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Stability Study of Mucoadhesive Microsphere Containing Nateglinide by Using Biodegradable Polymer Chitosan

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Aim: Stability Study of Mucoadhesive Microsphere Containing Nateglinide by Using Biodegradable Polymer Chitosan
Study Design: The investigation of the stability of Nateglindine containing mucoadhesive microsphere by using chitosan was carried out.
Methodology: The present study was performed to test the stability of microspheres formulation. The promising formulations were selected for in-vitro stability studies. Formulations were stored in screw-capped, amber color small glass bottles at 4±1°C, 27±2°C, and 42 ± 2°C for 45 days. After 0, 15, 30, and 45 days they were evaluated for the following parameters like particle size, and percent residual drug content.
Results: The particle size of the microspheres was found to increase slightly at 4±1°C from initial to 45 days which might be due to the agglomeration of particles. While at a higher temperature that

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is 27±2°C, an increased in particle size was observed to more as compared to particle stored at 4±1°C could be due to agglomeration of microspheres more at a higher temperature. As the period passed, the concentration of the drug in the formulation was decreased with time but at the highest (42±2°C) temperature degradation rate was maximum.

Conclusions: The stability study of microsphere containing Nateglinide concludes that the formulation CM-4326F was the best formulation in drug stability studies. As the period passed, the concentration of the drug in the formulation was decreased with time but at the highest (42±2°C) temperature degradation rate was maximum. Hence it was concluded that temperature 4±1°C or 27±2°C are suitable for storage of formulation because little changed was found in particle size and residual drug content.

Keywords: Microsphere; chitosan; stability study; nateglinide; diabetes mellitus; particle size.

1. INTRODUCTION

Nasal administration offers an interesting rug action that can be improved by developing new drug delivery systems, one such formulation being a mucoadhesive system. These systems remain in close contact with the absorption tissue, the mucous membrane, releasing the drug at the active site leading to increased bioavailability for both local and systemic effects. Over the last few decades, the application of mucoadhesive polymers in nasal drug delivery systems has gained interest among pharmaceutical scientists as a means of promoting dosage from residence time in the nasal cavity as well as for improving intimacy of contact with absorptive membranes of the biological system. In addition, the enhanced paracellular absorption following the swelling of the mucoadhesive polymers on the nasal membranes provides an important way for the absorption of the macromolecules through the nasal cavity [1, 2]. Nasal drug delivery can also provide a route of entry to the brain that circumvents the blood-brain barrier because the olfactory receptor cells are in direct contact with the central nervous system. Recently, the nasal mucosa is considered an attractive site for the delivery of vaccines not only because it has a relatively large absorptive surface and low proteolytic activity, but also because, the nasal vaccines are patient compliant and reduce the production costs compared with the parenteral products. When administered intranasal, vaccines can induce both local and systemic immune responses [3, 4]. Despite the high permeability of the nasal membrane, generally only small molecular weight drugs (<1000 Da) show adequate absorption in the nasal cavity most hydrophilic and macromolecular drugs such as insulin show low bioavailability or even no absorption. Some mucoadhesive polymers such as cellulose, polyacrylate, starch, and chitosan have proven to be effective in improving intranasal absorption of hydrophilic macromolecules. These polymers achieve this by increasing the drug residence time in the nasal cavity or enhancing intranasal absorption; some of them can serve both functions. Most of these polymers are generally recognized as safe pharmaceutical excipients and not absorbed, so they would not be expected to display systemic toxicity. Even though several challenges are still to be overcome, the encouraging results stimulate pharmaceutical researchers to exercise further efforts to develop new nasal formulations to replace the conventional parenteral products [5, 6].

Diabetes mellitus (DM) is one of the major diseases characterized by increased blood glucose levels. It is a chronic disease and most predominant in adults. It is generally associated with abnormality of glucose-receptor on β cells of Langerhans in the pancreas so they start responding at higher glucose concentration and reduce the sensitivity of peripheral tissues to insulin and excess secretion of hyperglycaemic hormones (glucagon). The symptoms in DM are polyuria, polydipsia, polyphagia, and fatigue, etc. This can be achieved by coupling bio-adhesion characteristics to microspheres and developing bio-adhesive microspheres. Bio-adhesive microspheres have advantages such as efficient absorption and enhanced bioavailability of drugs owing to a high surface-to-volume ratio, a much more intimate contact with the mucus layer. To eliminate the drawback of the short biological half-life of nateglinide, it is incorporated in the delivery system to sustain the release of the drug and subsequent absorption and maintenance of the blood glucose concentration [7, 8].

Microspheres are matrix systems that contain drugs throughout their structure and are candidates for controlled release. Microsphere can be defined as solid spherical particles

ranging from 1 to 1000 µm in size. These particles consist of the drug which is then distributed in a polymeric material. [9] The choice of methods for the preparation of microspheres depends on many factors such as the drug solubility, partition coefficient, polymer composition, molecular weight, stirring speed and stirring time, etc. For instance, the ionotropic gelation method may be a method of choice for the preparation of microspheres. Chitosan microspheres were prepared by the inotropic gelation method [10].

2. MATERIALS AND METHODS

2.1 Chemicals and Reagents

The drug nateglinide was obtained as a gift sample from Glenmark Pvt. Ltd., Mumbai, chitosan is obtained from a natural source and acetic acid, methanol, Tri-polyphosphate (TPP), Solvents, and other reagents were of analytical grade. Preparation of Chitosan Microspheres by Ionic Gelation Technique.

2.2 Preparation of Chitosan Microspheres by Ionic Gelation Technique

Chitosan solutions of various concentrations (1-5 % w/v) were prepared by dissolving chitosan in acetic acid (3% v/v) at room temperature. The drug nateglinide was dissolved into the methanol as solvent. This drug of the methanolic solution was added to chitosan solution and the mixture was stirred properly under magnetic stirring at 3000 rpm for 4 hrs. This chitosan drug solution was dropped into a stirring aqueous solution of various concentrations (1-4% w/v) of TPP solution. The dropping rate and falling distance were kept constant. The solution was stirred constantly for 4 hours on a magnetic stirrer followed by filtration through Whatman filter paper and rinsing with distilled water. The gel-like beads were obtained which were air-dried for 24 hrs followed by oven drying for 6 hrs at 40°C [11, 12].

2.3 Stability Studies

A well-designed stability testing plan is essential for the successful development of dosage form. Based upon the carrier system the storage stability study is a principal requirement. The purpose of stability testing is to provide evidence on how the quality of a formulation varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light. Degradation is likely to occur under tropical conditions of higher ambient temperature and humidity. The present study was performed to test the stability of microspheres formulation. The promising formulations were selected for in-vitro stability studies. Formulations were stored in screw-capped, amber color small glass bottles at 4±1°C, 27±2°C, and 42 ± 2°C for 45 days. After 0, 15, 30, and 45 days they were evaluated for the parameters like particle size, and percent residual drug content [13].

2.3.1 Effect of storage temperature on particle size

Particle size was determined using an optical microscope by calibration of stage and ocular micrometer. From the obtained data average change in particle size on aging was calculated. The prepared formulations were tested for particle size at 4±1°C, 27±2°C, and 42 ± 2°c temperatures. Formulations were stored in amber color glass bottles, and then they were evaluated after 15, 30, and 45 days for a change in particle size of formulation batch CM-4326F. An effect of Storage temperature on particle size is shown in Table 1 and Fig. 1 [14].

2.3.2 Effect of storage on drug content at different temperature

The stability of microspheres formulation on storage for drug content is important. The prepared formulations were tested for stability at 4±1°C, 27±2°C and 42 ± 2°C temperatures for 45 days. Formulations were stored in amber color glass bottles, and then they were evaluated after 15, 30, and 45 days for a change in residual drug content. For the determination of residual drug, microspheres CM-4326F was estimated spectrophotometrically using Shimadzu Model 1601 Spectrophotometer. An effect of Storage temperature on Drug content at different temperatures is shown in Table 1 and Fig. 2 [13-14].

3. RESULTS AND DISCUSSION

The stability of microspheres formulations on storage is of great concern. Stability studies were carried out with selected formulation CM-4326F which was stored in amber color glass bottles as a powder for 45 days at 4±1°C, 27±2°C, and 42±2°C and relative humidity 55±5% (RH

55±5%). The change was observed after 15 days interval for particle size and residual drug content. For the determination of residual drug content, microspheres were estimated spectrophotometrically using UV Visible spectrophotometer. The changed in particle size of formulations was determined by optical microscopy using calibrated ocular and stage micrometers. The particle size of the microspheres was found to increase slightly at 4±1°C from initial to 45 days which might be due to the agglomeration of particles. While at a higher temperature that is 27±2°C, an increased in particle size was observed to more as compared to particle stored at 4±1°C could be due to agglomeration of microspheres more at higher temperature and the same formulation were checked for residual drug content.

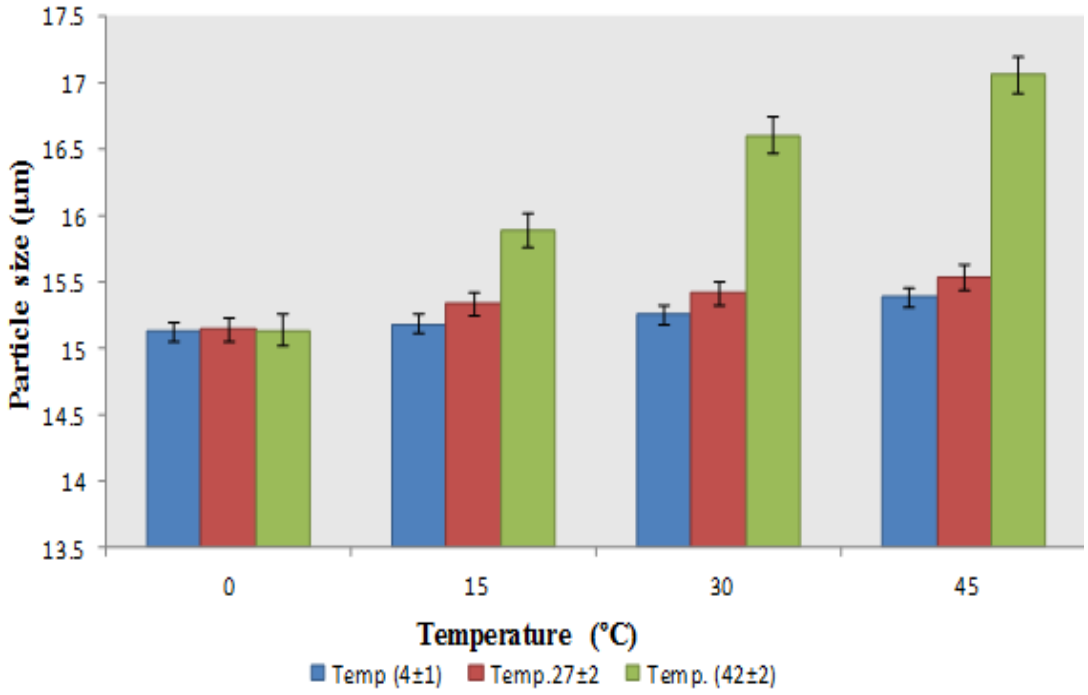

Fig. 1. Effect of storage temperature on particle size

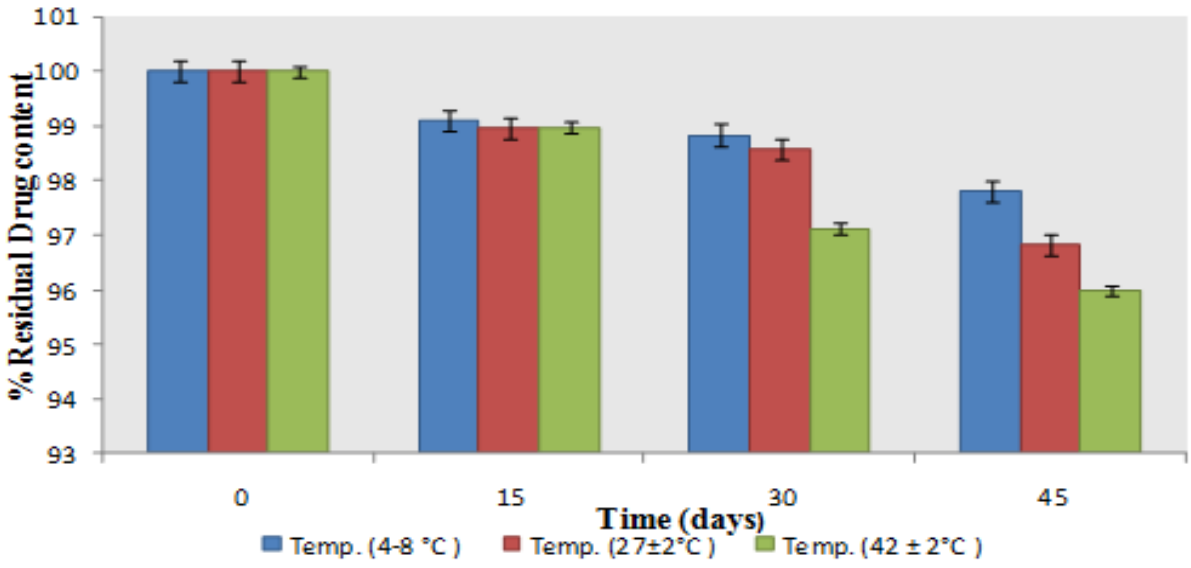

Fig. 2. Effect of different storage temperatures on % residual drug content

Table 1. Effect of Storage Temperature on Particle Size (µm) and % residual drug content

Formulation code	Initial observation			Observation After (15 days)			Observation (30 days)			Final Observation (45 days)		
CM-4326F	**4±1 °C**	**27±°C**	**42±2°C**	**4±1 °C**	**27±2°C**	**42±2°C**	**4±1 °C**	**27±2°C**	**42±2°C**	**4±1 °C**	**27±2°C**	**42±2°C**
Effect of storage The temperature on particle size	15.42±1.3	15.40±1.6	15.38±0.8	16.15±1.1	15.69±1.9	14.10±1.4	16.47±0.9	16.38±0.7	13.60±1.3	17.48±1.6	16.67±1.5	12.83±1.4
Effect of Temp. on % residual drug content	100	100	100	99.09±1.4	98.83±1.1	98.79±0.9	98.95±1.3	98.48± 1.2	96.83± 1.4	98.58±1.8	97.12±1.6	93.98± 1.5

The percent residual drug content of the selected formulation is shown in Table 1. It was observed that the formulation stored at 4.0±1°C was stable as very less drug was degraded (100 to 98.58±1.8%) on storage for 45 days while the product stored at 27±2°C, was quite stable as far as the residual drug content as about 97% on 45th day. The major change in residual drug content was observed at 42±2°C temperature on the 45th day and found to be 93.98± 1.5% (table 1). As the period passed, the concentration of the drug in the formulation was decreased with time but at the highest (42±2°C) temperature degradation rate was maximum. Hence it was concluded that temperature 4±1°C or 27±2°C are suitable for storage of formulation because little changed was found in particle size and residual drug content [8-10, 12-14].

4. CONCLUSION

The stability study concludes that the formulation CM-4326F was the best formulation in drug stability studies. As the period passed, the concentration of the drug in the formulation was decreased with time but at the highest (42±2°C) temperature degradation rate was maximum. Hence it was concluded that temperature 4±1°C or 27±2°C are suitable for storage of formulation because little changed was found in particle size and residual drug content. The particle size at and drug content at 4±1°C was found to be 17.48±1.6 µm and 98.58±1.8 % after 45 days of completion. The particle size at and drug content at 27±2°C was found to be 16.67±1.5 µm and 97.12±1.6% after 45 days of completion.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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