preparation to processing of bionanocomposites. Use of natural/bio-carrier in the preparation of bionanocomposite emphasizing wide usage in various filed of research. Among these different methods, melting or Fusion method is one of the simple and efficient method for the solubility enhancement.

Fusion or Melting Method

Fusion or melting method is subjected with main advantages that due to its simplicity and economy, which was proposed to prepare fast release solid dispersion. The physical mixture of a drug and a water-soluble carrier heated directly until it melts. The melted mixture then cooled and solidified rapidly in an ace bath under rigorous stirring. The final solid mass crushed, pulverized, and sieved. The melting point of binary system is dependent upon its composition, i.e., the selection of the carrier and the weight fraction of the drug in the system.

The formulation of nanosized particles could be useful to BCS class II drugs to enhance and improve their solubility, dissolution rate and ultimately bioavailability [11,20]. Nanonisation is beneficial not only due to the increase in Active pharmaceutical ingredients (API) dissolution but also the increase in saturation solubility. There are plentiful techniques to decrease the drug powder particle size to the nanoscale, pearl milling, nanocrystallisation [11], jet milling, nano-precipitation, high-pressure homogenization and supercritical fluid technology [11, 20,21]. Frequent stabilising techniques have been utilised for stabilizing nanoparticles, including an addition of one or more stabilizing materials[22, 23], ionic or steric stabilisation of hydrophobic drugs and polymeric stabilizers in wet combination[24]. From analysis of state-of-the-art techniques, it emerges that the

latest and most effective approaches to the solubilisation of water insoluble drugs are based on generating a drug dispersion (at molecular and/or nanoscale level) in a stabilizing media, preferably in solid-state form[25]. Bionanocomposites form a fascinating interdisciplinary area that brings together biology, materials science, and nanotechnology. New bionanocomposites are impacting diverse areas, in particular, biomedical science. The extraordinary versatility of these new materials springs from the large selection of biopolymers and fillers available to researchers. Existing biopolymers include, but are not limited to, polysaccharides, aliphatic polyesters, polypeptides and proteins, and polynucleic acids; whereas fillers include clays, hydroxyapatite, and metal nanoparticles. The interaction between filler components of nanocomposites at the nanometer scale enables them to act as molecular bridges in the polymer matrix. This is the basis for enhanced mechanical properties of the nanocomposite as compared to conventional microcomposites. Bionanocomposites add a new dimension to these enhanced properties in that they are biocompatible and/or biodegradable materials. BNCs prepared by use of microwave irradiation, which is a green and effective instrument for generating solid dispersions.

Microwave-Assisted Synthesis

The electromagnetic irradiation spectrum of Microwave irradiation (0.3–300 GHz) is lies between the IR and radio frequencies with correspond to wavelengths of 1 cm - 1 m. Microwave techniques were useful technique into the pharmaceutical field for various approaches like as tablets, agglomerates, formation of gel beads, nanomatrix, microspheres, film coats, and solid dispersions [18].

Microwave frequency: Microwave heating refers the use of electromagnetic waves ranges from 0.01m to 1m wave length of certain frequency to generate heat in the material. These microwaves lie in the region of the electromagnetic spectrum between mm wave and radio wave i.e. between IR and radio wave and they are defined as those waves with wavelengths between 0.01m to 1m, corresponding to frequency of 30GHz to 0.3GHz.

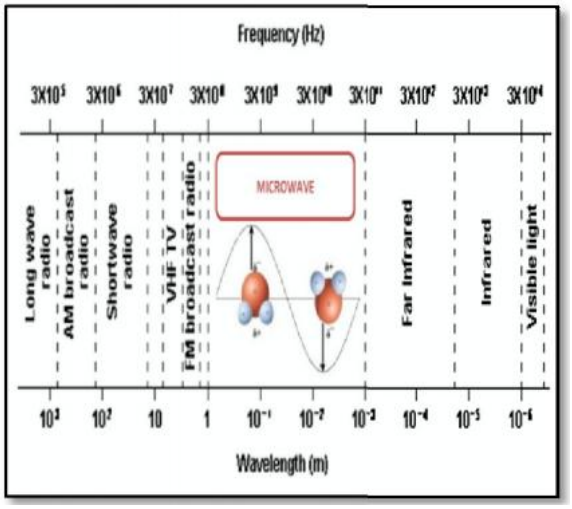

Figure 5: Microwave Frequency Region

Microwaves can be directly transformed into heat within the material. Therefore, it is capable to achieve uniform and rapid heating even in materials with low heat conductivity, such as polymers, because the transfer of energy does not depend on heat diffusion. This is very significant in the preparation of drug formulations because many excipients are polymers. This mechanism is employed extensively for making drug–polymer interaction, polymeric cross-linkages as well as structural modification of drug crystals via its effects of heating.

The technique offers simple, fast, economic, and efficient. Recently microwave assisted synthesis has emerged as new tool in particle size reduction and dissolution enhancement. Due to its ability to couple directly with the reaction molecule and by passing thermal conductivity leading to a rapid rise in the temperature, microwave irradiation has been used to improve many organic syntheses.

The basic principle behind the heating in microwave oven is due to the interaction of charged particle of the reaction material with electromagnetic wavelength of particular frequency. The phenomena of producing heat by electromagnetic irradiation are ether by collision or by conduction, sometime by both. All the wave energy changes its polarity from positive to negative with each cycle of the wave. This cause rapid orientation and reorientation of molecule, which cause heating by collision. The Difference between Conventional and Microwave assisted heating andenergy transfer comparison were reported in Table 1 and Fig. 6 respectively.

Sr. No.	Conventional Heating	Microwave assisted heating
1	Reaction mixture heating proceeds from a surface usually inside surface of reaction vessels	Reaction mixture heating proceeds directly inside mixture
2	The vessel should make physical contact with surface source which is at a higher temperature.	No need of physical contact of reaction with the higher temperature source.
3	Heating take place by electric or thermal source	Heating take place by electromagnetic wave
4	Heating mechanism – Conduction	Heating mechanism - dielectric polarization & conduction
5	Uniform heat applied to All the compound in mixture	Heating to Specific component can be possible
6	Heating rate is less	Heating rate is several fold high

Table 1: Difference between Conventional Heating and Microwave assisted heating

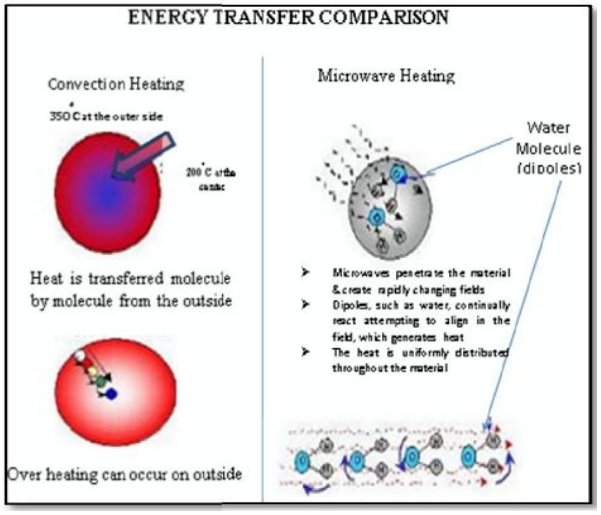

Figure 6: Energy Heat Transfer

Advantages of Microwave assisted synthesis:

Rapid volumetric heating
No overheating at the surface
Energy savings and Addressable heating
Higher yields and shorter preparation times
Lower operating costs
Small Narrow particle size distribution
High Purity

Mechanism of Microwave assisted synthesis:

Heating Mechanism: The mixture may be treated with high frequency electromagnetic waves. The heating starts from the interaction of electric field of the wave and charged particle in the mixture. Two basic principle mechanisms involve in the heating of mixture of drug and natural / bio carrier.

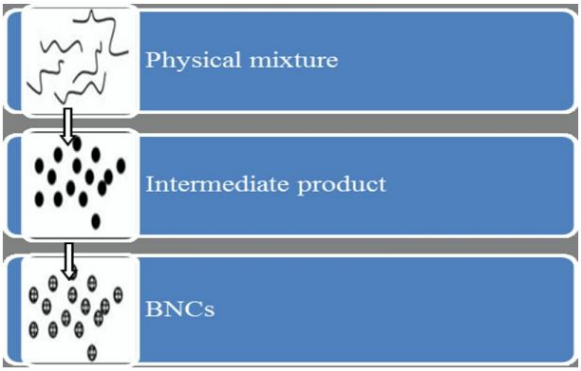

Figure 7: Mechanism of Microwave Assisted Synthesis

Dipolar Polarisation: Dipolar polarisation is a technique by which heat is generated between polar molecules. On exposure to the high electromagnetic field of appropriate frequency, polar molecules try to follow the field and orient themselves in phase with the field. The random motion of particles and random interaction generates heat. Microwave radiation has the appropriate frequency (0.3-30 GHz) to oscillate polar particles and enable enough inter-particle interaction.

Interfacial Polarization: This mechanism is important for system where a dielectric material is not homogenous, but consists of conducting inclusion of one dielectric in other.

Conduction mechanism: The mechanism generates heat through resistance to an electric current. The oscillating electromagnetic field produces an oscillation of electrons or ions in a conductor, resulting in an electric current. This current faces internal resistance, which heats the conductor.

Use of Natural Carriers in BNCs:

Biopolymers have used as drug carrier substrates in the past with several studies examining materials, such as sodium alginate, chitosan and gelatin results into formation of three-dimensional (3D) structure. Carbohydrate polymers are widely used in recent years in pharmaceutical and biomedical applications due to their biocompatibility and biodegradability. The polysaccharides represent one of the most abundant industrial raw materials and have been the subject of intensive research due to their sustainability, biodegradability and bio-safety. Different types of natural–origin carriers, especially proteins and polysaccharides (the systems more inspired on the extracellular matrix) that are being used in research, or might be potentially useful as carriers systems for active API as well as biomolecules with application in the solubility enhancement field and targeting several biological tissues. The combination of both applications into a single

material has proven to be very challenging though.

The earliest exclusive approach towards formation of nanocomposites was done by Kerc *et. al*. used silicon dioxide as the substrate for adsorption of drug, however, recrystallization of the drug was encountered as major problem due to the high mobility of drug molecules on inorganic surfaces[17]. Replacement of the inorganic surface with inert 3D matrixes (cyclodextrin and crospovidone), that possess suitable microstructural properties for preventing recrystallization of the drug[11]. The use of natural carriers in solubility and dissolution enhancement is a pioneering concept. Use of natural carriers as a composite material for incorporating drug in the nanocrystalline form with the help of microwave-induced diffusion (MIND), which is a green and effective way of generating nanocomposites. The carriers for BNCs are gelatin, acacia gum, cassia gum and ghatti gum or some other reported polymer. These carriers are selected on the basis of their wetting and good surfactant properties, which additionally support the enhancement of solubility and dissolution and ultimately bioavailability. Gelatin is a natural protein carrier that has a good dielectric property, the remaining carriers are carbohydrates, which also have good dielectric properties, indicating excellent efficacy of molecular heat transfer required for MIND.

Characterization of carriers:

Swelling characteristics:

Swelling index (SI) was expressed as a percentage and calculated according to the following equation:

$$\%\ Swelling = \frac{Xt - X0}{X0} \text{ X } 100$$

Where, *X*0 is the initial height of the powder in the graduated cylinder and *Xt* denotes the height occupied by swollen gum after 24 hours [17].

Viscosity determination:

The viscosity of the carrier dispersions is measured by viscometer using spindle 3 at 100 rpm [17].

Foaming index:

The foaming index of the carrier is measured to establish their surfactant properties. The foaming index can be calculated by the following equation:

$$Foaming\ Index = Vf - Vi$$

Where, Vf is the volume of 1% w/v solution of carrier after shaking and Vi is the volume of 1% w/v solution of carrier before shaking.

Preparation of physical mixtures for bionanocomposite:

A physical mixture of drug with natural carriers prepared by simple blending of drug with carrier in required ratios (drug: carriers) for 10 min.

Preparation of Bionanocomposites (BNCs):

For each sample, a physical mixture of API and natural carrier was made by uniform mixing. The weight-to-weight (w/w) ratio of drug to the carrier taken as per required by ratios keeping amount of mixture constant. Then 4 ml of water added for each gram of the drug–carrier mixture to make homogeneous slurry (the water added for hydration of the carrier). A fixed amount of the slurry (5 gm) placed in a glass beaker with a Teflon stirrer (transparent to microwaves) and treated with microwave irradiation for different times at power of 560 W. The temperature of the mixture at the end of treatment recorded using an inbuilt temperature measurement probe. The samples then ground in a glass mortar and sieved to achieve a particle size of 80–250 mm.

Evaluation of prepared BNCs:

Drug content analysis:

To identify the amount of drug incorporated in the BNCs, Drug extracted from the BNCs by dissolving them in adequate 25 ml solvent. The 0.2µ membrane filter used to filter the resulting solution. The drug content in the solvent extracts is analyzed by using UV-Visible spectrophotometer at its λmax, against the solvent as blank.

Solubility study:

The solubility of drug and physical mixture determined in pH 6.8 phosphate buffer. The solubility of drug, physical mixtures and BNCs determined by taking an excess amount of drug (30 mg) and BNCs (equivalent to 30 mg of drug) and adding them to 10 ml of solvent (pH 6.8 buffer), in Teflon-facing screw-capped vials. The samples were kept at equilibrium for a period of 48 h on an orbital shaking at 37- 0.5°C and 50 rpm. The supernatant fraction collected from the vials was filtered through a 0.2µ membrane filter and analyzed by UV-Visible spectrophotometer at a λmax. Ratio optimization (drug: carrier) done on the basis of the best solubility results obtained.

Powder dissolution test:

The powder dissolution test performed on BNCs following the USP XXIV Apparatus 2 (paddle) method in 900 ml of dissolution media maintained at 37± 0.5°C at. Powder containing 5 mg. API was added to dissolution media. All experiments were carried out in 3 steps. Dissolution profiles of BNCs were compared

with that of the pure drug at the same experimental conditions.

Drug dissolution kinetics:

To describe and explain drug dissolution rates, various mathematical models were useful. Efficacy of these models relies on the nature of the dosage unit.

Characterization of Bionanocomposites:

From the results obtained by solubility and dissolution studies, the BNCs, which noticed the better results, selected for further characterization.

Fourier-transform infrared spectroscopy:

Fourier-transform infrared (FTIR) spectra of pure API, pure carriers and BNCs of individual API with individual carriers are taken to access interaction, if any, between drug and gum in mixtures. BNCs of drug with each carrier mixed with potassium bromide (KBr) of IR grade in a ratio of 1:100 and compressed using a motorized pellet press at 15 tonnes pressure. The pellets then scanned using an FTIR spectrophotometer. The FTIR spectra of mixtures compared with that of the carriers and pure API to assess any change in the principal peaks of spectra of pure drug and carrier.

Differential scanning calorimetry:

Differential scanning calorimetry (DSC) studies of pure drug and carriers and BNCs of individual drug with individual carriers performed to assess what changes had actually occurred when BNCs formed and by what phenomenon these enhanced drug solubility. Accurately weigh the test sample in aluminium pans, approximately 2–4 mg, based on the drug content in the formulation, and seal. An empty aluminium pan used as a reference. DSC thermograms obtained by differential scanning calorimeter at a heating rate of 10°C/min from 0 to 300°C in nitrogen atmosphere.

X-ray diffraction studies:

X-ray diffraction (XRD) determines the drug and pure carriers. The BNCs of individual drug with individual carriers performed to assess the changes in the crystallinity made when the drug mixed with carriers. XRD patterns can be helpful to record using Philips diffractometer and Cu-ka radiation (l = 1.5418 Å), monochromatised by a secondary flat graphite crystal.

Scanning electron microscopy:

BNCs that showed the best results in the solubility and dissolution studies subjected to scanning electron microscopy (SEM) to investigate to confirm the changes made during the formation of BNCs. Samples prepared by mounting powder onto a brass stub using graphite glue and coated with gold under vacuum before use. Images recorded at the required magnification at an acceleration voltage of 10 kv using a scanning electron microscope.

Transmission electron microscopy:

The optimized ratio of BNCs showing the best results in the solubility and dissolution studies subjected to transmission electron microscopy (TEM) studies to confirm the formation of nanocrystals embedded in composites. The specimens for TEM mounted on a carbon-coated copper grid made of disc type with a thinned (electron transparency) central area of size 3 mm. The images obtained by using a PHILIPS CM200 transmission electron microscope at operating voltages 20–200 kv with a resolution of 2.4 A°.

Applications of Bionanocomposite:

Pharmaceutical Application:

Most of the drugs available in the market are having better permeability and therapeutic effect but due to its poor solubility or insolubility in aqueous medium affects the dissolution and its absorption in GI tract. The aqueous medium is available in GI tract and due to the hydrophobic nature of drug have poor solubility in such environment which may affect on its dissolutions and bioavailability. To control and overcome this poor solubility or insolubility problem of drug in water, the simple and convenient method has been adapted that is preparation of bionanocomposite by microwave irradiation method. The big challenging for the formulation scientist is regarding the poor aqueous solubility of drugs and thus there is need to subsequent conversion of such drug in bionanocomposite by using natural carriers. The present review revealed the enhancement of solubility and drug dissolution of poorly soluble drugs.

The effort taken towards the solubility enhancement were reported for Meloxicam which is poorly water soluble drug, its enhanced solubility and dissolution by various solid dispersion techniques using poloxamer 188 investigated the effect of different techniques of preparation of solid dispersion on *in-vitro* dissolution of meloxicam, by preparing solid dispersions by two methods namely, hot melt method and microwave assisted method. The best – fit model indicating the mechanism of dissolution from the formulation showing the highest release for was found to be Higuchi matrix release. The microwave assisted method was found to be better solubility than melting method for preparing solid dispersions. [26]

Bionanocomposite useful in Target-specific delivery, as it enhances the bioavailability of drug and also useful in development of biomedical science from the study many drugs are used for pharmacotherapy, while having a beneficial action, and also exhibit side-effects that may limit their clinical application. Therefore, there has been a long desire to achieve safe and selective delivery of drugs to target areas in the body in order to maximize the therapeutic potential and minimize the undesired side-effects. NSAIDs are categorized depending on the chemical structure including: Salicylatic acid derivatives e.g. aspirin, Fenamic acid derivatives e.g. Flufenamic acid, Acetic acid derivatives e.g. Sulindac and Propionic acid derivatives e.g. Naproxen, Flurbiprofen, Suprofen, and Indoprofen. NSAIDs drugs have analgesic and antipyretic effects and act as anti-inflammatory effects in high doses. NSAIDs act by interfere with cyclooxyganase enzyme and by controlling the production of prostaglandins responsible for inflammation and pain. Though, prostaglandins have other vital functions such as it protect the stomach from indigestion and ulcers, thus NSAIDs can have undesirable side effects in the gastrointestinal track and in some cases in the cardiovascular system. For the same bionanocomposite prepared to improve the solubility and target specific action studied by the hybridization technology.

An additionally, nanocarrier system is used to enhance the bioavailability of drugs at the disease site and especially depending on cellular internalization. The study of versatile nanocomposite formulation system of NSAIDs of the Arylalkanoic acids was carried out in the form where the hybridization technology can be adapted to prepare efficient drug nanocarriers. Hybridized drug-carriers can be made from a variety of organic and inorganic materials including biodegradable polymers and inorganic clays. Thus developments in drug nanotechnology with a great approach, layered double hydroxide (LDH) materials offer some unique advantages, as their medical properties support their different pharmaceutical applications. By the introduction of drug- LDH nanocomposite platform, the delivery system becomes an active participant rather than passive vehicle in the optimization of drug-therapy [27].

Further, the approach employed towards the enhancement of the solubility and improves dissolution for practically insoluble drug Glipizide. Enhanced solubility of practically insoluble drug glipizide and increased its dissolution which was obtained by preparing its bionanocomposites, using microwave-induced diffusion, which shows enhanced bioavailability of glipizide. The use of natural carriers such as gelatin, acacia, cassia and ghatti gum, with the help of microwaves. As the concentration of polymer in the composite increased, the solubility and dissolution of glipizide were enhanced. [21]

Solubility enhancement and improvement of dissolution rate of poorly water soluble raloxifene HCl (RLX) by using microwave induced fusion method were studied and the solubility of RLX was enhanced with increasing concentration of hydroxyl propyl methyl cellulose (HPMC E5 LV). HPMC E5 LV was used as a hydrophilic carrier to enhance the solubility and dissolution rate of RLX. After microwave treatment, the drug and hydrophilic polymer are fused together, and the conversion of drug from the crystalline form into an amorphous form. The mechanism involved in enhancing the solubility and dissolution rate of RLX in SDs attributed to the surfactant and wetting properties of HPMC E5 LV and the formation of molecular dispersions of the drug in the polymer. [28]

The drug release profile must also be improved and optimized as this property is crucial in oral drug bioavailability, particularly for drugs with low gastrointestinal solubility and high permeability. To optimize oral bioavailability of poorly water soluble drug nimodipine (NM), by the influence of modified gum karaya (MGK), in comparison with that of gum karaya (GK). The *in-vitro* release rate of NM from both cogrinding mixtures was significantly higher than that of physical mixtures or pure NM. The *in vivo* study revealed that the bioavailability of NM from pure drug was significantly lower when compared to the cogrinding mixtures. The oral bioavailability was found as NM powder greater than cogrinding mixtures of NM, GK greater than cogrinding mixtures of NM, MGK greater than NM solution.[23].

Furthermore, the use of synthetic polymer HPMCE3LV in the solubility enhancement for poorly aqueous soluble drug simvastatin and cost effective formulation produced. Physical mixture, co-grinding method, spray drying methods compared. Co-grinding method applied for preparation of drug polymer complex and compared with the solubility and dissolution of marketed preparation. The conversion of crystalline state of drug into amorphous state successfully by physically mixing, co-grinding

and spray drying, the drug with polymer, but co-grinding observed the best solubility enhancing capacity. The polymers having surfactant activity that enhances the solubility and dissolution rate of drug [29].

Biomedical application of Nanocomposite Hydrogels:

Nanocomposite Hydrogels stimulate native tissue microenvironment due to their porous and hydrated molecular structure. An emerging approach to reinforce polymeric hydrogels and to include multiple functionalities focuses on incorporating nanoparticles within the hydrogel network. A wide range of nanoparticles, such as carbon-based, polymeric, ceramic, and metallic nanomaterials can be integrated within the hydrogel networks to obtain nanocomposites with superior properties and tailored functionality. Nanocomposite hydrogels can be engineered to possess superior physical, chemical, electrical and biological properties. Such study focused on the most recent developments in the field of nanocomposite hydrogels with emphasis on biomedical and pharmaceutical applications [30]. Engineering complex tissues that can mimic native tissue functions hold enormous promise in treating organ failures resulting from injuries, aging, and diseases [31, 32].

A variety of nanoparticles such as carbon-based nanomaterials (carbon nanotubes (CNTs), graphene, nanodiamonds), polymeric nanoparticles (polymer nanoparticles, dendrimers, hyperbranched polyesters), inorganic/ceramic nanoparticles (silica, silicates, calcium phosphate), and metal/metal-oxide nanoparticles (gold, silver, iron-oxide) are combined with the polymeric network to obtain nanocomposite hydrogels.

Nanocomposite Hydrogels from Carbon-Based Nanomaterials:

Carbon-based nanomaterials such as CNTs and graphene are mainly used to incorporate multi functionality such as high mechanical, electrical conductivity, and optical properties to the synthetic or natural polymers [33]. Both CNTs- or graphene-based nanocomposite hydrogels are evaluated for applications such as actuators, conductive tapes, biosensors, tissue engineering scaffolds, drug delivery systems, and biomedical devices [34, 35]. The hydrophobic nature of CNTs shows problem in limited interaction with hydrophilic polymers. Other strategies implemented to enhance the solubility of the CNTs in aqueous solutions include the use of single-stranded DNA (ssDNA), proteins, and surfactants to modify the surface properties. Due to their high electrical conductivity, nanocomposites reinforced with CNTs can be used to engineer a range of electrically conductive tissues such as nerve, muscle, and cardiac tissues. Engineered cardiac tissues when released from the substrate spontaneously actuated and moved within a fluid environment due to the cyclical contraction of the cells.

Nanocomposite Hydrogels from Metal and Metal-Oxide:

Nanocomposite hydrogels containing metal or metal-oxide nanoparticles are extensively employed as imaging agents, drug delivery systems, conductive scaffolds, switchable electronics, actuators, and sensors [36].

However, new fabrication technologies will also be devised to recapitulate cellular microenvironment of native tissues within the nanocomposite hydrogels. Some following applications of nanocomposites have been growing at a rapid rate.

Drug delivery systems

Anti-corrosion barrier coatings

UV Protection gels

Lubricants and scratch free paint

New fire retardant materials

New scratch/abrasion resists materials

Superior strength fibers and films

Furthermore, bionanocomposite were investigated the functions of polymers and size of nanoparticles on the antibacterial activity of silver bionanocomposites (Ag BNCs). The silver nanoparticles (Ag NPs) were incorporated into biodegradable polymers that are chitosan, gelatin and both polymers via chemical reduction method in solvent in order to produce Ag BNCs.

The antibacterial activity of different sizes of silver nanoparticles was investigated against Gram-positive and Gram-negative bacteria by the disk diffusion method using Mueller-Hinton Agar.

The silver BNCs were studied as a function of the polymer weight ratio in relation to the use of chitosan and gelatin. The morphology of the Ag BNCs films and the distribution of the Ag NPs were also characterized, the diameters of the Ag NPs were measured and their size is less than 20 nm. The antibacterial activities of the Ag BNC films were studied against Gram-negative bacteria (E. coli and P. aeruginosa) and Gram-positive (S. aureus and M. luteus) by diffusion method using Muller-Hinton agar. Thus, the antibacterial activity of Ag NPs with size less than 20 nm was demonstrated and shown positive response against Gram-negative and

Gram-positive bacteria. The Ag NPs stabilized well in the polymers matrix. Silver nanoparticles (Ag NPs) have attracted intensive research interest for centuries because of their important biological applications especially in bactericidal effect which is the capability of killing about 650 types of diseases causing microorganisms [37]. It has a significant potential for preventing infections, healing wounds [38] and anti-inflammatory.

The repetitive Gly-Pro-Ala sequence in gelatin peptides' structure was reported to the antioxidative, antihypertensive as well as increasing calcium bioavailability is the reason of its wide research in bone engineering field [39]. Unique properties of gelatin which are nontoxicity, biodegradable, biocompatible, and non-immunogenic abilities lead itself capable for biomedical applications, for example in drug delivery as capsules, hydrogel, or microspheres [40]. Chitosan a polysaccharide biopolymer obtained from naturally occurring chitin is an excellent natural polymer due to its nontoxicity, biodegradability, biocompatibility, bioactivity, multifunctional groups and antimicrobial activity. It is mainly being examined in field of agriculture, food packaging industry, bone engineering, artificial skin, biomedical material and drug delivery [41].

Delivery of anticancer drugs:

Presently, there is still a great need for new treatments to eradicate cancer cells while causing much minimal damage to the normal cells. As a step forward in this direction, researchers around the world are taking great effort to incorporate nanotechnology into existing therapeutics and imaging in cancer treatment. Efficient delivery of anti-cancer drugs still stands a big challenge because of lack of specific site targeting and toxic effect of the candidate drug. Besides occurrence of multi drug resistance (MDR) is one of the major obstacle to the success of the tumor's chemotherapy [47,48]. Recently, some reports have shown that anticancer drugs could be readily modified on the biocompatible nanomaterials covalently or non-covalently that could afford the sustained drug delivery for the target cancer cell lines and reduce the relevant toxicity toward normal cells and tissues [49].The prepared biodegradable Poly (lactic acid)/ gold [PLA/Au] nanpcomposites by facilitating the uptake of anticancer drug in target cells. Studies revealed that daunorubicin fused with PLA/Au nanocomposites have a synergistic effect on the drug uptake in cancer cells and used in multidrug-resistant leukemia. From the specific nanostructure of the PLA nanofibers and the relevant nanocomposites used for the anticancer drug daunorubicin could be self-assembled on the surface of the newer PLA/Au nanocomposites and thus apply new promising carrier for nano-medicine in cancer treatment [50].

Application of Microwave:

The main and highlighted uses of Microwave are in the kitchen, packaged good, also have an enormous potential in pharmaceutical manufacturing. Microwave technology has a great excellence and use in pharmaceutical industry. A revolutionary microwave processing technology using 915 MHz microwave energy has been approved by USFDA. Being focused to pharmaceutical industries, the microwave heating has been used now-a-days in applications of Drying, Thawing, Sterilization, Drug Extraction, Chemical Synthesis, Hydro distillation etc. Its applications have been found to be extended in Preparation of Solid Dispersions, Coating of Tablets, Drying of Granules, Semisolid Formulations like Ointments, Cream, lotions etc. In today's competitive era microwave is one of the major tool for the rapid lead generation and optimization through which medicinal chemist will be able to deliver critically needed new chemical entities and candidate drug. The use of microwave open new route to control the physiochemical properties and drug delivery profiles of pharmaceutical dosage forms [51]. This review article is an attempt to reveal the involvement of application of microwave technology in the pharmaceutical process as well as pharmaceutical dosage form

Recently, Microwave widely used in pharmaceuticals and to prepare pharmaceutical dosage forms such as agglomerates, gel beads, microspheres, nanomatrix, solid dispersion, tablets and film coat. The microwave could induce drying, polymeric crosslinkages as well as drug-polymer interaction, and modify the structure of drug crystallites via its effects of heating or electromagnetic field on the dosage forms. The use of microwave opens a new approach to control the physicochemical properties and drug delivery profiles of pharmaceutical dosage forms without the need for excessive heat, lengthy process or toxic reactants. Alternatively, the microwave can be utilized to process excipients prior to their use in the formulation of drug delivery systems. The intended release characteristics of drugs in dosage forms can be met through modifying the

physicochemical properties of excipients using the microwave [18].

Further, the use of microwave mainly in microbiological, biomedical, analytical and drug discovery has been investigated. In present decade, the microwave has been utilized to process dosage forms such as polymeric gel beads, microspheres, nanomatrix, agglomerates, tablet, film coat and solid dispersion.

CONCLUSION:

Use of Microwave technology has been revealed by its tremendous application in the pharmaceutical industry. Further, this review focusing on evolution and acceptance are succeeding at developing rate for BCS class II drugs. The modern microwave preparation systems are all equipped with the necessary safety measures to ensure completely safe processing for both operator and products like BNCs. The preparation of BNCs for the enhancement of solubility of BCS class II drugs by using natural carrier will embed significant application, increase of drug dissolution rate ultimately improved bioavailability of such drugs. Microwave technology is now frequently utilized in many academic and industrial laboratories for routine synthetic transformations by using microwave irradiation. Hence, microwave technology utilized in pharmaceutical formulations and processes. Form the above discussed applications the BNCs are mainly useful for the solubility enhancing, increase drug dissolution and improved bioavailability of poorly water soluble drug.

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