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A REVIEW ON METFORMIN - ITS DIFFERENT TECHNOLOGIES FORMULATIONS

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***Abstract*—Diabetes mellitus, describes a group of metabolic diseases in which the person has high blood glucose. Metformin hydrochloride is an anti-diabetic drug from the biguanide class of oral antihyperglycemic agents.Half-life 6.2 hours. Duration of action is 8-12 hours. Metformin decreases blood glucose levels by decreasing hepatic glucose production, decreasing intestinal absorption of glucose. Metformin hydrochloride and gliclazide were prepared by using different concentration of polymers of various grades of HPMC, Carboxy methyl cellulose, Calcium phosphate dibasic anhydrous, Micro crystalline cellulose, PVP, Lactose monohydrate. Different types of pellets i.e. Metformin pellets, coated Metformin pellets and disintegrate pellets were shown independent influence on the formulation. In order to evaluate the pHs effect on the transdermal drug delivery, HPMC/PVA based TDS-patch was prepared. Floating tablet Metformin HCl have been shown sustained release there by proper duration of action at a particular site and are designed to prolong the gastric residence time after oral administration.**

***Index Terms*— Biguanides, Different technologies, Bilayer, floating, Effervescent tablets, Reservoir Pellets.**

I. INTRODUCTION

DIABETES

Diabetes is a chronic disease in which body does not make or properly use insulin, a hormone that is needed to convert glucose and other food in to energy. Diabetes mellitus, describes a group of metabolic diseases in which the person has high blood glucose (blood sugar), either because insulin production is inadequate, or because the body's cells do not respond properly to insulin, or both.

There are three types of diabetes:

A. Type 1 Diabetes

The body does not produce insulin. Some people may refer to this type as insulin-dependent diabetes, juvenile diabetes, or early-onset diabetes. People usually develop type 1 diabetes before their 40th year, often in early adulthood or teenage years. Approximately 10% of all diabetes cases are type 1.

B. Type 2 Diabetes

The body does not produce enough insulin for proper function, or the cells in the body do not react to insulin (insulin resistance). Approximately 90% of all cases of diabetes worldwide are of this type. Some people may be able to control their type 2 diabetes symptoms by losing weight, following a healthy diet, doing plenty of exercise, and monitoring their blood glucose levels.

C. Gestational Diabetes

This type affects females during pregnancy. Some women have very high levels of glucose in their blood, and their bodies are unable to produce enough insulin to transport all of the glucose into their cells, resulting in progressively rising levels of glucose. Diagnosis of gestational diabetes is made during pregnancy.

II. METFORMIN HYDROCHLORIDE

FUNCTIONAL CATEGORY

Metformin hydrochloride is an anti-diabetic drug from the bigunaide class of oralantihyperglycemic agents.

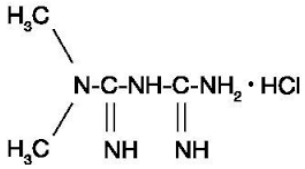

Fig: structure of metformin

Class: Guanidine's
Chemical name: (diamino methyl dine)-3,3-dimethyl-gunadine1
Molecular Formula: C4H12ClN5
Molecular weight: 165.63gm/mol
IUPAC name: N-N-dimethylimidocarbonimidic diamide hydrochloride
Category: Anti diabetic agent
Description: white to off white crystalline powder, odourless
PKa: in acid (12.4)
Solubility: freely soluble in water, slightly soluble in alcohol practically insoluble in acetone and in methylene chloride
Half-life: 6.2 hours. Duration of action is 8-12 hours.

ABSORPTION AND BIOAVAILABILITY

The absolute bioavailability of a metformin hydrochloride 500 mg tablet given under fasting conditions .approximately 50-60%. Studies using single oral doses of metformin tablets of 500 mg and 1500 mg.This is due to decreased absorption rather than an alteration in elimination.

METABOLISM AND ELIMINATION

Intravenous single-dose studies in normal subjects demonstrate that metformin is excreted unchangedin the urine and does not undergo hepatic metabolism nor biliary excretion. Renal clearance is approximately 3.5 times greater than creatinine.

PHARMACODYNAMICS

Metformin is an oral anti hyperglycaemic agent that improves glucose tolerance in patients withNIDDM, lowering both basal and postprandial plasma glucose. Metformin is not chemically or pharmacologically related to any other class of oral anti hyperglycaemic agents. Unlike sulfonylureas, metformin does not produce hypoglycaemia in either patient with NIDDM or healthy subjects and does not cause hyper insulinemia. Metformin does not affect insulin secretion.

MECHANISM OF ACTION

Metformin's mechanisms of action differ from other classes of oral antihyper-glycemic agents. Metformin decreases blood glucose levels by decreasing hepatic glucose production, decreasing intestinal absorption of glucose, and improving insulin sensitivity by increasing peripheral glucose uptake and utilization. These effects are mediated by the initial activation by metformin of AMP-activated protein kinase (AMPK), a liver enzyme that plays an important role in insulin sign along, whole body energy balance, and the metabolism of glucose and fats. Increased peripheral utilization of glucose may be due to improved insulin binding to insulin receptors. Metformin administration also increases AMPK activity in skeletal muscle. AMPK is known to cause GLUT4 deployment to the plasma membrane, resulting in insulin-independent glucose uptake.

ADVERSE REACTION

Adverse reactions of a more intense character including epigastric, discomfort, nausea, and vomiting followed by diarrhoea, drowsiness, weakness, dizziness, malaise and headache might be seen.

III. TECHNOLOGIES DEVELOPED FOR METFORMIN

A. Bilayer tablets

1) Sustained Release Bilayer Tablet of Metformin Hydrochloride with Metoprolol Tartrate

The drug of choice for type2 diabetes mellitus is Metformin hydrochloride and for Hypertension is Metoprolol tartrate, to reduce the prevention of cardiac problems in diabetic patients. The formulations of tablets .were prepared by using release retarding agents like HPMC K100, Eudragit S 100 for sustained release (SR) layer and super disintegrates like Cross povidone, Sodium starch glycol ate (SSG) for immediate release (IR) layer. Both sustained and immediate release granules were evaluated for flow property. Bilayer tablets were evaluated for weight variation, hardness, thickness, swelling index and in-vitro drug release for 12 hours.

2) Bilayered Floating Tablets of Metformin Hydrochloride

Gastro retentive floating drug delivery systems (GFDDS) of Metformin HCl, an antidiabetic drug with an oral bioavailability of only 50% (because of its poor absorption from lower gastrointestinal tract) have been designed to increase its residence time in the stomach without contact with the mucosa was achieved through the preparation of floating bilayer matrix tablet by direct compression technique, by using HPMC as release retardant, and NaHCO3 as gas generating agent to reduce floating lag time.

3) Metformin Hydrochloride and Gliclazide Bilayer Tablets

In the present work bilayer tablets of metformin hydrochloride and gliclazide were prepared by using different concentration of polymers of various grades of HPMC, Carboxy methyl cellulose, Calcium phosphate dibasic anhydrous, Micro crystalline cellulose, PVP, Lactose monohydrate. The bilayer tablet contributing initial loading dose and dissolves rapidly, the remainder of the drug in the extended release was constant rate till the end of the dissolution process.

B. Floating tablets

1) Metformin HCl Floating Tablet using Pectin as a Natural Polymer

Floating tablet Metformin HCl have been shown sustained release there by proper duration of action at a particular site and are designed to prolong the gastric residence time after oral administration. Five batches of tablets were prepared by the wet granulation by using HPMCE15 (floating agent) and Pectin (obtained in nature) as polymers along with sodium bicarbonate as gas generating agent.

2) Optimization of a metformin effervescent floating tablet containing hydroxypropylmethylcellulose and stearic acid

A simplex lattice experimental design has been used comprising different levels of hydroxypropylmethylcellulose (HPMC), stearic acid (SA), sodium bicarbonate (SB) as tablet matrix components, and hardness (H), t60%, FLT as response variables. Two models have been applied to decide which composition will result in Fickian diffusion or in overlapping of two dissolution mechanisms, diffusion and matrix erosion. Three of EFT showed the two dissolution mechanisms but most of EFT showed Fickian diffusion only.

C. Pellets

1) Metformin Tablet from Reservoir Pellets

In this study tablets prepared by using three different types of pellets i.e. Metformin pellets, coated Metformin pellets and disintegrate pellets were shown independent influence on the formulation. The reservoir pellets coated with ethyl cellulose

and Eudragit RS 100 the release is depends on the thickness of coating and compaction pressure. HPMC K4M and MCC pH 101 used as a binder in all formulations, PEG 400 as plasticizer, magnesium stearate and talc as a lubricant.

D. Transdermal patch

1) n vitro Transdermal Delivery of Metformin from a HPMC/ PVA Based TDS-patch at Different pH (12)

In order to evaluate the pHs effect on the transdermal drug delivery, HPMC/PVA based TDS-patch was prepared. In vitro transdermal dissolution was performed at 32 oC at different pHs. Comparatively higher release rate was found in case of pH 7.4 than those of others. pHs 5.4 and 8 showed almost the same release pattern. The release fashion was Higuchi type of diffusion controlled release. This result showed that neutral pH would accumulate the maximum drug from such a TDS patch, where the skin pH (around 5.4)

E. Sustained release Tablets

1) Design and Evaluation of Bull's Eye (In-Lay) Tablet of Glipizide and Metformin Hydrochloride

In-lay tablet comprises of glipizide immediate release layer formulated with neem gum as disintegrating agent and metformin hydrochloride for sustained release formulated with different grads of HPMC (HPMC K4M, HPMC K15M, HPMC K100M) in which SR layer surrounded by glipizide immediate release granules. The drug-excipient compatibility studies were conducted by FT-IR studies.

2) Metformin Hydrochloride Using Hydrophilic Synthetic and Hydrophobic Natural Polymers

The overall objective of this study was to develop an oral sustained release metformin hydrochloride tablet by using hydrophilic Eudragit RSPO alone or its combination with hydrophobic natural polymers Gum copal and gum damar as rate controlling factor.The drug release study revealed that Eudragit RSPO alone was unable to sustain the drug release. Combining Eudragit with gum Copal and gum Damar sustained the drug release for more than 12 h. Kinetic modelling of in vitro dissolution profiles revealed the drug release mechanism ranges from diffusion controlled or Fickian transport to anomalous type or non-Fickian transport.

IV. METFORMIN HYDROCHLORIDE MATRIX TABLETS BY SINTERING TECHNIQUE AND ITS EVALUATION

When given, a divided dose of 0.5-3 gm daily, it increases the hepatic glucose production thereby increasing the peripheral glucose uptake and utilization and shows a significant bioavailability about 50-60%. Since metformin hydrochloride is widely chosen as the first line drug in the treatment of type2 DM, because of its minimal risk and maximum efficacy, the formulation of metformin hydrochloride matrix tablet was taken in to consideration. Matrix tablets reduce the frequency of dose administration, and are found to have increased patient compliance. A relatively recent technique called sintering technique is involved in the formulation which aims to extend the release of metformin hydrochloride from the matrix tablets.

A. Metformin Hydrochloride Matrix Tablet Using Natural Polysaccharide

The sustained release matrix tablet of Metformin Hydrochloride was prepared by wet granulation technique using Tamarind pulp polysaccharide. The polysaccharides obtained after extracted from natural source and evaluated for their colour, viscosity and ph. The prepared tablet was evaluated for their hardness, friability, drug content, In vitro dissolution, swelling studies. In vitro drug release profiles of Metformin Hydrochloride Tablet using Tamarind pulp polysaccharide formulation release of drug from the Tablet exhibited a sustained & controlled pattern over an extended time period.

B. Formulation and Evaluation of Swelling Restricted Matrix Tablet Containing Metformin Hcl

Metformin Hcl was formulated as restricted swelling matrix tablet by using HPMC K100 and CMC in ratio of 50:50 in order to obtain a sustained release formulation. Matrix tablets containing 500mg of metformin were prepare by direct compression method. The drug polymer ration influenced the release of drug from the formulations. An increase in polymer decreased the drug release. F13 partially coated swelling matrix tablet further retarded the release of drug.

V. CONCLUSION

Floating tablet Metformin HCl have been shown sustained release there by proper duration of action at a particular site and are designed to prolong the gastric residence time after oral administration. Metformin pellets and disintegrate pellets were shown independent influence on the formulation. Bilayer tablet concept has long been utilized to develop sustained released formulation. Such tablet has a fast releasing layer and may contain one (bi-layer), to sustain the drug release. However, the blood level is maintained at steady state as the release from sustaining layer. This review includes bilayer tablet of metformin, Fixed dose combination, Floating bilayer tablet of metformin and glicazide as well as Floating bilayer tablet of metformin.

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