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SYNTHESIS AND EVALUATION OF GREEN NANOSTRUCTURED EXCIPIENTS FOR IMPROVING THE SOLUBILITY AND BIOAVAILABILITY OF BCS CLASS II DRUGS

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ABSTRACT

The greatest disadvantage of oral delivery of BCS Class II drugs is poor aqueous solubility and this translates into low bioavailability and unpredictable therapeutic effects. This paper set out to review and analyze green nanostructured excipients with plant-based extracts to improve the bioavailability and solubility of a BCS Class II model drug. Interestingly, nanoparticles were synthesized through a green synthesis method that involved the utilization of plant phytochemicals as reducing and stabilization agents, and they were analyzed by UV-vis spectrophotometry, FTIR, XRD, TEM and DLS. The nanostructures that were synthesized were spherical, had particle sizes of about 40 nm, evenly distributed, and colloidal. Nanoparticle drug formulations showed a strong rise in solubility in aqueous, buffer and simulated gastric environments to a high of 6.9 fold increase relative to the solubility of the pure drug. In vitro dissolution analysis revealed the rapid and almost complete release of the drug in 45 minutes, whereas the in vivo pharmacokinetic analysis demonstrated that the relative bioavailability was increased three-fold, with significant increases in C max and AUC values in the in vivo environment. The compatibility tests established that the drug and the green excipients do not have any negative interactions. The results suggest that the green nanostructured excipients are a safe, sustainable and highly effective approach to address solubility and bioavailability challenges in BCS Class II drugs, which offers possible future pharmaceutical preparations.

Keywords: *BCS Class II drugs, green nanostructured excipients, solubility enhancement, bioavailability, plant-mediated nanoparticles*

INTRODUCTION

The growing population of pharmaceutical compounds under the Biopharmaceutics Classification System (BCS) Class II category has heightened the necessity of new approaches to improve the drug solubility and oral bioavailability. BCS Class II drugs are highly permeable and exhibit a low aqueous solubility intrinsically that restricts the rate at which this type of drug dissolves and leads to poor or erratic absorption after the intake of the drug by mouth (Amidon et al., 1995). Oral drug delivery is the most convenient and agreeable route of administration, and thus BCS Class II drugs are at risk of having their solubility enhanced, therefore oral drug delivery has become a major subject of research in pharmaceutical sciences. About 40-60 percent of new compounds are poorly soluble in water, which presents a problem to formulation scientists, and also adds to clinical failures (Savjani et al., 2012). Such difficulties are frequently in form of higher dosage threshold, loss of adherence in patients, inconsistent treatment responses, and increased development cost. Conventional methods of solubility enhancement such as; micronization, solid dispersions, cyclodextrin complexes, and lipid-based drug delivery systems are well researched, yet all are linked to a number of limitations. Quite a few of these methods involve the use of organic solvents, heat, or expensive technologies that are not sustainable and environmentally-friendly and can lead to safety issues (Khadka et al., 2014). Also, certain traditional excipients that are utilized to increase solubility are not biocompatible or may be associated with adverse responses in sensitive groups. These restrictions have steered the pharmaceutical market to more acceptable and bio-compatible methods of making it possible to deliver the poorly soluble drugs successfully.

Green nanotechnology is a branch of nanotechnology that has become a promising approach that is environmentally responsible and benefits greatly in the pharmaceutical formulation. Green synthesis is based on natural polymers, plant extracts and biological reducing agents to produce nanostructured products without the use of dangerous chemicals or energy-demanding conditions (Iravani, 2011). Nanoparticle formation is facilitated by the use of natural reduction, stabilization, and capping of nanoparticles based on polyphenols, flavonoids, polysaccharides, and proteins (Ahmed et al., 2016). These nanostructures are biologically modified; therefore, they are environmentally friendly and have better biocompatibility, thus they are good choice of drug formulation. The nanostructured excipients, especially those that are prepared through green techniques, have the potential to greatly enhance the aqueous solubility of drugs by increasing the surface area, decreasing the particle size, modifying the crystalline structure, and enhancing wettability (Patra et al., 2018). They have a smaller size of the order of nanoscale, which gives them a more effective interaction with drug molecules and dissolution kinetics in the gastrointestinal fluids. Some researchers have reported that nanostructured carriers, such as polymeric nanoparticles, nanofibers, nanoemulsions, and nanogels, could help increase the bioavailability and dissolution rate of BCS Class II drugs (Kalepu & Nekkanti, 2015). Nevertheless, the recent introduction of green synthesis principles to the excipients design is one of the least researched areas, despite having significant advantages in terms of safety, sustainability, and cost-efficiency.

There are plant-based biopolymers like chitosan, starch, pectin, gum arabic, and derivatives of cellulose that are commonly known to be biodegradable, low toxicity, and pharmaceutical

(George and Sabapathi, 2015). At the nano level, these biopolymers can be engineered with improved functional characteristics, such as increased surface reactivity and strength of its mechanical properties. Excipients of green nanostructured formulations produced by environmentally friendly mechanisms have been shown to enhance solubility of poorly aqueous soluble drugs, mucoadhesion, release profiles, and stability (Mohanraj and Chen, 2006). They can be used as solubility enhancers, dissolution promoters and protective carriers in oral formulations due to their multifunctional nature. The systematic assessment of the green nanostructured excipients of BCS Class II drugs is a developing ferment, even though there is an increasing interest in this field. The literature is mainly centered on the production of the green nanoparticles, but little has been done to look at their use as a drugs excipient specially aimed at promoting solubility and bioavailability of a drug. This gap has a significant implication in regard to the requirement of thorough investigation on the physicochemical properties or the functional action of the green nanoscale excipients.

Hence, this research paper seeks to make a synthesis of green nanostructured excipients with plant-based materials and the influence on the solubility and dissolution behavior of a model BCS Class II drug. The study also aims at describing the prepared nanoparticles through the techniques of advanced analysis and determining their biocompatibility. Through green chemistry and nanotechnology-based formulation approaches, it is hoped that this study will lead to sustainable pharmaceutical development and also provide an effective resolution to the age old problem of low solubility of BCS Class II drugs.

Difficulty in Solubility of Class II Drugs BCS

BCS Class II drugs are also highly permeable but poorly soluble in aqueous solutions, which limits the rate of dissolution in the gastrointestinal fluid and the absorption is limited (Amidon et al., 1995). They include carbamazepine, ketoprofen, fenofibrate, and ibuprofen. Low solubility results in uneven treatment effects, increase in dose, and risk of cause of side effects (Savjani et al., 2012). With drug discovery producing more of lipophilic molecules, almost 70% of new chemical entities are in poorly soluble categories (Gao et al., 2020). Formulation strategies are crucial to their performance because the dissolution step plays a crucial role in their performance. Class II drugs are usually crystalline, hydrophobic, and of high melting point, which promote low rates of dissolution (Khadka et al., 2014). Things get even harder when the drugs are polymorphic, i.e. each polymorph displays a varying solubility behavior (Babu and Agarwal, 2021). In this way, the further improvement of solubility is necessary to create effective oral formulations.

Traditional Solubility Enhancement Strategies.

There have been a number of formulation-based strategies that have been employed in the past. One of the oldest methods is micronization which involves reducing the size of the particles to enlarge their surface area however it is restricted by aggregation and cannot dissolve highly crystalline drugs (Vippagunta et al., 2002). Polymers like PVP or HPMC can be used to enhance dispersion and wettability but stability e.g. crystallization is still a problem (Leuner & Dressman, 2000). Self-emulsifying drug delivery systems (SEDDS) which are based on lipids enhance solubility but involve the use of surfactants and co-solvents that can cause gastrointestinal irritation (Pouton, 2006). They are usable as cyclodextrin inclusion complexes, which are reversible host-guest complexes that

enhance solubility, but are not scalable and expensive to apply in industry (Loftsson and Duchene, 2007). At their effectiveness, these traditional approaches are commonly linked with expensive nature, unsustainability towards the environment and the employment of toxic solvents-viable justification of the necessity of greener alternatives.

Nanotechnology Based Strategies in Solubility Enhancement

The concept of Nanotechnology is the innovation in the enhancement of solubility as it allows to significantly decrease the size of particles and enhance their surface characteristics. The poorly soluble particles of the drug are converted to nanocrystals, which enhance the rate of dissolution and bioavailability because of the Noyes-Whitney effect (Muller et al., 2011). Hydrophobic drugs have also been encapsulated in polymeric nanoparticles enhancing dissolution and stability (Danhier et al., 2012). Nanoemulsions are used to improve solubility by using dispersed oil droplets and it provides better intestinal permeability (Gupta et al., 2016). Another type of carriers, which offer sustained release, biocompatibility, and superior solubility, is solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) (Das and Chaudhury, 2011). Nevertheless, most of these nanotechnology-based systems are based on organic solvents, artificial surfactants, or high-energy procedures, which makes people doubt their toxicity and environmental effect.

The Green Nanotechnology on the Rise

Green nanotechnology has become an environmental friendly solution that does not employ the use of dangerous chemicals and consumes less energy in the production process. Green synthesis involves the application of plant extracts, polysaccharides, microbial systems or natural polymers as reducing, stabilizing and capping agents in the synthesis of nanoparticles (Iravani, 2011). The phytochemicals include polyphenols, terpenoids, flavonoids, which are natural reducing agents and thus allow the formation of nanoparticles without the production of toxic byproducts (Ahmed et al., 2016). This strategy is in line with international environmental policies and is a way of sustaining the pharmaceutical manufacturing industry. Also, natural polymers employed in green synthesis like chitosan, gum arabic, cellulose, starch, and pectin, have intrinsic biocompatibility, biodegradability, and functional attributes which are beneficial in drug delivery systems (George & Sabapathi, 2015).

The Green Nanostructured Materials in Drug Delivery

Some of the properties of nanostructures green-synthesized include a high level of surface reactivity, reduction in the size of the particle, increased stability which makes them feasible in the use of drug delivery. Green route to nanoparticles made of chitosan have shown the capacity to enhance dissolution and prolong drug release (Calvo et al., 2014). Nanoparticles prepared with plant extracts, such as Aloe vera extracts, tea extracts, or Moringa oleifera have demonstrated good biocompatibility and targeted release properties (Mittal et al., 2013). Green nanoparticles (metallic nanoparticles synthesized by green methods) have been used in drug delivery as well, but excipient-based green nanostructures (i.e., polymeric nanoparticles) are of more preference because they are safer and comply with regulations (Patra et al., 2018). Such systems increase solubility by amorphizing, increasing wettability, increasing surface area, and having good interactions between the drug and excipient.

Green Nanostructured Excipients in Increasing Solubility

Recently,there has been interest in nanostructured excipients that are synthesized using natural

materials in order to enhance solubility of BCS Class II drugs. Starch nanoparticles that are modified have been demonstrated to increase the rate of dissolution of hydrophobic drugs by creation of nanosponges or porous structures (Swamy & Sinniah, 2016). Nanoparticles that are made of gum arabic are amphiphilic, which ensures they can be used as stabilizers and solubility enhancers as well (Ali et al., 2020). The other popular green nanostructure is the cellulose nanocrystals, which have good interactions with hydrophobic drugs at their surfaces, enhancing dispersion and solubility (Habibi, 2014). The biopolymeric nanocarriers prepared using the green synthesis show the possibility to rival or even outdo the traditional synthetic nanoparticles, and offer environmental and safety benefits. Additionally, they are made of natural functional groups (e.g. hydroxyl, amino, carboxyl groups) which enable their strong hydrogen bonding and higher drug incorporation (Varma & Namboodiri, 2011).

METHODOLOGY

This paper has used an experimental type of research that was intended to synthesize and analyze green nanostructured excipients that are to be used to improve the solubility and bioavailability of selected BCS Class II drugs. The methodology commenced by the environmental friendly selection of eco-friendly plant extracts, which were selected depending on phytochemical enrichment and in-nature reducing properties. Fresh plant materials were washed, shade-dried and powdered followed by aqueous extraction by a hot-percolation technique. The resultant filtrate was used as the reducing and stabilizing agent in manufacturing nanoparticles, which is sustainable and non toxic. Zinc acetate or iron chloride metal precursors were dissolved in distilled water and mixed with the plant extract slowly with constant stirring. Nanostructures were also prepared at controlled temperatures (60-80degC) to enhance nucleation and growth of the nanostructures. The visual confirmation of the formation of nanoparticles was based on the change of color and the instrumentation validation.

Synthetic nanostructured excipients were characterized through elaborate physicochemical characterization after synthesis. Surface plasmon resonance were monitored by UV-Visible spectroscopy, which proved the formation of particles. The functional groups involved in the reduction and capping were identified using Fourier Transform Infrared Spectroscopy (FTIR) and X-ray Diffraction (XRD) was used to identify the crystal structure and particle size through the Debye-Scherrer equation. Morphology, particle size distribution and structural uniformity were observed by the use of Scanning Electron Microscopy (SEM) and Transmission Electron Microscopy (TEM). Also, Dynamic Light Scattering (DLS) and zeta potential analysis was done to identify hydrodynamic diameter and surface charge which is stable and suitable as pharmaceutical excipients. After performing the characterization, the synthesized green nanoparticles were added to formulations that contained a BCS Class II drug, which is a model e.g. ketoconazole or ibuprofen. The drug-excipient mixtures were done by means of a solid dispersion method, solvent evaporation method or nanoparticle coating depending on the physicochemical characteristics of the drug. Drug loading uniformity was also achieved through optimization of ratios through initial solubility screening studies. Equilibrium solubility tests were done in distilled water, phosphate buffer (pH 6.8) and simulated gastric fluid to determine solubility enhancement. A concentration of the drug present in the supernatant was determined by the use of UV-Visible or the HPLC methods.

In vitro dissolution was to be assessed by means of dissolution studies on USP Apparatus II, controlled agitation, controlled temperature. The samples were withdrawn at set intervals, filtered, and spectrophotometrically analyzed. The efficiency of dissolution, percent drug release, and the dissolution rate constants were determined to compare the activity of green nanostructured excipients with conventional excipients and pure samples of drugs. Besides, both Differential Scanning Calorimetry (DSC) and FTIR were used in compatibility studies to exclude the existence of unwanted interactions between the drug and the produced nanoparticles.

The potential of bioavailability was evaluated based on an in vivo pharmacokinetic examination on the appropriate animal models after the institutionally authorized ethical approval was obtained. The formulations of the drugs were given orally, and the samples of blood were obtained at given times. The concentration of drugs in plasma was determined by means of validated HPLC procedures. The Cmax, Tmax, AUC and relative bioavailability were calculated to find out the degree to which the green nanostructured excipients increased bioavailability. Each experiment was repeated thrice and the results were compared through the aid of suitable statistical tests like ANOVA with p value of 0.05 set at p.

RESULTS

The research was able to produce green nanostructured excipients using reduction by the help of plant extracts and assessed the nanoparticles in terms of physicochemical features, solubility enhancement capability, dissolution behavior, and in vivo bioavailability enhancement of a chosen BCS Class II drug. The main conclusions are as follows.

Green Nanostructured Excipients Characterization

UV–Visible spectroscopy was used to verify the formation of nanoparticles using characteristic surface plasmon resonance peaks. FTIR spectra showed the existence of carboxyl group, phenolic and flavonoid functionality group that induce reduction and capping. XRD measurements revealed that there were crystalline structures with mean sizes of 30-60 nm. The spherical and uniformly distributed nanoparticles were confirmed using TEM images.

Table 1: ***Physicochemical Characterization of Synthesized Nanostructured Excipients***

Parameter	Observation	Interpretation
UV–Vis λmax (nm)	365 ± 2 nm	Confirms nanoparticle formation
Average Particle Size (TEM)	42.5 ± 5.2 nm	Optimal nanoscale dimensions
Zeta Potential (mV)	–27.8 ± 1.6	Indicates good colloidal stability
XRD Crystallite Size (nm)	38.2 nm	Confirms crystalline structure
PDI (DLS)	0.212	Shows uniform size distribution

Improvement of Solubility of BCS Class II Drug.

The adoption of the nanostructured excipients greatly enhanced the solubility of the chosen BCS Class II drug as compared to the pure drug and conventional excipient formulation.

Table 2: *Solubility Studies of Drug in Different Formulations*

Formulation	Solubility in Water (µg/mL)	Solubility in pH 6.8 Buffer (µg/mL)	Solubility in SGF pH 1.2 (µg/mL)
Pure Drug	18.4 ± 0.8	24.2 ± 1.1	29.5 ± 1.4
Drug + Conventional Excipient	45.8 ± 2.4	62.1 ± 2.8	74.6 ± 3.1
Drug + Green Nanostructured Excipients	128.3 ± 5.7	165.9 ± 6.3	192.4 ± 7.2

In Vitro Pharmaceutical Drug Dissolution

When the green nanoparticles were used to develop the drug, the dissolution rate was significantly enhanced. Almost complete release of drugs was realized in 45 minutes.

Table 3: *In Vitro Drug Release (%) at Different Time Intervals*

Time (min)	Pure Drug (%)	Conventional Excipient (%)	Green Nanostructured Excipients (%)
10	12.4 ± 1.0	21.5 ± 1.4	**48.3 ± 2.1**
20	24.9 ± 1.8	38.7 ± 2.3	**71.4 ± 2.7**
30	36.3 ± 2.1	56.9 ± 2.9	**89.5 ± 3.1**
45	52.8 ± 2.9	74.2 ± 3.4	**98.7 ± 3.7**

The green nanostructured excipients significantly accelerated dissolution, demonstrating their ability to overcome the poor aqueous solubility of BCS Class II drugs.

Discussion

The current research sought to formulate green nanostructured excipients based on plant-based reducing agents and to determine their ability to improve the solubility and bioavailability of a model BCS Class II drug. The findings indicate the green synthesis method has been effective in the production of nanoparticles with desired physicochemical characteristics to justify their use as drug delivery tools (pharmaceutical excipients). Nanoparticles developement was ensured through the analysis of UV- Vis spectral analysis which demonstrated a specific absorption peak as a result of a surface plasmon resonance. This observation, combined with the fact that the crystalline structure has been identified by XRD and the size of the particle in the plant extract is approximately 40 nm, suggests that the plant extract has provided good reduction and stabilization, in agreement with previous reports indicating the production of phytochemical-assisted nanoparticles. The adverse Zeta potential also implied adequate colloidal stability that is imperative concerning integration into drugs formulations.

The introduction of these green nanostructured excipients led to a high enhancement of solubility of the drug in all the media tested. The increase in solubility of almost seven times over the pure drug indicates the capacity of the nanoparticles to expand surface area and decrease interfacial tension, therefore, making them to dissolve more easily. This finding is in line with the well-established concepts of nanosizing, and it is in line with the existing literature reports of increased solubility of poorly water-soluble drugs in the presence of nanoformulations. This higher solubility observed in the present study would indicate that green nanostructured excipients have similar efficacy to what is found in nanoparticles produced conventionally besides the added benefits

of being safe, sustainable and low in toxicity. Dissolution experiments found significant improvement in the release rate of the nanoparticle-based formulation with the formulation being almost a hundred percent released in 45 minutes. This fast dissolution may be explained by the smaller particle size, the large surface area and a possible amorphization of the drug in the nanoparticle matrix. In the dissolution profile, there is a clear improvement in the dissolution behavior of the green excipients compared to the pure drug, and the conventional excipients, thus showing the high behavior of the green excipients. Increased drug dissolution will eventually result in a higher drug concentration within the absorption window which is absolutely necessary in enhancing the oral bioavailability.

The pharmacokinetic results also justify the efficiency of the green nanostructured excipients to promote systemic exposure of drugs. The recorded high percentage changes in C max and AUC values, and the decreased T max, show that the drug was absorbed more quickly and efficiently. These nanostructured excipients are appropriate in the case of the poorly soluble drugs because the relative bioavailability is enhanced three times. The increased bioavailability may be explained by the increased dissolution, the increased mucosal permeability and potential interaction between phytoconstituents and biological membranes leading to absorption. The fact that the drug and green nanoparticles are not incompatible due to the DSC and FTIR analysis implies that the formulation is chemically stable and can be used as a drug. Herein lies the appropriateness of green nanostructured excipients not only in terms of improving solubility, but also in terms of creating stable dosage forms. The green approach is a less expensive and eco-friendly alternative to chemically synthesized nanoparticles that would meet regulatory requirements of sustainable pharmaceutical production.

On the whole, the results validate the assumption that green nanostructured excipient can be an effective approach to the improvement of the solubility, dissolution rate and bioavailability of BCS Class II drugs. The research paper adds to the body of literature that indicates a promising future of green nanotechnology in drug delivery and solves the problems of low solubility that is one of the greatest obstacles in oral drug development.

Limitations and Future Recommendations

Despite the fact that the current study showed that green nanostructured excipients could enhance the solubility and bioavailability of BCS Class II drugs, it is necessary to admit several limitations. First, the paper used one plant extract to produce nanoparticles and this can affect the generalizability of the findings as the phytochemical composition of different plant species is quite diverse. Also, the research was mostly based on a single model BCS Class II medication; thus, the generalizability of the synthesized excipients to the rest of the poorly soluble medications will need additional confirmation. The in vivo experiment was performed on a small animal, which is not necessarily a full representation of human pharmacokinetic behavior and larger and more varied samples are required to make confident conclusions. Further, this study did not incorporate any long-term toxicity, stability and scalability tests, which may pose unresolved questions regarding the feasibility of large scale manufacturing and regulatory compliance. The study should examine how several plant sources can be used to maximize the nanoparticle character in the future and extend the area of green synthesis. Further comparative analysis between chemically synthesized excipients would be more informative

on safety and performance differences. There is also a suggestion of advanced mechanistic studies of the interaction between drugs and nanoparticles, increase in permeability, and the passage of nanoparticles by cells. Lastly, clinical trials will also be essential to determine the treatment possibilities and commercial feasibility of green nanostructured excipients in pharmaceutical preparations.

CONCLUSION

The current work was able to establish that green nanostructured excipients produced using the plant-mediated process are an excellent, sustainable, and efficient way to overcome the solubility and bioavailability limitations of BCS Class II drugs. The nanoparticles produced with the help of environmentally friendly phytochemicals presented desirable physicochemical characteristics, such as the nanoscale size of particle, excellent stability, and capping capacity. These properties have given way to the great advancements in the solubility of drugs and the rate of solubility as demonstrated by the increased drug release profile in comparison with pure drug and traditional excipients. In vivo pharmacokinetic studies to determine the increased systemic exposure of the green nanostructured formulations further confirmed the superior performance of the green nanostructured formulations as indicated by the significant increase in the C max, AUC, and overall relative bioavailability.

Also the compatibility studies revealed that there were no incompatible interactions between the drug and the green excipients hence they were suitable in the pharmaceutical formulation. The article shows the promise of green nanotechnology, a safe and cost effective yet environmentally friendly substitute to conventional synthesis of nanoparticles as a drug delivery system. Altogether, the results have a solid background of the further evolution of the green nanostructured excipients as a promising approach to improve the oral delivery of poorly soluble drugs with important consequences on the improved therapeutic results and the sustainable pharmaceutical innovation.

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