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Preparation and characterization of antidiabetic drug loaded polymeric nanoparticles

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ABSTRACT

The aim of present work was preparation and characterization of Glipizide loaded polymeric nanoparticles. Nanoparticles were prepared by solvent evaporation method. The prepared nanoparticles were characterized by particle size, entrapment efficiency, drug loading, FTIR analysis and In vitro diffusion are been performed. The particle sizes, entrapment efficiency and drug loading of the prepared nanoparticles were ranging from 201.1to 427.5 nm, 59.78% to 79.53% and 23.135% to 37.11%. From thirteen formulations, F13 formulation showed best release of at the end of 10 h.

Key words: Nanoparticles, Glipizide, Eudragit RL 100, solvent evaporation method

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INTRODUCTION

Diabetes mellitus is a metabolic disorder characterized by hyperglycemia. This may be associated with absolute or relative deficiencies in insulin secretion and/or insulin action. Non-insulin-dependent diabetes mellitus (NIDDM) is a heterogeneous disorder and mainly occurs in adults. Most of them diabetic patients have NIDDM. Glipizide is a second generation sulfonylurea oral hypoglycemic agent that used in the treatment of NIDDM. [1]

Nanoparticles are solid particles having particle size in the range 10-1000 nm. Nanoparticles are classified in to two categories, depending on the method of preparation i.e. nanospheres and nanocapsules. They are able to absorb and/or encapsulate a drug, thus protecting it against chemical and enzymatic degradation. Nanospheres are matrix systems in which the drug is physically and uniformly dispersed while nanocapsules are vesicular systems in which the drug is confined to a cavity surrounded by a unique polymer membrane. [2] Nanoparticles can offer many advantages over conventional dosage form such as limiting fluctuations within therapeutic range, reducing side effects, decreasing dosing frequency, and improving patient compliance. [3]Nanoparticles as drug carriers can be formed from both biodegradable as well as non-biodegradable polymers. Biodegradable polymers such as Eudragit RL100 have been used in various clinical applications. Solvent evaporation method was used to formulate Eudragit RL100 loaded nanoparticles due to the biocompatibility of this polymer. The method of preparation of nanoparticles by solvent evaporation is widely applied in pharmaceutical industries to obtain the controlled release of drug.

The aim of the present study was to formulate, optimize and characterize Eudragit RL100 sustained release nanoparticles containing Glipizide by solvent evaporation method for improved bioavailability. [4]

MATERIALS AND METHODS

MATERIALS

Glipizide was obtained as gift a sample from international test centre, (Panchkula, India). Eudragit RL100 polymer was a kind gift sample from Evonik Degussa India Private Limited, Mumbai. All other chemicals and materials were of analytical grade and were used as procured.

EXPERIMENTAL DESIGN

The effect of formulation variables on the nanoparticles formulation was characteristics and to optimized by using a3^2 full factorial design. The design and statistical analysis were performed by Design-Expert Software. A number of preliminary experimentations were conducted to determine the experimental factors and factor levels. Response surface methodology (RSM) was used for the analysis of results. The amount of PLA polymer (X1,mg) and the concentration of PVA (X_2,%w/v) was classified to low, medium, and high values for the independent variables as described in Table 1. The studied responses were entrapment efficiency (EE), particle size (nm), and drug loading (DL). The 3^2 full factorial design and observational data are shown in Table 2. The significance of the model was determined by the comparisons of statistical parameters, and the best model (suggested) was decided based on reasonable agreement between adjusted R^2 and predicted R^2, higher values of adjustedR^2 and predicted R^2 model p value (should be less than 0.05). Three-dimensional (3D) response plots resulting from the equations were constructed using Design-Expert software. [5]

Table No. 1: Process variables and their levels for full - factorial design

Independent variables	Levels		
	Low (−1)	Medium (0)	High (1)
X_1	50	100	150
X_2	0.15	0.30	0.45

PREPARATION OF NANOPARTICLES

Nanoparticles containing Glipizide were prepared by solvent evaporation method. Solvent evaporation method involves two steps. The first step required emulsification of the polymer solution into an aqueous phase containing surfactant. During second step, evaporation of polymeric solvent is carried out, inducing polymer precipitation as nanospheres. [6] Drug was dissolved in Dichloromethane (DCM) and acetone (5ml each) and polymer was dissolved in DCM (10 ml) separately. This organic solution was then added into aquoues phase containing polyvinyl alcohol (dissolved in water) with constant stirring on magnetic stirrer at room temperature thus the oil -in-water (o/w) type emulsion was formed. Formulated nanoparticles were sonicated for 6min by using probe sonicator. Then this formed emulsion was stirred for 4-5 hr using magnetic stirrer for the evaporation of organic solvent. The nanoparticles were collected by centrifugation for 30 minutes at 10000 rpm (Remi, Mumbai). The final emulsion was then kept for lyophilization (freeze-drying) for 48 hrs. The obtained free flowing nanoparticles were stored in desiccator for further analysis. [7]

PHYSIOCHEMICAL CHARACTERIZATION OF NANOPARTICLES

PARTICLE SIZE

Freeze-dried Nanoparticle formulations were reconstituted in distilled water. The particle size and zeta potential of the Eudragit RL100 loaded Glipizide nanoparticles were determined by Particle Size Analyzer (Zetasizer Ver System; Serial Number: MAL 1051945; Malvern Instruments Ltd, Malvern, UK). The results of particle size of different formulation are shown in table 2.

DRUG LOADING (DL %) AND ENTRAPMENT EFFICIENCY (EE %)

The entrapment efficiency and drug loading of nanoparticles were determined by the separation of nanoparticles from the supernatant after centrifugation at 10000rpm for 30 minutes .The amount of free Glipizide in the supernatant liquid was measured by spectrophotometer at 276 nm. The Glipizide entrapment efficiency (EE) and drug loading (DL) of the nanoparticles were calculated from the following equations. [8]

$$\text{Entrapment efficiency} = \frac{\text{Total amount of drug} - \text{Amount of free drug} \times 100}{\text{Total amount of drug added}}$$

Drug loading = $\frac{\text{Total amount of drug – Amount of free drug} \times 100}{\text{Total weight of the Nanoparticle taken}}$

FOURIER TRANSFORMS INFRARED SPECTROSCOPY (FTIR)

The FT-IR spectra of pure Glipizide and Eudragit RL100 nanoparticles loaded with Glipizide were recorded to check drug polymer interaction and stability of drug. [9]

DRUG RELEASE STUDIES

The drug release studies of prepared nanoparticles were evaluated *in- vitro* by using Dissolution Test Apparatus, Type-II at 37±0.5 °C and at a paddle speed of 100 rpm. The Dissolution test was carried out in a 900 ml dissolution medium of phosphate buffer pH 6.8 up to 10 hrs. 5 ml sample were withdrawn from the dissolution medium at different time intervals and drug release was determined with Double beam ultraviolet spectrophotometer at 276 nm. The withdrawn samples were replenished with 5mL of fresh media. [10, 11]

RESULTS AND DISCUSSION

The responses observed for all formulations were particle size (Y_1), Entrapment efficiency (Y_2) and Drug loading (Y_3). Thirteen formulations of Glipizide loaded Eudragit nanoparticles were prepared according to a 3^2 full factorial design.

TABLE (2): Experimental Design of EuRL100 nanoparticles and Results for the various measured responses

Run	Amount of polymer EuRL100(mg) X_1	Amount of surfactant PVA(%w/v) X_2	Particle size(nm) Y_1	Entrapment efficiency (%) Y_2	%Drug loading Y_3
1	50	0.45	210.5	59.78	23.13
2	100	0.3	356.4	72.96	33.97
3	100	0.45	201.1	67.45	33.23
4	100	0.3	326.8	72.43	34.15
5	100	0.3	274.9	71.68	34.76
6	150	0.45	303.7	69.86	35.19
7	150	0.3	385.9	73.32	36.32
8	50	0.15	378.8	69.12	30.18
9	50	0.3	232.8	62.97	28.65
10	100	0.3	265.2	70.97	34.93
11	100	0.3	239.8	71.11	34.02
12	100	0.15	427.5	74.68	35.12
13	150	0.15	425.6	79.53	37.11

PARTICLE SIZE

Particle size was found to increase, by increasing the amount of polymer. This would be attributed to the fact that a viscous polymer solution is more difficult to break up into smaller droplets at the same input power of mixing which led to an increase in particle size. Moreover at a higher amount of polymer, solidification of nanoparticles is faster leading to the formation of a viscous polymer consistency in the nanodroplets. An increase in concentration of the surfactant (polyvinyl alcohol, PVA) led to a decrease in particle size of nanoparticles. The amount of surfactant plays an important role in the protection of the particles because it prevents the agglomeration of particles.

PERCENTAGE ENTRAPMENT EFFICIENCY AND PERCENTAGE DRUG LOADING

The entrapment efficiency (EE) and drug loading (DL) of the different formulations (with their codes) is given in Table 2. As the concentration of polymer increased, entrapment efficiency and drug loading also increased, which can be explained by the increased viscosity of the organic phase with increase in the amount of polymer and resulting in less drug loss during the evaporation process. But the entrapment efficiency was found to decrease with an increase in surfactant concentration. When the concentration of surfactant is increased, it helps in solubilizing the drug in the aqueous phase. Due to this, when organic solvent is added to the aqueous phase, a greater amount of drug is soluble in the aqueous phase and assists in drug leakage from the nanoparticles

RESPONSE SURFACE ANALYSIS

Response surface plot the combined effect of Eudragit RL100 polymer and PVA surfactant on particle size of nanoparticles is shown in fig.1. Response surface plot in fig.2 and fig. 3 shows combined effect of Eudragit RL100 polymer and PVA surfactant on entrapment efficiency and drug loading.

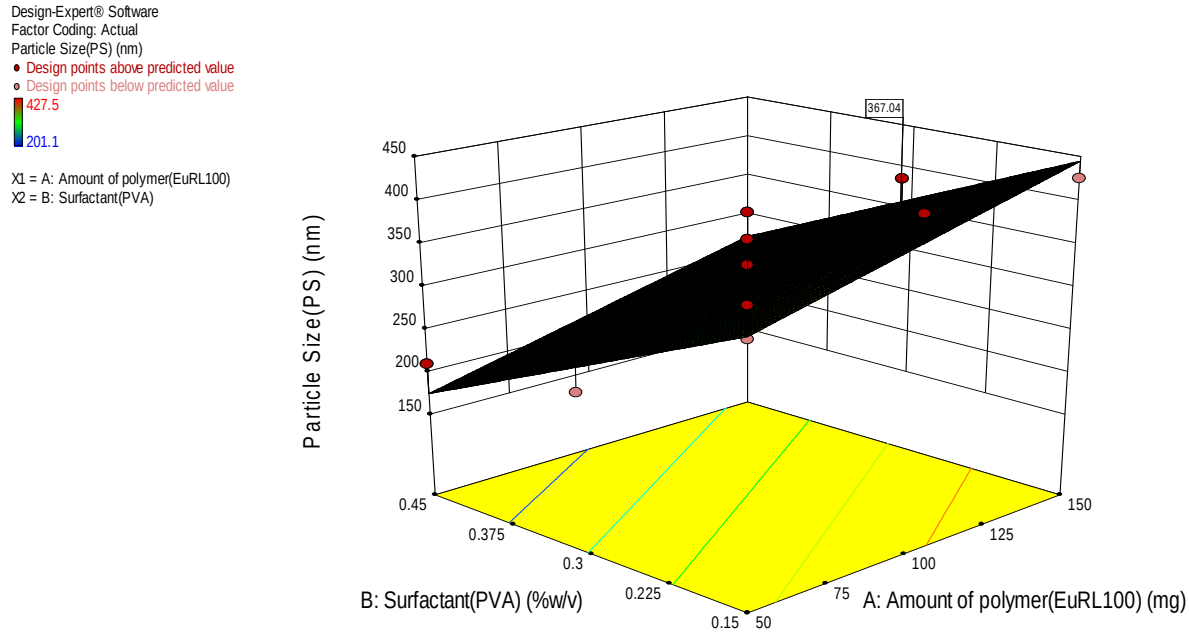

Fig 1: Response surface plot showing the combined effect of EuRL 100 and PVA on particle size of nanoparticles

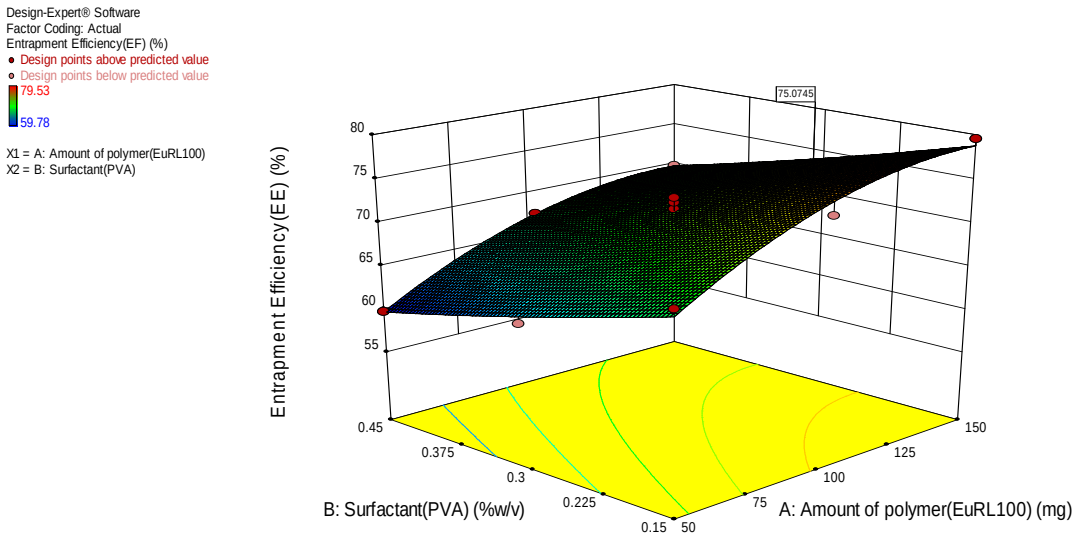

Fig. 2: Response surface plot showing the combined effect of EuRL 100 and PVA on % entrapment efficiency of nanoparticles

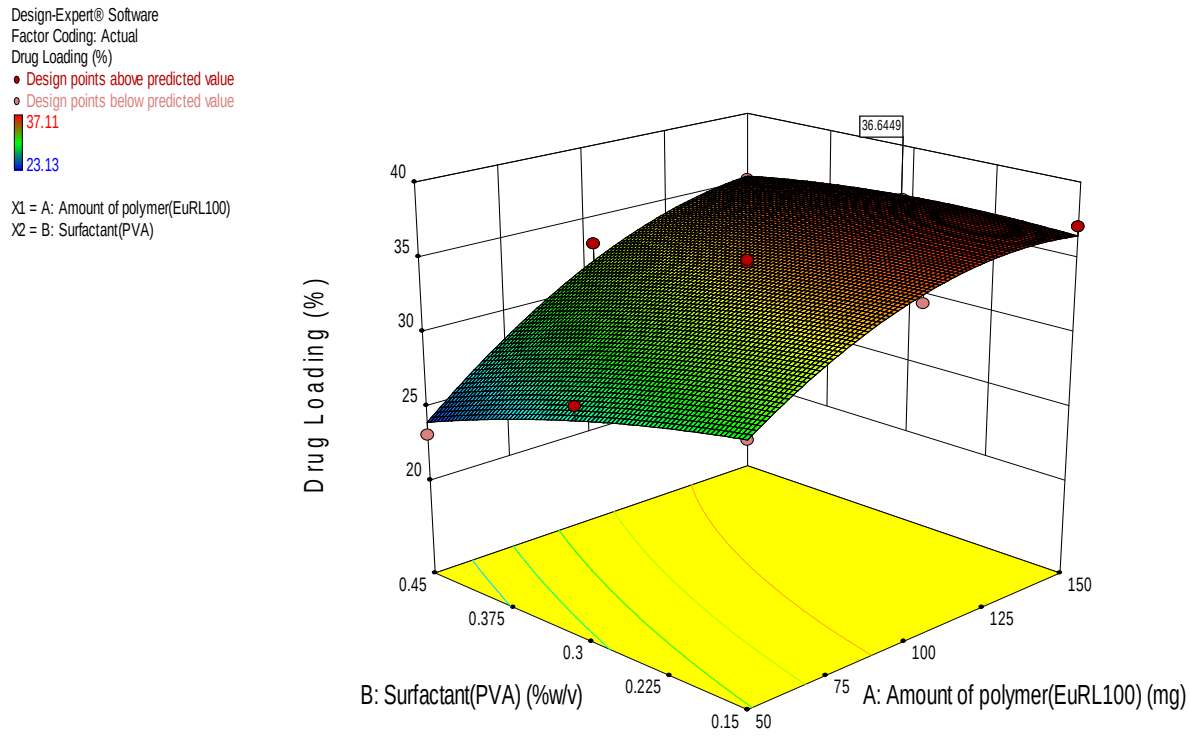

Fig. 3: Response surface plot showing the combined effect of EuRL 100 and PVA on % drug loading of nanoparticles

FOURIER TRANSFORMS INFRARED SPECTROSCOPY (FTIR)

The spectrum of Glipizide and physical mixture of Glipizide with Eudragit RL100 is shown in fig.4 and Fig.5.

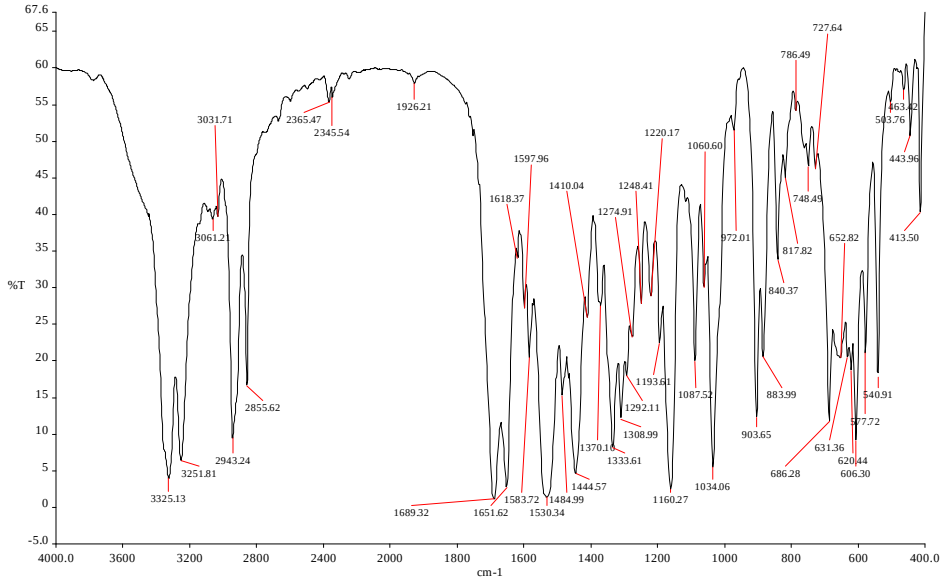

Fig. 4: FTIR spectrum of Glipizide

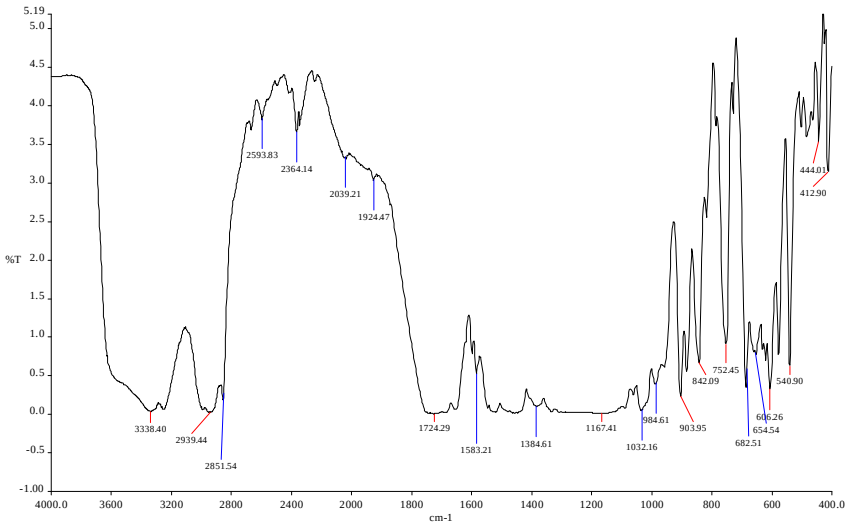

Fig. 5: FTIR spectrum of physical mixture of Glipizide with Eudragit RL100

IN VITRO DRUG RELEASE STUDIES

The release profile of Glipizide loaded nanoparticles showed the cumulative drug release from 64.31 – 78.56. The nanoparticles displayed a biphasic drug release pattern with initial burst release followed by sustained release of drug. The burst release may be ascribed to the drug associated with the surface of particles. The result displayed that the release was depend on the concentration of polymer. An increase in the polymer concentration caused a decrease in the release rate because polymer increases the density of the molecule in the given space; as a consequence of which release is reduced. However the percent cumulative drug release increased with increase in surfactant concentration which could be attributed to the decrease in particle size and increase in surface area available in the dissolution.

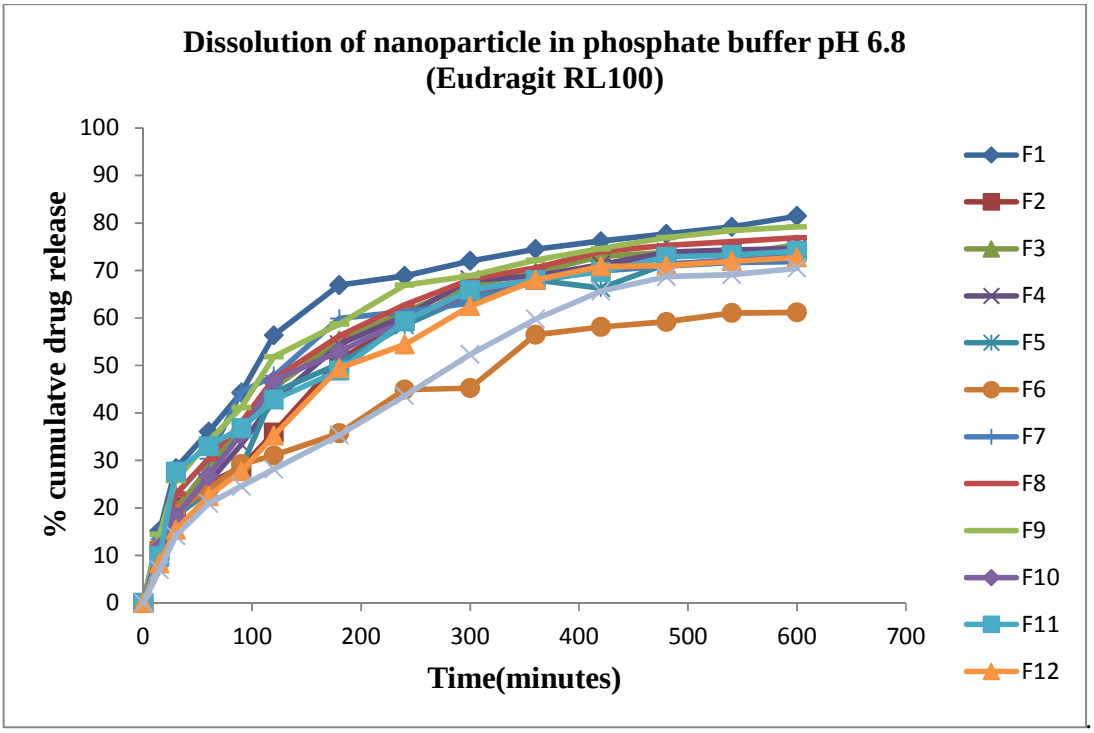

Fig.6: Drug Release Profile of F1 – F13

CONCLUSION

The nanotechnology based systems may improve drug therapy of patients as demonstrated by *in vitro studies*. Various nano systems have been shown the ability to improve bioavailability of antidiabetic activity of several drugs, while reducing their toxicity and potentially simplifying drug regimens. The above objectives were achieved by formulating Glipizide loaded Eudragit RL100 nanoparticles by solvent evaporation method used for the treatment of diabetes by enhancing the bioavailability. Thus the formulation F13 has showed the sustained release formulation for the treatment of diabetes by decreasing the dose and frequency of administration and thereby reducing the side effects and improving the patient compliance.

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