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Formulation and evaluation of Repaglinide loaded Nanoparticles

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ABSTRACT

Nanoparticles loaded with Repaglinide were prepared using gelatin as the polymeric matrix and glutaraldehyde, PVP, PEG 2000 and PEG 10000 as the cross linking agents. A method of desolvation precipation was used for obtaining the nanoparticles, using acetone as the desolvating agent in each formulation. All the formulations (F1 to F4) were characterized for yield, entrapment efficiency, particle size and *in vitro* drug release. The order of the particle size obtained using various cross-linking agents was glutaraldehyde < PVP < PEG2000 < PEG 10000. The highest particles size was obtained in F4 (2228.37 nm) while the lowest was in F1 (242.73 nm). The yield of the nanoparticles was also affected by the choice of the cross-linking agent and ranged from 56-74%. The drug entrapment efficiencies of different formulations were in the range of 63.24 to 38.52 %. Glutaraldehyde and PVP were able to sustain the relesae of repaglinide for upto 24 h and 12 h respectively whereas PEG 2000 and PEG 10000 formualations released drug within 8 and 6 h of the study respectively.

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Introduction

Polymeric nanoparticles as drug delivery vehicles offer a multitude of advantages, including increased oral bioavailability of drugs and reduced dosage frequency ((Dass & Choong, 2006)). A variety of anticancer, antimicrobial, antituberculosis, peptide and protein based drug formulations with nano drug carriers have been researched for their therapeutic effectiveness (Srivastava et al, 2005; Jain et al, 2005). Inspite of the wide spread research, sustained release formulations with nanopolymeric carriers could be found only in small numbers in the market, with most of them in the form of ointments or wound healing bandages. Chitosan, gelatin and alginate nanoparticles are easy to prepare and customize. In addition to their excellent drug binding capacity, they have been demonstrated to possess biocompatibility and proved to be safe for oral consumption. The chitosan and alginate nanoparticles of repaglinide have been reported by some researchers. Hence the gelatin nanopolymeric materials were chosen to be used as drug carriers for formulations.

Diabetes mellitus is a metabolic disorder characterized by hyperglycemia that may result from defects in insulin secretion or action or both. Repaglinide is an oral antihyperglycemic agent used for the treatment of non-insulin-dependent diabetes mellitus (NIDDM) (drugbank, 2021). It lowers blood glucose levels by stimulating the release of insulin from the pancreas. This action is dependent upon functioning beta (β) cells in the pancreatic islets.The commonly prescribed dose of repaglinide in adults with type 2 diabetes is 1mg tablets 4 times a day and it exhibits bioavailability of 56%. Previously attempts have been made to improve the bioavailabilty of repaglinide. Some of these have been successful in the initial stages with promising results (Wu et al, 2019; Gautam & Mishra, 2018; Sharma et al, 2017; Mali and Bathe, 2017). Hence an attempt has been made to provide sustained release of repaglinide from the gelatin nanoparticles to minimize the dosing frequency. The objectives of the present study includes formulation of gelatin nanoparticles loaded with repaglinide and study the sustained release effect of the nanoparticles (*in vitro*).

Material and Methods

Repaglinide was obtained as gift sample from Torrent Pharmaceuticals Limited, Ahmedabad. Gelatin was procured form Oxford Lab fine chemicals, Mumbai and was used as obtained. All other chemicals and reagents used were of analytical grade and used as obtained .

Preformulation Studies (Martin 2006)

Preformulation studies are an important tool for determination of physical and chemical properties of the drug before incorporating it in formulation development. The nature of the drug highly affects the processing parameters like method of preparation, loading efficiency, compatibility and pharmacokinetic response of the formulation. Organoleptic properties, solubility, loss on drying, melting point and calibration curve studies were performed as part of preformulation analysis .

Formulation of gelatin nanoparticles

Four batches of gelatin nanoparticles of Repaglinide were prepared using four different crosslinking agents and a fixed amount of gelatin (Table 1).

Gelatin (1 g) was dissolved in deionized water (20 mL) with stirring under gentle heating at 60°C. Acetone (20 mL) was quickly added to the gelatin solution as a de-solvating agent to precipitate the high molecular weight Gelatin (one-step de-solvation method). The obtained precipitated gelatin was redissolved by adding 20 mL of water with the aid of gentle heating to 60°C, adjusting the pH of the solution to 7.0 with phosphoric acid. Thereafter, the crosslinking agent (glutaraldehyde/PVP/PEGs) was added while stirring and the stirring was continued for further 1 h. Repaglinide was added at this point to the mixture while stirring and acetone (75 mL) was added drop-wise under stirring at 500-1000 rpm to form the repaglinide loaded gelatin nanoparticle. The solution was cooled to about 0°C and centrifuged at 1200 rpm for about 20 min. The solution was rinsed with distilled water and lyophilized to obtain powder of gelatin nanoparticle (two-step de-solvation method) (Sailaja et al. 2011; Ahmed O Elzoghby 2013).

Characterization and evaluation of nanoparticles

Determination of Yield

The lyophilized nanoparticles were collected and weighed accurately. The percentage yield was then calculated using formulae given below:

$$\% \text{ yield} = \frac{\text{Mass of the lyophilized nanoparticles} * 100}{\text{Total weight of drug and polymer}}$$

Determination of particle size of microspheres

The particle size of each formulation batch was determined using a laser diffraction particle size analyzer.

Determination of drug entrapment in the nanoparticles

The various formulations of the nanoparticles were subjected to drug content analysis. 50 mg of the microspheres of each batch were accurately and dispersed in 10 mL methanol and sonicated at 125 Watts power for 2 min. The suspension was then centrifuged at 6000 rpm for 2 min. The supernatant was diluted appropriately in water and analyzed using UV visible spectrophotometer at 245 nm. The percentage drug entrapment was calculated.

***In-vitro* release study**

USP type II dissolution apparatus (paddle type) was performed at 50 rpm in 900 mL 0.1N HCl, maintained at 37 ± 0.5°C. 50 mg of nanoparticles were placed in the dissolution vessel for studying the rate and extent and dissolution. 5 mL of the sample was withdrawn at a predetermined interval and the volume of dissolution medium was maintained by adding equal volume of fresh dissolution medium. The absorption of the withdrawn sample was measured spectrophotometrically with suitable dilution and the corresponding concentration was determined from the calibration curve. The percentage of drug released at varioustime intervals was calculated and plotted against time.

Results and Discussion

Performulation parameters

The physical characterization of the drug was performed according to the reported procedure and the results obtained are presented in Table 2.

Percentage Yield of nanoparticles

The various formulations of the pre-

pared nanoparticles were evaluated for the percentage process yield. The percentage yield varied from 56-74% (Table 3). The yield of the nanoparticles was also affected by the choice of the crosslinking agent suggesting glutaraldehyde and PVP to be better cross linkers in comparison to the PEGs used in the study.

Particle size of nanoparticles

The particle size of various formulations was determined Malvern particle size analyzer (Table 3). The particles size was widely influenced by the choice of the cross-linking agent. It was observed that the smallest particles were obtained from the use of glutaraldehyde. The order of the particle size was glutaraldehyde < PVP < PEG2000 < PEG 10000.

Entrapment of drug

The drug entrapment of various formulations of Repaglinide was carried out as per the procedure and performed in triplicate. The drug entrapment efficiencies of different formulations were in the range of 63.24 to 38.52 % (Table 3). Glutaraldehyde and PVP were able to entrap the drug in efficient amounts owing to their good crosslinking capabilities. On the other hand the PEGs used in the study exhibited poor entrapment of Repaglinide.

***In vitro* drug release study**

The *in vitro* drug release study of the nanoparticles was evaluated in 0.1N HCl. The % release, % cumulative drug release calculated and the cumulative release data was subjected to kinetic modeling studies. From the release data it could be inferred that only glutaraldehyde and PVP were able to sustain the relesae of repaglinide for upto 24 h and 12 h respectively whereas PEG 2000 and PEG 10000 formualations released drug within 8 and 6 h of the study respectivley.

Release kinetic Study

The release kinetic was mathematically modeled to determine the type of release behavior exhibited by the drug from the nanoparticles. The zero order, first order, Higuchi and Korsemeyer-Peppas model were studied. The plots were used to determine the release behavior.

The linear regression coefficients obtained from the release kinetic curves revealed that the release of drug from the nanoparticle matrix followed primarily the Korsemeyer-Peppas model. The release of drug from the nanoparticles obeyed Korsemeyer-Peppas model suggesting an initial Fickian release due to swelling of the gelatin matrix and later non-Fickian release due to erosion of the swollen matrix

Conclusion

In the present study, nanoparticles loaded with Repaglinide were prepared by desolvation method using gelatin as the polymer and glutaraldehyde, PVP, PEG 2000 and PEG 10000 as the cross lining as well as release retarding agent. The results obtained showed that this methodology was able to produce reproducible nanoparticles suitable for sustained release of drug from the formulations. Additionally, it can be concluded that the nanoparticles produced from gelatin using glutaraldehyde as the cross linking agent is an excellent delivery system that has higher ability to sustain the release behavior of the drug for our 24 h, providing a once a day administration possibility of the drug.

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Table 1. Composition of different batches of gelatin nanoparticles

S.No.	Ingredient	Batch Code			
		F1	F2	F3	F4
1	Repaglinide (mg)	10	10	10	10
2	Gelatin (g)	1	1	1	1
3	Glutaraldehyde (g)	1	-	-	-
4	PVP (g)	-	1	-	-
5	PEG 2000 (g)	-	-	1	-
6	PEG 10000 (g)	-	-	-	1
7	Deionized water	qs	qs	qs	qs

Table 2. Preformulation characters of Repaglinide

Color	Odor	Melting Point	LOD	Solubility
Off-white crystal-line pow-der	Tasteless	240-242° C	0.27%	Soluble in 0.1N HCl & 0.1N NaOH; slightly soluble in methanol and ethanol; insoluble in water

Table 3. Characteristics of nanoparticles formulations

Formulation	Yield	Average Parti-cle Size (nm)	Entrapment Efficiency (%)
F1	74.02	242.73	63.24
F2	71.29	1080.77	54.11
F3	62.37	1262.40	33.18
F4	56.14	2228.37	18.52

Figure 1. Zero order of Repaglinide from nanoparticles

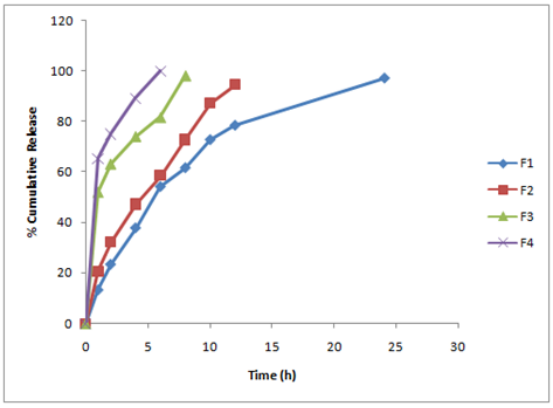


Figure 2. First order of Repaglinide from nanoparticles

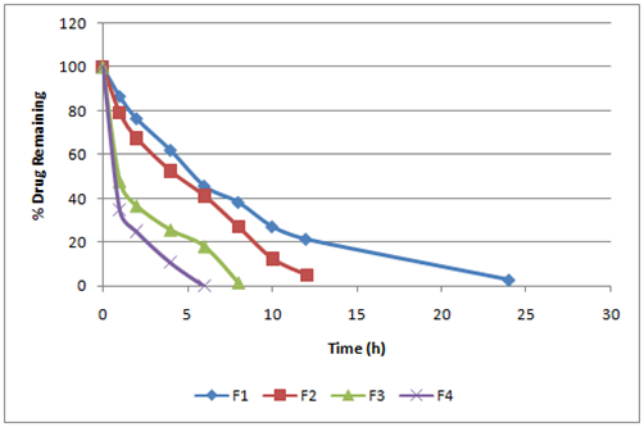


Figure 3. Higuchi plot of release of Repaglinide from nanoparticles

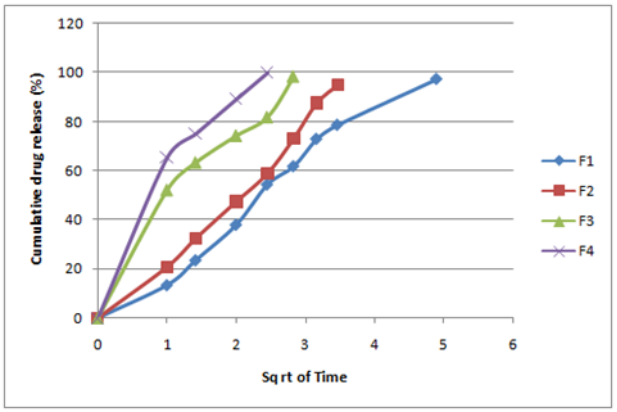
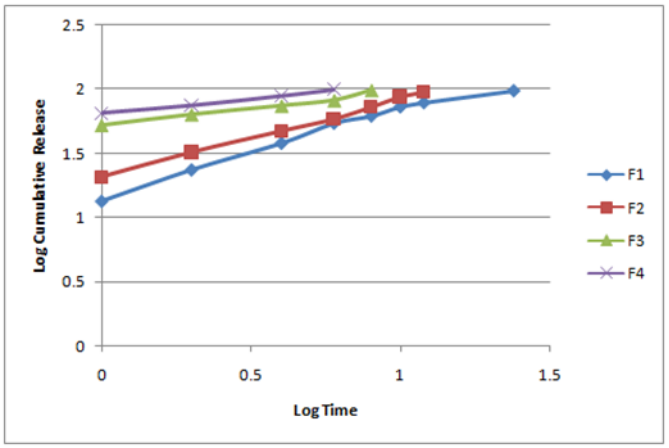


Figure 3. Korsemeyer-Peppas plot of release of Repaglinide from nanoparticles



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