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DESIGN OF NANOSUSPENSIONS OF NATEGLINIDE USING POLYMERS AND STUDY OF INVITRO DRUG RELEASE

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ABSTRACT

Nano suspensions are colloidal dispersions containing drug nanoparticles stabilised by surfactants that are utilised in the production of nanomedicine. They are also known as biphasic systems because they are made up of pure drug particles distributed in an aqueous medium and a suspended particle having a diameter of less than 1 micron. The majority of medications used today are lipophilic, and many are insoluble in water due to functional groups, particle size, chemical makeup, and other factors, including anti-diabetic pharmaceuticals like Nateglinide. As a result, the goal of this research is to generate nano-suspensions of nateglinide using poloxamer as a polymer and to test their improved bioavailability. On the generated formulations, physical parameters such as drug entrapment efficiency, drug content, yield, surface morphology, and in vitro drug release studies were assessed. In vitro studies in a phosphate buffer with a pH of 1.2 found that the nanosuspension formulation released more drug than the pure drug. As a result, nanosuspensions might be a feasible alternative to standard delivery routes for drugs with limited water solubility, potentially improving their biopharmaceutical efficacy..

Keywords: Excoecaria agallocha L., Rheumatoid arthritis, Anti-inflammatory, Anti-arthritic, Formalin induced arthritis.

INTRODUCTION

Diabetes is a kind of metabolic disease marked by hyperglycemia, a negative nitrogen balance, and, in rare circumstances, ketonemia. The thickening of the capillary basement membrane, which is followed by an increase in vessel wall matrix and cellular proliferation, is one of the most prevalent pathological alterations.[1] This causes vascular problems such as lumen narrowing, early atherosclerosis, glomerular capillary sclerosis, retinopathy, neuropathy, and peripheral vascular insufficiency, as well as retinopathy, neuropathy, and peripheral vascular insufficiency. Nano suspensions are colloidal dispersions that contain nano-sized drug particles stabilised by surfactants and are used to make nanomedicine. [2]

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They're also known as biphasic systems since they're made up of pure drug particles dispersed in an aqueous medium with a diameter of less than 1 micron and a suspended particle with a diameter of less than 1 micron. According to the National Institutes of Health, nano suspensions can be used to increase the solubility of drugs that are poorly soluble in both aqueous and lipid environments.[3]

The majority of today's drugs are lipophilic, and many of them are poorly soluble in water due to functional groups, particle size, chemical nature, and other considerations, especially anti-diabetic pharmaceuticals like Nateglinide, which are poorly soluble in water. The bioavailability and efficacy of this medication are significantly limited due to its low water solubility. It has now been established that reducing the particle size of any drug enhances its solubility, and hence its bioavailability. Other methods have been used to do this, including nano suspension, micronization, surfactants, complexation, and so on. As a result, nano suspension technology is

considered as part of the operation. [Muller et al., 2000]. Nateglinide is indicated only in type II DM as an alternative to sulfonyl ureas, or to supplement metformin/long acting insulin. The solubility of Nateglinide was aimed to be improved by using nano suspensions, that is expected to boost the rate of dissolution and absorption .

MATERIALS

Nateglinide drug was a gift sample, polymers and other chemicals were bought from SD Fine Chem Ltd.

METHODS

Solubility of Nateglinide

Excess quantities of Nateglinide were added to water and buffer solutions with varied pH (1.2, 4.5, and 7.2) buffers in triplicate to test drug solubility. The flask-containing liquids were shaken for 24 hours on a rotary shaker. After 24 hours, the solutions were examined using a UV spectrophotometer at 247 nm, the absorption maxima obtained before, and medication concentrations were computed.

FTIR studies

The FTIR analysis was used to confirm the likelihood of chemical bond interaction between the medication and the polymer. A PerkinElmer 1600 spectrophotometer with a resolution of 2 cm-1 was used to create the FTIR spectrum. The samples were scanned with an average of 8 scans per sample in the spectral band between 4000 and 400 cm-1. To form a disc, solid powder samples were oven dried at roughly 300°C, coarsely crushed, mixed with potassium bromide (1:10 by weight), and pressed at 15000 psig (using a Carver Laboratory Press, Model C, Fred S. Carver Inc., WIS 53051). To boost the signal level and eliminate moisture, the detector was properly purged with clean dry nitrogen gas. The spectrum GX series model software was used to analyse the data.[5]

Formulation of nanosuspensions

Nanosuspension was prepared by the solvent evaporation technique. Nateglinide was dissolved in a methanol (6 ml) at room temperature. This was poured into 20 ml water containing different amounts of Ploxamer F-68 maintained at a temperature of 30–40°C and subsequently stirred at ranging agitation speed for 1 hr to allow the volatile solvent to evaporate (Remi, High speed stirrer, India.). Addition of organic solvents by means of a syringe positioned with the needle directly into surfactant containing water Organic solvents were left to evaporate under a slow magnetic stirring of the nanosuspension, at room temperature for 2 hours.[4]

Evaluation of Nateglinide Nanosuspension

Surface morphology

Scanning Electron Microscopy (SEM) was performed to evaluate the particle surface morphology and shape. A concentrated aqueous suspension was applied to a slab and vacuum dried. A gold coating 20 nm thick was used to shade the sample in an evaporator. A JSM-5200 Scanning Electron Microscope (Tokyo, Japan) was used to take the photos, which were operated at 10 kV.

Calculation of process yeild

Gravimetry was used to calculate the nanosuspension manufacturing yieldFixed amounts of nanoparticle suspension were centrifuged (16,000g, 30 min, 15oC) and the sediments were dried. Standard equations were used to obtain the percentage process yield (percent P.Y.).

Estimation of entrapment of drug

The Nanosuspension was centrifuged at 5000 rpm for 15 minutes with a specified amount of medication (10mg/20ml) included. Separation of the supernatant solution The absorbance was measured using a UV spectrophotometer at 247 nm using 2 percent w/v tween 80 as a blank . 5ml of supernatant was distributed with 100 ml of 2 percent w/v tween 80 solutions, and the absorbance was measured using a UV spectrophotometer at 247 nm using 2 percent w/v tween 80 The quantity of medication in the supernatant that was not entrapped was calculated. From the drug unentrapped, the amount of drug entrapped and the percentage entrapment were calculated. The standard deviation was calculated for three trial.
[6]

RESULTS:

Table 1: Formulation of Nateglinide nanosuspension

Ingredients	NSN-1	NSN-2	NSN-3	NSN-4	NSN-5	NSN-6
Nateglinide (mg)	10	10	10	10	10	10
Methanol (ml)	8	8	8	8	8	8
Polymer (%w/v)	0.25	0.5	0.75	0.25	0.5	0.75
Surfactant (ml)	1	1	1	2	2	2
Distilled water (ml)	20	20	20	20	20	20

Table 2: Drug content and entrapment parameters of formulations

Formulation batches	Percentage drug content (%)	Entrapment efficiency	Percentage yield
NSN-1	98.59±0.91	64.28±2.57	53.35±2.97
NSN-2	99.28±0.28	67.46±4.69	64.74±2.74
NSN-3	99.26±0.45	69.45±4.49	71.19±2.45
NSN-4	99.74±0.67	86.74±3.08	79.99±3.65
NSN-5	98.91±0.51	80.08±4.99	73.85±2.66
NSN-6	98.24±0.85	75.91±2.55	71.25±2.27

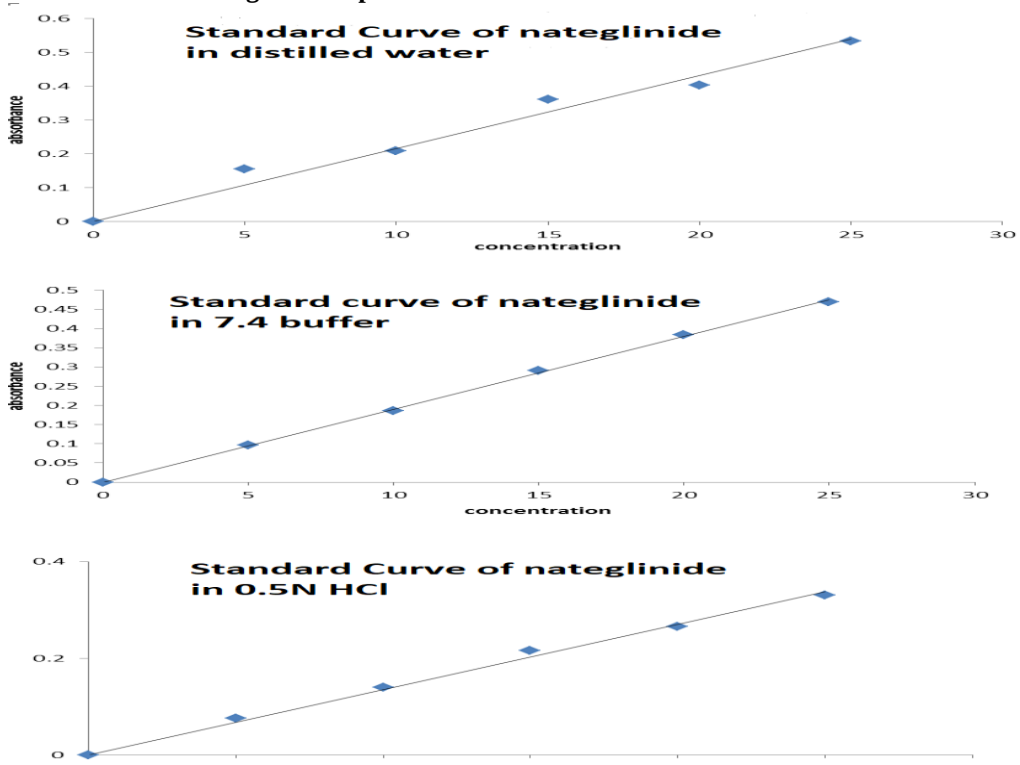
Table 3: Invitro drug release from formulations

Time (min)	% drug release (Mean± S.D)					
	NSN-1	NSN-2	NSN-3	NSN-4	NSN-5	NSN-6
0	0	0	0	0	0	0
5	20.92±0.74	24.12±5.47	19.04±2.37	26.29±3.96	25.13±3.17	22.16±3.17
15	35.68±0.69	36.86±5.16	29.36±3.87	37.96±3.28	38.16±3.07	31.62±2.06
30	69.04±0.28	55.74±4.11	55.29±3.46	60.01±2.47	56.11±2.47	48.13±2.44
60	81.98±3.65	62.16±4.42	65.46±2.63	77.38±1.76	75.11±3.81	69.13±2.56
90	96.32±6.09	75.94±3.85	79.38±3.24	87.16±1.99	82.34±4.18	80.29±1.97
120	97.09±6.18	80.63±3.74	81.62±2.84	93.26±2.49	86.13±4.69	84.87±2.75

Table: 4. Model fitting of the prepared formulations

Formulation	Zero order	First order	Higuchi	Peppas	'n' values
NSN-1	0.8435	0.8391	0.8901	0.9293	0.3609
NSN-2	0.8471	0.9992	0.9959	0.9995	0.4593
NSN-3	0.8369	0.9736	0.9905	0.9896	0.5055
NSN-4	0.8238	0.9811	0.9923	0.9957	0.4313
NSN-5	0.8261	0.9958	0.9931	0.9979	0.4518
NSN-6	0.8849	0.9978	0.9981	0.9965	0.4869

Figure 1: Calibration curve of Nateglinide in pH 7.2 buffer & 0.5 N HCl



Drug release studies

In the donor compartment, a 10 mL quantity of the nanosuspension containing medication was introduced, which was sufficient for generating sink conditions for the experiment. The receptor compartment was kept at 37°C with gentle agitation using a magnetic stirrer and contained 20 mL of 0.2M Phosphate buffer solution with a pH of 7.4. Aliquots of 1mL were removed at certain time intervals and replaced with the same amount of new phosphate buffer A single beam UV spectrophotometer was used to determine the quantity of medication released by measuring the absorbance at 247 nm (Genesis 10 UV, Thermo electron Corporation, USA)

RESULTS AND DISCUSSION

The composition of nateglinide nanosuspension was determined using various drug polymer ratios, as indicated in Table 1. Process yield, surface morphology, particle size, drug entrapment, zeta potential, in vitro drug release, and release kinetic data were all assessed in the formulations.[7]

The FTIR spectra of Nateglinide revealed peaks corresponding to several bonds, such as 1636.84 cm-1 for C=O stretching, 2931.53 cm-1 for C—H stretching, 1221.13 cm-1 for —CH3, and 3313.87 cm-1 for N—H stretching. Similar peaks for the polymer, Polymer, were discovered, with 1109.52 cm-1 for C=O stretching, 2883.56 cm-1 for C—H stretching, and 1339.81 cm-1 for O—H stretching. The peaks corresponding to C=O at 1641.21 cm-1 of the drug had been changed to 1625.17 cm-1 and –CH3 at 1214.38 cm-1 had been pushed to 1219.07 cm-1, suggesting strong bonds between drug and polymer, but no other distinguishing new peaks had been found, indicating no chemical interaction.

The medication particles were reduced to nano size in the nanosuspension formulation. There was no drug loss throughout the formulation process, hence the formulation was theoretically deemed to contain 100 percent drug content. All of the formulations' % drug content, drug entrapment efficiency, and percentage yield were determined, and the findings were displayed in table (2). Formulation F4 had the greatest percentage drug content of 99.43 percent, while Formulation F6 had the lowest percentage drug content of 98.6 percent. However, the pure drug solution yielded 99.93 percent.

When compared to other formulations, NSN-4 had a high drug entrapment efficiency. This might be attributed to the existence of optimal polymer and tween 80 concentrations; nevertheless, when comparing the formulations NSN-1, NSN-2, and NSN-3, it is obvious that increasing the polymer concentration improved drug entrapment efficiency. It's interesting to note that NSN-4, NSN-5, and NSN-6 are not the same. This might be because the drug has been trapped by the polymer and the tween, causing the drug molecules to become smaller and ionised in water. In the formulations NSN-1, NSN-2, and NSN-3, tween80 is present in low quantities, and the drug cannot be reduced to smaller particle sizes or high polymer ratios, resulting in drug molecule capture.

Formulation NSN-4 has the highest percentage yield (78.5%), followed by NSN-5, NSN-3, and NSN-3. This suggests that NNF4 is the best formulation, as the polymer concentration is optimal and the tween concentration is within acceptable limits. The yield is reduced as the tween concentration is reduced. The differences between pure Nateglinide and the optimised nanosuspension formulation were clearly visible in SEM micrographs. Nateglinide particles were discovered to be big and very irregular. Particles vanished after formulation, and the medication became tiny and homogenous. This might be because the surfactant employed to stabilise the drug particles was hydrophobically adhered to the crystal surface. As a result, we may conclude that the strategy used to increase solubility is suitable. The in vitro drug release profile of the produced Nateglinide nanosuspension was investigated using several graphical models. Plots showing percent medication released as a function of time for all formulations are shown in the release data for NSN-1, NSN-2, NSN-3, NSN-4, NSN-5, and NSN-6. Nateglinide in vitro release was seen to have a very fast first burst, followed by a very gradual drug release. A rapid first release shows that some medication was localised on the nanoparticles' surface. When compared to other formulations, NSN-4 showed the best release and was deemed the best formulation.

The resulting dissolving data were fitted into several kinetic release models such as zero order, first order, Peppas, and Higuchi to characterise the release kinetics of all six formulations. For both the model and the drug equation, these values were compared. The drug release from all formulations follows Peppas release and Higuchi model, as demonstrated by greater R2 values. The release mechanism was anomalous diffusion since it was validated as Peppas model. All of the batches' diffusion exponent (n) values were within 0.5, indicating that the drug release mechanism was pure Fickian diffusion. The Peppas model is frequently used to determine if a release mechanism is Fickian diffusion, non-Fickian diffusion, or zero order diffusion. The 'n' value can be used to describe various release mechanisms.

CONCLUSION

For medications with low water solubility, nanosuspensions might be a viable alternative to traditional delivery techniques, with the potential to improve biopharmaceutical efficacy. This study lays the groundwork for future research targeted at assessing medication bioavailability and bioequivalence in vivo, as well as their biological profiles in blood serum. The solubility of various drugs might be increased using the nanosuspension technique, which is the purpose of this study. The approach employed to improve the solubility of

Nateglinide was found to be successful and yielded a positive result throughout the experiment.

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