RESEARCH ARTICLE

Development and Optimization of Nateglinide Loaded Polymeric Sustained Release Microspheres

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ABSTRACT
This research study aims to develop and characterize of polymeric sustained release microspheres of Nateglinide (NTG), anti-diabetic drug known for its shorter half-life, which leads to poor bioavailability and frequent dosing. NTG polymeric microsphere developed by Emulsion-Solvent Diffusion-Evaporation method. Ethyl cellulose was used as rate retarding material. The polymeric microsphere were characterised for % yield, encapsulation efficiency, drug release, FTIR, and SEM. The developed NTG polymeric microspheres were smooth and spherical with porous nature and showed entrapment efficiency in range of 59.43% - 88.47 % with highest percent yield of 98.75%. FTIR spectra showed drug excipient compatibility while optimized formulation F5 showed complete drug release up to 24 hrs. These results indicate that NTG microspheres offer a safe and effective drug delivery system with prolonged release, which can enhance bioavailability, improve patient compliance, and reduce dosing frequency.
Keywords: Nateglinide, Sustained drug delivery, Shorter Half-life, Polymeric Microspheres.
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INTRODUCTION

The oral route is considered as effective ways to deliver medications. However, because it is restricted to particular areas of the gastrointestinal tract, it is linked to a comparatively short systemic half-life and limited absorption.[1] Frequent dosage regimen is required to maintain therapeutic efficacy due to these pharmacokinetic constraints. The effectiveness of drug therapy is primarily defined by the ability to attain and sustain the desired concentration of the drug in the bloodstream or target tissues.[2, 3] These setbacks of conventional drug delivery system demand the need for Novel drug delivery including nanoparticles, microspheres, liposomes etc. Novel drug delivery systems (NDDS) offer significant advantages over traditional systems by providing controlled, sustained, and targeted drug release. These systems maintain therapeutic drug levels over extended periods, improving efficacy and reducing side effects therefore suitable for drugs with shorter half-life.[4] NDDS reduce the frequency of administration, enhancing patient compliance, especially for chronic conditions. Advanced formulation considerations including nanoparticles, liposomes, and hydrogels enable precise control over drug release, optimizing both pharmacokinetics and pharmacodynamics. By addressing the limitations of conventional dosage forms, NDDS improve treatment outcomes and offer more effective, patient-friendly therapies.[5,6] Microspheres typically ranges from 1 µm to 1000 µm are a promising approach in sustaining the release of drugs with short half-lives. These spherical micro particles, typically made from biodegradable polymers, encapsulate the drug and control its release through diffusion or degradation of the polymer matrix. For drugs with a short half-life, microspheres can significantly prolong the drug's bioavailability in the bloodstream, reducing the need for frequent dosing and enhancing patient compliance. By providing a controlled, steady release, microspheres help maintain a consistent drug concentration, improving therapeutic efficacy and minimizing side effects. This is especially beneficial for drugs that require precise dosing, such as those used in chronic diseases or critical care. Additionally, microspheres can be engineered for targeted delivery to specific tissues or organs, further optimizing the therapeutic outcome. Overall, microspheres offer a versatile and effective strategy for enhancing the pharmacokinetics of short half-life drugs. Nateglinide, an oral hypoglycemic agent for type 2 diabetes, has very short half-life of 1.5 hours, necessitating frequent dosing to maintain effective blood glucose control. Starlix (Nateglinide) is available in 60 mg and 120 mg oral tablets, to be taken 1 hr–30 minutes before meals. The recommended dose of NTG is 120 mg three times a day, either alone or with Metformin or a Thiazolidinedione. Frequent dosing is necessary to achieve effective glucose control and provide patient relief. This can be challenging for patients, leading to suboptimal adherence and fluctuating glucose levels. Formulating Nateglinide as a sustained-release (SR) microsphere formulation offers several advantages.[11] By encapsulating

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Table 1: Formulation of NTG loaded polymeric Microspheres

Sr. No	Formulation Code	NTG (mg)	EC (mg)	PVA (%)
1	F1 (1:1)	100	100	1.5
2	F2 (1:2)	100	200	1.5
3	F3 (1:3)	100	300	1.5
4	F4 (1:4)	100	400	1.5
5	F5 (1:5)	100	500	1.5

Table 2: Percent Yield of NTG loaded polymeric Microspheres.

Sr. No.	Formulation Code	% Yield
1	F1	59.86
2	F2	73.23
3	F3	87.98
4	F4	98.75
5	F5	88.78

Table 3: Entrapment Efficiency of NTG loaded polymeric Microspheres.

Sr. No.	Formulations	% EE
1	F1	59.43
2	F2	65.49
3	F3	77.00
4	F4	88.21
5	F5	88.47

the drug in microspheres, it can be released gradually over an extended period, ensuring more consistent plasma concentrations with reduced dosing frequency. This controlled release minimizes the risk of blood glucose fluctuations, which are common with short-acting formulations, and helps maintain stable glycemic control throughout the day. Additionally, SR microspheres improve patient convenience and adherence by reducing dosing frequency.[12] The use of polymer-based matrices or lipid-based systems in microspheres further optimizes the pharmacokinetics of Nateglinide, allowing for a steady therapeutic effect. Ultimately, the sustained-release microsphere formulation can improve both clinical outcomes and patient quality of life by providing stable blood glucose control, reducing side effects, and enhancing treatment adherence, all while ensuring better management of type 2 diabetes.[13] The present investigations aim to formulate the Nateglinide-loaded microspheres using biodegradable polymers as the encapsulating material. Ethyl Cellulose, polymeric materials also allow for control over drug release profiles, including delayed, prolonged, or triggered release. Furthermore, these microspheres can be engineered to enhance biological behaviors like targeted delivery and optimizing the therapeutic potential of the drug.

EXPERIMENTS

Materials

Nateglinide (NTG) was gifted by Kilitch Drugs (INDIA) LTD, Mumbai, India. Ethyl cellulose (EC) 10 cp, Dichloromethane (DCM), n-hexane purchased from Merck India. Poly-vinyl Alcohol (PVA), Ethanol obtained from SD fine chemicals, Mumbai.

Methods

Development of NTG loaded polymeric Microspheres

The Emulsion-Solvent Diffusion-Evaporation technique was employed to develop NTG-loaded polymeric microspheres. NTG and Ethyl Cellulose were mixed in varying concentration ratios (1:1, 1:2, 1:3, 1:4, and 1:5) as shown in Table 1. Both ingredients were dissolved in solution mixture of DCM and ethanol (1:1). This organic phase was poured in syringe and dropwise addition was done in to PVA solution (1.5%) in distilled water under continuous stirring. The stirring was continued at 1000 rpm using a overhead stirrer to remove the organic solvents. Subsequently, N-hexane was introduced during stirring to harden the microspheres. The filtration was performed to separate out dried microspheres using Whatman filter paper. Final drying was performed in a desiccator for 24 hours.[14]

Evaluation of NTG loaded polymeric Microspheres

Percentage Yield[15]

% yield was determined by below formula

$$\% \text{ Yield} = \frac{\text{Wt of microspheres}}{\text{Wt. of drug}} + \text{Wt of Polymer X } 100$$

FTIR Spectrophotometry Analysis:

This study was performed for pure NTG and final NTG microsphers to understand the compatibility between drug and excipients. The both samples were mixed with KBr and pellets were made and loaded in FTIR. The samples were scanned between 4,400–500 cm-1.[16]

Drug Encapsulation/ Entrapment Efficiency

Microspheres equivalent to 10 mg were dissolved in DCM solvent to dissolve outer polymeric coating. The extraction of the drug was performed by addition of 6.8 phosphate buffer. The solution was stirred till to remove the organic phase from the system. Final solution was filtered through and analysed at 210 nm using UV spectroscopy.[17]

$$\% \text{ Encapsulation efficiency} = \frac{\text{Actual Drug}}{\text{Theoratical Drug}} \text{ X } 100$$

FESEM Analysis

The outer morphology of formulation was studied using FESEM analysis. The SEM instrument was operated at working distance of 8.6–8.7 mm and an accelerating voltage of 1.0 kV.[18,19]

Drug release study

Study was done in USP type I apparatus with 6.8 phosphate buffer at 100 RPM and at temp was maintained at 37 ± 0.5°C. The samples (3 ml) were withdrawn at specific time intervals and same quantity of fresh buffer was added each time to maintain the sink condition. The sampling was done at known time points and analysed at 210 nm using UV spectroscopy. The drug release was calculated based on absorbance.[20]

RESULT AND DISCUSSION

Percentage Yield

The total % yield of microspheres for all batches was found to be ranged between 59.86% to 98.75 % as shown in Table 2.

It was noted that as the drug-to-polymer ratio increased (from F1 at 1:1 to F4 at 1:4), the overall yield also increased. However, a further increase in the drug-to-polymer ratio (F5 at 1:5) resulted in a slight decrease in the percentage yield. This could be due to maximum viscosity of the solution, which led to greater adhesion of the polymer solution to the magnetic stirrer bead and the inner walls of the container, ultimately reducing the microsphere yield. The formulation with the optimum drug: polymer content F4 (1:4), exhibited the highest percentage yield (98.75 %) compared to the other formulations.

FTIR Spectrophotometry Analysis

A drug-excipient compatibility study was conducted through this study to evaluate the interaction among pure drug polymers used in the formulation, specifically NTG and NTG polymeric microspheres. No new or additional peaks were observed (Figure 1), indicating excellent compatibility between drug and polymer. However, a decrease in peak intensity was noted, likely due to the higher amount of polymers used in the formulations. These findings suggest that the polymers were compatible with the drug and did not interfere with its chemical structure. The results of this study are shown in Figure 1, highlighting the absence of significant chemical interactions. The stability testing of pharmaceutical formulations is a complex, time-consuming, and costly process, requiring scientific expertise to ensure the drug's efficacy, safety, and quality over time.

Drug Encapsulation/ Entrapment Efficiency

From the given data in **Table 3** it could be observed that F 5 batch showed maximum entrapment efficiency and Microspheres gave the highest drug content. Polymers based on % EE could be arranged from F5 to F1. Thus, it was analysed that the percentage entrapment efficiency and polymer concentration are directly proportional to each other. Drug entrapment efficacy only slightly increases with batch F 5 as compared to F4 despite of higher polymer level than F4. This signifies that addition of more polymer may not significantly affects entrapment efficiency.

SEM Analysis

The SEM images revealed a smooth surface morphology with a varied size distribution within each batch. The

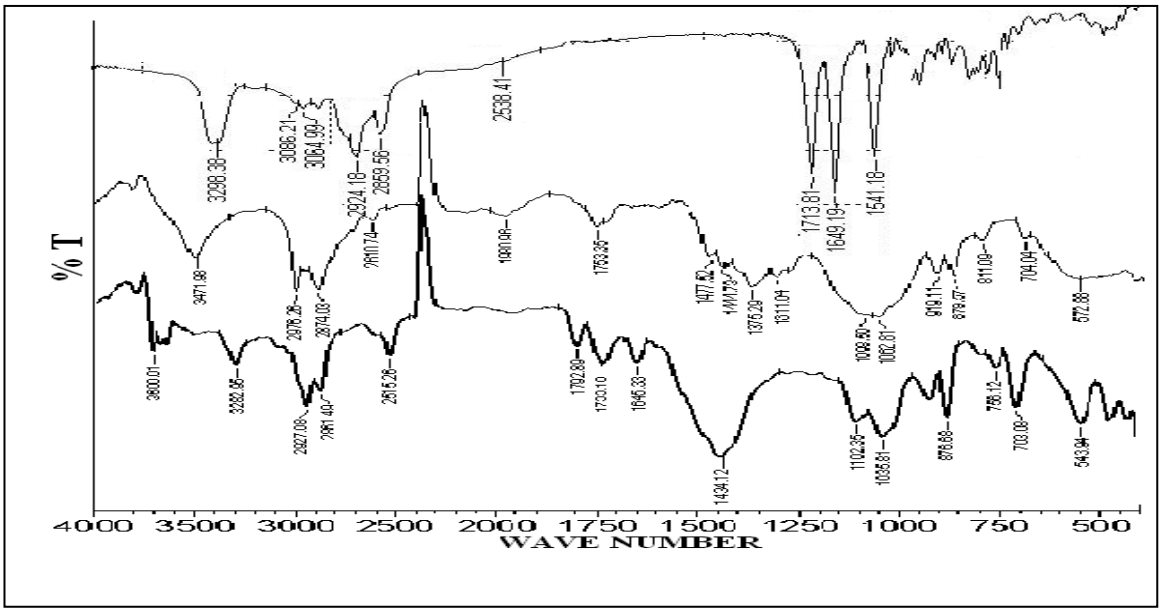

Figure 1: FTIR spectra of NTG, EC and NTG loaded microsphers.

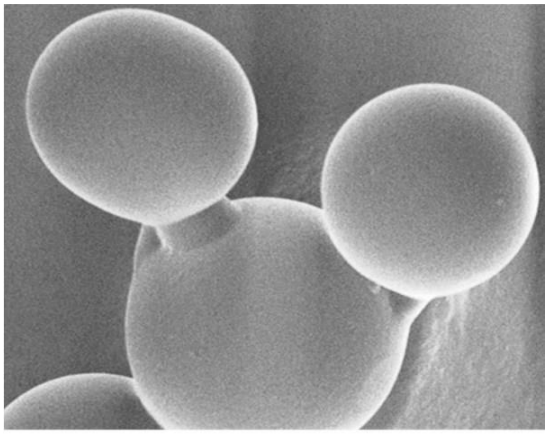

Figure 2: SEM image of NTG loaded polymeric Microspheres showing smoother surface with slightly porous nature.

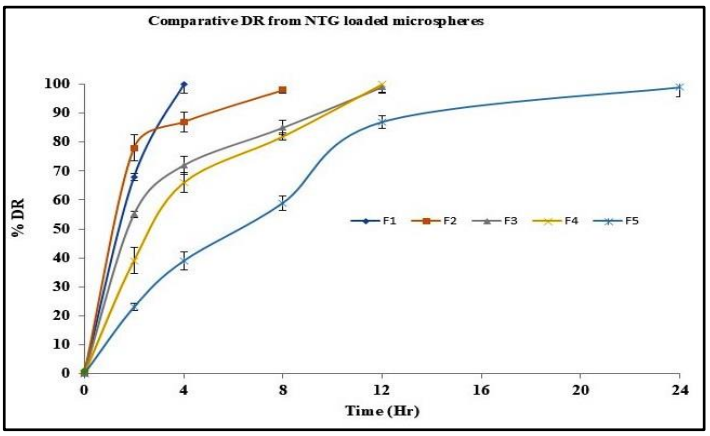

Figure 3: Comparative release of microspheres.

microspheres displayed a dense, smooth external surface. The outer surface of microcapsules also displayed some porosity which might be the result of partial breakdown of polymeric chain likely due to solvent evaporation that occurred after the formation of a smooth, dense outer layer. Figure 2 illustrates the shape and surface morphology as observed through SEM. This leads to the leaching or metabolism of the drug from the beads into the gastric fluid, which can be clearly seen in In-vitro drug release.

Drug release

This study helps to track and record release of drug and also study the release pattern. Therefore, polymer will allow the drug to get released in sustained manner sometimes up to 48 hr. The Figure 3 shows % drug release as a function of time at interval for batch F1to F5.

All the formulation (F1-F5) successfully release drug from the polymeric membrane. Only difference was found in the time period up to which they continuously releasing drug. Formulation F1 (100%), F2 (98%) and F3(99%) release in 10hr, 15 hr, 19 hrs respectively, while F4 showed 100% drug release sustained up to 24 hrs.as compared to F5 (98%) in 20hrs. The Formulation F5 was found to be suitable for delivering the drug as sustained manner.

CONCLUSION

This present investigation describes preparation of SR polymeric NTG microspheres using an Emulsion-Solvent Diffusion-Evaporation. The microspheres were smooth, spherical, and free from pores on their surface. NTG was found to be in a highly disordered, amorphous state, uniformly distributed within the microspheres. Thus, formulated microspheres exhibited highest entrapment efficiency of (88.47) along with satisfactory percentage yield (98.75%). The optimized formulation F4 showed 100% of total drug release up to 25hrs which confirms the slow and prolong release of drug from the formulation. In conclusion, the short half-life of NTG can be addressed by formulating it into sustained-release microspheres, thereby reducing dosing frequency and enhancing patient compliance.

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