DESIGN AND CHARACTERIZATION OF MUCOADHESIVE GLIPIZIDE MICROSPHERES

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Summary

The objective of the present investigation was to design and characterization of mucoadhesive glipizide microsphere using carbopol 974 as polymer. Glipizide is a second-generation oral anti-diabetic drug used in type-2 diabetes (Non-Insulin dependent diabetes mellitus) that can acutely lower the blood glucose level in humans by Stimulation the release of insulin from the pancreas. Its shot biological half life (0.3+0.7 hours) necessitates that it be administered in 2 or 3 doses of 2.5 to 10 mg of per day. Microspheres were prepared by simple emulsification phase separation technique using glutaraldehyde as a crosslinking agent. Twenty preliminary trail batches F1-F20 of microspheres were prepared by using different volume (10 to70 ml) of glutaraldehyde as cross linking agent ,cross linking time 1 to 4 hours and polymer-to- drug ratio 3:1. From these batches the optimized formulation is selected based on the percentage of mucoadhesion and sphericity of microspheres. On the basis of the preliminary trials 3^2 full factorial design were employed, to study the effect of independent variable X_1 (polymer-to- drug ratio 1:1, 3:1 and 6:1) and the stirring speed X_2 (500, 1000 and 1500rpm) on dependent variables percentage mucoadhesion, drug entrapment efficiency, particle size and t80. The drug polymer compatibility studies were carried out using FTIR. The stability studies were

conducted for the optimized formulation. The optimized formulation exhibited a high drug entrapment efficiency of 60%, swelling index 0.42, Percentage of mucoadhesive after 1hour 62% and the drug release was also sustained for more than 12 hours.

Keywords: Mucoadhesive microspheres, Glipizide, Carbopol 974, Glutaraldehyde.

Introduction

A primary object of using muco adhesive formulations orally would be to achieve a substantial increase in length of stay of the drug in the GI tract. Stability problem in the intestinal fluid can be overcome. Therapeutic effect of drugs insoluble in the intestinal fluids can be improved[5]. Muco adhesive microsphere carrier systems are made from the biodegradable polymers in sustained drug delivery. Recently, dosage forms that can precisely control the release rates and target drugs to a specific body site have made an enormous impact in the formulation and development of novel drug delivery systems[1-3]. Microspheres form an important part of such novel drug delivery systems. They have carried applications and are prepared using assorted polymers[1]. However, the success of these microspheres is limited owing to their short residence time at the site of absorption. It would therefore be advantageous to have means for providing an intimate contact of the drug delivery system with the absorbing membranes[6-9]. This can be achieved by coupling bioadhesion characteristics to microspheres and developing bioadhesive microspheres. Bioadhesive microspheres have advantages such as efficient absorption and enhanced bioavailability of drugs owing to a high surface-to-volume ratio a much more intimate contact with the mucus layer and specific targeting of drugs to the absorption site[10-13].

Glipizide is a second-generation oral anti-diabetic drug used in type-2 diabetes (Non-Insulin dependent diabetes mellitus) that can acutely lower the blood glucose level in humans by stimulation the release of insulin from the pancreas. It's shot biological half life (0.3+0.7 hours) necessitates that it be administered in 2 or 3 doses of 2.5 to 10 mg of per day[18,20,21]. Carbopol 974 is a synthetic good muco-adhesive and biodegradable polymers.

Thus the development of controlled-release dosage forms would clearly be advantageous. Moreover, the site of absorption of Sulfonyl ureas is in the stomach. Dosage forms that are retained in the stomach would increase the absorption, improve drug efficiency, and decrease

dose requirements. Thus, an attempt was made by using synthetic mucoadhesive polymer (Carbopol 974) by using Glipizide as a drug. On the basis of the preliminary trials a 3^2 full factorial design were employed for all the polymers batches, to study the effect of independent variable X_1 (polymer-to- drug ratio1:1, 3:1 and 6:1) and the stirring speed X_2 (500, 1000 and 1500rpm) on dependent variables percentage mucoadhesion, drug entrapment efficiency, particle size and t80. The drug polymer compatibility studies were carried out using FTIR. The stability studies were conducted for the optimized formulation.

Materials and Method

Glipizide was obtained as gift sample from Madras Pharmaceuticals, Chennai. Carbopol 974 was obtained from Zydus Cadila, Ahamedabad. 0.5% Span 85. Acetic acid, Petroleum ether, Light and heavy Liquid paraffin, Glutaraldehyde of analytical grade are used.

UV Spectrophotometer, Scanning Electron Microscopy, USP XXIV, Basket apparatus (Dissolution), HPLC, Image analyser, Sieve analyser, Optical Microscope, Propeller stirrer (1000 rpm), USP Tablet disintegration apparatus.

Preparation of microspheres

Microspheres were prepared by simple emulsification phase separation technique by using Carbopol 974 as polymer and different volume of cross linking agent (Glutaraldehyde) is added as per method described in Thanoo et al[14].

Carbopol 974 (1.5 gms) was dissolved in 150 ml of 1% v/v aqueous acetic acid solution and the drug (500mg) was dispersed in the polymer solution. Twenty preliminary trial batches were prepared using the polymer to drug ratio 3:1 and stirring was performed using a propeller stirrer at 1000 rpm kept constant. The resultant mixture will be extruded through a syringe (No.20) in 1 lit of liquid paraffin (Heavy and light 1:1 ratio). Containing 0.5% Span 85 and stirring was performed using propeller stirrer. After 15 min cross linking agent glutaraldehyde (25% v/v aqueous solution) was added and stirring was continued. The amount of cross linking agent and cross liking time was varied 10- 70ml and 1 to 4 hours. In factorial design batches B1-B9, the optimized amount of glutaraldehyde was used as a cross linking agent and cross linking time. The Polymer –to-Drug ratio (1:1, 3:1 and 6:1) and Stirring speed (500, 1000 and 1500rpm) were varied in nine batches. Microspheres thus obtained were filtered and washed several time

with petroleum ether (80:20) to remove traces of oil. They were finally washed with water to remove excess of cross linking agent. The microspheres were then dried at room temperature (at 25^0C and 60% RH for 24 hours).

Evaluation of microspheres

Drug content

According to literature review the assay for second generation oral-anti diabetic drugs like Glipizide was estimated by ultraviolet visible (UV/VIS) spectrophotometric method. Aqueous solution of drug was prepared in phosphate buffer (pH 7.4) and absorbance is measured on ultraviolet visible spectrophotometer at 276 nm[22]. The method is validated for linearity, accuracy and precision. The method obeys Beer's law in the concentration range of 5- 50 mcg/ml, a standard drug solution was analysed repeatedly, the mean error (accuracy) and relative standard deviation (Precision) were determined.

Drug entrapment efficiency

50 mg of microspheres were crushed in a glass mortar and pestle, and the powdered microspheres was suspend in 10 ml of phosphate buffer solution (pH 7.4). After 24 hours, the solution filtered and the filtrate is analysed for the drug content. The drug entrapment efficiency is calculated using the following formula; Practical drug content/Theoretical drug content x 100.

Particle size

The particle size of the microspheres was determined by using optical microscopy method[23]. Approximately 50 microspheres are counted for particle size using a calibrated optical microscope.

Swelling Index of Microspheres

For estimating the swelling index, the 100 microspheres was suspended in 5ml of simulated gastric fluid USP (pH 1.2). The particle size would be monitored by microscopy technique every 1 hour using an optical microscope. The increase in particle size of the microspheres will be noted for up to 8 hours and the swelling index is calculated as per method described by Ibrahim.

In-Vitro Wash-off test for Microspheres

The mucoadhesive properties of the microspheres are evaluated by in-vitro wash-off test reported by Lehr et al. A 1cm by 1cm piece of rat stomach mucosa was tied onto a glass slide (3inch by 1inch) using thread. Microspheres are spread onto the wet rinsed tissue specimen, and the prepared slide is hung onto one of the groves of a USP tablet disintegrating test apparatus. The disintegrating test apparatus is operated such that the tissue specimen was given regular up and down movements in a beaker containing the simulated gastric fluid USP (pH 1.2). At the end of 30 minutes, 1 hour, and at hourly intervals up to 10 hours, the number of microspheres still adhering onto the tissue is counted.

Drug release study

The drug release study will performed using USP XXIV basket apparatus[22]. At 37^0C+0.5^0C and 50rpm using 900ml of phosphate buffer (pH7.4) was a dissolution medium. Microspheres equivalent to 10 mg of glipizide were used for the test. Five ml of sample was withdrawn at predetermined time intervals and filtered through a 0.45 micron membrane filter, diluted suitably and analyzed. Spectrophotometrically an equal amount of fresh medium was replaced immediately after withdrawn of the test sample. Percentage drug dissolved at different time intervals was calculated using the Lamberts-Beer's law equation. The t80 was calculated using the weibullequation.

Scanning electron microscopy

A scanning electron photomicrograph of drug-loaded mucoadhesive microspheres was taken. A small amount of microspheres was spread on glass stub. Afterwards, the stud containing the sample was placed in the scanning electron microscope chamber. The scanning electron photomicrograph is taken at the acceleration voltage of 20kv chamber pressure or 0.6mm Hg, Original magnification X 800[11].

Stability testing

Formulations of glipizide loaded microspheres were tested for stability studies. Both the formulations were divided into 3 sample sets and stored at:

4 ± 1^0C, 25 ± 2^o C & 60 ± 5% RH and 37 ± 2^oC & 65 ± 5% RH.

After 30 days, the drug release of selected formulations was determined by the method discussed previously in vitro drug release studies and percentage entrapment efficiency was also carried out for the same formulation.

Release kinetics and mechanism

To know the release mechanism and kinetics of Glipizide, optimized formulation was attempted to fit in to mathematical models and n, r^2 values for zero order, First order, Higuchi and Peppas models were represented. The peppas model is widely used, when the release mechanism is not well known or more than one type of release could be involved. The semi-empirical equation (Peppas *et al*., 1985) shown as equation.

Mt/M∞ = ktn

Where, *M*t/*M*∞ is fraction of drug released at time't', k represents a constant, and n is the diffusional exponent, which characterizes the type of release mechanism during the dissolution process. For non-fickian release, the value of n falls between 0.5 and 1.0; while in case of fickian diffusion, n = 0.5; for zero-order release (case II transport), n = 1; and for supercase II transport, n > 1. Observation of all the r^2 values indicated that the highest r^2 (0.9756) value was found for Zero order release. According to 'n' value it is one, so it follows non-fickian diffusion with zero order release (case II transport).

3^2 full factorial design layouts

A statistical model incorporating interactive and polynomial terms was utilized to evaluate the responses.

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_1^2 + b_{22}X_2^2$$

Where, Y is the dependent variable, b_0 is the arithmetic mean response of the nine runs, and bi is the estimated coefficient for the factor X_1. The main effects (X_1 and X_2) represent the average result of changing one factor at a time from its low to high value. The interaction terms (X_1X_2) show how the response changes when two factors are simultaneously changed. The polynomial terms (X_1^2 and X_2^2) are included to investigate non-linearity. On the basis of the preliminary trials a 3^2 full factorial design was employed to study the effect of independent variables i.e. drug:polymer ratio (X_1) and the stirring speed at rpm (X_2) on dependent variables % mucoadhesion, drug entrapment efficiency, particle size and the time required for 80% drug dissolution (t_{80}).

Result and Discussion

The mucoadhesive microspheres of an oral anti-diabetic drug glipizide were prepared by simple emulsification phase separation technique. Carbopol 974 was selected as a synthetic

polymer for the preparation because of its biodegradable and mucoadhesive properties. Acetic acid from 1% to 8% v/v was used to prepare polymer solution. But no effect of concentration of acetic acid was observed on percentage mucoadhesion or drug entrapment efficiency, therefore 1% v/v of acetic acid was used.

Polymer concentration is important factors, mention in Lee et al and based on Viscosity of polymers solution. Three different concentrations 0.5%, 1% & 2% v/v were selected. From this 1% concentration show a maximum sphericity was observed so we select 1% w/v of polymer in 1% v/v acetic acid solution and 1:1 Heavy and light paraffin was used as dispersion medium and 0.5% v/v of Span 85 was added as a surfactant to dispersion medium.

The volume of cross linking agent (10-70ml) and stirring time were varied from 1 to 4 hours. From 20 preliminary trial batches F1-F20, spherical free flowing microspheres were obtained by using 60-70 ml of glutaraldehyde F9-F20, shown in the Table I.Microspheres batches F1-F4 prepared by using 10 ml glutaraldehyde showed very irregular shaped microspheres and percentage of mucoadhesion also good but drug entrapment efficiency is not good. Batches F5-F8 prepared by using 20ml of glutaraldehyde showed good mucoadhesion properties and Drug entrapment efficiency. Batches F9-F12 was prepared by using 40ml of glutaraldehyde showed spherical free flowing microspheres and also shows good mucoadhesion and 60% of drug entrapment efficiency. Batches F13-F16 was showed 68% of drug entrapment efficiency and also showed 81% mucoadhesion. The batches F17-F20 was showed spherical free flowing microspheres and showed 68% of drug entrapment efficiency and decrease in mucoadhesion take place. As the cross linking agent increases, the mucoadhesiveness is decreases and crosslinking time did not show a significant effect on the percentage of drug entrapment efficiency, shown in Table I.

From these preliminary trial batches the best optimized formula is selected. On the basis of the preliminary trials 3^2 full factorial design were employed, to study the effect of independent variable X_1 (polymer-to- drug ratio 1:1, 3:1 and 6:1) and the stirring speed X_2 (500, 1000 and 1500rpm) on dependent variables percentage mucoadhesion, drug entrapment efficiency, particle size and t80.The results depicted in Table II clearly indicate that all the dependent variables are strongly dependent on the selected independent variable as they show a wide variation among the nine batches. The polynominal equations can be used to draw conclusions after considering the magnitude of coefficient and the mathematical sign it carries (ie.positive or negative).The

dependent variables indicate a good fit. All the nine batches B1-B9 were prepare by using 60ml of glutaraldehyde and 3hours crosslinking time shown in Table II. The in vitro wash of test for percentage mucoadhesion after 1 hour varied from 38 to 64 and showed good correlation coefficient. Indicates that the effect of X_1(polymer-to-drug ratio) is more significant thanX_2 (stirring speed). Moreover, stirring speed had a negative effect on percentage mucoadhesion (the stirring speed increased means the % of mucoadhesion is decreased).This finding may be attributed to the change in particle size that affects mucoadhesion. Similar results were obtained for swelling index. Thus, the polymer concentration increased the swelling index also increased. The swelling index varied from 0.287 to o.664 and showed good correlation coefficient.Thus, we can conclude that the amount of polymer and stirring speed directly affect the percentage mucoadhesion and swelling index.

The drug entrapment efficiency varied from 28% to 60% and showed good correlation coefficient. Indicates that the effect of X_1(polymer-to-drug ratio) is more significant thanX_2 (stirring speed). Moreover, stirring speed had a negative effect on drug entrapment efficiency (the stirring speed increased means the particle size and drug entrapment efficiency was decreased). Mucoadhesive microspheres of all the nine batches shows spherical and free flowing. They range in particle size from 46 to 69. The stirring speed has negative effect on t_{80} because as the particle size increased the drug release decreases. Batch B5 is the optimized formulation and they are spherical free flowing shown in Fig 1.

In vitro drug release studies were carried out the percentage drug dissolved at different time interval was calculated using the Lambert's-Beer's equation. The t_{80} was calculated using the weilbull equation. The average values of t_{80} for batches B1 to B9 are mentioned in Table II
The stability studies were carried out by storing the optimized formulations at $4^0 \pm 1^0$c, 25 $\pm 2^0$c & 60 $\pm$ 5% RH and 37$\pm 2^0$c & 65$\pm$5%RH for one month. Two parameters namely percentage entrapment efficiency and invitro release studies were carried out. The drug release at 4 ± 1^0c. showed 90.78% and percentage entrapment efficiency 70.34%, the drug release at 25 $\pm 2^0$c & 60 $\pm$ 5% RH showed 94.56% and percentage entrapment efficiency 70.45% and the drug release at 37 $\pm 2^0$c & 65 $\pm$ 5% RH showed 89.78% and percentage entrapment efficiency 67.89%.

In vitro drug release of the optimized formula B5 is given in Table III and Model fitting for the release profile of formulations was shown in table IV.

Conclusion

The results of a 3^2 full factorial design revealed that the polymer-to-drug ratio and stirring speed significantly affected the dependent variables percentage mucoadhesion, drug entrapment efficiency, particle size, swelling index. As the concentration of glutaraldehyde increases, the mucoadhesiveness decreases and there was no significant effect in time. Stirring speed has negetive effect on t80.The microspheres of the best batch exhibited a high percentage mucoadhesion of 62% after 1 hour and 60% drug entrapment efficiency. The microsphere of glipizide could sustain the release of the drug for more than 12 hours.

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Table No. I Preliminary Trial Batches of glipizide mucoadhesive microsphere by using Carbopol 974

Batchcode	Vol. of glutaraldehyde (ml)	Cross linking time(h)	% Mucoadhesion after 1 hr.	Drug Entrapment Efficiency (%)	Sphericity of microsphere
F1	10	1	88	36	Very Irregular
F2	10	2	82	38	
F3	10	3	77	40	
F4	10	4	71	42	
F5	20	1	84	49	Slightly Irregular
F6	20	2	78	53	
F7	20	3	71	55	
F8	20	4	65	58	
F9	40	1	75	55	Spherical from following
F10	40	2	69	57	
F11	40	3	62	59	
F12	40	4	61	60	
F13	60	1	87	61	
F14	60	2	83	62	
F15	60	3	79	68	
F16	60	4	62	70	
F17	70	1	61	68	
F18	70	2	54	70	
F19	70	3	47	74	
F20	70	4	41	76	

Note: All batches were prepared by polymer to drug ratio of 3:1 at 1000 rpm speed

Table No. 11 Formulation of Carbopol 974 loaded glipizide mucoadhesive microsphere by using 3^2 full Factorial design layouts

Batch Code	Variable levels in coded from		% Mucoadhesion After1h	Drug Entrapment Efficiency (%)	Swelling Index	Particle Size	T80 (min.)
	X_1	X_2					
D1	-1	-1	46	38.14	0.318	50.0	243
D2	-1	0	40	33.68	0.306	46.5	236
D3	-1	1	38	28.25	0.287	44.3	223
D4	0	-1	64	51.32	0.492	59.4	211
D5	**0**	**0**	**62**	**60.35**	**0.424**	**58.1**	**232**
D6	0	1	58	58.25	0.380	51.3	241
D7	1	-1	52	46.15	0.664	69.0	478
D8	1	0	48	37.45	0.644	65.5	448
D9	1	1	42	31.65	0.582	61.8	401

Note: All batches were prepared by using 60ml glutraldehyde and crosslinking time 3h

Translation of coded levels in actual units			
Variables level	**Low (-1)**	**Medium (0)**	**High (+1)**
Polymer: Drug Ratio (X_1)	1:1	3:1	6:1
Stirring speed rpm (X_2)	500	1000	1500

Table No. III In-vitro Release profile Glipizide mucoadhesive microsphere formulation Carbopol 974 B5

Time	Root Time	Log time	Abs	CDR	% CDR	Log % CDR	% Drug Retained	Log % Drug Retained	(%Retained)$^{1/3}$
1	1	0	0.0278	4.712	23.56	1.372	76.44	1.883	4.243
2	1.414	0.3010	0.0320	5.948	29.74	1.473	70.26	1.846	4.126
3	1.752	0.4771	0.0363	7.236	36.18	1.558	63.82	1.804	3.996
4	2	0.6020	0.0400	8.448	42.24	1.625	57.76	1.761	3.865
5	2.236	0.6989	0.0450	9.996	49.98	1.698	50.02	1.699	3.684
6	2.441	0.7781	0.0496	11.506	57.53	1.759	42.47	1.628	3.488
7	2.645	0.8450	0.0565	13.638	68.19	1.833	31.81	1.502	3.168
8	2.828	0.9030	0.0645	15.642	78.21	1.893	21.79	1.338	2.793

Table No. IV Model Fitting for the Release Profile of Formulations R= correlation coefficient; n= slope (≤0.5 – fickian diffusion; 0.5<n<1 – non fickian diffusion; 1 – Case – II transport; >1 – super case –IItransport

Formulation Code	Zero Order	First Order	Higuchi Matrix	Korsmeyer-Peppas		Hixon-Crowell	Best Fit Model
	R	R	R	R	N	R	
Carbopol 974	0.988	0.921	0.943	0.953	0.572	0.950	Zero

Fig No.1 scanning electron microphotograph of glipizide loaded Carbopol 974 mucoadhesive microspheres