FORMULATION AND DEVELOPMENT OF NOVEL INSITU NASAL GEL CONTAINING GLIBENCLAMIDE NANOPARTICLES

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ABSTRACT

In order to provide an alternative, patient compliant and controlled release of sulfonylureas, nasal route is one of the best options among other routes for type-II diabetes mellitus. Glibenclamide (GLB) was selected since its oral absorption is affected by presence of food and it undergoes extensive first-pass metabolism. GLB loaded solid lipid nanoparticles (SLN) were prepared using stearic acid and Poloxamer 188 by hot homogenization technique. Carbomer 934P was incorporated as a gelling agent in the formulation with menthol as nasal decongestant and permeation enhancer. The formulation of pH 6.2-6.4 was optimized using central composite design. The optimized formulation showed drug diffusion of about 90.59% over 24 hours in bio-relevant nasal dissolution test apparatus using saline phosphate buffer pH 6.4 at 34 ± 0.5°C. Particle size analysis was done using scanning electron microscope (SEM) and it was found in the range of 290-420nm.

***Keywords*:** glibenclamide, solid lipid nanoparticles, stearic acid, in-situ nasal gel, controlled release

1. INTRODUCTION

The prevalence of diabetes is seen more than 125 million persons in world today, among them up to 45% of newly diagnosed have type II Diabetes Mellitus which is readily treated with oral sulfonylureas because of its added advantages over other antidiabetic drugs. Majority of antidiabetic drugs in which patients are administered via oral route. Most of the diabetic geriatrics patient are tired of taking anti-diabetic tablet or capsule since they are required to be taken 2 or 3 times a day. So in order to provide an alternative route (non-swallowing) and compliance to patient (controlled release), nasal delivery of sulfonylureas is one of the best options among other routes. Glibenclamide was selected as a model drug in present investigation since its oral absorption is affected by presence of food and it undergoes extensive first-pass metabolism [1]. Additionally by preparing nanoparticles of glibenclamide, we can achieve dose reduction from 5 mg to 3 mg per day which is ideal for nasal delivery [2].

2. EXPERIMENTAL

2.1 Preparation and evaluation of blank solid lipid nanoparticles

Hot homogenization technique [3] was carried out at temperatures above the melting point of stearic acid. A pre-nanoemulsion of the melted stearic acid (70°C) was formed by adding it to 100 ml of aqueous Poloxamer 188 solution which was maintained at the same temperature under stirring at 4000 rpm by high-shear mixing device for 5 minutes. The prepared nanosystem was converted to nanoparticles by sudden cooling at room temperature under stirring.

The concentrations of stearic acid and poloxamer 188 are shown in Table 1 according to 3^2 factorial design.

Batch	Stearic acid (gm)	Poloxamer 188 (gm)
D1	5	1
D2	4	1
D3	3	1
D4	5	1.5
D5	4	1.5
D6	3	1.5
D7	5	2
D8	4	2
D9	3	2

Table 1: 3^2 Factorial Design for preparation of blank Stearic acid SLN by hot homogenization technique

The blank nanoparticles were evaluated for various parameters like re-dispersion, settling rate, particle size distribution (under microscope) and sedimentation after one month. SEM of these formulations was taken at 8000X magnification, 30 Kv current.

On the basis of ease of re-dispersion, settling rate, small and uniform particle size Distribution (from SEM 220 to 280 nm), **Batch D7** was selected for formulation and development of glibenclamide nanosuspension.

2.2 Preparation and evaluation of drug loaded solid lipid nanoparticles

Drug loaded SLN were prepared by the same procedure as preparation of blank SLN. Here, the drug was dispersed in melted stearic acid maintained at 70°C, which was used for further proceedings [4].

Central Composite design was used for preparation of Glibenclamide SLN. The design is shown in following Table 2.

Batch Code	Drug	Stearic acid	Poloxamer
	(gm)		
K1	2	3	1
K2	2	5	1
K3	2	3	2
K4	2	5	2
K5	2	4	1.5
K6	2	2.59	1.5
K7	2	5.41	1.5
K8	2	4	0.79
K9	2	4	2.21

Table 2: Design lay-out of central composite design

The prepared drug loaded SLNs were evaluated for various parameters like re-dispersion, settling rate, particle size distribution, sedimentation, % drug release and % drug loading. The results are shown in Table 3.

The in-vitro dissolution study was carried out using modified dissolution test apparatus which is shown in Figure-1.

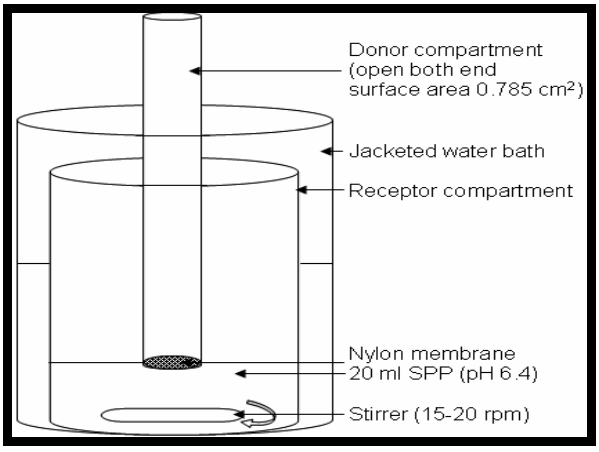

Figure 1: Bio-relevant Nasal Dissolution test apparatus

2.3 Optimized formulation

From the above matrix of central composite design, contour plots were drawn, superimposed and the optimum concentrations of stearic acid and Poloxamer 188 were found to be 3.6 and 1.7 % respectively. The optimized batch was evaluated for % drug loading and % drug release (See Table 3).

Finally, the in-situ gel was formed using Carbomer 934P. The in-vitro dissolution study was carried out using bio-relevant test apparatus in saline phosphate buffer pH 6.4 at 34 ± 0.5°C [5]. Finished formulations were characterized for its pH, viscosity, re-dispersion, in vitro drug diffusion and particle size analysis [6].

Final formulation is mentioned in following Table 4.

3. RESULTS AND DISCUSSION

SEM of **Batch D7** was taken at 8000X magnification, 30 Kv current which is shown in Figure-2. The particle size distribution lies in the range from 220 to 280nm.

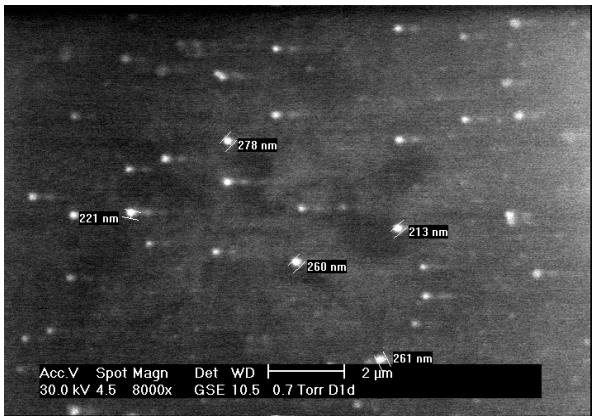

Figure 2: SEM image of Batch D7

The results of % drug release and % drug loading of K1 to K9 batches are shown in following Table 3 along with the respective graph of comparative release profile of batch K1 to K9 as shown in Figure 3

Batch Code	% Drug release	% Drug loaded
K1	78.87	41.40
K2	65.57	56.87
K3	81.25	43.67
K4	70.62	63.79
K5	82.16	52.26
K6	90.82	35.51
K7	62.67	69.69
K8	79.52	46.09
K9	84.32	53.66

Table 3: % drug release and % drug loading of central composite design batches

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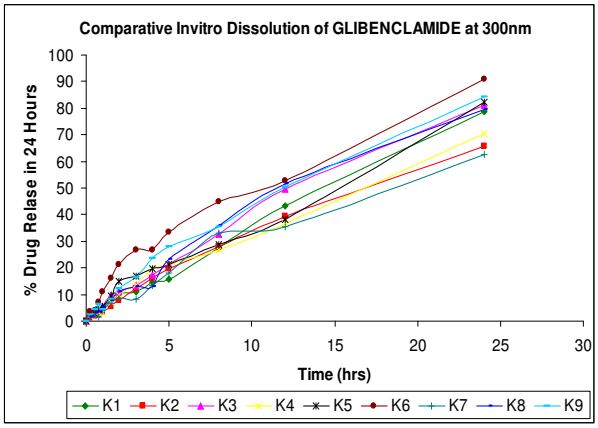

Figure 3: Comparative release profile of K1-K9

Contour plots were drawn from matrix of central composite design which are shown in figure 4 and 5.

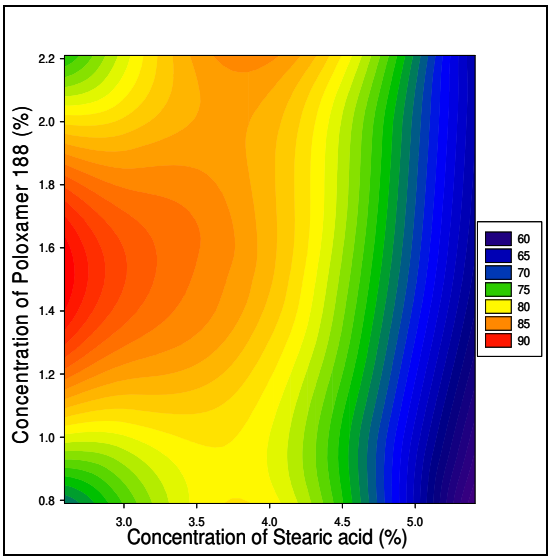

Figure 4: Contour plot of percent drug release

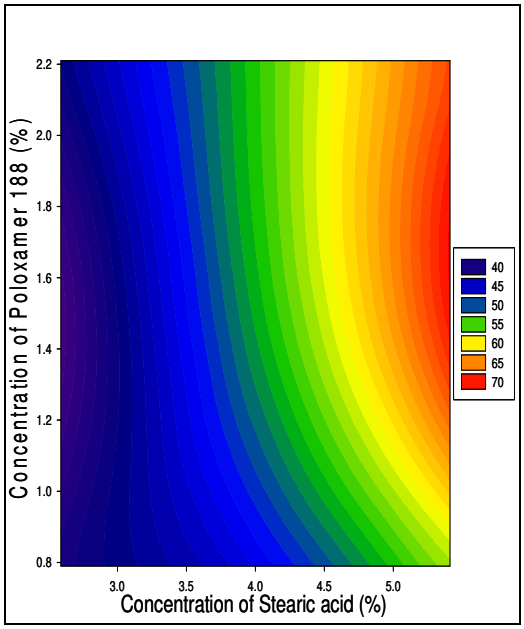

Figure 5: Contour plot of percent drug loaded

In order to get an optimized batch with greater than 85 % of Glibenclamide release in 24 hrs and % Glibenclamide loading greater than 50 %, superimposing of both curves was done and figure is plotted below in Figure 6.

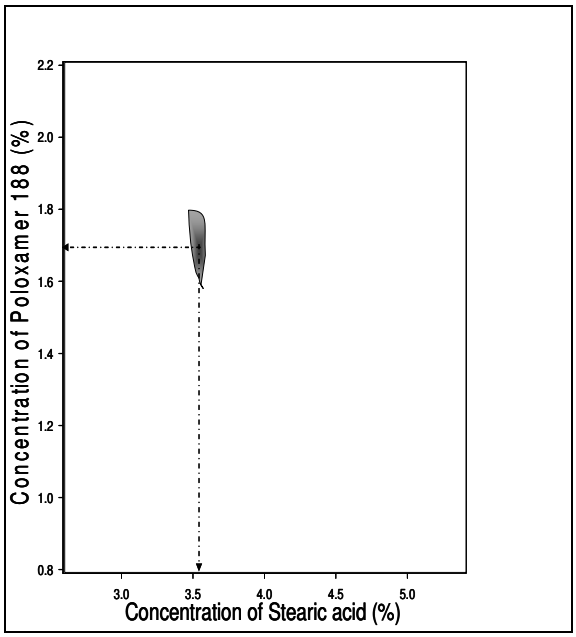

Figure 6: Contour plot of percent drug loaded

From superimposed curve, it was found that 3.6 % of Stearic acid and 1.7 % of Poloxamer 188 are optimized concentrations for preparing desired batch.

The check point batch was prepared and showed good diffusion of about 90.59% in 24 hours, particle size of 290 to 420nm (shown in figure 7) and pH 6.2 The formulated dosage form of Glibenclamide was stable, since the stability study was carried out for two months at 40°C ± 2°C and 75% RH ± 5% RH [7] [8].

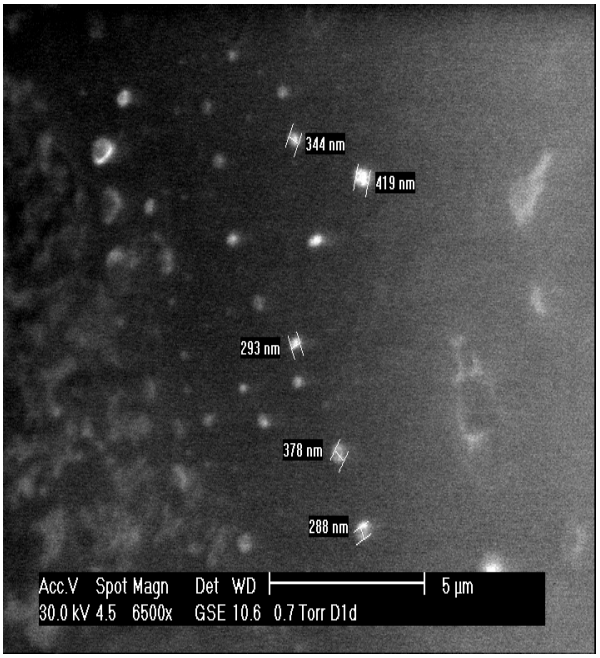

Figure 7: SEM image of check point batch

4. CONCLUSION

Novel In-situ nasal gel containing glibenclamide nanoparticles can change the current medical therapy provided to diabetic geriatrics by pharmacist and offers them a best advantages since the patient experience difficulty in swallowing oral solid unit dosage form along with the disadvantage which mentioned earlier regarding oral administration of glibenclamide. Glibenclamide loaded solid lipid nanoparticles dispersion is an ideal dosage form for controlled mode of nasal drug delivery, and also can be used for other such low dose drug molecules.

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Sr No.	Ingredients	Function	Qty	Qty limit as per IIG guide
1	Glibenclamide	API	2 g	--
2	Poloxamer 188	Surfactant	1.7 g	0.6 mg (S/C) to 2.5% (Oral)
3	Stearic acid	Release retardant	3.6 g	5.4mg (oral) to 30% (Topical)
4	Menthol	Nasal decongestant	0.1 g	0.05% (Nasal)
5	Carbomer 934P	Gelling agent	0.5 g	0.9 to 1.5% (Topical)
6	Benzalkonium chloride	Preservative	0.05 g	0.05% (Nasal)
7	Distilled water	Vehicle	100 ml	--

Table 4: Final formulation