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A Review on Nanohybrids: Technique for Solubility Enhancement of Poorly Water Soluble Drugs

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ABSTRACT

In order the drug bioavailable in human body must absorb it, and in oral treatments absorption takes place, after drug dissolution by diffusion of the molecules through gastrointestinal membranes. It was found that BCS class –II drug has poor aqueous solubility in GI tract greatly influences the drug release; particularly it affects the bioavailability of drug. Solubilization of water insoluble drug is a big issue of pharmaceutical research. Nanohybrids are 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. In nanohybrids there is use of natural and synthetic polymers. The present review mainly focusing on the simple and convenient method of preparation of nanohybrids with the help of Microwave irradiation Method by using natural/synthetic carriers such as acacia, gelatin, cassia, ghatti gum, and HPMC, MC 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 nanohybrids 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 nanohybrids, which will help in formulation of drug with improved bioavailability.

Keywords: BCS Class II, Nanohybrids, Solubilization, Enhancement of solubility, Optimized drug dissolution and drug release.

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1. INTRODUCTION

The oral route is the major way of dosing both existing and new drugs. Most of the drugs which administrated by oral route are absorbed by passive diffusion through the gastro-intestinal (GI) cellular membranes. The solubility and permeability are the most important tools for determining the oral bioavailability of specific drugs within the GI tract, which have aqueous environment. According to US pharmacopoeia more than 40% of the drugs are poorly soluble or insoluble in aqueous environments.[1] The enhancement oral bioavailability of poorly water-soluble drugs represent an actual challenge for pharmaceutical research, with the aims of improving drug therapeutic effectiveness as well as creating new market opportunities. The BCS class II drugs are water-insoluble (solubility equal or less than 100 µg of solute per 1 ml of solvent) but have high membrane permeability is only limited by dissolution. The energy-driven step is dissolution of crystalline solid in a process. In general, the kinetics of the process depends on solute, solvent chemical nature, microstructure and on the system conditions. It is possible to show that the dissolution rate of a crystalline drug in a given dissolution environment can be increased by forcing it to assume a microstructure by the theories of dissolution and non-electrolytes solubility characterized in nanoscale (short range) periodicity. The latest and most effective approaches to water-insoluble drugs solubilization are based on generating a drug dispersion (at molecular and/or nanoscale level) in a stabilizing media, preferably in solid-state form. Our main approach is that the enhancing effects of Microwave (MW) heating on mass transport might provide a green, effective instrument for generating such dispersions.

Nanohybrids are 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 hybrid is consists of two materials of varying natures and combination of those shows improved in their properties greater than that of individual. The melting or fusion technique is one of the simple and efficient technique in the preparation of nanohybids or/and bionanocomposites for the solubility and dissolution enhancement. Particle size

reduction provides more surface area for absorption and rapid dissolution. Microwave radiation consists of electromagnetic waves with frequencies between the infrared and radio waves, which is in the range of 0.3–300 GHz.It passes through materials and oscillate their molecules, which generating heat. The ability of microwave to penetrate any substance, which produced the heating a sample at any point at a given time .The first and unique attempt was proposed by Kerk et al in the direction of bioavailability enhancement. The pharmaceutical nanocomposites which prepared by MW processing which was silicon dioxide substrate with isolated molecular clusters which adsorbed on the surface. Nevertheless, it seems that re-crystallization is not definitively inhibited, as drug molecules have high mobility on inorganic surfaces. These approach consisting the replacement of inorganic surface with inert 3D-matrixes that having the suitable microstructure properties to prevent re-crystallization of the drug. The cross-linked polyvinylpirrolidone (Crospovidone) is first chosen matrix which constrains the drug into stable molecular clusters and/or nanocrystals by its 3D network. The other matrix like cyclodextrin, is a torus-shaped molecule that forms molecular complexes with the drug. [2]

2. Biopharmaceutical classification system [3,4]

Class I - High Permeability, High Solubility:

These drugs are having high absorption number and high dissolution number. The rate limiting step is drug dissolution and if dissolution is very rapid then gastric emptying rate becomes the rate limiting step. e.g. metoprolol

Class II – High Permeability, Low Solubility:

These drugs have a high absorption number and a low dissolution number. In vivo drug dissolution is then a rate limiting step for absorption except at a very high dose number. These drug exhibit changeable bioavailability and need the improvement in dissolution for increasing the bioavailability. These compounds are suitable for design the SR and CR formulations. In vitro- in vivo correlation (IVIVC) is usually projected for class II drugs. e.g. Phenytoin

Class III- High Solubility, Low Permeability:

Permeation throughout the intestinal membrane is the rate-determining step for these drugs. as absorption is permeation rate limited, bioavailability is independent of drug release from the dosage form. These drugs generally show low bioavailability and permeability enhancement is generally essential. These drugs are challenging for controlled release development. e.g.Cimitidine

Class IV- Low Solubility, Low Permeability:

Drugs of this class show poor and unpredictable bioavailability. The overall bioavailability is govern by several factors such as rate of dissolution, intestinal permeability, gastric emptying, and so on. These drugs are generally not appropriate for oral drug delivery or moreover some special drug delivery technologies such as nanosuspensions will be needed

Thus, from the BCS, most of the drugs go 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. 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. The Noyes–Whitney equation shows factors in dissolution rate with surface area. 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 . 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.

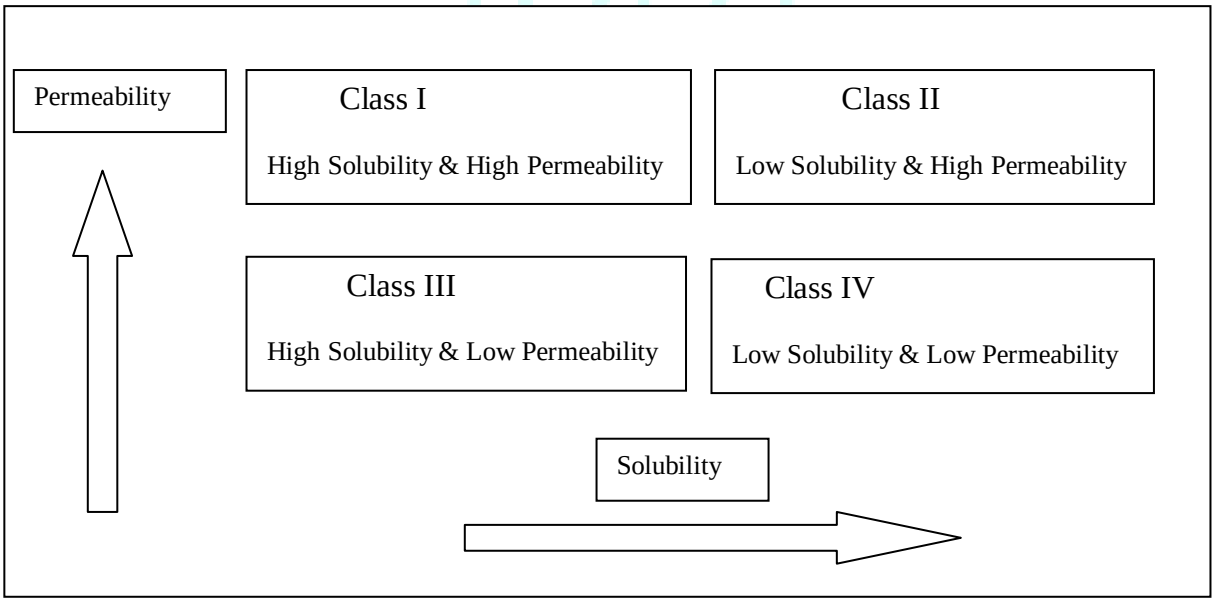

Figure 1: BCS Classification System

3. Technique for solubility enhancement: [5, 6, 7]

1] Physical Modifications.

Particle size reduction like micronization and nanosuspension, alteration in the crystal habit like polymorphs, amorphous form and co crystallization, drug dispersion in carrier like eutectic mixtures, solid dispersions, solid solutions and cryogenic technique.

2] Chemical Modifications.

Adjust of ph; make use of of buffer, derivatization, complexation, and salt formation.

3] Miscellaneous Methods.

Supercritical fluid process, use of adjuvant like surfactant, solubilizers, cosolvency, hydrotrophy, and novel excipients.

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.

3.Mechanism of solubilisation :[8,9,10]

The process of solubilisation involves the

1] Breaking of inter-ionic or intermolecular bonds in the solute

2] The separation of the molecules of the solvent to provide space in the solvent for the solute

3] Interaction between the solvent and the solute molecule or ion.

4. Nanohybrids:

Nanohybrids are 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. Hybrids are 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 / bio and synthetic carrier in the hybrid by nanotechnology and their evaluating parameters as drug release profile by in-vivo and in -vitro and bioavailability in biological system hence termed nanohybrids.[12,13]

4.1 Classification of nanocomposites: [11]

Nanohybrids are subtypes of polymer based nanocomposites

[Inorganic/Organic polymer nanocomposites]

A] Polymer based nanocomposite:

Polymer/ceramic nanocomposite

Inorganic/ Organic hybrid nanocomposites

Polymer/ Layered silicate Nanocomposites

Polymer/polymer Nanocomposites

Biocomposites/ bionanocomposite

B] Non polymer based nanocomposite:

Metal/Metal Nanocomposite

Metal/Ceramic nanocomposites

Ceramic/Ceramic Nanocomposites

Inorganic / Organic hybrid nanocomposites:

Hybrid inorganic/organic materials are not just physical mixtures; they can be broadly defined as nanocomposites with organic and inorganic components thoroughly mix. Indeed, hybrids are either homogenous system derived from monomers and miscible organic/inorganic components, or heterogenous systems (nanocomposites) where at least one of the components has the scale of nanometer.

4.2 Method used for solubility enhancement/ preparation of nanocomposites [14]:

A) Solution intercalation

In this system, the bio-polymer or bio-prepolymer, such as starch and protein is added into the solvent which is completely soluble in solvent. The inorganic nano fillers such as silicate platelets are swollen in a solvent such as water, chloroform or toluene. When the biopolymer and solution of swollen nanoparticles are mix, the polymer chains intercalate and move the solvent within the interlayer of the silicate. Upon solvent exclusion the intercalated structure remnants, resulting in a creation of biopolymer/ layered silicate bio-nanocomposite.

B) In situ intercalative polymerization

In this method, the nanoparticle is discrete in a liquid monomer or a monomer solution, so the polymer development can occur between the intercalated sheets. Polymerization can be completed either by heat or radiation, by the diffusion of a suitable initiator, or by an organic initiator or catalyst.

C) Melt intercalation

The melt intercalation technique has become the ordinary method for the preparation of polymer/layered silicate bio-nanocomposites. There are lots of advantages compare with solution intercalation and in situ intercalative polymerization. In this process, the polymer is heated at specific temperature to obtain a molten mass and mixed with nanoparticle. It can be done by the extruder.

D) Template synthesis

In this method, biomolecules, parts and whole cells, microorganisms offer as the template for inorganics which are generate from a precursor. The templating bio organics is in nanosized particle which is entrapped in mesoporous matrix. This technique is highly adaptable. This is a simple and easy procedure and relevant for large scale production. This method mostly required water soluble polymers and the resulting product may be probability of contagion due to side product .

4.3 Microwave assisted synthesis [15, 17]

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.

Microwave frequency:

Microwave heating refers the make use of of electromagnetic waves ranges from 0.01m to 1m wave length of definite frequency to create 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.

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 capacity to couple directly with the reaction molecule and by passing thermal conductivity leading to a fast rise in the temperature, microwave irradiation has been used to progress 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.

Reaction mixture heating proceeds directly inside mixture.

No need of physical contact of reaction with the higher temperature source.

Heating take place by electromagnetic wave

Heating mechanism - dielectric polarization & conduction

Heating to Specific component can be possible.

Heating rate is several folds high.

4.4 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

4.5 Mechanism of microwave assisted synthesis: [16]

A) 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.

B) 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 generate heat. Microwave radiation has the proper frequency (0.3-30 GHz) to oscillate polar particles and allow enough inter-particle interaction.

C) 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.

D) 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.

4.6 Use of natural/synthetic polymers in nanohybrids : [18,19]

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 threedimensional (3D) structure. Carbohydrate polymers are widely used in recent years in pharmaceutical and biomedical applications due to their biocompatibility and biodegradability. The polysaccharides characterize one of the most abundant industrial raw materials and have been the topic of thorough 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. Replacement of the inorganic surface with inert 3D matrixes (cyclodextrin and crospovidone), that possess suitable microstructural properties for preventing recrystallization of the drug. 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. Synthetic Polymer to be used are HPMC, PVP, MC, Polypropylene, Polystyrene etc. because having characteristics such as inert, Thermally stable, high tensile strength and excellent dielectric properties , chemically inert etc.

4.7 Characterization Of Polymers: [20,21]

1] Swelling Characteristics:

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

$$SI = \frac{H_F - H_i}{H_i}$$

Where, X0 is the initial height of the powder in the graduated cylinder and

Xt denotes the height occupied by swollen gum after 24 hours .

2] Viscosity Determination:

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

3] 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 Nanohybrids:

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 Nanohybrids :

For each sample, a physical mixture of API and natural/synthetic 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.

4.8 Evaluation of Prepared Nanohybrids:

A) Drug content analysis:

To identify the amount of drug incorporated in the Nanohybrids, Drug extracted from the nanohybrids 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.

B) Solubility study:

The solubility of drug and physical mixture determined in pH 6.8 phosphate buffer. The solubility of drug, physical mixtures and nanohybrids determined by taking an excess amount of drug (30 mg) and nanohybrids (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.

C) Powder dissolution test:

The powder dissolution test performed on nanohybrids 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 nanohybrids were compared with that of the pure drug at the same experimental conditions.

D) 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.

4.9 Characterisation of Nanohybrids:

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

A) Fourier-transform infrared spectroscopy:

Fourier-transform infrared (FTIR) spectra of pure API, pure carriers and nanohybrids of individual API with individual carriers are taken to access interaction, if any, between drug and gum in mixtures. Nanohybrids 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.

B) Differential scanning calorimetry:

Differential scanning calorimetry (DSC) studies of pure drug and carriers and nanohybrids of individual drug with individual carriers performed to assess what changes had actually occurred when nanohybrids 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.

C) X-ray diffraction studies:

X-ray diffraction (XRD) determines the drug and pure carriers. The nanocomposites 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 magnification at an acceleration voltage of 10 kv using a scanning electron microscope. diffractometer and Cu-ka radiation (l = 1.5418 Å), monochromatised by a secondary flat graphite crystal.

D) Scanning electron microscopy:

nanohybrids 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

E) Transmission electron microscopy:

The optimized ratio of nanohybrids 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°.

5. APPLICATION[14]

1. The nanocomposite materials are also good candidates for catalysts, gas-separation membranes, contact lenses and bioactive implant materials. [21]

2. Bionanocomposites are used in fabrication of scaffolds, implants, diagnostics and biomedical devices and drug-delivery systems. It also used in the cosmetics industries.

3. Ahemad et al (2017), focused on the medical speciality and Cumulative applications of Chitosan centred bionanocomposites. He demonstrated the various schemes for the preparation of chitosan nanocomposites from different functional material, focusing on their application specifically in tissue engineering, drug and gene delivery, wound healing and bio imaging.

4. Selvakumar et al (2015), developed the enriched adhesion of talc/ZnO nanocomposites on cotton fabric assisted by aloe-vera for bio-medical application mostly used on baby diaper. [22]

5. Sajid et al (2012) synthesized and characterized the silica nanocomposites for bone applications. [23]

6. Stodolak et al (2009), studied on nanocomposite fibres and find out its medical applications. She successfully modified the calcium alginate fibres with the nanofiliers which creates an opportunity in tissue regeneration by using the fibres as bioactive materials. [24]

7. Tamayo et al (2016), developed the copper polymer nanocomposites which is excellent and cost effective biocide controllingor inhibiting the growth of microorganisms and preventing foodborne diseases and nosocomial infections. [25]

8. Polymer nanocomposites used in gene delivery for purpose of aanticancer drug delivery, pDNA transfection, siRNA and DOX delivery, CPT drug and report. [26]

9. It is used as actuators in artificial muscle. [27]

10. Kendre et al (2017), developed the Bosentan nanocomposite by using amphiphilic graft co-polymer-carrier which is soluplus to enhanced the solubility, dissolution and bioavailability. He prepared the graft co-polymer-based nanocomposite formulation by using the single-emulsion technique. [28]

11. Kumar et al (2010), prepared and characterized the bio-nanocomposite films based on soy protein isolate and montmorillonite using melt extrusion. These bio-nanocomposite films could potentially be used for packaging of high moisture foods such as fresh fruits and vegetables to replace some of the existing plastics such as low density polyethylene (LDPE) and polyvinylidene chloride (PVDC). [29]

12. Cherian et al (2011), developed the cellulose nanocomposites with the help of nanofibres which is isolated by pineapple leaf fibers. The developed composites were utilized to fabricate various versatile medical implants. Pineapple leaf fibers derived nanocellulose embedded polyurethane has beenutilized as an attractive and readily available range of materials for the fabrication of vascular Prostheses and used for to make heart valves and coronary stent in the cardiovascular system. Bionanocomposites mostly applicable in development of cardiovascular system. [30, 31]

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