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Preparation and evaluation of repaglinide nanosuspensions

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ABSTRACT

Diabetes is a chronic disease that is featured by an increase in the blood glucose levels, glucosuria and at times, ketonemia. Current drug Repaglinide is a newer drug that is synthesized to control the blood sugar levels post meals. The most tangible problems that are concurrent with the use of repaglinide is its very low solubility and thereby causing little bioavailability dose inconsistency. Various methods have been developed through the years to improve the dissolution of the drug. One of those methods is the concept of nanosuspensions. These are colloidal suspensions of nano-sized drugs particles that are stabilized by surfactants. Nanosuspensions are defined as dual phasic systems that contain a pure drug which is dispersed in a polar vehicle with a diameter of the particle, which is less than 1 μm in size. Nanosuspension was adopted to improve the solubility of repaglinide to enhance its dissolution rate and absorption. As per the results, it can be said that the nanosuspensions of repaglinide were prepared and represented as a promising new formulation for oral delivery. Invitro study in pH 1.2 phosphate buffer showed that the prepared formulations have a better drug release when compared to the pure drug.

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INTRODUCTION

Diabetes is one of those metabolic disorders that is typically characterized by an increase in blood glucose level, glycosuria and ketonemia. This widely spread disease and its complications result in thickening of vascular tissue, PVD, neuropathy and retinopathy. The blood sugar-lowering drugs are beneficial when used orally significant drawback of insulin being it is given in the form of injection. So recently there are three new classes of drugs that had been synthesized like alpha-glucosidase inhibitors, meglitinide analogues and thiazolidinediones. Out of those drugs, repaglinide is the first member of the more modern class of drugs that are designed to lower the postprandial glucose [1].

The most prevalent problem faced by those drugs are very low solubility and thereby causing the oral delivery very inefficient leading to low bioavailability and improper dose and release proportionality. Research attempts are being put towards enhancing the oral bioavailability of repaglinide kind of lipophilic drugs to improve the clinical effect. Out of those methods to improve the solubility and bioavailability, Nano suspensions have been a promising method to facilitate the above problem. These are dispersion systems of colloids of nanosized drug molecules which are dispersed in aqueous medium with the surfactants. They are also defined as the biphasic systems that contain drug particles with a diameter of less than 1 micrometre. So it can be advocated that the nanosuspensions can be adopted to improve the water solubility of drugs

Table 1: Formulation of repaglinide nanosuspension

Ingredients	F1	F2	F3	F4	F5	F6	F7
Repaglinide (mg)	8	8	8	8	8	8	8
Methanol (ml)	6	6	6	6	6	6	_
poloxamer (%w/v)	0.25	0.5	0.75	0.25	0.5	0.75	_
Tween 80 (ml)	1	1	1	2	2	2	–
Aqueous solvent (ml)	20	20	20	20	20	20	20

Table 2: Solubility data of repaglinide in various solvents

S. No.	Solvent	Solubility
1.	Distilled water	0.034 mg/ml
2.	pH 1.2 Buffer	0.105 mg/ml
3.	pH 4.5 Buffer	0.19 mg/ml
4.	pH 7.2 Buffer	0.420 mg/ml

Table 3: %drug content, entrapment efficiency and %yield of Nanosuspension

Formulation batches	Percentage of drug content (%)	Entrapment efficiencymean±S.D	% yield mean±S.D
F1	99.3	63.3 ±0.43	52.6 ± 3
F2	98.7	66.3 ± 0.58	63.4 ± 4
F3	99.2	68.1± 0.38	70.8 ± 2
F4	99.43	85.2 ± 0.52	78.5 ± 4
F5	98.89	79.0 ± 0.45	72.4 ± 2
F6	98.6	74.0 ± 0.96	70.4 ± 2
F7	99.93	—	—

both in aqueous and lipid solubility [2].

Most of the drugs prescribed now are lipophilic and many of them are poorly soluble in water because of their functional groups, particle size, chemical nature etc. especially in consideration to antidiabetic drugs, repaglinide. This drug has poor water solubility, thereby limiting its bioavailability and efficacy. Now it was found that particle size reduction of any drug will improve its solubility so will be the bioavailability. For achieving this, many techniques like Nanosuspension, micronization, surfactants, complexation, etc.; have been in use. So, nanosuspension technique is taken into consideration for the process. Nanosuspension was adopted to improve the solubility of repaglinide to enhance its dissolution rate and absorption [3].

MATERIALS & METHODS

Materials

All the chemicals that are used in the experiments were procured from SD Fine Chem LTD., Mumbai, India. Cipla labs gifted drug Repaglinide, Mumbai and the polymer poloxamer is gifted by Azing Pharmaceuticals.

Preformulation Studies

Drug solubility study

Drug solubility tests were done three repetitions by adding excessive amounts of repaglinide to the aqueous medium and buffer solution by maintaining the different pH's like 1.2pH, 4.5pH and 7.2pH as buffers. These flasks that contain different solutions were placed on a rotary shaker for approximately 24hrs and after which they were visualized and analysed with UV at 247nm. This absorption maximum was determined already and the concentrations of drug in those above different solutions were identified [4].

Compatibility analysis

FTIR

The obtained sample was analyzed by FT-IR spectrum. It was compared with the standard FTIR spectra of the pure drug and comparisons are made

Table 4: Drugrelease from all the formulations in 120 min

S. No.	Time (min)	% drug release (Mean± S.D)						
		F1	F2	F3	F4	F5	F6	F7
1.	0	0	0	0	0	0	0	0
2.	5	22.570± 0.325	22.889± 0.053	17.203± 0.456	26.747± 0.587	23.281± 0.353	20.424± 0.514	10.000± 0.878
3.	15	33.402± 0.569	36.007± 0.223	30.149± 0.731	37.407± 0.392	36.309± 0.367	29.882± 0.478	16.673± 1.234
4.	30	69.864± 0.716	54.122± 0.136	53.075± 0.760	58.013± 0.405	54.558± 0.324	46.464± 0.292	19.137± 0.457
5.	60	81.261± 1.013	71.251± 0.235	63.926± 0.447	76.668± 0.384	73.353± 0.578	67.338± 0.349	21.285± 0.802
6.	90	94.367± 0.564	87.726± 0.285	77.741± 0.356	89.455± 0.546	85.291± 0.637	80.195± 0.432	24.761± 0.588
7.	120	95.987± 0.313	89.438± 0.570	78.941± 0.338	98.080± 0.254	91.802± 0.481	84.800± 0.275	27.123± 0.346

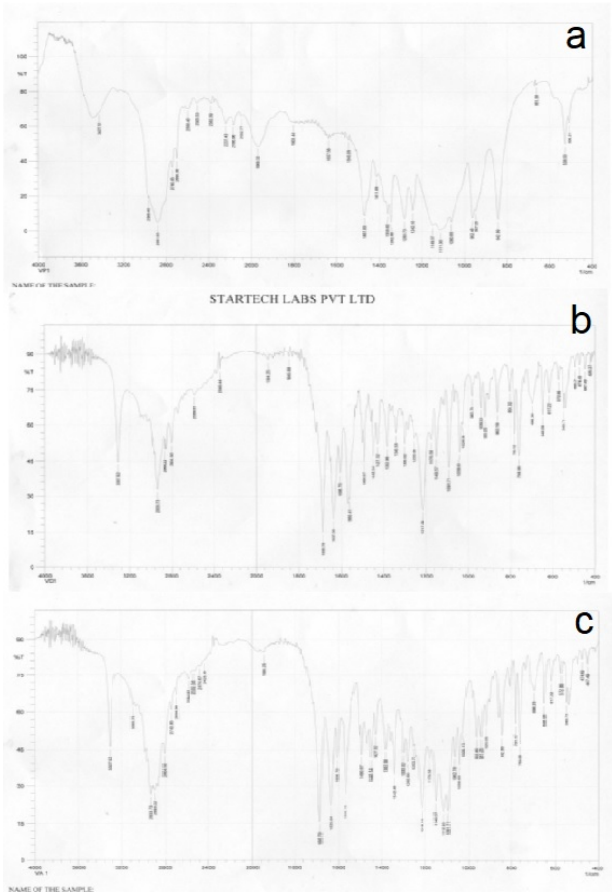

Figure 1: FTIR studies; a. polymers; b. drug; c. formulation

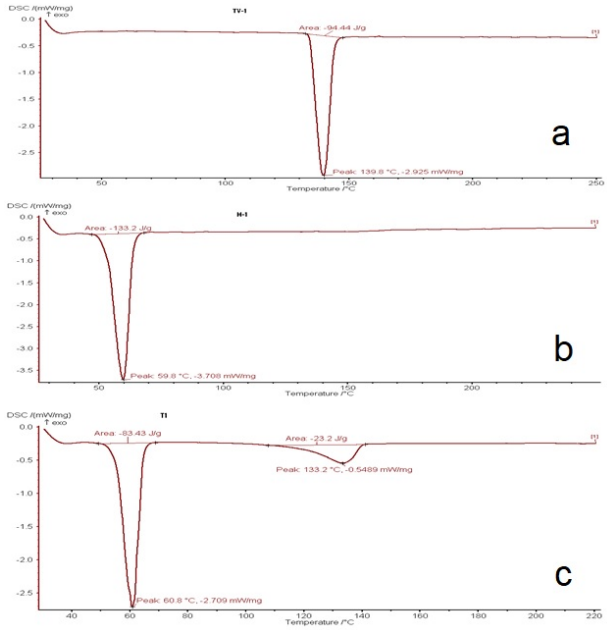

Figure 2: DSC studies; a. Drug; b. Polymer; c. formulation

to check the compatibility of polymer with the drug. The FTIR spectrum was performed by using a PerkinElmer 1600 spectrophotometer with a resolution of 2 cm^{-1}.

Differential Scanning Colorimetry

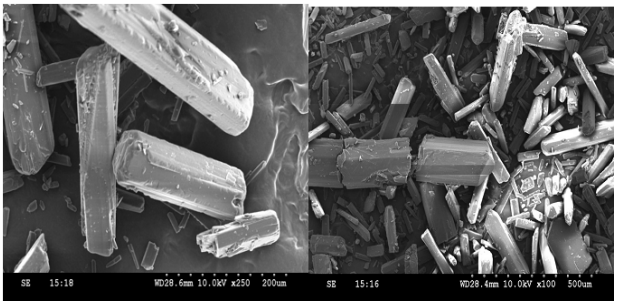

Figure 3: SEM photographs of pure drug

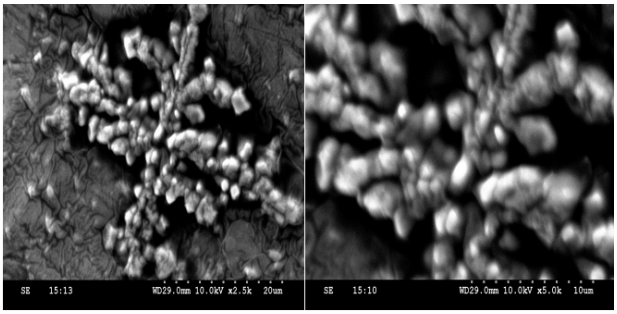

Figure 4: SEM photographs of nanosuspension

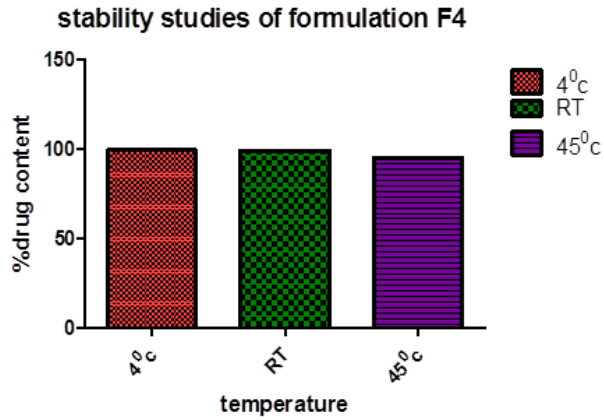

Figure 5: Stability Study: Comparison of % Drug Content of Formulation F4 at 4ºC, Room temperature(29ºC) and 45ºC ± 2ºC / 75% RH

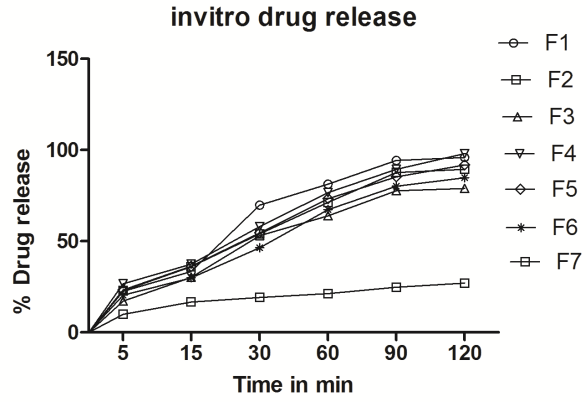

Figure 6: Drug releases from all formulations in 120 min.

DSC (model 822e, USA) with a Mettler MT-50 balance was used to analyze the thermal behaviours of samples.

Formulation of nanosuspensions

Nanosuspensions were made using the solvent evaporation method. The drug was solubilized in 6ml of methanol at normal temperature. The solution was poured into 20ml aqueous solution that contains varying amounts of Lutrol F 68 that was maintained at 30–40°C and stirred for 1hr to facilitate the evaporation of the methanol. The organic solvents were added with the help of a syringe with a needle into the water and surfactant mixture. Non-polar solvents were allowed to evaporate under a continuous stir of the nanosuspension, at ambient temp for 2hours

Evaluation of prepared formulations

Scanning Electron Microscopy

SEM was sued to visualize the morphology of the prepared nanosuspensions. JSM-5200 Scanning Electron Microscope was used to take the pictures.

Determination of yield

The percentage yield of the prepared nanosuspensions was calculated using the gravimetric method. A pre-fixed volume of nanoparticles was sedimented using a centrifuged, and this sedimentation was dried and weighed.

The percentage yield was calculated:

$$\%\ yield\ = \frac{Weight\ of\ Nanoparticles}{Total\ weight\ of\ solids} x100$$

Determination of % drug Entrapment Efficiency

The prepared suspension was taken with the known amount of the drug that is 10 mg/ 20 ml and this is subjected to centrifugation at 5000rpm. The floating liquid is taken 5ml and mixed with 100ml of tween-80 suspension. This was then allowed to be visualized under UV at 247nm. The readings are noted and the experiments are performed in trials of triplet [5] .

$$Loading\ efficiency\ = \frac{Total\ amount\ of\ drug - amount\ of\ unbound\ drug}{Nanoparticles\ weight}$$

Stability studies

These formulations were tested for the stability by the method prescribed by Joseph et al.

***I n-vitro* drug release**

The *in-vitro* drug release studies have been performed using the Static Franz diffusion cell. Cellulose membrane was used as a compartment with

10mL of the prepared suspension as a donor. The receptors contain 20 mL of 0.2 moles Phosphate buffer pH7.4 which was presented at ambient temperature with continuous agitation. A specific aliquot of 1ml was withdrawn from the medium which was immediately replaced with buffer. The drug releases were calculated bu UV at 247nm.

RESULTS AND DISCUSSION

Preformulation study

FTIR spectrum of repaglinide was characterized with various peaks corresponding to multiple bonds like 1637.56 cm^{-1} for C=O stretching, 2933.3$cm^{-1}$for C—H stretching, 1217.41 $cm^{-1}$for $-CH_3$, 3307.92 cm^{-1} for N—H stretching. Similarly corresponding peaks for the polymer, Leutrol F-60 had been obtained and inferred as 1111 cm^{-1} for C=O stretching, 2881.65 cm^{-1} for C—H stretching and 1342.46 $cm^{-1}$for O—H stretching. The peaks that correspond to C=O at 1637.56 of the drug had been shifted to 1635.64 $cm^{-1}$and $-CH_3$ at 1217.41 cm^{-1}had been shifted to 1215.15 cm^{-1} indicating that there are strong bonds between drug and polymer. Still, there were no other distinctive new peaks seen indicating that there is no chemical interaction between them. That the drug molecules have been bound by surfactant. The groups are shown in Figure 1and Figure 2. The thermograms of colorimetry were analysed for pure drugs and nanosuspensions. The drug showed a melting point at 139.8°C were in the formulation graph showed no peak. It is precise drug release and entrapment studies The %drug, entrapment & %yield of formulations were estimated and the results were given in table 3. Among all, F4 showed a high %drug of 99.43% and the lowest was found in F6, that is 98.6%. But the pure drug suspension gave the yield of 99.93%, which can be considered as an assay of repaglinide.

Interestingly it is not similar in the case of F4, F5, and F6. This might be due to the reason that drug might have got captured into the polymer and the tween making the drug molecules to lower particle size and is ionized in water [6] .

SEM

The SEM micrographs were shown in Figure 3and Figure 4.

In-vitro Dissolution studies

The release data obtained for formulations F1, F2, F3, F4, F5, F6 and F7 were tabulated in Table 4., and Fig. 5 shows plots of percent of drug released as a function of time for all formulations.

The percentage drug released for F1 and F4 after 2 hours was more than the release of F2, F3, F5 and F6. The percentage drug release after 2 hours was 95.987%, 89.438%, 78.941%, 98.080%, 91.802% and 84.800% for F1, F2, F3, F4, F5 and F6 respectively.

Stability

There was a reduction in drug content when stored at 45ºC ± 2ºC / 75% RH. At higher temperature, there might be chances for drug degradation that decreased the drug release. The results were given in Figures 5 and 6.

CONCLUSION

Nanosuspension was adopted to improve the solubility of repaglinide to enhance its dissolution rate and absorption. As per the results, it can be said that the nanosuspensions of repaglinide were prepared and represented as a promising new formulation for oral delivery. Invitro study in pH 1.2 phosphate buffer showed that the prepared formulations have a better drug release when compared to the pure drug.

CONFLICT OF INTEREST

Authors declared no conflict of interest.

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