Original Article

BUDESONIDE COMPATIBILITY STUDY WITH EXCIPIENTS FOR PREPARATION OF NANOPARTICLE

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ABSTRACT

Objective: As a condition of acceptance and approval of any pharmaceutical product, stability studies ensuring the durability of the consistency, stability and efficacy of the product during the shelf life are taken into consideration. These studies should be conducted according to the guidelines provided by ICH, WHO and other agencies as intended.

Methods: The aim of this research was to evaluate the stability of the budesonide solution in some solutions and excipients and to further study the production of budesonide nanoparticles. In order to study the Budesonide stability mixture of solvent and polymers were used. To study the effect of temperature and relative humidity on the stability of budesonide preparations, prepared mixtures were stored under Accelerated (40 °C±2 °C/75 percent RH±5 percent RH), Intermediate (30 °C±2 °C/65 percent RH±5 percent RH), Long-term (25 °C±2 °C/60 percent RH±5 percent RH) and at 2-8 °C.

Results: Budesonide showed good compatibility at defined stability conditions in one month. Such type of preformulation compatibility study is necessary in preparation of nanoparticles.

Conclusion: It would be helpful in screening and identifying a suitable solvent, polymer and mixture at a desired concentration.

Keywords: Budesonide, Nanoparticles, Surfactant, Poloxamer, Glycerol Monostearate, Stability, Quality

INTRODUCTION

Budesonide is a potent glucocorticosteroid with a strong topical anti-inflammatory activity and low systemic effects, which was commonly used by inhalation for the treatment of asthma. Structurally, budesonide is a 16a, 17α-acetal prepared with n-butyrdehyde by reacting 16α, 17α-dihydroy steroid (16α-hydroxyprednisolone) [1]. Budesonide is a combination of two epimers (22R and 22S) due to the insertion of the alkyl chain at the C22 atom (Fig. 1). The two epimers tend to have similar pharmacological effects, but in vitro studies have shown that the anti-inflammatory effects of the R-epimer are two to three times stronger. While budesonide has been widely used in the United States, the European Pharmacopeia has the only pharmacopeia monograph for budesonide (EP). The EP monograph for budesonide notes that the R: S epimer ratio should be in the range 60:49 to 40:51.

The stability of drugs is influenced not only by their chemistry but also by their climatic conditions, such as room temperature, moisture content, light, etc. is likely to be unstable. However, knowledge about compatibility testing is still very limited. The objective of this article was to evaluate the stability of the budesonide solution in mixture of solvent and polymers and to further study researchers in the production of budesonide nanoparticles [6-8].

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MATERIALS AND METHODS

Materials

Based on their versatility and physicochemical properties, solvents and excipients have been selected. Glycerol Monostearate (GMS) was obtained from CDH Pvt. Ltd., Mumbai, Poloxamer 188 from BASF, Mumbai and Ethanol from New Neeta Chemicals, Pune.

Methods

Specific proportions of the different formulations of solvent, water, GMS and Poloxamer 188 were prepared as shown in table 1. In addition, the compatibility study was observed with respect to appearance (coarser particle size, aggregates) at Accelerated (40 °C±2 °C/75% RH±5% RH), Intermediate (30 °C±2 °C/65% RH±5% RH), Long-term (25 °C±2 °C/60% RH±5% RH) and at 2-8 °C for 1 mo. The effect of relative humidity and temperature on individual components like ethanol, GMS, poloxamer 188 and mixtures was studied.

Fig. 1: Structure of budesonide
**Table 1: Varied mixtures for preparation of nanoparticles**

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Mixtures</th>
<th>RH±5% RH</th>
<th>RH±5% RH</th>
<th>RH±5% RH</th>
<th>RH±5% RH</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ethanol: Water</td>
<td>Clear Solution</td>
<td>Clear Solution</td>
<td>Clear Solution</td>
<td>Clear Solution</td>
</tr>
<tr>
<td>2</td>
<td>Ethanol: Water + Budesonide</td>
<td>Clear Solution</td>
<td>Fine Particle Observed</td>
<td>Few particles observed</td>
<td>Fine Particle observed</td>
</tr>
<tr>
<td>3</td>
<td>Ethanol: Water + Glycerol Monostearate</td>
<td>Clear Solution</td>
<td>Fine Particle</td>
<td>Clear Solution</td>
<td>Clear Solution</td>
</tr>
<tr>
<td>4</td>
<td>Ethanol: Water + Budesonide + Glycerol Monostearate</td>
<td>Clear Solution</td>
<td>Fine Particle</td>
<td>Clear Solution</td>
<td>Clear Solution</td>
</tr>
<tr>
<td>5</td>
<td>Ethanol: Water + Poloxamer 188</td>
<td>Clear Solution</td>
<td>Fine Particle</td>
<td>Clear Solution</td>
<td>Clear Solution</td>
</tr>
<tr>
<td>6</td>
<td>Ethanol: Water + Budesonide + Poloxamer 188</td>
<td>Clear Solution</td>
<td>Fine Particle</td>
<td>Clear Solution</td>
<td>Clear Solution</td>
</tr>
<tr>
<td>7</td>
<td>Ethanol: Water + Glycerol + Poloxamer 188</td>
<td>Clear Solution</td>
<td>Fine Particle</td>
<td>Clear Solution</td>
<td>Clear Solution</td>
</tr>
<tr>
<td>8</td>
<td>Ethanol: Water + Glycerol + Poloxamer 188</td>
<td>Clear Solution</td>
<td>Fine Particle</td>
<td>Clear Solution</td>
<td>Clear Solution</td>
</tr>
</tbody>
</table>

**Effect of poloxamer 188**

Poloxamer 188, a poly (ethylene oxide) (PEO) and poly (propylene oxide) (PPO) triblock copolymer, forms a membrane against various stresses. Poloxamers have been used as functional biomaterials for the treatment of cancer, such as drug delivery vectors for heat-sensitive hydrogels and chemosensitizing agents. The stabilizing characteristics of the membrane have been demonstrated in many scenarios by Poloxamer 188 (P188), 8,400 g/mol PEO-PEO-PEO triblock copolymer comprising two segments of 75 PEO units on either side of a segment of 30 PPO units [13-15]. Poluronic's is, therefore, a new form of nanomedicine that can increase solubility, increase circulation time, and release drugs to target sites. In aqueous medium, it can typically form cylindrical aggregates which exhibit a higher solubilization capacity than the spherical micelles produced by the hydrophilic Pluronic. Pluronic has a well-known colloidal steric stabilizing effect with a high ratio of EO/P0 [16-19].

**Table 2: Impact on mixtures when kept for accelerated (40 °C±2 °C/75 percent RH±5 percent RH), intermediate (30 °C±2 °C/65 percent RH±5 percent RH) and at 2-8 °C for one month**

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Mixtures</th>
<th>30 °C±2 °C/65% RH±5% RH</th>
<th>40 °C±2 °C/75% RH±5% RH</th>
<th>25 °C±2 °C/60% RH±5% RH</th>
<th>2-8 °C</th>
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<tr>
<td>1</td>
<td>Ethanol: Water</td>
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</tr>
<tr>
<td>3</td>
<td>Ethanol: Water + Glycerol Monostearate</td>
<td>Clear Solution</td>
<td>Fine Particle</td>
<td>Clear Solution</td>
<td>Clear Solution</td>
</tr>
<tr>
<td>4</td>
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<td>Fine Particle</td>
<td>Clear Solution</td>
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<td>Clear Solution</td>
<td>Fine Particle</td>
<td>Clear Solution</td>
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</tr>
</tbody>
</table>

**Effect of glycerol monostearate**

As an effective stabilizer, polar and non-polar compounds which can form water-in-oil or oil-in-water emulsions act as a shared solvent. These properties also make it helpful as a dispersing agent for pigments in oils or solids in fats, or as a solvent for phospholipids such as lecithin [20, 21]. When using glycerol monostearate in a formulation, the possibility of polymorph formation should be considered. Dispersible and foamy, the alpha form is useful as an emulsifying or preservative agent. For wax dyes, the denser and more stable beta form is suitable. To formulate the SLNs, GMS, a non-polar lipid (C18:1H2O0), was used. The goal behind the selection of GMS was its high drug entrapment efficiency, as the presence of high amounts of mono- and triglycerides in GMS allows the drug to solubilize in the lipid fraction, and the less specified mixture [22, 23]. of acyglycerol adds greater reach. For drug molecules to become entangled. An increase in particle size was caused by an increased volume of GMS. The tendency to fuse at high lipid concentrations can be explained by the fact that the size of nanoparticles strongly depends on the lipid concentration [24, 25].

The main knowledge prior to formulation is the solubility of drugs in mixtures of ethanol and water. The concentration of ethanol should be kept as low as possible in pharmaceutical preparations. The time consuming and the expensive experimental process is used to refine the composition of solvent mixtures to dissolve the chosen amount of a drug in a given volume of the solution. The size of the particles is increased in the order of ethanol, isopropanol and acetone by nanoparticles prepared using glycerol monostearate. The effects of the solvent also depend on the type of medication. The miscibility of the solvent and the aqueous phases is a prerequisite for the solvent injection process [26, 27].

**Ethanol: water and budesonide**

At room temperature, budesonide has very low solubility in water. With adjustable polarity, water is a solvent. When the water temperature is high, the polarity of the water decreases. To measure polarity, the dielectric constant is used. The polarity of water is reduced from 84 to 45 at 150 °C. Decreasing the polarity allows water to dissolve a number of hydrophobic organic compounds. In order to improve the temperature solubility of water, the solubility of organic compounds in water can be improved by adding organic solvents mixed with the solution. The dielectric constant of the mixture of solvents is decreased by adding organic solvents to the mixture like, ethanol [4, 9, 28]. With the addition of ethanol, the solubility of drugs increased, reached maximum values, and then again decreased in ethanol. The same was found in the combination of ethanol; water and ethanol; water+budesonide forming the fine particles at 2-8 °C [3, 9, 10, 29].

**Ethanol: water+glycerol monostearate**

This showed that there is a level of concentration where the intermolecular interaction between GMS and budesonide effectively occurs. The pH of the solution led the development of lamellar structures in the mixture, regardless of the ratio between GMS and budesonide. It promoted the formation of crystal-like structures leading to the formation of fine particles at 40 °C±2 °C/75% RH±5% RH and 25 °C±2 °C/60% RH±5% RH one-month conditions.
Ethanol: water+budesonide+glycerol monostearate and ethanol: water+budesonide+glycerol monostearate+poloxamer 188

Clear solution was obtained at 40 °C±2 °C/75% RH±5% RH for Ethanol: Water+Budesonide+Glycerol Monostearate and at 30 °C±2 °C/65% RH±5% RH for Ethanol: Water+Budesonide+Glycerol Monostearate+Poloxamer 188. The other conditions exhibited presence of fine particles which can be controlled by varying the concentration of the surfactant and the solvent used in the formulation. The observed fine particles may be because of an heterogeneous network of crystalline particles was formed by the mixture of GMS, promoting non-uniform bond strength and the resulting "ductile-like" rupture [22]. As the gel is sheared, the system might collapse into smaller clusters of aggregates, but with the reduction in shear, the reestablishment of these clusters into an organized and cohesive network would be hampered as the shear forces have overcome the Brownian motion of suspended crystals [14, 30]. Nanoparticles are affected by the initial amount of drug used. The pH of the aqueous medium can also be changed by increasing the concentration of the drug, especially when the drugs have pH-dependent groups, and these changes in pH can lead to precipitation of the drug and increase the PS and PDI. Therefore, as used, drugs generally buffer the aqueous phase to preserve the pH. Additionally, the amount of drug present is generally much smaller than the amount of aqueous phase. In such cases, by increasing the concentration of the drug, the pH of the aqueous phase will not be significantly changed [11-13]. Due to the increase in free surface energy, aggregation occurs so that the particles begin to interact with each other, causing changes in the particle size. As a dispersing medium, the use of a surfactant serves as a steric stabilizer and inhibits the incorporation of particles to prevent the formation of aggregates. A change in particle size is caused by the presence of these aggregates [26, 28-30].

Ethanol: water+glycerol monostearate+poloxamer 188

Crystal growth was observed when kept for 30 °C±2 °C/65% RH±5% RH whereas a clear solution was obtained in rest of the conditions. This may be observed due to particle aggregation induced by surface-bound surfactants, an increase in surfactant concentration contributes to a higher PDI. This was accompanied by an observation that, as increased drug molecules attempt to build up the system, there is a need for surfactants to stabilize the system [4].

CONCLUSION

The various mentioned combinations have advantages and disadvantages of its own at a specific concentration. Many factors should be considered when choosing an appropriate mixture prepare nanoparticles for its efficacy, quality and safety. Budesonide in few mixtures showed good compatibility at defined stability conditions in one month. Such type of preformulation compatibility study is necessary in preparation of nanoparticles. It would be helpful in screening and identifying a suitable solvent, polymer and mixture at a desired concentration.

ACKNOWLEDGEMENT

The authors are grateful to BASF, Mumbai for providing the gift sample of Poloxamer 188.

FUNDING

Nil

AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICTS OF INTERESTS

The authors declare that there is no conflict of interests regarding the publication of this manuscript.

REFERENCES


