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EXTENDED RELEASE TABLET OF METFORMIN: A REVIEW

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Abstract
Extended release dosage forms cover a wide range of prolonged action preparations that provide continuous release of their active ingredients for a specific period of time. Metformin Hcl is ant hyperglycemic agent used in the treatment of type 2 Non Insulin Dependent Diabetes Mellitus. The extended release formulation of Metformin Hcl (MER), prolongs drug absorption in the upper gastrointestinal tract and permits once daily dosing in patient with Type 2 Diabetes Mellitus .This newer formulation may enhance patient compliance with oral therapy compared to conventional immediate release (MIR) Metformin Hcl in Type 2 Diabetes Mellitus Extended release formulation of Metformin Hcl presents significant challenges due to its poor inherent compressibility, high dose and high water solubility.

Keywords: Metformin, Extended Drug Release, Diabetes, Diseases, characterization, Evaluation.

Introduction

Oral Drug delivery has been known for decades the most widely utilized route of administration among all the routes that have been employed for the systemic delivery of drug via various pharmaceutical products of different dosage forms. The reasons that the oral route achieved such popularity may be in part attributed to its case of administration as well as the traditional belief that by oral administration of the drug is well absorbed.

All the pharmaceutical products formulated for systemic delivery via the oral route of administration irrespective of the mode of delivery (immediate, sustained or controlled release) and the design of dosage forms (either solid dispersion or liquid), must be developed within the intrinsic characteristics of Gl physiology. Therefore, a fundamental understanding of various disciplines, including GI physiology, pharmacokinetics, pharmacodynamics and formulation design, is essential to achieve a systemic approach to the successful development of an oral pharmaceutical dosage form.

Sustained or controlled drug delivery occurs when embedded within a polymer that may be natural or semi-synthetic or synthetic in nature. The polymer is judiciously combined with the drug or other active ingredients in such a way that the active agent is released from the material in a predetermined fashion and releases the drug at a constant rate for the desired time period.

Solid dispersion (SD), in which compounds are dispersed into water-soluble carriers, has been generally used to improve the dissolution properties and the bioavailability of drugs that are poorly soluble in water. Solid dispersion has also been applied for the controlled release of drugs. Previous reports have shown that by using solid dispersions it is possible to precisely control the rate of

release of an extremely water-soluble drug, such as oxprenolol hydrochloride and that of phenacetin and diclofenac sodium as well. These studies have shown that there is a linear relationship between the rate of release.

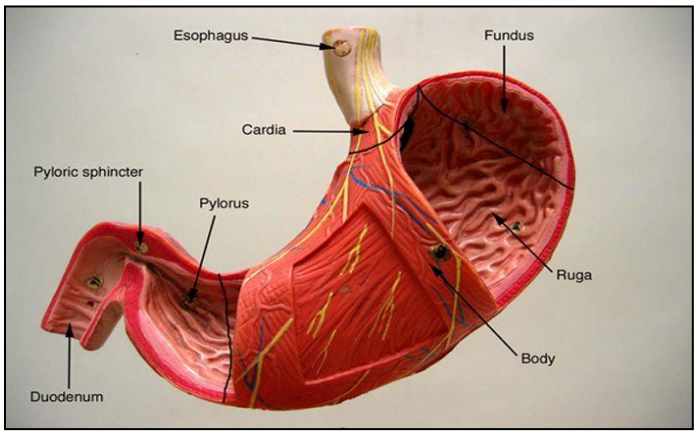

Fig. No. 1: Anatomy of Stomach

Advantages of tablet

- Large scale manufacturing is feasible in comparison to other dosage forms. Therefore, economy can be achieved.
- Accuracy of dose is maintained since tablet is a solid unit dosage form.
- Tailor made release profile can be achieved.
- Longer expiry period and minimum microbial spillage owing to lower moisture content. As tablet is not a sterile dosage form, stringent environmental conditions are not required in the tablet department.
- Ease of packaging (blister or strip) and easy handling over liquid dosage form.
- Easy to transport in bulk. Emergency supply can be carried by patients.
- Organoleptic properties (taste, appearance and odour) are best improved by coating of tablet.
- Product identification is easy and mark

Disadvantages of tablet

- It is difficult to convert a high dose poorly compressible API into a tablet of suitable size for human use.
- Difficult to formulate a drug with poor wettability, slow dissolution into a tablet.
- Slow onset of action as compared to parenteral, liquid orals and capsules.
- The amount of liquid drug (e.g., Vitamin E, Simethicone) that can be trapped into a tablet is very less.
- Difficult to swallow for kids, terminally ill and geriatric patients.

Materials

HPMC K4M, HPMC K15M HPMC K100M was purchased from Dow Chemical's (Midland, MI, USA); metformin HCl, PVP K30, Talc and magnesium stearate, IPA, Carbopal 71G, Microcrystalline Cellulose and Aerosil.

All other solvents and reagents were purchased from Merck chemicals, India, and were of analytical grade.

Physicochemical characterization of granules

The granules were evaluated for various physicochemical parameters including angle of repose, bulk density, tap density, compressibility index and Hausner ratio.

1)Angle of repose

The fixed-funnel method was used to determine angle of repose. The granule formulation was carefully poured through a funnel until the apex of the conical pile just touched the tip of funnel. The height (h) of the pile of the powder and the radius (r) of its conical base were measured and applied to compute the angle of repose (θ) as in Eq 1

$\theta = \tan^{-1} h/r$ …… (1)

2)Bulk and tap densities

A 30 g quantity of the granule samples was placed in a 100 ml dry measuring cylinder and volume, Vo, occupied by it, without tapping, was determined. The cylinder was then given 500 taps using a tap density apparatus (model ETD-1020, Electrolab, India,) and the resulting volume, V500, was noted determined [15-16]. The bulk and tap densities were calculated using Eq 2 and 3, respectively.

Bulk density = W/Vo…… (2)

Tapped density = W/V500 ……..… (3)

Where W is the weight of the granules.

3)Compressibility index

This parameter was calculated fitting bulk and tap density data (TD and BD, respectively) into Eq^{n} 4 [15-16]. Compressibility (C %) = 100 (TD – BD)/TD.… (4)

4)Hausner ratio

This parameter was calculated as the ratio of tap density to bulk density of the granules [15-16].

Physicochemical characterization of tablets

The tablets were evaluated for assay, hardness and friability.

1)Determination of drug content

Randomly selected tablets (20) from each batch were weighed and powdered. A quantity of the powder, equivalent to 100 mg of metformin HCl, was transferred to a 100 ml volumetric flask and extracted with water. A quantity (1 ml) of filtered solution was diluted to 100 ml with water and the absorbance measured at 233 nm (model UV1201, Shimadzu). Each measurement was carried out in triplicate and the mean taken. Drug concentration was calculated from the calibration curve of a standard (concentration range: 0 to 10 µg/ml).

2) **Determination of tablet hardness**

The hardness of each of 10 tablets randomly selected from each batch was measured with a tablet hardness tester, and the mean and standard deviation evaluation.

3)Determination of tablet friability

Tablet Friability was assessed using a friabilator (model EF-2, Electrolab, India) at 25 rpm for 4 min. The weight of ten tablets before and after the test, and the percent loss in weight recorded as friability.

Technologies to achieve oral controlled drug delivery

There are various methods employed for the fabrications of oral controlled release delivery systems. Ritschel has given the detailed report of these techniques. These are as follows:

a. Hydrophilic matrix

b. Plastic matrix

c. Barrier resin beads

d. Fat embedment

e. Repeat action

f. Ion-exchange resin

g. soft gelatine depot capsules

h. Drug complexes

Evaluation of controlled release tablets

Before marketing a controlled release, product must to assure the strength, safety, stability and reliability of a product by forming in-vitro and in-vivo analysis and correlation between the two. Various authors have discussed the evaluating parameters and procedures for controlled release formulations.

A. In vitro methods

a. Beaker method

b. Rotating disc method

c. Rotating bottle method d. Rotating basket method

e. Oscillating tube method

f. Dialysis method

g. USP dissolution method

B. In vivo methods

Once the satisfactory in vitro profile is achieved, it becomes necessary to conduct in-vivo evaluation and establish in-vitro in-vivo correlation. The various in-vivo evaluation methods are:

a. Clinical response b. Blood level data

b. Urinary excretion studies

c. Toxicity studies

d. Radioactive tracer techniques

e. Nutritional studies

f. Stability studies

Adequate stability data of the drug and its dosage form is essential to ensure the strength, safety, identity, quality, purity and in vitro in vivo release rates, which they claim to have at the time of use. A controlled release product should a predetermined amount of the drug at specified time intervals, which should not change on storage. Any considerable deviation from appropriate release would render the controlled release product unless. The in vitro and in vivo release rates of controlled release products may be altered by atmospheric or accelerated conditions, such as temperature and humidity. The stability programmes of controlled release products include storage at both nominal and accelerated conditions such as temperature and humidity to ensure that the product will withstand these conditions.

Diseases

1)Metformin during Pregnancy and Lactation

It has been shown that pregnancy may alter the function of drug-metabolizing enzymes and drug transporters in a gestational stage. The activities of several hepatic cytochrome P450 enzymes such as CYP2D6 and CYP3A4 are increased, whereas the activity of some others, such as CYP1A2, may be decreased. The activities of some renal transporters, including organic-cation transporter and P-glycoprotein increase during pregnancy. However, significant gaps still exist in our understanding of the spectrum of drug metabolism and transport genes affected, gestational age-dependent changes in the activity of encoded drug metabolizing and transporting processes, and the mechanisms of pregnancy-induced alterations.

The pharmacokinetics of metformin is also affected by pregnancy, which is related to the changes in renal filtration and net tubular transport, which can be estimated roughly by the use of creatinine clearance. At the time of delivery, the fetus is exposed to variable concentrations of metformin from negligible to as high as maternal concentrations. However, infant exposure to metformin through the breast milk is low.

Metformin appears to be effective and safe for the treatment of gestational diabetes mellitus, particularly for overweight or obese women. It has been suggested that metformin is safe during pregnancy. However, as metformin crosses the placenta, its use during pregnancy raises concerns regarding potential adverse effects on the mother and fetus. Furthermore, patients with multiple risk factors for insulin resistance may not meet their treatment goals with metformin alone and may require supplementary drugs such as insulin. However, there are potential advantages for the use of metformin over insulin in gestational diabetes mellitus with respect to maternal

weight gain and neonatal outcomes. Furthermore, the use of metformin throughout pregnancy in women with polycystic ovary syndrome decreases the rates of early pregnancy loss and preterm labor; hence protecting against fetal growth restriction. There have been no demonstrable teratogenic effects, intrauterine deaths or developmental delays with the use of metformin. Therefore, the evidence supports the efficacy and safety of metformin during pregnancy with respect to immediate pregnancy outcomes. However, because there are no guidelines for the continuous use of metformin in pregnancy, the duration of treatment is based on clinical judgment and experience on a case-by-case basis.Recently, the Endocrin Society has not only confirmed the use of metformin during pregnancy but also has recommended it as a first-line treatment of cutaneous manifestations, for prevention of pregnancy complications, or for the treatment of obesity. It should be noted that not all references allow the use of metformin in the first trimester of pregnancy. Therefore, it is suggested that metformin therapy be used for glycemic control only for those women with gestational diabetes who do not have satisfactory glycemic control despite medical nutrition therapy and who refuse or cannot use insulin or glyburide in the first trimester.

2) Metformin and Diabetes

Numerous studies and clinical trials have demonstrated that metformin monotherapy or combination therapy with other glucose-lowering drugs is effective in treating T2D. A report from 1995 illustrated that metformin is able to lower plasma glucose levels, and in the decades that followed, new roles of metformin in diabetes have been discovered. In the 1995 study, by Defronzo et al., 289 diabetes patients were treated with metformin or placebo. After 29 weeks, the metformin group showed lower mean fasting plasma glucose and HbA_{1c} levels. In a 1997 study by Garber, 451 diabetic individuals were given different dosages of metformin (ranging from 500 mg to 2,000 mg daily). After 14 weeks, it was found that metformin's efficacy is dose-dependent. In 2006, a 5-year randomized and double blind clinical trial in which metformin was compared with glibenclamide and rosiglitazone, other anti-diabetic drugs, was published. The results showed that the fasting plasma glucose levels were decreased the least by rosiglitazone and the most by glibenclamide, with metformin showing intermediate effects.

In some cases, metformin is used in combination with other anti-diabetic drugs or reagents. For example, in a 29-week study of 632 individuals, the combination of metformin and glibenclamide showed better glucose control than metformin alone. Glimepiride showed similar results in a clinical trial with 372 individuals. Another study showed that metformin and troglitazone lead to a stronger reduction in fasting plasma glucose and postprandial glucose levels after 3 months of treatment than treatment with metformin alone. Moreover, studies demonstrated that combination therapy of metformin with DPP4 inhibitors, SGLT2 inhibitors, or GLP1 receptor agonists also showed effective glucose control, without an additional risk of hypoglycaemia. Combination of metformin and insulin is another way to treat diabetes. In a trial with 96 patients, this combination exhibited better control of glucose levels and weight gain than treatment with metformin alone. In another study, with 390 patients, the combination with insulin also exhibited better glucose control than treatment with metformin alone.

Moreover, metformin improves insulin sensitivity and decreases fasting insulin levels in cognitive impairment patients with abnormal glucose metabolism. Metformin is a rational treatment choice for pregnant women with T2D, gestational diabetes (GDM), and polycystic ovarian syndrome (PCOS). Metformin was shown to have a stronger reducing effect on the body weight of PCOS patients than rosiglitazone. On the basis of *in vitro* and *in vivo* studies, including animal studies and clinical trials, the use of metformin in pregnancy is becoming increasing common globally. Nevertheless, the safety is controversial. Studies showed that children exposed to metformin may have a higher prevalence of obesity, BMI, abdominal fat volume, or blood pressure. Other research suggested that patients taking metformin for more than 10 years had an increased risk of beta cell failure and insulin resistance. Although long follow-up studies may be required to explore the possible effects of metformin on human cells and tissues, metformin is undoubtedly the preferred treatment option for diabetes patients.

Metformin exerts its anti-hyperglycemic effects mostly by suppressing hepatic glucose production through AMPK-dependen or -independent pathways. On the one hand, metformin inhibits gluconeogenesis through AMPK-dependent activation of SHP (small heterodimer partner) and inhibition of phosphorylation of CBP (CREB binding protein), thus suppressing the expression of gluconeogenic genes, such as *G6Pase* (glucose 6 phosphatase), *PEPCK* (phosphoenolpyruvate carboxykinase), and *PC* (pyruvate carboxylase). Moreover, activation of AMPK leads to the inhibition of mTORC1 (mammalian target of rapamycin complex I), which also results in the suppression of gluconeogenesis. On the other hand, metformin inhibits hepatic glucose production in an AMPK-independent manner. Studies showed that metformin attenuates the ability of glucagon or inhibits mitochondrial GPD (glycerol-3-phosphate dehydrogenase), subsequently leading to an impairment of lactate utilization for gluconeogenesis. Recently, a study also demonstrated that metformin directly targets FBP1 (fructose-1,6-bisphosphatase-1), the rate controlling enzyme in gluconeogenesis, inhibiting hepatic glucose production. Other studies suggested that metformin could also enhance GLUT1 (glucose transporter 1) mediated glucose transport into hepatocytes through activating IRS2 (insulin receptor substrate two), decreasing plasma glucose levels. Besides decreasing liver glucose production, metformin also decreases glucose levels through increasing (i) GLUT4(glucose transporter 4) mediated glucose uptake in skeletal muscles and (ii) absorption of glucose in the intestines. Metformin also stimulates GLP-1 (glucagon-like-peptide-1) release, thereby enhancing insulin secretion and lowering plasma glucose levels. Moreover, recent studies suggested that gut macrobiotic may be a target site of metformin. An increasing number of studies have showed dysbiosis of the gut microbiota in T2D patients. In a randomized, double blind study, scientists found that metformin affects the composition and function of the gut microbiota, providing new insight in the mechanism underlying metformin's anti-diabetic effects. After a short-time administration of metformin, the *Bacteroides fragilis* count in the gut decreased, which resulted in an increase in GUDCA (glycoursodexoycholic acid) levels. The elevation of GUDCA levels suppresses intestinal FXR (farnesoid X receptor), which improves glucose tolerance.

3) Metformin and Cancer

Accumulating evidence indicates that metformin inhibits growth, survival, and metastasis of different types of tumor cells, including those from breast, liver, bone, pancreas, endometrial, colorectal, kidney, and lung cancers. Metformin's anti-cancer properties

depend on its direct and indirect regulation of cells' metabolism. The direct effects are mediated by AMPK-dependent and -independent pathways. (i) Metformin activates AMPK, which leads to the inhibition of mTOR signaling, and as a result, protein synthesis is disturbed, and cell growth and proliferation is suppressed. For example, crosstalk between G protein-coupled receptors (GPCRs) and insulin receptor signaling systems may be inhibited by metformin: possibly contributing to the inhibition of pancreatic cancer proliferation. P53 is considered as a critical tumor suppressor gene in human cancers. Research showed that p53 is involved in the anti-cancer effects of metformin. Metformin activates AMPK and then induces p53 phosphorylation to prevent cell invasion and metastasis. (ii) Metformin also inhibits mTORC1, a key regulator of cell growth that can integrate intracellular and extracellular stimuli, in an AMPK-independent manner. Additionally, metformin suppresses mitochondrial complex I, thereby preventing the generation of reactive oxygen species (ROS) and further decreasing DNA damage, suppressing cancer development. Previous studies also suggested that metformin can suppress cancer development by activating autophagy and apoptosis through an AMPK-independent pathway.

Considering the indirect beneficial effects of metformin in cancer, studies indicated that metformin could regulate angiogenesis, fibroblasts, tumor-associated macrophages, and immunosuppressant, changing the tumor microenvironment. As an anti-diabetic drug, metformin decreases plasma glucose levels, thereby inhibiting cancer cell proliferation and survival. Other studies reported that metformin could activate the immune response against cancer cells or decrease NF-κB (nuclear factor-κB) activity, which results in a reduction in the secretion of pro-inflammatory cytokines. In addition, microRNA has been suggested to mediate one of the anti-cancer actions of metformin. Studies showed that metformin could induce DICER expression *in vitro* and *in vivo*, a crucial enzyme in the regulation of microRNA biogenesis. Recently, a study found that metformin combined with fasting-induced hypoglycemia synergistically impairs tumor metabolic plasticity and growth via the PP2A/GSK3β/MCL-1 axis. It has been suggested that tumor cells alternate between glycolysis and oxidative phosphorylation (OXPHOS) to adapt to metabolic challenges. Dietary limitation through intermittent fasting (IF) is an emerging approach to inhibit tumor development, while metformin is an OXPHOS inhibitor. It has been found that combination of metformin and intermittent fasting showed the strongest reduction in tumor growth without causing any weight loss or toxicity. This suggests more potential strategies to treat tumors with metformin may be developed in the future.

4) Breast Cancer

Breast cancer (BC) is one of the most common malignancies occurring in females. It is driven by a multitude of cellular pathways and its incidence increases with age. Cellular glucose metabolism is linked tightly with the proliferation and development of breast cancer. Several studies suggested that metformin reduces the incidence of breast cancer in T2D patients. Cancer cells show enhanced glucose uptake and metabolism and prefer glycolysis over OXPHOS, which is called the "Warburg effect." The noted specialty of metformin is to decrease glucose levels, thereby limiting the availability of energy for cancer cells. Metformin was also shown to decrease FAS expression, an essential component of the fatty acid synthesis pathway, thus affecting the survival of cancer cells.

Triple negative breast cancer (TNBC) is a kind of breast cancer that is difficult to cure, due to the lack of approved targeted therapies and effective chemotherapy with low toxicity. BACH1 (BTB and CNC homology 1) was reported to be the main regulator of glycolysis and OXPHOS in TNBC, and is therefore related to the Warburg effect. A previous study has showed that heme could suppress the expression of BACH1 and is helpful in the treatment of TNBC. Recently, a study indicated that combination therapy of heme and metformin significantly inhibits tumor growth and strongly suppresses TNBC. These findings provide us with new insight in the use of metformin combined with other drugs to treat tumors.

5) Blood Cancer

In the progression and treatment of multiple myeloma (MM), AKT signaling occupies an important place. In MM, AKT expression is always high, even in the advanced stages. Studies showed that metformin inhibits AKT/mTOR signaling, thereby impairing MM cell proliferation. Furthermore, metformin could also inhibit GRP78 (glucose regulatory protein 78) to further impair autophagosome formation and increase apoptosis, strengthening the anti-myeloma effects of brotezomib.

Leukemia comprises 2.8% of all cancers and 3.4% of cancer-related deaths worldwide. The aberrant activation of the PI3K/AKT/mTOR pathway is one of the most common biochemical features of leukemia. Metformin inhibits AKT/mTOR signaling, and might therefore be an effective approach to treat leukemia. Metformin has a beneficial role in human lymphoma by inhibiting mTOR signaling without the involvement of AKT, and the suppression of mTOR subsequently leads to the suppression of growth of B cells and T cells.

6) Colorectal Cancer

Colorectal cancer (CRC) is also one of the most common cancers in the world, with an increasing incidence in low and middle income countries. Recently, numerous studies, including fundamental research, clinical trials, and epidemiological studies, showed that metformin might be a candidate chemoprevention drug to decrease the risk of CRC development. In 2004, a report had demonstrated the relationship between metformin and CRC, and in the following years, the beneficial effects of metformin on the regulation of CRC development were reported in several studies. Metformin may exert its pharmacodynamic effects through the gut-brain-liver axis, but these mechanisms require further exploration. In the intestine, metformin increases glucose uptake and lactate concentrations. Metformin administration increases the bile acid pool in the intestine, which may affect GLP-1 secretion and cholesterol levels. In addition, metformin changes the microbiome, affecting the regulation of metabolism, such as glucose homeostasis, lipid metabolism, and energy metabolism. These changes contribute to the inhibition of the development and progress of CRC.

7) Endometrial Cancer

Endometrial cancer is the fifth most common malignancy in women with the incidence rising in both developed and developing countries. Disordered metabolism caused by metabolic syndrome like obesity and hyperglycemia is related to the development of endometrial cancer. Metformin is an effective anti-diabetic drug, studies have demonstrated the beneficial effect of metformin on endometrial cancer development. Studies showed metformin administration improves survival rate in diabetic patients with endometrial cancer. The mechanisms involved in the effect of metformin in treating endometrial cancer are mainly mitochondrial OXPHOS

suppression and AMPK activation, which subsequently inhibiting a variety of metabolic pathways, including STAT3, ZEB-1, ACC, mTOR, and IGF-1. These leads to protein synthesis and fatty acid synthesis decreased, apoptosis and autophagy increased, cell proliferation and cell cycle progression decreased, which all have a contribution to the suppression of endometrial cancer.

8) Melanoma

Melanoma is the most aggressive skin cancer and is responsible for almost 80% of the skin cancer-related deaths. Due to its strong invasive ability, melanoma often metastasizes to the lymph nodes, liver, lungs, and even the central nervous system. Because of its strong resistance to therapies and the ability to escape from the immune response, melanoma is a difficult public health problem. Currently, two antibodies for the treatment of melanoma are available, i.e., ipilimumab (anti-CTLA-4) and nivolumab (anti-PD-1). However, 55–60% patients do not respond to these treatments, and new treatment strategies are urgently required. Metformin can induce cell cycle arrest in the G0–G1 phase in melanoma cells. Another study indicated that metformin can attenuate melanoma growth and metastasis through inhibiting the expression of TRB3 (tribbles pseudokinase 3) in non-diabetic and diabetic mouse models. Because of the activation effect of AMPK, metformin could influence melanoma cell death and proliferation and the tumor microenvironment. It will be interesting to investigate the effects of combination treatment of metformin with current therapies or other drugs to treat melanoma.

9) Bone Cancers

Compared with cancers initiating in bone tissue itself, invasion of metastatic cancers, especially breast, lung, and prostate cancers, into bones is more common . All types of bone cancers influence the osteolytic process, and osteoblastic metastases occur through osteoclast activation or stimulant factors which are responsible for osteoblastic proliferation, differentiation, and formation RANKL (receptor activator of nuclear factor kappa-B ligand) is important in the suppression of osteoclast proliferation and differentiation, which is inhibited by AMPK upon metformin treatment. Moreover, metformin suppresses bone cancer cell proliferation, migration, and invasion via the AMPK/mTOR/S6 or the MMP2/MMP9 signaling pathway

10) Metformin and Obesity

The incidence of obesity has rapidly increased in recent years due to changes in lifestyle. Obesity is a multi-factor chronic disease accompanied with other related metabolic syndromes, such as diabetes, fatty liver diseases, and CVDs. Obesity is caused by an imbalance between energy intake and expenditure (Accumulating evidence suggests that metformin may be a potential therapy for obesity and its related metabolic dysfunctions. In non-diabetic individuals, metformin was shown to exert weak but beneficial effects on weight loss. In mice, metformin treatment for 14 weeks significantly prevented high-fat diet induced obesity and the associated inflammatory response through increasing the expression of FGF21 (fibroblast growth factor, a key metabolic hormone that improves lipolysis in white adipose tissue to prevent fat accumulation Moreover, metformin may prevent obesity in mice by increasing metabolic activity of brown adipose tissue (BAT), a tissue with abundant mitochondria.

Marketed Product List

Brand Name	Strength (mg)	Manufactured by
Bigesense XR	500	Zydus Cadila Healthcare ltd.(CND)
Cetapin XR	1000	Sanofi Aventis Pharma India
Cetapin XR	500	Sanofi Aventis Pharma India
Duomet ER	500	Biochem Pharmaceuitical industries ltd.
Exermet	1000	Cipla ltd.
Exermet	500	Cipla ltd.
Exermet	850	Cipla ltd.
Glumet-XR	500	Cipla ltd(Protec)

Metaday	1000	Wockhardt ltd(SSD)
Mesite-XR	500	Sanofi Aventis Pharma India(Onsite)
Mesite-XR	1000	Sanofi Aventis Pharma India(Onsite)
Metaday	500	Wockhardt ltd(SSD)
Sumet ER	500	Intra Labs India Pvt. ltd
Carbophage XR	500	Merc ltd
Diamicron XR CP	500	Serdia Pharmaceuticals India Pvt ltd.
Teniva-M	500	Intas Pharmaceutical ltd
Janumet XR CP	1000	MSD Pharmaceutical ltd
Glumetza	500	Santraus INC
Fortamet	500	Healing Pharma India Private ltd

Conclusion

Metformin hydrochloride is a biguanide antihyperglycemic agent used in the treatment of non-insulin dependent diabetes mellitus ("NIDDM").It has intrinsically poor permeability in the lower portion of the gastrointestinal tract leading to absorption almost exclusively in the upper part of the gastrointestinal tract. With poor oral bioavailability, low half-life and higher water solubility. The marketed immediate release products need to be administered 2-3 times daily. The current Metformin therapy is associated with high incident of GI side effects seen in about 30% of patients.

Hence, in the present work extended-release tablets of Metformin hydrochloride were developed with objective; that the tablet has a longer transit time in the stomach and acts as an in vivo reservoir that releases drug at a slow rate continuously over a prolonged time for absorption in the stomach and the intestine.

Metformin is a valuable drug for the treatment of T2DM, with minimal significant side effects. It provides benefits beyond its action as an oral hypoglycaemic agent and insulin sensitiser. Data from both clinical and bench studies indicate that metformin has a direct action on the endothelium and thus provides protection against the development of hyperglycaemia-induced vascular disease. The cellular mechanisms involved in the vasoprotective effects of metformin and its actions in the liver and skeletal muscle still have to be further elucidated, but seem to involve a reduction in oxidative stress that may or may not be secondary to an action on mitochondrial complex 1. They possibly involve the activation of AMPK and/or other pathways, such as those mediated by the deacetylase Sirtuin 1 and the regulation of eNOS. Although there is a vast dataset on metformin-mediated activation of AMPK being a contributor to the insulin-sensitising and hepatic gluconeogenesis inhibitory actions of metformin, some data are contradictory, suggesting that AMPK-independent actions are also important.

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