RESEARCH ARTICLE

Formulation and Characterization of Glibenclamide Nanoparticles as an Oral Film

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ABSTRACT
Glibenclamide (GLB), which belongs to Class-II (BCS), has poor oral bioavailability attributable to its insufficient aqueous solubility. The study’s major goal was to manufacture GLB as nanoparticles to increase its low water solubility and low bioavailability, as well as to load it as an oral film to give immediate action and enhance hypoglycemic effectiveness by avoid first pass metabolism. GLB nanoparticles were prepared by the solvent anti-solvent precipitation technique with different stabilizing agents such as PVP K15, soluplus, HPMC E15, poloxamer 188 and tween 20 as co-stabilizers, using different drug:stabilizer: co-stabilizer ratios of 1:1:0, 1:2:0 and 1:1:2, respectively. The optimized formulations of GLB nanoparticles were evaluated for particle size, polydispersity index and size distribution, zeta potential, entrapment efficiency, release study, x-ray diffraction, and surface morphology by SEM. The optimized formula was F10 exhibited a lower particle size of 61.6, a high dissolution rate, and no drug-excipient interaction. In this study, we focused on the casting of the optimized formula of GLB nanosuspension directly to oral thin film using the PVA polymer by solvent casting method without the need for solidification by freeze dryer. This technique maintains stability of NPs and overcomes the main obstacle of nanoparticle formulation, which is form aggregation upon standing. These results may indicate that GLB NPs released immediately from the oral film give immediate action and enhance hypoglycemic effectiveness in addition to increasing bioavailability of GLB by enhancing solubility and dissolution rate and avoiding first-pass metabolism by hepatic enzymes.

Keywords: Glibenclamide, Nanoparticle, Oral film, Particle size, Soluplus, Solvent anti-solvent precipitation method.

INTRODUCTION
Recently, “Nanotechnology” has become very important and widely utilized in the modern pharmaceutical industry to solve the bioavailability problem of poorly water-soluble drugs, which has long been a difficult challenge in the pharmaceutical industry. Pharmaceutical nanoparticles are defined as submicron size, solid structure and less than 1-micrometer, usually from 1 to 1000 nm.¹ Nanoparticles offer several advantages, such as increasing surface area by particle size reduction, which enhances aqueous solubility, dissolution rate and bioavailability. Also, nanoparticles can be formulated as sustained, controlled release, site-specific drug delivery and reduce the toxicity and side effects of drugs.²⁻³ There are several types of nanoparticles, for example nanosuspension, polymeric nanoparticles as well as lipid nanoparticles, etc.⁴ The top-down method and the bottom-up method are the two general ways for producing nanomaterials and creating nanoparticles. The top-down methods decrease the large drug particle size to a small size without using organic solvents. These methods are called high-pressure homogenization as well as media milling.⁵ The bottom-up approach involves dissolving the medication in an organic solvent system such as methanol mixed with a miscible anti-solvent system such as water, and the drug precipitates due to its low water solubility.⁶ Glibenclamide nanoparticles were prepared using the Solvent anti-solvent precipitation approach, which is a straightforward bottom-up process. GLB, often known as glyburide, is a sulfonylurea anti-diabetic medication of the second generation used to control type 2 diabetes mellitus (T2DM). It promotes hypoglycemia by boosting insulin secretion by activating-cells in the pancreas. Corresponding to the biopharmaceutics classification system, it belongs to class II drugs (BCS). Because of its poor bioavailability, which is due to its low water solubility, its slow dissolution rate is the rate restricting step, delaying
oral absorption and resulting in partial bioavailability. It may be difficult to incorporate poorly soluble medications into oromucosal films, but the reduction in particle size may promote solubility. These oromucosal films provide rapid absorption in emergency situations, resulting in a faster onset of action, which can be beneficial. They are normally designed to have a fast onset of action and do not require the use of water. The hepatic first-pass metabolism is largely bypassed by this pathway, which may result in enhanced bioavailability since it directly enters the systemic circulation. Patient compliance and adherence improved as a result of reduced frequent doses. We attempted to create GLB-loaded nanoparticles by employing a solvent anti-solvent precipitation technique to improve GLB solubility and stability, and then pouring them directly onto an oral film without the necessity for freeze drying in this investigation. This may be considered as a novel technique for stabilization and solidification of nanoparticles.

MATERIALS AND METHODS:

Materials
GLB was sent to me as a gift sample by Pioneer Company for Pharmaceutical Industries, Iraq. Soluplus® supplied by BASF SE, Germany. PVP K 15 was purchased from Fluka, Germany. Poloxamer 188 Eastman Chemical company, USA. HPMC E 5 and HPMC E15 were purchased from Baoji, China. Tween 20 and Methanol were purchased from THOMAS BAKER, India. PVA® was purchased from Alfa Aesar, Germany.

Methods

Preparation of Glibenclamide Nanoparticles
GLB nanoparticles were made using the solvent evaporation technique, also known as the solvent anti-solvent precipitation method. It’s a technique that works from the bottom up. A precise of raw GLB 5 mg was dissolved in 2 mL of methanol, forming an organic phase. The aqueous phase is made by dissolving a certain amount of stabilizer (PVP K, Soluplus®, HPMC E15 and Poloxamer 188) and co-stabilizer (Tween 20) in 20 mL of distilled water. The organic phase was injected drop by drop into 20 ml of aqueous solution containing different types of stabilizer alone or in combination with co-stabilizer using a plastic syringe with the needle, at a rate of 1-mL/min with mechanical agitation of 800 revolutions per minute (rpm), and then left on a magnetic stirrer for about 30 minutes to allow the volatile solvent to evaporate. After that, they were subjected to 1-minute of probe sonication. Then the optimized formula with the lowest particle size was lyophilized using (lyophilizer, Copley UK) after adding the mannitol as a cryoprotectant to generate the nanoparticle powder. The ratio of drugs: stabilizer: co-stabilizer used to prepare GLB nanoparticles: 1: 0, 1: 2: 0 and 1: 1: 2 as seen in the Table 1.

Characterization of GLB Nanoparticle Particle Size Distribution and Polydispersity Index
The size of all manufactured GLB nanoparticles was measured by the 90 Plus particle size analyzer (Brookhaven Instruments), utilizing the dynamic light scattering method at a scattering angle of 90 degrees and a temperature of 25°C without dilution. The polydispersity index can be determined with this apparatus. PDI is an important test for determining particle size homogeneity inside a sample. The PDI is also known as the heterogeneity index. The PDI numerical value ranges from 0–1, as the PDI nears zero, the particles are more homogenous. A bigger PDI value indicates that the particle sample has a wider size distribution. Also, the surface area of prepared nanoparticles can be measured by this device.

Determination of Zeta Potential
Zeta potential was measured for the optimized formula of GLB NPs using (Zeta plus, Brookhaven Instruments). It is an indicator of surface charge which determines the stability of NPs. The minimum degree required for electrostatic nanosuspension stability is ± 30 mV, and the minimum degree required for steric stabilization is ± 20 mV. Measurements were carried out on the optimized formulation at room temperature.

Entrapment Efficiency
The entrapment efficiency was evaluated for optimized formulas of freshly formulated nanoparticles at a drug:

Table 1: The composition of Glibenclamide nanoparticles made with various stabilizers for various drugs: stabilizer: co-stabilizer ratio.

<table>
<thead>
<tr>
<th>F. code</th>
<th>GLB (mg)</th>
<th>Stabilizer type</th>
<th>Stabilizer (mg)</th>
<th>Drug: stabilizer: co-stabilizer ratio</th>
<th>Co-stabilizer tween-20 (mg)</th>
<th>Stirring speed</th>
<th>P.S. (nm)</th>
<th>PDI</th>
</tr>
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<tbody>
<tr>
<td>F1</td>
<td>5 mg</td>
<td>PVP K15</td>
<td>5 mg</td>
<td>1:1:0</td>
<td>0</td>
<td>800</td>
<td>211</td>
<td>0.005</td>
</tr>
<tr>
<td>F2</td>
<td>5 mg</td>
<td>Soluplus®</td>
<td>5 mg</td>
<td>1:1:0</td>
<td>0</td>
<td>800</td>
<td>94</td>
<td>0.005</td>
</tr>
<tr>
<td>F3</td>
<td>5 mg</td>
<td>HPMC E15</td>
<td>5 mg</td>
<td>1:1:0</td>
<td>0</td>
<td>800</td>
<td>339</td>
<td>0.005</td>
</tr>
<tr>
<td>F4</td>
<td>5 mg</td>
<td>PXM-188</td>
<td>5 mg</td>
<td>1:1:0</td>
<td>0</td>
<td>800</td>
<td>826</td>
<td>0.005</td>
</tr>
<tr>
<td>F5</td>
<td>5 mg</td>
<td>PVP K15</td>
<td>10 mg</td>
<td>1:2:0</td>
<td>0</td>
<td>800</td>
<td>433</td>
<td>0.005</td>
</tr>
<tr>
<td>F6</td>
<td>5 mg</td>
<td>Soluplus®</td>
<td>10 mg</td>
<td>1:2:0</td>
<td>0</td>
<td>800</td>
<td>192</td>
<td>0.024</td>
</tr>
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<td>F7</td>
<td>5 mg</td>
<td>HPMC E15</td>
<td>10 mg</td>
<td>1:2:0</td>
<td>0</td>
<td>800</td>
<td>795</td>
<td>0.228</td>
</tr>
<tr>
<td>F8</td>
<td>5 mg</td>
<td>PXM 188</td>
<td>10 mg</td>
<td>1:2:0</td>
<td>0</td>
<td>800</td>
<td>1162</td>
<td>0.008</td>
</tr>
<tr>
<td>F9</td>
<td>5 mg</td>
<td>PVP K15</td>
<td>5 mg</td>
<td>1:1:2</td>
<td>10 mg</td>
<td>800</td>
<td>189</td>
<td>0.314</td>
</tr>
<tr>
<td>F10</td>
<td>5 mg</td>
<td>Soluplus®</td>
<td>5 mg</td>
<td>1:1:2</td>
<td>10 mg</td>
<td>800</td>
<td>61.6</td>
<td>0.423</td>
</tr>
<tr>
<td>F11</td>
<td>5 mg</td>
<td>HPMC E15</td>
<td>5 mg</td>
<td>1:1:2</td>
<td>10 mg</td>
<td>800</td>
<td>847</td>
<td>0.005</td>
</tr>
<tr>
<td>F12</td>
<td>5 mg</td>
<td>PXM 188</td>
<td>5 mg</td>
<td>1:1:2</td>
<td>10 mg</td>
<td>800</td>
<td>1017</td>
<td>0.005</td>
</tr>
</tbody>
</table>
stabilizer: co-stabilizer ratio of 1:1:0 and 1:1:2. It was centrifuged at 15,000 rpm for 30 minutes via an ultracentrifuge. A concentration of drug not corporate was calculated by measuring the absorbance of the supernatant solution at 300 nm by a UV-visible spectrophotometer.\textsuperscript{13}

**In-vitro** Dissolution of Prepared GLB NP

**In-vitro** drug release studies were done for pure GLB and optimized formulas of GLB NPs. It was carried out using the diffusion bag method via USP type II dissolution apparatus (paddle type). The nanosuspension volume corresponding to 5 mg GLB was put in a dialysis bag (Mw cutoff 12,000-14,000) that was soaked in buffer pH 6.8 for 24 hours before being used, then fixed to the paddle of a USP dissolution device Type II rotating at 75 rpm in dissolution media containing 900 mL of phosphate buffer 6.8 with 1% w/v SLS at 37°C. At various time intervals, 5 mL of dissolving medium was drawn through a syringe, filtered through a 0.45 mm filter syringe, and refilled with an equal volume of new dissolution media.

UV spectrophotometric (cary 100 conc varian) was used to determine the drug concentration at 300 nm.\textsuperscript{14}

**Crystallinity and Surface Morphology**

**X-ray Diffraction (XRD)**

The X-Ray diffraction technique is done to evaluate the molecular arrangement of a crystalline substance. This test was conducted on both pure GLB and GLB-loaded nanoparticles (XRD6000 Shimadzu Japan). The patterns were recorded in the 5–90 range and the operational voltage for x-ray diffraction was 40 kV and the current was 30 mA. As a result of this test, it was determined that if the newly formed structures are crystalline or amorphous.\textsuperscript{15}

**Scanning Electron Microscopy**

The pure GLB powder and GLB nanoparticles of the optimized formula were examined by scanning electron microscopy. The SEM uses an electron beam to determine surface topography, outer layer morphology and compositional chemistry.\textsuperscript{16}

**Preparation of GLB NPs as Oral films**

Oral films of optimized GLB nanosuspension were prepared via the solvent casting method using poly vinyl alcohol polymer (PVA), which is a type of hydrophilic polymer. A homogenous solution of PVA was prepared by gradual addition and dissolving 400 mg of PVA in 20 mL of hot water at (60°C) with continuous stirring on a magnetic stirrer in about 60 minute to form a homogenous polymeric solution and then left to cool.\textsuperscript{17} Then 30% w/w glycerin as plasticizer was added to the polymeric solution with continuous stirring for about 1-hour. The remaining excipients, such as mannitol as a cooling agent, and vanilla as a flavoring agent, were dissolved in 2 mL of hot water, then poured into the polymeric solution. After that the selected GLB nanosuspension preparation (equal to 80 mg of GLB) was added to the polymeric solution with continuous stirring for an additional hour and kept aside to remove the entrapped air bubbles. The final uniform dispersion was cast on a 9 cm diameter Petri dish without air bubbles and dried overnight in a 40°C oven (Memmert, Germany). After drying, the film was removed from the petri dish with the help of a sharp blade, then cut to an appropriate size of 2 & 2 cm\textsuperscript{2}. Each film contained GLB dose equivalent to 5 mg. After that, it was sealed in aluminum foil until further evaluation.\textsuperscript{18}

**In-vitro** Dissolution Study of Oral Film Incorporating GLB NPs

A film with a diameter of 2x2 cm\textsuperscript{2} was placed at the bottom of 900 mL of phosphate buffer pH 6.8 with SLS 1% w/v (dissolving media) at 37°C and rotated at 50 rpm using the USP dissolution apparatus type II (paddle type). To maintain sink condition, a 5 mL sample was collected at a fixed interval (1,2,3,4,5,6,7,8,9,10,15,30 minutes) and replaced with the same volume of phosphate buffer pH 6.8. Then the sample was filtered at 0.45 mm and analyzed at 300 nm by a UV spectrophotometer using (cary 100 conc varian). All reading was carried out in triplicate.\textsuperscript{19}

**RESULTS AND DISCUSSION**

**Particle Size and Poly Dispersity Index**

Because these variables affect nanoparticle saturation solubility, release rate, and bioavailability, the mean particle size and polydispersity index are two critical particular parameters. PDI readings typically range from 0 to 0.05 (monodisperse average), 0.05 to 0.08 (almost monodisperse), 0.08 to 0.7 (mid-range polydispersity), and more than 0.7 (high polydispersity) (very polydisperse). Except for poloxamer 188, all of the created GLB nanoparticle formulations have a particle size on the nano scale. The particle size of all formulas, as well as the polydispersity index (PDI), can be seen in Table 1.

**Type of Stabilizer Influences Particle Size and PDI**

Four various polymers (PVP K15, Soluplus®®, HPMC E15 and PXM188) were used to analyze the effect of the polymer type on GLB nanoparticles at two different ratios of 1:1 and 1:2 to prepare the formulas (F1-F8), as presented in Figure 1. The particle size of formulas F1-F4 ranged from (94–826 nm) at a drug: stabilizer ratio of 1:1, while for F5–F8 at a drug: polymer ratio of 1:2, the particle size ranged from (192–1162). As indicated in table 1, F2 and F6, which are prepared with soluplus stabilizer in two ratios of 1:1 and 1:2, have the smallest particle sizes. This was strongly influenced by the viscosity of the polymeric dispersion in the presence of different stabilizers and followed the following pattern: Soluplus®® > PVP K15 > HPMC E15 > Poloxamer 188. It can be seen that the nanoparticles prepared by using Soluplus®® as a stabilizer give the smallest particle size than the other stabilizers because Soluplus®® is an excellent excipient made of polyvinyl caprolactam and polyvinyl acetate, which represent the hydrophobic moiety, and polyethylene glycol (PEG) that represents the hydrophilic moiety.

It can stabilize the nanosuspension more efficiently due to its amphipathic nature, so it is considered a surface-active and wetting agent commonly used to provide steric stabilization.\textsuperscript{20}
PVP K15 is a nonionic stabilizer. It creates a protective wall on the surface and disrupts the intimate particle interaction. Also, it has amphiphilic parts that provide steric stabilization for nanoparticles. So, the PVP K15 based formulation provided a smaller particle size than the formulation based on HPMC E15, which had a larger particle size. HPMC E15 is a nonionic stabilizer, a bigger molecule that stabilizes the system by steric stabilization and hydrogen bonding between the drug particles and HPMC E15. But due to high viscosity, it forms a thick broad layer covering drug particles, increasing the particle size. While the largest particle size is shown in the formulation containing poloxamer 188 in all drug:stabilizer:co-stabilizer ratios of 1:0, 1:2:0 and 1:1:2 this is attributed to weak adsorption and affinity of poloxamer 188 to GLB particles. So the obtained data suggest that it is not suited as a primary stabilizer for GLB nanoparticles formulation. Table 1 shows that a polydispersity index value between 0.4 and 0.005 suggests a narrow distribution with strong stability.

**Effect of Stabilizer Concentration**

The average particle size of prepared GLB nanoparticles is affected by changes in stabilizer amount. The effect of stabilizer amount on particle size can be either positive (increasing particle size) or negative (decreasing size of particles). It can also affect the non-ionic stabilizers’ adhesion affinity to the particle surface. When the drug:stabilizer ratio was adjusted from 1:1 to 1:2, the size of manufactured GLB nanoparticles increased in general. As demonstrated in Figure 3, the lowest particle size was attained with a drug:stabilizer ratio of 1:1, which was attributed to the amount of stabilizer being sufficient to coat particles and prevent aggregation to ensure nanoparticles stability. The increase in particle size could also be related to increased viscosity, which slows particle movement in the solution and makes it difficult to handle newly created nanoparticles. As a result, a high concentration of stabilizer causes ostwald ripening, while a low concentration causes particle aggregation. So, the formulation with a ratio 1:1 drug to stabilizer had the smallest particle size.

**Effect of a Combination of Stabilizers with Co-stabilizers**

The combination of stabilizer and co-stabilizer play a very important role in maintaining uniformly stabilized nanoparticles and preventing aggregation for a longer time. A blend of co-stabilizer (tween 20, a nonionic surfactant that stabilizes the dispersion system by steric influence) and stabilizer in formulas F9-F12 was illustrated in Figure 4. It provided the best reduction in particle size due to its adsorbed on the external surface of freshly prepared hydrophobic drug (GLB) and provided a mechanical barrier against crystal growth to inhibit agglomeration. It can be found from Table 1 that the formula F10 has the lowest particle size. It was found the P.S of formula F10 (61.6 nm) using soluplus as a stabilizer and tween 20 as a co-stabilizer was decreased when compared to the formula F2 (P.S is 94 nm), which contains just stabilizer, as well as the formula F1 (211 nm), which contains only PVP K15, which will be reduced to 189 nm when combined with co-stabilizer tween 20. This indicates that this mixture (containing tween-20) has a strong surface attraction, which
could result in a persistent thermodynamic wall at the drug particle’s interfacial surface, restricting agglomeration of nanoparticles. Whereas the P.S of the formulations F11 (847) and F12 (1017), that were stabilized by HPMC E15 and poloxamer 188, respectively, increased with the addition of tween-20. This finding suggests that co-stabilizer combinations may obstruct transportation from an organic solvent to an aqueous anti-solvent, resulting in particle agglomeration.

Zeta Potential

The Zeta potential was done for an optimized formula for determining the stability of nanoparticles by measuring the surface charge of nanoparticles in colloidal solution. The zeta potential of the optimized formula (F10) of GLB was -29mV as shown in Figure 6. As a result, it was determined that the system met the physical stability requirements for colloidal systems.

Effect of Entrapment Efficiency

The entrapment efficiency was evaluated for optimized formulas of freshly prepared nanoparticles at a drug: stabilizer: co-stabilizer ratio of 1:1:0 and 1:1:2. It must have been centrifuged at 15,000 rpm for 30 minutes via an ultracentrifuge. A UV-visible spectrophotometer was used to measure the concentration of drug unincorporated by measuring the absorbance of the supernatant solution at 300. The optimized formulas (F2 and F10) show that entrapping efficiency ranged from 91% and 98% respectively. Formulation (F10) containing soluplus with tween 20 as co-stabilizer showed the highest entrapment, up to 98%, because it has a higher affinity for entrapment GLB from the outer aqueous layer into the inner surfactant layer. Also, it could be attributed to decreased partitioning of GLB into the external aqueous layer because it is a lipophilic drug.

In-vitro Dissolution of GLB Nanoparticles

An *in vitro* dissolution analyze was done for raw GLB and optimized formulas (F2 and F10). This study was performed in phosphate buffer solution (pH 6.8) in the presence of SLS 1% w/v using the diffusion bag method. The *in vitro* release of the optimized formulas F10 exhibited an interesting faster release of more than 95% after 30 minutes with a primarily burst effect drug release within 10 min, while F2 reached 84% after 30 min and raw GLB released only up to 31% after 30 min, as shown in Figure 7. These results established that pure GLB was more difficult to dissolve in phosphate buffer solution pH 6.8 because it is a hydrophobic, weak acid with pKa 5.3. In this study, the enhancement in dissolution rate and solubility of GLB loaded nanoparticles were attributed to the reduced particle size of GLB-NPs and corresponding to the Noyes-Whitney equation the dissolution rate enhanced as the particle size decreased due to increased surface area. These results demonstrated that the dissolution rate of F10 was higher compared to the dissolution rate of F2 because it contains nonionic surfactants (tween 20) that increase surface wetting.

X-ray Diffraction

It was examined for pure GLB and the GLB NPs formula that was optimized to estimate possible changes in the crystalline structure of GLB as presented in Figures (8 and 9), respectively. Sharp peaks at 2 scattered angles of 10,12,16,19, 20, 23, and 27 were found in pure GLB patterns, indicating the drug’s crystalline composition. In the nano formulation, the intensity of these peaks was reduced. This suggests that after nanonization, the drug form’s crystalline character has decreased mostly. It was found that there was a clear difference in the crystallinity of the nanoparticles from that of pure GLB. It could be due to the variations in particle size and crystal pattern upon precipitation.
Scanning Electron Microscopy of GLB (SEM)

SEM could be used to estimate surface morphology for pure GLB and GLB nanoparticles as shown in Figures 10 and 11. There is a clear difference between pure GLB and GLB nanoparticles lyophilized powder. The pure GLB was presented as an irregular tabular crystal shape, while GLB nanoparticle showed a regular and uniform shape with a particle size generally lower than the pure GLB and with a narrow particle size distribution.29

In-vitro Dissolution Study of GLB Nanoparticles Loaded as Oral Film

A dissolution study was conducted for pure GLB film and GLB loaded as nanoparticle film. In the current work, a challenge was achieved by converting nanosuspensions directly into thin films without the need for solidification by various methods such as spray drying and freeze drying, which solve the main
drawback of nanoparticles, which tend to form aggregates upon standing. From two optimized formulas, F2 and F10 we selected F10 and converted it to an oral film. The percent of drug released from the film loaded with pure drug was found to reach 25% after 2 min, while the percentage of GLB from film loaded GLB nanoparticle in first two minutes was 54% and reach to 98% after 5 minute, which was better than film contain pure drug. The improvement in the percent of drug released from the GLB nanoparticle film could be attributable to a reduction in particle size, which increased the surface area of the dissolving medium as seen in Figure 12. This finding is in agreement with the Noyes–Whitney equation, which already suggests that a rise in saturation solubility and a decrease in particle size cause an increase in dissolution rate and thus bioavailability.30

CONCLUSION
Because the drug used in this study was Class II (BCS), saturation solubility was a problem and the dissolving rate was a rate-limiting step. It was concluded that the formulation of GLB as NPs increased saturation solubility and dissolving rate due to particle size reduction. So, with nanoparticles, maximum drug release was achieved in minutes. suggesting superior performance over commercially available formulations. Also, it can be found that formulation of nanoparticles loaded directly as oral thin film without the need for freeze drying may be considered as a novel technique for stabilization and solidification of nanoparticles. Therefore, the transformation of nanoparticles into oral film stabilizes nanoparticles by keeping them at nano size and overcomes the main draw-back of nanoparticles, which is that they tend to aggregate and form large particle size upon standing. Also, the incorporation of GLB NPs into oral films is an appropriate method for providing rapid absorption in emergency situations, resulting in a faster onset of action because the hepatic first-pass metabolism is largely bypassed by this pathway, which may result in enhanced bioavailability since it directly enters the systemic circulation.

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