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Anti-Hyperglycaemic Effect of Glipizide Implants In Alloxan Induced Diabetic Rabbits

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***Abstract:-*Diabetes mellitus is a chronic metabolic disorder characterized by hyperglycemia caused by defective insulin secretion, resistance to insulin action or combination of both. Frequent administration of ant diabetic drug dosage form leads to some side effects and affect on patients compliance, so there is need to develop a sustained release dosage form to enhance patients compliance and reduced dosing frequency. So attempt has been made to prepare and evaluate sub dermal biodegradable implants of Glipizide.**

Keywords:-*Diabetes, Implants, Glipizide, Alloxan Induced, Ant hyperglycemic.*

I INTRODUCTION

The primary goals of DM management are to reduce the risk for micro vascular and macro vascular disease complications, to ameliorate symptoms, to reduce mortality, and to improve quality of life. Near normal glycemia will reduce the risk for development of micro vascular disease complications, but aggressive management of traditional cardiovascular risk factors (i.e., smoking cessation, treatment of dyslipidemia, intensive blood pressure control and ant platelet therapy) are needed to reduce the likelihood of development of macro vascular disease. Evidence based guidelines, as published by the ADA, can help in the attainment of these goals. [1]

Hyperglycemia not only increases the risk for micro vascular disease, but contributes to poor wound healing, compromises white blood cell function, and leads to classic symptoms of DM. Diabetic ketoacidosis and hyperosmolar hyperglycemic state are severe manifestations of poor diabetes control, invariably requiring hospitalization. Reducing the potential for micro vascular complications is targeted at adherence to therapeutic lifestyle intervention (i.e., diet and exercise programs) and drug-therapy regimens, as well as at maintaining blood pressure as near normal as possible.[2]

II EXPERIMENTAL METHOD

2.1 Preparation of Implants

Gelatin based drug implants were prepared aseptically by using following method.

Weighed quantity of gelatin and sodium alginate (70:30, 80:20 and 90:10 % w/w) were sprinkled on the surface of the water in a beaker on continuous stirring to avoid formation of lumps and allowed to hydrate for 15 minutes. Glycerin (18%w/w) as a plasticizer was added and heated over a water bath at 60^0 C until gelatin dissolves.

In other beaker drug was dissolved in the little quantity of Chloroform Then this drug solution was added in the above gelatin, sodium alginate solution. (formulae shown in table no. 1) Homogeneous mixture of drug and polymers solution was poured into glass Petri dish (10cmX10cm) to a 3mm height and allowed to congeal for 30 minutes by placing the petri dish in ice cooled water and dried at room temperature for 72 hours. After drying the implants were cut into size of 3 mm thickness and 6 mm length by a sterile stainless steel cutter. All prepared formulations were stored at aseptic chamber. [3]

TABLE I FORMULAE OF IMPLANTS

Ingredients	Formulation		
	F1	F2	F3
Glipizide	1.5% w/w	1.5% w/w	1.5% w/w
Gelatin & Sodium alginate Mix.	30% w/w	30% w/w	30% w/w
Glycerin	18% w/w	18% w/w	18% w/w
Chloroform	2% v/v	2% v/v	2% v/v
Water q.s	100 gms.	100 gms.	100 gms.

F1 = Gelatin: Sodium Alginate- 70%: 30% w/w
F2 = Gelatin: Sodium Alginate- 80%: 20% w/w
F3 = Gelatin: Sodium Alginate- 90%: 10 % w/w

2.2. in-vivo evaluation studies of drug action for antihyperglycemic effect

The approval of the Institutional Animal Ethical Committee was obtained for the study. In vivo evaluation of drug implants was carried out in alloxan induced diabetic rabbits by measuring the lowering of blood glucose levels at predetermined time intervals after their implantation into subcutaneous tissue at thigh region. [4-11]

2.2.1 Animals

Male Rabbits weighing around 2.5 kg were procured from Mahadevappa Rampure Medical College, Gulbarga, Karnataka. The animals were housed individually in cages under environmentally controlled conditions (temperature 37ºC and 12 hr lighting cycle). The animals were fed as usual with a standard rabbit diet that is commercially available and had access to water *ad libitum*.

2.2.2 Induction of Diabetes in Experimental Animals

Male rabbit after fasting for 24hr prior to treatment, 140-150mg/kg of body weight alloxan monohydrate solution (3 % alloxan prepared with normal saline solution and sterilized by filtration) was injected into the marginal ear vein of rabbits, which were then kept in different cages and supplied food and drink *ad libitum*. 72 hr later, rabbits had stabilized with a blood glucose concentration above 250-280 mg/dl were used for the study.

2.2.3 Screening of Animals

Four groups of rabbits, five in each received the following treatment schedule.

Group I: Diabetic control

Group II: Glipizide Implants (1mg/kg body weight, subcutaneously)

Group III: Glipizide Implants (2mg/kg body weight, subcutaneously)

Group IV: Glipizide Implants (4mg/kg body weight, subcutaneously)

2.2.4 Collection of Blood Samples and Blood Glucose Determination

Blood samples were collected from the marginal ear vein at an interval of 24 hrs (1 day) up to 12 days and were analyzed for blood glucose by GOD/POD method by using Glucose estimation kit from Span Diagnostic Ltd., Mumbai.

2.2.5 Statistical Analysis

All the data expressed as mean ± SEM were evaluated by one-way analysis of variance (ANOVA). Value of $p<0.05$ were considered as statistically significant.

III RESULTS AND DISCUSSION

In this set of experiment, dose response relationship of Glipizide implants (F3) hardened with formaldehyde for 6 hr, were studied at different doses (1, 2 & 4mg/ kg body weight) in alloxan induced diabetic rabbits (R1, R2 & R3) for a period of 12 days.

In vivo study data revealed that, in rabbits (R1) group maximum reductions in blood glucose level were observed from a period of 3rd to 5th day and it was found to be 189±2.27, 176±3.31 and 198±3.14 respectively. In rabbits (R2) group a maximum reductions in blood glucose level were observed from 3rd to 7th day, and it was found to be 174±3.11, 172±3.45, 167±3.38, 170±3.22 and 173±3.70 respectively. A maximum reduction in blood glucose level of rabbits (R3) group was observed as 174±4.42, 169±3.63, 169±4.97, 168±3.54, 163±3.56, 170±3.02 and 169±3.12 from 3rd day to 9th day respectively.

The result showed that, Glipizide implants at a dose of 4mg/kg body weight were found to produce an optimal reduction in blood glucose level of alloxan induced diabetic rabbits group (R3).

TABLE II REDUCTION IN BLOOD GLUCOSE OF RABBITS (R1) WITH 1MG/KG BODY WEIGHT GLIPIZIDE IMPLANTS

Time (Days)	Reduction in blood glucose (mg/dl) of Rabbits group (R1)					
	Animal 1	Animal 2	Animal 3	Animal 4	Animal 5	Mean ±SEM
1	240	241	239	241	240	240±3.47
2	206	204	205	205	206	205±2.91
3	190	189	187	190	190	189±2.27 *
4	176	177	176	178	174	176±3.31 *
5	198	198	199	197	199	198±3.14 *
6	214	216	213	215	214	214±4.87
7	241	243	240	242	241	241±3.93
8	240	241	239	241	241	240±3.87
9	249	249	249	250	250	249±3.21
10	254	255	257	256	255	255±3.46
11	258	257	259	256	257	257±4.57
12	261	262	261	262	261	261±4.32

TABLE III REDUCTION IN BLOOD GLUCOSE OF RABBITS (R2) WITH 2MG/KG BODY WEIGHT GLIPIZIDE IMPLANTS

Time (Days)	uction in blood glucose (mg/dl) of Rabbits group (R2)					
	Animal 1	Animal 2	Animal 3	Animal 4	Animal 5	Mean ±SEM
1	240	242	241	243	241	241±3.65
2	201	198	199	198	200	199±2.34
3	174	175	173	174	176	174±3.11*
4	171	173	171	173	174	172±3.45*
5	166	168	167	167	169	167±3.38*
6	169	171	170	170	172	170±3.22*

7	173	175	172	173	174	173±3.70*
8	215	213	216	214	214	214±4.38
9	229	227	230	231	230	229±4.31
10	244	242	245	247	245	244±4.73
11	252	253	254	253	255	253±4.64
12	261	263	261	263	261	261±4.73

TABLE IV REDUCTION IN BLOOD GLUCOSE OF RABBITS (R3) WITH 4MG/KG BODY WEIGHT GLIPIZIDE IMPLANTS

Time (Days)	Reduction in blood glucose (mg/dl) of Rabbits group (R3)					
	Animal 1	Animal 2	Animal 3	Animal 4	Animal 5	Mean ±SEM
1	241	239	241	240	240	207±3.49
2	207	209	207	206	208	174±4.42*
3	172	174	174	175	177	169±3.63*
4	168	170	169	169	171	169±4.97*
5	169	170	171	168	169	168±3.54*
6	169	168	170	168	167	163±3.56*
7	163	162	164	163	165	170±3.02*
8	169	170	170	171	172	169±3.12*
9	168	169	169	170	171	215±4.71
10	215	217	215	214	216	243±4.35
11	244	243	241	244	245	257±4.62
12	257	256	258	257	259	

TABLE V DOSE RESPONSE RELATIONSHIP OF GLIPIZIDE IMPLANTS IN ALLOXAN INDUCED DIABETICS RABBITS

Time (Days)	Reduction in blood glucose level (mg/dl) (mean±SEM) (n=5)			
	Diabetic control	(R1) 1mg/kg b.w Glipizide	(R2) 2mg/kg b.w Glipizide	(R3) 4mg/kg b.w Glipizide
1	264±4.38	240±3.47	241±3.65	240±3.48
2	265±3.90	205±2.91	199±2.34	207±3.49
3	261±4.12	189±2.27*	174±3.11*	174±4.42*
4	262±4.46	176±3.31*	172±3.45*	169±3.63*
5	258±3.57	198±3.14*	167±3.38*	169±4.97*
6	262±3.83	214±4.87	170±3.22*	168±3.54*
7	264±3.21	241±3.93	173±3.70*	163±3.56*
8	260±3.54	240±3.87	214±4.38	170±3.02*
9	261±4.34	249±3.21	229±4.31	169±3.12*
10	259±3.18	255±3.46	244±4.73	215±4.71
11	258±3.91	257±4.57	253±4.64	243±4.35
12	258±3.78	261±4.32	261±4.73	257±4.62

A 25% reduction in blood glucose level is considered as a significant ant hyperglycemic effect. The ant hyperglycemic effect was maintained from 3rd to 9th days. (results tabulated in table no. 5)

The sustained ant hyperglycemic effect observed over longer periods, due to the slow release and absorption of Glipizide over longer periods of time.

IV CONCLUSION

In vivo studies of Ant hyperglycemic effect in alloxan induced diabetic rabbits were revealed Glipizide implants produced an optimal percentage reduction in blood glucose levels of rabbits group (R3) at dose of 4mg/kg body weight.

Use of biodegradable polymers in implantable dosage forms has added advantage for prolonged therapeutic activity. In the present investigation gelatin and sodium alginate were used for formulation of drug implants and to sustain the drug release for prolonged period of time by cross linking with formaldehyde. Glipizide drug implants can be used as ant hyperglycemic dosage forms for the treatment of diabetes mellitus. As they meet the criteria such as improved therapeutic outcome and minimum incidence of adverse effects

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