International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 6 Nov-Dec 2021, pp: 300-305 www.ijprajournal.com ISSN: 2249-7781

In-Vitro Antidiabetic Activity of Ibutilide and Sotalol Using Alpha-Amylase Inhibition Assay

Pavithra P[1], Pavazhaviji P[2]
[1]*Student, Mother Theresa Post Graduate & Research Institute of Health Sciences, Puducherry.*
Corresponding Author: Pavithra P

Submitted: 10-11-2021 Revised: 24-11-2021 Accepted: 27-11-2021

ABSTRACT: Diabetes mellitus is a serious complex chronic condition that is a major source of ill health worldwide. This metabolic disorder is characterized by hyperglycemia and disturbances of carbohydrate, protein and fat metabolisms, secondary to an absolute or relative lack of the hormone insulin.Reasons for this include increase in sedentary lifestyle, consumption of energy rich diet , obesity , etc.The key enzymes for carbohydrate metabolism are pancreatic ∝-amylase and ∝-glucosidase which convert consumed polysaccharides to monosaccharides.This enzyme action causes postprandial blood glucose level elevation due to absorption of formed glucose from polysaccharides in the small intestine. Drugs having an inhibitory action on both of these enzymes possess an ability to control of postprandial blood glucose level specifically in type-2 diabetic patients. Currently available drugs in this category are acarbose and miglitol which competitively inhibit above enzymes.Ibutilide is a potent drug when compared to Acarbose and Sotalol, because it exhibits 33% inhibition of ∝-amylase activity at 25µg concentration. However, only at 300µg concentration of Sotalol exhibit 33% inhibition of ∝-amylase activity.Our present study reveals that Ibutilide andSotalol possesses pancreatic ∝-amylase inhibitory activity which is comparable to that of acarbose. So, Further studies will be carried out to confirm the antidiabetic activity of these drugs.

KEYWORDS: Diabetes mellitus,Ibutilide, Sotalol, Acarbose, Potassium channel.

I. INTRODUCTION:

Diabetes mellitus is a chronic metabolic disorder of carbohydrate, lipid and protein metabolism characterized by hyperglycemia and hyperlipidemia due to insufficient or complete cessation of insulin synthesis or secretion and/or peripheral resistance to insulin action [1]. The hallmark of diabetes mellitus is polyuria-excessive urine production**,** polydipsia-excessive thirst and polyphagia-excessive eating [2].Diabetes is a condition primarily defined by the level of hyperglycaemia giving rise to risk of microvascular damage (retinopathy, nephropathy and neuropathy). It is associated with reduced life expectancy, significant morbidity due to specific diabetes related microvascular complications, increased risk of macrovascular complications (ischaemic heart disease, stroke and peripheral vascular disease), and diminished quality of life [3].The pathogenesis of diabetes mellitus and its complications is managed by insulin and oral administration of hypoglycaemic drugs such as sulfonylureas and biguanides[4]. However, on chronic usage most of these agents produced several side effects, including hypoglycemic coma, insulin resistance, hyper-sensitivity, cholesterol, jaundice, abdominal pain, anorexia and metallic taste [2].

POTASSIUM CHANNELS:

Potassium channels are the most widely distributed type of ion channel and are found in virtually all living organisms. They form potassium-selective pores that span cell membranes. Furthermore, potassium channels are found in most cell types and control a wide variety of cell functions.Potassium channels function to conduct potassium ions down their electrochemical gradient, doing so both rapidly (up to the diffusion rate of K^+ ions in bulk water) and selectively (excluding, most notably, despite the sub-angstrom difference in ionic radius). Biologically, these channels act set or reset the resting potential in many cells.In excitable cell, such as neurons, the delayed counter flow of potassium ions shapes the action potential.By contributing to the regulation of the action potential duration in cardiac muscle, malfunction of potassium channels may cause life-threatening arrhythmias. Potassium channels may also be involved in maintaining vascular tone.They also regulate cellular processes such as the secretion of hormones (e.g., insulin release from

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 6 Nov-Dec 2021, pp: 300-305 www.ijprajournal.com ISSN: 2249-7781

beta-cells in the pancreas) so their malfunction can lead to diseases (such as diabetes)[5, 6].

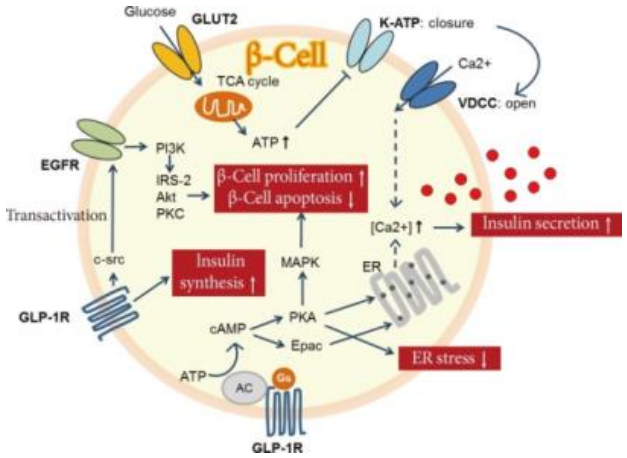

Figure:1 Potassium channel

ROLE OF POTASSIUM CHANNEL BLOCKERS IN DIABETES MELLITUS:

Type II DM is at present one of the most challenging health care problems, which requires optimum management. At present the treatment of diabetes mellitus includes insulin, sulfonylureas, biguanides, glucosidase inhibitors, DPP-4 inhibitors, thiazolidinediones, GLP-1 receptor agonists, amylin agonists, medical nutrition therapy and lifestyle modification. Insulin, a hypoglycaemic hormone, is secreted from human pancreas by glucose entry into cell through GLUT-2. Increased glucose results in inhibition of ATP-sensitive K+channel resulting in depolarisation of cells. It increases Ca++ entry through voltage sensitive L-type calcium channels into the cells and also releasing Ca++ from intracellular binding sites, such as the internal surface of the cell membrane, sarcoplasmic reticulum and mitochondria of the cell resulting in release of insulin by degranulation of stored vesicles. Many of the drugs used for diseases other than diabetes, interact with receptors. Involved in insulin secretion, causing hypo or hyperglycemia. Hence, they should be evaluated for their effect on blood glucose.

Amiodarone has long been referred to as a prototype of Class III anti-arrhythmic agents because it was demonstrated in early experimental studies in 1970s that this compound prolongs both APD and the refractory period of cardiac muscle when administered chronically. It exerts multiple actions by blocking delayed rectifier potassium channels, blocks inactivated sodium channels, inhibits calcium channels and has non-competitive beta adrenergic blocking property also. With this background amiodarone was evaluated in albino wistar rats for effect on glucose metabolism by its action on calcium and potassium channel blocking activity.Amiodarone is both calcium and potassium channel blocker; both these channels are indicated in glucose metabolism. Release of insulin requires closure of potassium channels and subsequent opening of calcium channels in beta cells of pancreas. This study has shown hyperglycemic effect of amiodarone in albino wistar rats through glucose challenge. Hence further studies are required to assess effect of amiodarone on glucose levels, as on one hand it has a pro insulin secreting effect by blocking potassium channels.Therefore, release of insulin requires closure of potassium channels and subsequent opening of calcium channels in beta cells of pancreas. So, potassium channel blockers such as Ibutilide, Bretylium, Sotalol, and Amiodarone may have the capacity to stimulate insulin secretion which can be results in hypoglycaemia. Hence, the aim of the present study is to determine the effect of Ibutilideand Sotalol using in-vitro antidiabetic method such as alpha-amylase inhibition assay[7, 8].

IBUTILIDE:

Ibutilide is a Class III antiarrhythmic agent comes under potassium

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 6 Nov-Dec 2021, pp: 300-305 www.ijprajournal.com ISSN: 2249-7781

channel blockers that is indicated for acute cardioconversion of atrial fibrillation and atrial flutter of a recent onset to sinus rhythm. It exerts its antiarrhythmic effect by induction of slow inward sodium current, which prolongs action potential and refractory period (physiology) of myocardial cells. Because of its Class III antiarrhythmic activity, there should not be concomitant administration of Class Ia and Class III agents[9 -11].

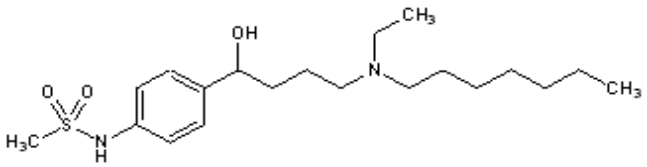

Figure:2 Structure of Ibutilide

SOTALOL:

Sotalol is a medication to treat abnormal heart rhythms. It is a non-selective competitive beta –adrenergic receptor blocker that also exhibits class III antiarrhythmic properties by potassium channel blocking capacity[12, 13].

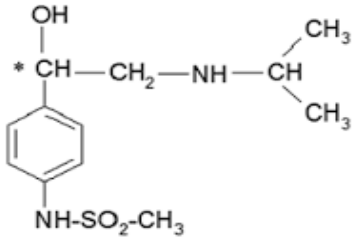

Figure:3 Structure of Sotalol

IN-VITRO MODELS:

i. Alpha-Amylase Inhibition Assay[14, 15]:

A total of 500 µl of test samples (Ibutilide and Sotalol) and standard drug (Acarbose) (100-1000µg/ml) were added to 500 µl of0.20 mM phosphate buffer (pH 6.9) containing α-amylase (0.5mg/ml) solution and were incubated at 25°C for 10 min. After these, 500 µl of a 1% starch solution in 0.02 M sodium phosphate buffer (pH 6.9) was added to each tube. The reaction mixtures were then incubated at 25°C for 10 min. The reaction was stopped with 1.0 ml of 3, 5 dinitrosalicylic acid colourreagent. The test tubes were then incubated in a boiling water bath for 5 min, cooled to roomtemperature. The reaction mixture was then diluted after adding 10 ml distilled water and absorbance was measured at 540 nm. Control represent 100% enzyme activity and were conducted in similar way by replacing extract with vehicle

Percentage inhibition (I %) was calculated by

I % = (Ac-As)/Ac X 100,

where Ac is the absorbance of the control and As is the absorbance of the sample.

II. RESULTS AND DISCUSSION:

✓ **IN-VITRO ANTIDIABETIC ACTIVITY OF IBUTILIDE AND SOTALOL**

Ibutilide produced -26.08, 7.24, 23.18, 30.43 and 33% inhibition of ∝-amylase activity at 5, 10, 15, 20 and 25µg concentrations respectively. Sotalol exhibited 0, 24.6, 33.3, 36.2 and 46.3 % inhibition at 100, 200, 300, 400 and 500µg concentrations respectively. The standard drug

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 6 Nov-Dec 2021, pp: 300-305 www.ijprajournal.com ISSN: 2249-7781

acarbose exhibited 5.9, 26.0, 34.78, 46.37 and 71.0% inhibition of ∝-amylase activity at 100, 200, 300, 400 and 500µg concentrations respectively. Ibutilide is a potent drug when compared to Acarbose and Sotalol, because it exhibits 33% inhibition of ∝-amylase activity at 25µg concentration. However, only at 300µg concentration of Sotalol exhibit 33% inhibition of ∝-amylase activity.

Table:1 In-Vitro antidiabetic activity of Acarbose using ∝-amylase method

S.NO	CONCENTRATION	ABSORBANCE	% INHIBITION OF ∝-AMYLASE
1.	100µg/ml	0.058	15.9
2.	200µg/ml	0.051	26
3.	300µg/ml	0.045	34.78
4.	400µg/ml	0.037	46.37
5.	500µg/ml	0.020	71

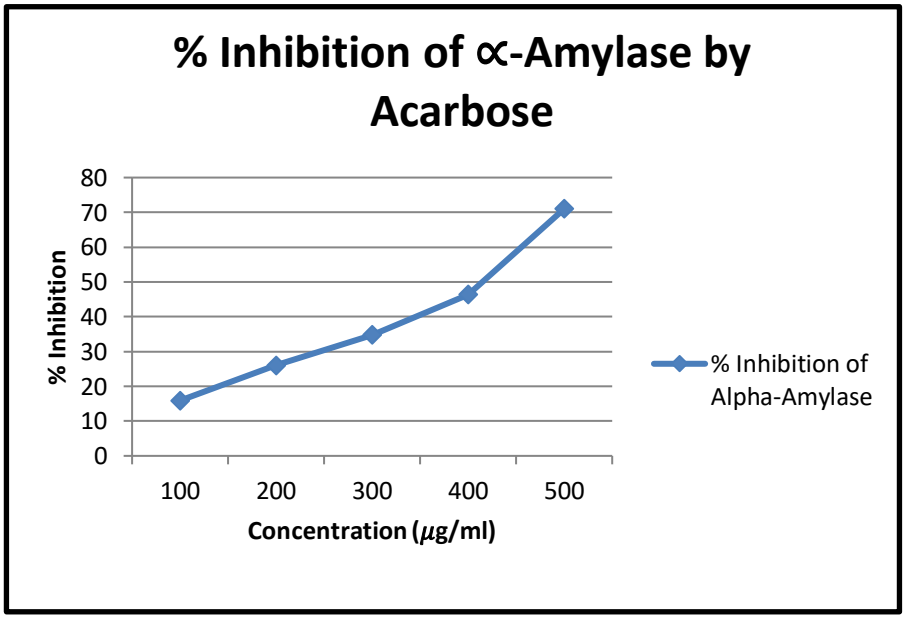

Figure: 4 In-Vitro antidiabetic activity of Acarbose using ∝-amylase method

Table: 2 In-Vitro antidiabetic activity of Ibutilide using ∝-amylase method

S.NO	CONCENTRATION	ABSORBANCE	% INHIBITION OF ∝-AMYLASE
1.	5µg/ml	0.087	-26.08
2.	10µg/ml	0.064	7.24
3.	15µg/ml	0.053	23.18
4.	20µg/ml	0.048	30.43

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 6 Nov-Dec 2021, pp: 300-305 www.ijprajournal.com ISSN: 2249-7781

5.	25µg/ml	0.046	33

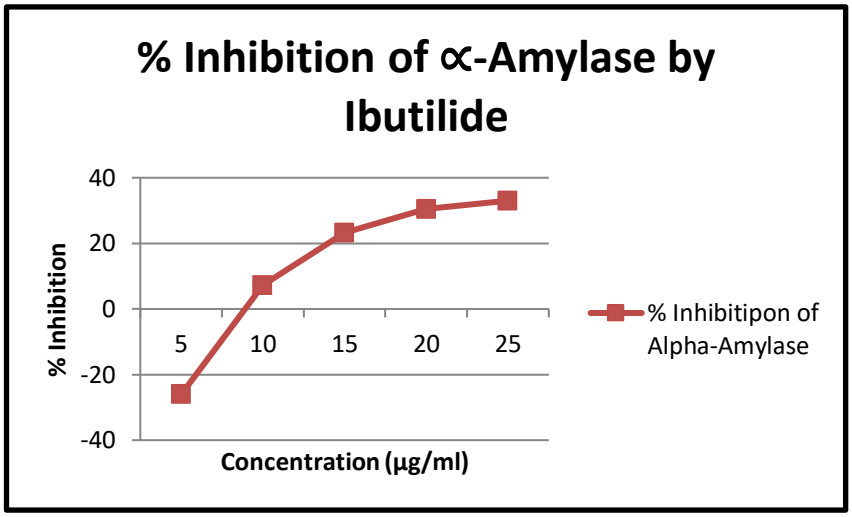

Figure:5In-Vitro antidiabetic activity of Ibutilide using ∝-amylase method

Table:3In-Vitro antidiabetic activity of Sotalol using ∝-amylase method

S.NO	CONCENTRATION	ABSORBANCE	% INHIBITION OF ∝-AMYLASE
1.	100µg/ml	0.069	0
2.	200µg/ml	0.052	24.6
3.	300µg/ml	0.046	33.3
4.	400µg/ml	0.044	36.2
5.	500µg/ml	0.037	46.3

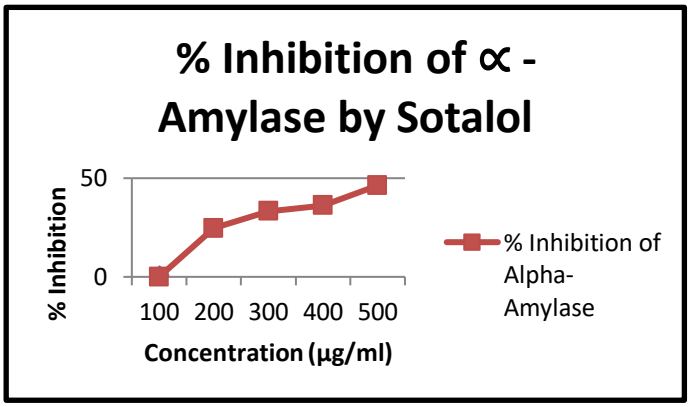

Figure: 6 In-Vitro antidiabetic activity of Sotalol using ∝-amylase method

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 6 Nov-Dec 2021, pp: 300-305 www.ijprajournal.com ISSN: 2249-7781

III. CONCLUSION:

Diabetes mellitus is a serious complex chronic condition that is a major source of ill health worldwide. This metabolic disorder is characterized by hyperglycemia and disturbances of carbohydrate, protein and fat metabolisms, secondary to an absolute or relative lack of the hormone insulin.The number of people in the world with diabetes has increased dramatically over recent years.Present number of diabetics worldwide is 150 million and this is likely to increase to 300 million or more than by the 2025.Reasons for this include increase in sedentary lifestyle, consumption of energy rich diet , obesity , etc.The key enzymes for carbohydrate metabolism are pancreatic ∝-amylase and ∝-glucosidase which convert consumed polysaccharides to monosaccharides.This enzyme action causes postprandial blood glucose level elevation due to absorption of formed glucose from polysaccharides in the small intestine. Drugs having an inhibitory action on both of these enzymes possess an ability to control of postprandial blood glucose level specifically in type-2 diabetic patients. Currently available drugs in this category are acarbose and miglitol which competitively inhibit above enzymes.Our present study reveals that Ibutilide andSotalol possesses pancreatic ∝-amylase inhibitory activity which is comparable to that of acarbose. So, Further studies will be carried out to confirm the antidiabetic activity of these drugs.

BIBLIOGRAPHY

1. Das P K, Bhattacharya S, Pandey J N and Biswas M. Antidiabetic activity of Trapanatansfruit peel extract against streptozotocin induced diabetic rats. Global Journalof Pharmacology, 2011; 3(5):186-190.
2. Sharma U S and Kumar A. Antidiabetic effect of Rubusellipticus fruit extracts in alloxan induced diabetic rats. Journal of Diabetology, June 2011; 4:2.
3. Hogan P, Dall T and Nikolov P. Economic costs of diabetes in the U.S. in 2002. Diabetes Care. American DiabetesAssociation, 2003; 26: 917-932.
4. Velraj M, Singh M, Ravichandiran V, Nirmala S, and Ragala S. Antidiabetic activity of ethyl acetate and ethanolic extract of Scindapsusofficinalis fruit in alloxan induced diabetic rats.International Journal of PharmTech Research,July-Sept 2011;3(3):1305-1310.
5. "Potassium channel", WWW.Wikipedia.Com
6. "Potassium channel blockers", WWW.Wikipedia.Com
7. Sibgatullah M and Suresha R N. Evaluation of Amiodarone for Its Effect on Glucose Metabolism in Euglycemic Albino Wistar Rats. International Journal of Recent Trends in Science And Technology, 2013;3(8):178-181.
8. Wasada T. Adenosine triphosphate–sensitive potassium [K^+ (ATP)] channel is coupled with insulin resistance in obesity and type-2 diabetes mellitus. Intern. Med., 2002; 41(2):84-90.
9. "Ibutilide", Pubchem.htm
10. "Ibutilide", Drugs.Com.htm
11. "Ibutilide", DrugBank
12. "Sotalol", Pubchem.htm
13. "Sotalol", DrugBank
14. Banerjee A, Maji B, Mukherjee S, Chaudhuri K and Seal T. In-vitro antidiabetic and anti-oxidant activities of methanol extract of Tinosporasinensis. Journal of Applied Biology and Biotechnology, 2017 3(5):61-67.
15. Lakshmidevi N and Dsouza D. Models to study in-vitro antidiabetic of plants : A review. International journal of Pharma and Biosciences, 2015;6(3):732-741.