



EVALUATION OF GLYCEMIC CONTROL WITH FLOATING TABLETS OF METFORMIN HCL IN ALLOXAN INDUCED DIABETIC RATS

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ABSTRACT

Metformin HCL is an oral anti-diabetic drug in the biguanide class. Metformin HCL improves glycemic control primarily through its suppression of hepatic glucose production. The Floating tablets of Metformin HCL containing Xanthan gum has to be selected for the present evaluation. The present evaluation of glycemic control with floating tablets of Metformin HCL in alloxan (110 mg/kg of Alloxan monohydrate, i.p) induced diabetic rats. The result suggested that frequent dosing and possible incomplete absorption of the drug can be avoided with Metformin HCL floating tablet (FM3). Therefore, it concluded that drug (Metformin HCL) suitable for floating drug delivery system with a new choice of an economical, safe and enhances the bioavailability formulation in the management of type II diabetes mellitus.

Keywords:-Metformin Hydrochloride, Floating Tablets, Alloxan Monohydrate, Glycemic Control.

INTRODUCTION

Metformin HCL is an oral anti diabetic drug in the biguanide class. It is the first line drug of choice for the treatment of Type II diabetes particularly in over weight and obese people and those with normal kidney function (Tripathi KD *et al.*, 2009). Metformin HCL improves glycemic control primarily through its suppression of hepatic glucose production (hepatic gluconeogenesis). The Sustained release preparation of Metformin HCL not only will offer improved patient's compliance but also may improve the pathophysiology of the disease. By sustained release tablets, we can minimize the drug dose. Therefore the best formulation (FM3) has to be selected for the present evaluation of glycemic control with floating tablets of Metformin HCL in alloxan induced diabetic rats.

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MATERIALS AND METHODS

Materials

Metformin Hydrochloride was a Gift sample from Medley Pharmaceuticals, Gujarat.

Methods

Preparation of Metformin Hydrochloride Floating tablets

Tablets were prepared by wet granulation method. Metformin Hydrochloride (500 mg) was mixed with required amount of polymers and other excipients (Table I). All the excipients were passed through sieve no. 40, mixed and granulated with 10% solution of PVP K-30 in isopropyl alcohol. The wet mass was passed through sieve no.16 and dried at 45°C for 2 hrs. Dried granules were passed through sieve no. 20 and mixed with magnesium stearate and talc (Raju DB *et al.*, 2010). In vitro release studies were carried out by using USP paddle dissolution test apparatus. The Floating tablets of

Metformin HCL containing Xanthan gum (FM3) showed satisfactory results with invitro drug release profile (Mohamed Raffick M *et al.*, 2012), short buoyancy lag time and total buoyancy time more than 12 hrs and the drug release (FM3) has better control over release of drug when compared to marketed product. The best formulation (FM3) has to be selected for the present evaluation of glycemic control with floating tablets of Metformin HCL in alloxan induced diabetic rats.

INVIVO STUDIES

Anti-diabetic Activity

The method of Dash *et al* was followed. The FM3 Metformin Hcl (100 mg/kg, p.o) was suspended in 1% w/v CMC in distilled water, pure drug Metformin Hcl (100mg/kg, p.o) and Marketed Drug (Metformin Hcl SR(Glyciphage SR), 100 mg/kg, p.o), suspended in 1% w/v CMC in distilled water used as reference control during the study. All the test samples were administered through p.o route.

Alloxan-induced diabetes test

The acclimatized rats were kept fasting for 24 h with water *ad libitum* and injected intraperitoneally a dose of 110 mg/kg of Alloxan monohydrate in normal saline. Rats were considered diabetic when the blood glucose level was raised beyond 150 mg/dl of blood. This condition was observed at the end of 48 h after Alloxanisation (Shivananda N *et al.*, 2006).

Experimental Design

The rats were segregated into four groups of six rats in each. Group I - diabetic control and rats received only vehicle (2 ml/kg, p.o) 1% CMC once daily for 7 days, Group II - rats received FM3 Metformin Hcl (100 mg/kg, p.o) suspended in 1% w/v CMC once daily for 7 days, Group III - rats received pure drug Metformin Hcl 100 mg/kg, p.o suspended in 1% w/v CMC once daily for 7 days and Group IV - rats received Marketed Drug (Metformin Hcl SR 100 mg/kg, p.o) suspended in 1% w/v CMC once daily for 7 days. Blood glucose levels were examined after 2, 12, 24, 72, 120 and 168 hrs of administration test drugs.

Determination of blood glucose

Glucometer (Accu - Chek) was used for the determination of the blood glucose levels of the rats. Blood samples were obtained from the cut tail tip of the conscious rat and glucose test strip soaked with blood and then inserted to be read by the glucometer. Blood glucose levels were examined after 2, 12, 24, 72, 120 and 168 hrs of administration test drugs.

Histopathological studies

The freshly excised pancreas were washed with saline and preserved in 10% formaldehyde solution for histopathological studies. The sections of pancreas stained with hematoxylin and eosin, were assessed for histopathological changes such as congestion, fibrotic changes, hemorrhage and necrosis. The microscopic slides were photographed.

Statistical analysis

The data were expressed as mean \pm standard error mean (S.E.M).The Significance of differences among the groups was assessed using one way and multiple way analysis of variance (ANOVA). The test followed by Dunnet's test *P* values less than 0.05 were considered as significance.

RESULT AND DISCUSSION

Effect of FM3, Metformin Hcl & Metformin Hcl SR (Glyciphage SR) on blood glucose level

There were observable changes in blood glucose level of treated and untreated rats. Treatment of diabetic rats with the FM3, Metformin Hcl & Metformin Hcl SR significantly decreased the blood glucose level compared to untreated diabetic rats. Treatment of diabetic rats with the FM3 significantly reduces the blood glucose levels compare than Metformin Hcl & Metformin Hcl SR treated rats.

Histopathological studies

The islets of alloxan induced diabetic rats showed extensive necrotic changes followed by fibrosis and atrophy (Fig.No.1, Group-I). The Alloxan diabetic rats treated with Metformin Hcl minimum degree of necrotic and fibrotic changes of islets of langerhans. (Fig.No.1, Group-III) The necrotic and fibrotic changes were not detected in the rats were treated with FM3 and Metformin Hcl SR. (Fig.No.1, Group-II and IV).

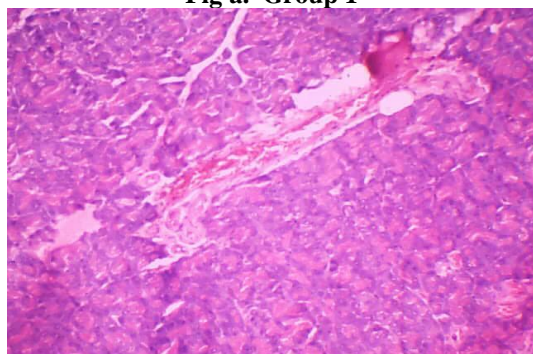
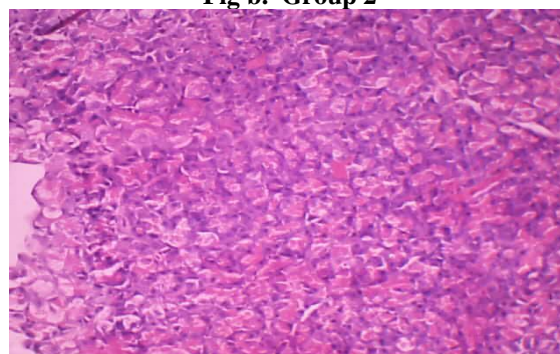
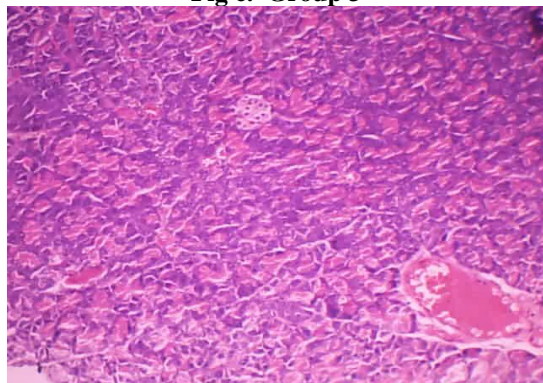
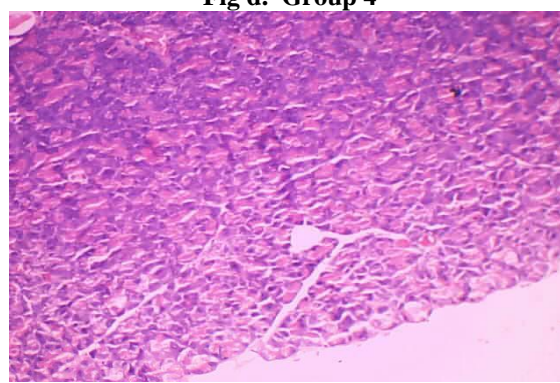
CONCLUSION

Metformin HCL floating tablet formulation (FM3) was subjected for invivo studies (anti diabetic activity) using alloxan induced diabetic in Rats model. From the above results, The FM3 (formulation containing Xanthan gum) shown very significant reduction of blood glucose level (at 168hrs, 99 ± 2.79), when compared to control (at 168hrs, 373.83 ± 4.20) and Marketed product (Metformin HCL 500mg SR tablets (Glyciphage SR)) (at 168hrs, 105.5 ± 1.77).

The invivo study of Metformin HCL floating tablet (FM3) was found that the glycemic control is best (formulation containing Xanthan gum) when compared with control (Rednick AB and Tucker SJ, 1970) and Marketed product (Metformin HCL 500mg SR tablets (Glyciphage SR)). The result suggested that frequent dosing and possible incomplete absorption of the drug can

Table 1. Fasting plasma glucose levels of alloxan-induced diabetic rats at intervals during daily oral administration of FM3, Metformin Hcl & Metformin Hcl SR (Glyciphage SR)

Groups	Treatment	Initial	2hr	12hr	24hr	72hr	120hr	168hr
I	Diabetic control + 1% w/v CMC soln p.o	252.17±2.37	302.33±3.08	327.83±2.96	355.17±1.66	358.17±4.08	365±4.19	373.83±4.24
II	Diabetic control + FM3 Metformin Hcl (100 mg/kg p.o)	253±2.16	198.17±2.73**	146±1.65**	124.17±1.66**	112.33±2.57**	106.83±0.91**	99±2.79**
III	Diabetic control + Metformin Hcl (100 mg/kg p.o)	247.33±2.68	217.5±2.19**	200.83±1.62**	178±2.08**	143.5±2.72**	134.5±2.22**	124.67±1.41**
IV	Diabetic control + Metformin Hcl SR (100 mg/kg p.o)	245.5±2.32	216.17±1.49**	184.83±1.35**	135.33±1.17**	114.83±1.68**	107.33±1.59**	105.5±1.77**

Fig 1. HISTOPATHOLOGICAL STUDIES OF PANCREAS**Fig a. Group 1****Fig b. Group 2****Fig c. Group 3****Fig d. Group 4**

be avoided with Metformin HCL floating tablet (FM3) (Lachman L *et al.*, 2003; Jose Gutierrez Rocca *et al.*, 2003). Therefore, it concluded that drug (Metformin HCL) suitable for floating drug delivery system with a new choice of an economical, safe and enhances the bioavailability formulation in the management of type II diabetes mellitus.

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