POLYMERIC EVOLUTION OF METFORMIN FOR SUSTAINED RELEASE EFFECT AND BETTER OUTCOME

Pragati Pundir[1*], Smriti Ghori[1] Dr Meenakshi Dhaiya[2], Dr. Mojahid ul islam[3] Dr Prabhakar Vishvakarma[4]

Abstract

During the preceding forty years, type 2 diabetes has been treated with the biguanide metformin, a medication utilized all around the world. Metformin was first approved in Canada in 1972 and received subsequent FDA approval in the US in 1995. By increasing the sensitivity of the liver and muscles to insulin, it enhances glycemic management. As metformin doesn't really increase insulin release, it has no connection to hypoglycemia. Metformin's enhanced metabolic regulation does not promote excess weight and may even lead to weight decrease. Other fibrinolytic disorders, hyperinsulinemia, insulin resistance, dyslipidemia, increased plasminogen activator inhibitor 1 levels, and dyslipidemia are all positively impacted by metformin. In spite of the fact that metformin lowers insulin resistance, the cellularmode of action is not fully known. Conventional drug was effective but caused an immediate effect that drastically decrease the blood sugar level and can cause dizziness and even rapid fatigue to the patient, Lactic acidosis, allergic reactions, changed the taste, cobalamin insufficiency, hypoglycemia and GI intolerance are the most prevailed metformin adverse medication responses. Acute complications of diabetes or extreme chronic conditions (including cardiacliver, and renalfaliure) should not be used with metformin. Moreover patient has to take the repetitive dosage of the drug over a certain period of time while in the modern day extended or sustained release formulation are in action for a longer period of time, different types of polymers are used to design such tablets to encapsulate them with the ability to release an optimum amount of drug at the particular interval of time to keep the dosage level steady for longer period.

Keywords: Diabetes, Metformin, Conventional Drug, Extended-release formulations

[1*, 2,3,4 Department] of Pharmacy, IIMT College of medical sciences, IIMT University Meerut 250001, Uttar Pradesh, India.

***CorrespondingAuthor-** Pragati Pundir[1*]
[*]Department of Pharmacy, IIMT College of medical sciences, IIMT University Meerut 250001, Uttar Pradesh, India.

DOI:- 10.48047/ecb/2023.12.si5a.0451

INTRODUCTION

Changes in lifestyle and globalisation have resulted in significant changes in societies, democratic structures, the eco system, and human psychology over the last 50 years. Diabetes and obesity have increased significantly in both advanced and emerging countries (1) with socially disadvantaged groups and Indigenous peoples bearing the heaviest burden. Diabetes stands as hot topic on the international health agenda as a worldwide epidemic and a risk to global economies, and public health, and the same has been mentioned by Edwin Gale in "the diabetes apocalypse"(2).

Diabetes and its repercussions are the outcome of the interplay of intricate genetic and environmental systems within a complex socioeconomic system with numerous psychosocial and environmental effects. In this Evaluation, we came across some of the major challenges, that the diabetes epidemic, particularly the, Non-insulin dependent(type 2) diabetes, has been posed to community in the current century.(3) These challenges include substantial growth in the frequency of, NIDDM and the disease's increased amount in youth or newer generation, including teenagers. We also emphasise the significance of the intrauterine environment and epigenetic factors, along with the financial influence of the diabetes epidemic to people and country alike. Diabetes has a massive impact on the economy. Diabetes-related global healthcare expenditure in 2010 was approximated to be $376 billion, accounting for 12% of total global healthcare spending.(4)

Diabetes had a straightforward healthcare expense of $176 billion in the United States in 2012. Outpatient medication and supplies spending grew from around $18 billion to $50 billion, offering a concrete instance of the rise in the expense of diabetes in a civilized nation. Cost information in low- and middle-income countries is scarce but desperately needed. According to the observations of a study (5) from China, the straightforward health bills ofNon-insulin dependent (type 2) diabetes and its drawbacks were estimated to be $26 billion in 2007, with an expected increase to $47.2 billion by 2030. In developing countries, controlling blood sugar accounts for roughly half of all medical spending. More than half of annual diabetes healthcare costs in the poorest countries is for pharmaceuticals that lower blood sugar levels in order to prevent life-threatening hyperglycemia (6).

Evaluation of Diabetes in INDIA

The Indian Council of Medical Research (ICMR, New Delhi) lead the very initial national survey on the incidence of NIDDM in India in mid of 1972 and 1975 4. Approximately 35,000 people over the age of 14 were screened using a 50 g glucose load. Diabetes was evaluated using a capillary blood glucose level greater than 170 mg/dl. The frequency was 1.5% in the rural population, and 2.1% in the urban population, while people over the age of 40 had a prevalence of 5% in the metropolitan and 2.8% in the nonmetropolitan areas (7). Further research revealed a notice able rise in the incidence of this disease, in various communities of India. Research performed in a small municipality in the southern part of India in 1988 reported that the prevalence of 5%. In the same research, the frequency of reduced glucose tolerance was 2%. In the mid of 1989 and 1991, a national study was carried out in various rural sections of the nation among specified town communities (8). This investigation, which used the terms and conditions of WHO from 1985 to recognize diabetes, found a crude prevalence of 2.8%.

Eluru's research study, which glanced at the frequency of diagnosed hypoglycemia in four small towns in Andhra Pradesh, found a 1.5%frequency. The frequency of known disease was 6.1% in individuals over the age of 40, which was unusually elevated at that point for a rural area with a poor socioeconomic background and low health awareness(9). A study conducted in Chennai in 1988 found a frequency of 8.2% in urban areas and 2.4 percent in rural areas.

The National Urban Diabetes Survey (NUDS), a population-based research was performed in the 6 Indian urban town and tried to recruit 11,216 peoples aged 20 and up from all socio-economic status strata (10). Diabetes was defined using the WHO criteria after an orallytolerared test for glucose was performed using capillary glucose. According to the study, the age-standardized frequency of NIDDM is 12.1%. This research also discovered that the frequency in South India is elevated by 13.5 percent in Chennai, 16.6 percent in Hyderabad, and 12.4 percent in Bangalore, compared to 11.7 percent in eastern India (Kolkata), 11.6 percent in Indian Subcontinent (New Delhi), and 9.3 percent in Maharashtra (Mumbai). The research additionally discovered many patients withweakened glucose tolerance (IGT), with 14% at elevated danger of diabetes (11).

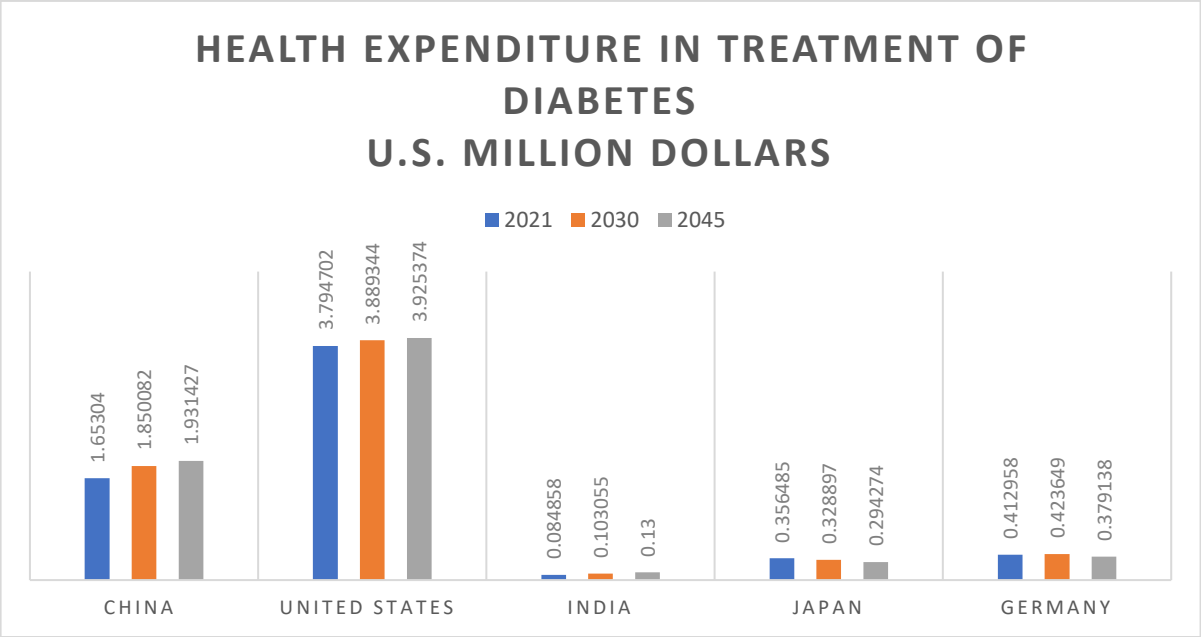


Fig. 1 Total Health Expenditure in Diabetes Treatments (12)

Tablets

Tablets are solidified dosage forms that are basically manufactured with the aid of suitable excipients. Depending on the manufacturing method, and their use they may differ in weight, hardness, size, thickness, shape, disintegration and dissolution parameters, and other aspects. Majorly tablets are used for drug administration orally. Many of these are prepared with various colourants and coatings. Some tablets, such as those delivered through another route of administration, such as buccally, vaginally, or sublingually, are designed with properties specific to their mode of administration. Tablets are mostly made via compression, with a few exceptions made through moulding. Compressed tablets are made with tablet machines that can compact granulated material under high pressure.

The dimensions and shape are obtained by the use of different shaped punches and dies. Molded tablets are made on a big scale using tablet technology, or on a small scale by working personels pressing wet powder material into a mould, from which the formed tablet is expelled and allowed to dry. Some tablets are grooved, to be easily divided into two or more pieces. This allows the patient to administrate smaller quantities as required, or, if recommended, to take the pill in a small or divided dosage. Because all tablets are not scored, they should not be broken or cut by the patients else drug-release features will be reduced by changing the tablet's physical dimensions.

Tablets are manufactured in various shapes and size: Circular, Flat, Biconvex, etc

TYPES OF TABLETS:

There are mainly two class undr which tablets are classified

Orally admistrated tablets.

Non-orally adminidstrated tablets

1) Orally administrated tablets : these are those tablets which are administrated through the oral route.

Buccal tablets

Sublingual tablets

Dental cone

Effervescent tablets

Dispensing tablets

Sustained released

Enteric-coated tablet

Chewable tablets.

Simple uncoated tablets

Film coated tablets

2**)Non-Oral Administrated**

Vaginal

Transdermal

METFORMIN TABLETS EVOLUTION

Galega officinalis (also called as professor-weed, French lilac, Italian fitch, and goat's rue,) is a herb flowering in summers, native to most temperate regions with white, blue, or purple flowers. The herb has also been used to increase milk in cows and has been utilised as a medication in plague outbreaks to enhance sweating of the infected persons.(13) Yet, the plant proved much too poisonous for broad agricultural use Muller and Rein wein documented early clinical investigation

with galeginesulfate in 1927. They tested self-administration of 109 mg galegine sulphate, then monitored glucose level of blood for 25 hours. They then widend the study to include more healthy people and, eventually, diabetes sufferers. There was a hypoglycemic effect in all three subjects (very less in the normoglycemic persons, but notable in diabetic patients).(14)

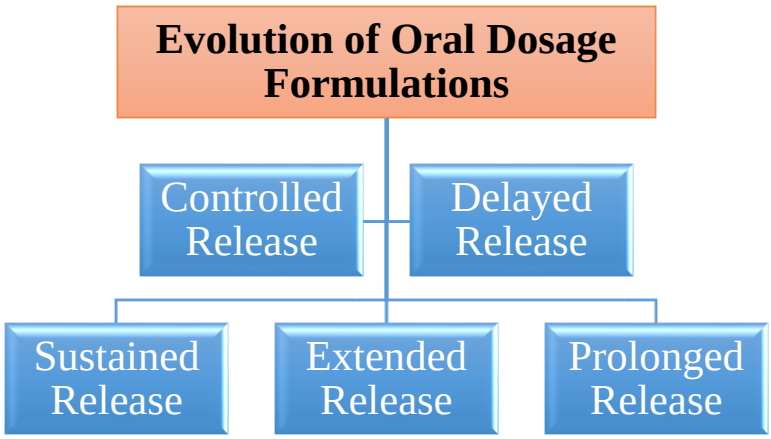


Fig. Evolution of Oral Dosage Forms

Over the following decades, additive observations on the anti-diabetic actions of Galega officinalis extracts were made by Leclerc and his research colleges, and also Parturier and Hugonot. They were successful in enhancing the safety and administration of galegine-based treatment, albeit their value was restricted by response variability and short duration of effect.

Metformin was examined in many tests in Paris in 1957 and was proven to reduce the glucose level in the blood of patients with Non-insulin-dependent (type 2) diabetes but not in normoglycemic persons. Metformin, unlike sulfonylureas (another kind of oral diabetes medication), did not boost insulin secretion but instead inhibited the release of glucose from the liver. Metformin had gastrointestinal side effects in those studies.

Metformin's advantages were again discovered in 1995. Several research was carried out, with the UK Prospective Diabetes Study being very important. It was a multicenter, randomized clinical research that tracked 3867 personnel for decades. Metforminreduces the risks of myocardial infarction and all-cause mortality regardless of its ability to glucose control.

Correspondingly, metformin became the first-line therapy for obese Non-insulin-dependent (type 2) diabetic patients. Prospective and retrospective trials validated the drug's and cardioprotective properties, and anti-atherosclerotic actions, but it took another decade for these findings to be converted into official guidelines. Diabetes specialists in the United States and Europe agreed in 2012 that metformin is the medicine of first choice for all people with type 2 diabetes.

Sustained Release Drug Delivery System

It encompasses any medication administration approach that enables drug dissolution across a prolonged amount of time that is not time dependent. Sustained dose forms are commonly made using a polymer that is hydrophilic in nature. The primary objective of a perfect drug delivery system is to administer the appropriate amount of medication at scheduled times and at the appropriate site of action in order to preserve the optimal therapeutic concentration of drug in the blood plasma.

Mechanism of release of Oral Sustained Release Drug Delivery System

- **Diffusion Sustained:** The mechanism of diffusion depicts the transfer of the drug molecules from an area with a high concentration to a region of lesser concentration.(15)
- **Dissolution Sustained:** A medicine with a slow un-going dissolving extent is intrinsically maintained, and for pharmaceuticals with high water solubility, dissolution can be reduced by proper salt or derivative synthesis, or by using a coating that dissolves in natural or alkaline environments. This prevents the medicine from being released from the dose form unless it attains the greater pH than that of the gut.(16)
- **Ion Exchange:** The ion exchange resins are unable to dissolve in water they are cross-linked polymers with ionisable functional groups. The resins were originally employed in a variety of medicinal applications, most notably to mask

flavours and controlled release mechanisms. When ionisable medications are exposed to the resin for an extended period of time, they create an irreversible compound. When suitable ions come into contact with ion-exchanged groups, a resin bound medication is removed.(17)

- **Osmotic Pressure:** The osmotic pressure differential between within the container and the outside space must be enhanced in this manner to regulate withdrawal. Keeping an osmotic agent swamped in the compartment is the easiest and also most reliable approach to maintain a consistent osmotic pressure. With the use of this technique, hydrophilic medications may be released with zero order.(18)
- **Density Alteration:** The majority of medications are either alkaline solutions or weak acids. Sustained drug release formulation is pH dependent. However, buffers could be in corporated into the preparation to enable maintaining a consistent pH, resulting in pH-independent drug release. These buffers include salts of citric acid, amino acids, tartaric acid, pthalic acid, and phosphoric acid.(19)

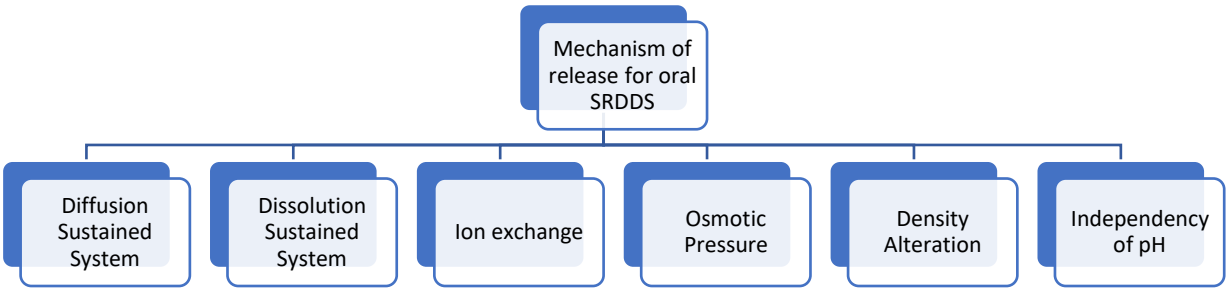


Fig. Mechanism used in release for oral SRDDS

METFORMIN SUSTAINED RELEASED TABLETS

Methodology

Vama Pharmaceuticals supplied the metformin hydrochloride (Nagpur, India). S. D. Fine Chem. Laboratories supplied microcrystalline cellulose (Avicel pH 101). (Mumbai, India). Colorcon,(Mumbai) provided HPMC K100M as a gift sample, and Dabur Research Foundation provided Guar gum as a gift sample (New Delhi). All of the other constituents were laboratory ingredients that were used without additional trials.

Analysis of the physical correlation between polymer and drug

A Fourier transform infrared spectrophotometer was used to scan the specimen over a wave number range of 4000-400 cm cm^{-1} that has unadulterated API. (FT-IR, Shimadzu 8400S; Japan). The drug's spectra changed in the presence of a polymer, indicating a physical involvement of the drug molecule with the polymer. A differential scanning calorimeter was used to conduct research of undressed and spray-dried metformin hydrochloride specimens. The thermal scanning was carried out in nitrogenous surroundings, with a rate of 10°C/min within a temperature range between 30-300°C. The reference material was alumina. The onset of melting point and enthalpies of fusion of specimen are spontaneously estimated by the equipment.

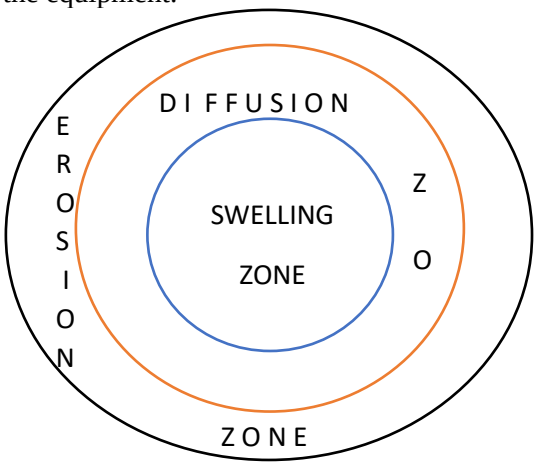


Fig. 2 Matrix Diffusion Sustained Release Drug Delivery System

Formulation of Tablets of Metformin Hydrochloride Matrix

The direct compression approach was used to create several matrix-inserted formulations of metformin HCl utilizing varied quantities of polymers, either in combination or alone. A determined amount of medication, filler (MCC), and polymer (HPMC, Guar Gum) were completely intermixed together. As a lubricant, Magnesium Stearate was added up, the required quantity of the mixture was and then compressed

using the eight-station rotatory press(Rimek Minipress Ahmedabad, by applying a constant compression force with 14mm flat-faced punches at a compressed force that is required to formulate the perfect tablet of hardness 7-8 kg/cm^2. Each tablets were kept in the seal-packed container for further use.

Code for formulation	Metformin(mg)	HPMC K 100M (mg)		Gaur Gum (mg)	Micro Crystalline Cellulose(mg)	Mg. sterate (mg)	Total (mg)
Formulation 1	500	100		-	390	10	1000
Formulation 2	500	150		-	340	10	1000
Formulation 3	500	200		-	290	10	1000
Formulation 4	500	-		100	390	10	1000
Formulation 5	500	-		200	290	10	1000
Formulation 6	500	150		50	290	10	1000
Formulation 7	500	100		100	290	10	1000

Table. 1: Constituents used in formulating different SR tablets of Metformin HCl

Assessment of the Formulated Tablets

The variation in weight, friability, thickness, hardness, and content of the drug of the manufactured matrix tablets were all measured immediately after preparation. (20,21) An electronic balance was used to assess the weight fluctuation of the pills (n = 20 tablets) (Sansui AJ 22OE, Japan). The Monsanto hardness instrument was used to measure the hardness of the tablets (n = 6). (Campbell Electronics, Bombay). Friability (n = 10) was measured for 240 seconds at 25 rpm in a Roche friability appartaus (Campbell Electronics) (Campbell Electronics). A vernier caliper was used to measure the thickness of the tablets. A UV/Visible spectrophotometer was used to measure the absorbance value of the standard and the specimen ata wavelength of **233 nm** (Shimadzu 1601).(15,16)

In vitro studies for release of the drug

Drug release tests were carried out at 370.5°C aided by the IP-1 dissolving apparatus, paddle-type, For the first 2 hours, 0.9L of 0.1 M HCl was utilised, followed by phosphate buffer of pH 6.8 solutions for 12 hours. The sinkcriteria was continued throughout the trial. To keep the volume constant, samples (10 mL) were taken at constant intervals and restored with the same volume of prewarmed (370.5°C) fresh dissolving vehicle. The withdrawn samples were filtered using a 0.45-mm membrane filter, and the drug concentration in each sample was measured using a UV spectrophotometer at 233 nm. The dissolving test was done three times.

Drug Release Kinetics

The dissolving profile of the investigated tablets was evaluated using various 1storder, 0 order and Higuchi square root kinetic equations in order to drug release mechanism. Higuchi's equation had the best match with the highest correlation (r2 = 0.98) across all formulations. Nevertheless, two considerations limit Higuchi's equation's application to matrix systems.(22,23,24) This model does not account for the impact of matrix expansion (due to hydration) and slow matrix disintegration. As a result, the dissolution profile was also fitted using the well-known exponential Korsmeyer-Peppas equation,(24)that is frequently used to characterise drug behaviour in polymeric systems.

$m_t/m_\infty = k.t^n$

i.e.m_t/m_∞ = amount of API released

t = time required to release

k= characteristic kinetic constant of the polymer.

n= diffusion coefficient which indicates the mode of release.

The limit considered in this study were n = 0.45 and n = 0.85.Values of n between 0.45 and 0.85 might be interpreted as indicative of both processes (polymer relaxation and drug diffusion in the hydrated matrix), also known as anomalous transport.

For comparing release data of various equations with a difference in mode of release (n-values), an (MDT) mean dissolution time was estimated aid by the following formulation.(25)

Mean dissolution time = (N/N+1). $K^{-1/N}$

where N = exponential release

k = rate constant for release

The dissolution records has been statistically analysed to determine and discriminate between dissolution data using the dissolution similarity factor 2.(24) The formula for calculating 2 is shown below.

$$f_2 = 50 \log \left\{ \left[1 + \frac{1}{n} \sum_{t=1}^{t} Wt \left(R_t - T_t \right)^2 \right]^{-0.5} \times 100 \right\}$$

where, n = count of dissolution time point

W_t = voluntary weight factor

R_t = standard dissolution point at t time`

T_t = trial dissolution point at t time

The f2 value in the 50-100 range suggests that the dissolution is comparable. The two values of 100

show that both the test and standard patterns are equal, while lowering the number indicates that the disparity between the release profiles is increasing.

Electronic Microscopic Characterisation

A scanning electron microscope was used to obtain electronic micrographs of drug metformin Hcl tablets prior & post dissolution (model JSM T200, Japan). Prior to inspection, the sample were vacuum coated with gold in an environment of argon. The electron microscope was set at a 30 kV acceleration voltage.

Statistical Evaluation

The obtained information was given to ANOVA(two way), and then forwarded to the Bonferroni post-tes t, to analyse the statistical difference using the programme Graph pad prism, and P 0.001 was declared significant in all cases.

COMBINATIONS OF METFORMIN

1.) Repaglinide and metformin

NIDDM is defined by low insulin secretion and reachability for treating type 2 diabetes, many kinds of oral anti-diabetic medicines are now licensed. Traditionally, a step-by-step treatment approach from monotherapy to combination therapy has been employed; although, the incidence failure of treatment with monotherapy has resulted in a shift towards early treatment with combination medicines that address the two major faults in glycemic control. Repaglinide (a prandial glucose regulator that stimulates insulin release) with metformin is one such combo therapy (an insulin sensitizer that reduses hepatic glucose output, elevate peripheral glucose uptake and utilisation and minimizes weight gain many clinical studies have found that combining repaglinide with metformin is well tolerated and leads in larger reductions in haemoglobin A1c and fasting plasma glucose levels when compared to either monotherapy. Because of its lower proclivity for hypoglycemia, repaglinide may be a better option to combination treatment with sulphonylureas and metformin.

When monotherapy is no longer effective, the combination regimen of repaglinide with metformin should be evaluated as a beneficial alternative in the treatment of individuals with NIDDM (type-2).

2.) Sitagliptin and metformin.

Nauck, directly compared sitagliptin (100mg) dose, one dose everyday added to continued metformin (1500 mg/dl) treatment to adjunct of glipizide 5 mg daily to a maximum of 20 mg to metformin. Sitagliptin was not lesser to glipizide in this 52-week analysis of 1172 individuals. Nevertheless, manysubjects dropped out of the sitagliptin arm, skewing the outcome in sitagliptin's favour in the per-protocol determination. In both groups, HbA1c fell by 0.67% from a baseline of 7.5%. In the sitagliptin group, 63% of patients achieved a HbA1c of less than 7%, whereas 59% in the glipizide group. Fasting glucose was lowered by 10.0 mg/dl in sitagliptin-treated people and 7.5 mg in placebo-treated people. Hypoglycemic episodes were substantially more common in the glipizide group (n = 657 events, 32% of subjects) than in the sitagliptin group (n = 50 events, 5% of subjects) (p 0.001). Body weight increased by 1.1 kg in glipizide-treated patients whereas it decreased by 1.5 kg in sitagliptin-treated patients (between-treatment difference -2.5 kg, 95% CI -3.1 to -2.0; p 0.001). (26) .

3.) Rosiglitazone and metformin

Glucose control and insulin resistance enhanced similarly from baseline in both groups (p0.05). The rosiglitazone/metformin combination therapy significantly improved hsCRP, IL-6, WBC, adiponectin, systolic and diastolic arterial pressure (p0.05) and MET group (p0.05). Compared to the RSG+MET group, metformin monotherapy substantially lowered BMI (p0.001), TC (p=0.012), and LDL (p=0.020). Notably, serum vaspin concentrations were reduced from baseline in both the RSG+MET (0.960.75 ng/ml, p0.001) and the MET (0.920.57 ng/ml, p=0.001) groups. HbA1c, FPG, WHR HOMA-IR, IL-6, insulin. (only in the MET+RSG group), and lipid mass were all linked with changes in vaspin. HbA1c, HOMA-IR,FPG, and insulin remained non-independent predictors of serum vaspin level increases in conventional multiple regression analysis (R2=0.836, p=0.004).

4.) Vildagliptin

According to the results of 3-6 months test, combined therapy with vildagliptin 50mg two times every day with metformin enhanced HbA1c notably more than monotherapy with metformin and vildagliptin individually in subjects with NIDDM, whose disease was inadequately maintained by metformin monotherapy or who were treated naïve. Furthermore, in patients with poorly controlled NIDDM, vildagliptin 50mg two times every day plus metformin was found to be non-inferior to glimepiride with metformin, gliclazide with metformin, or pioglitazone with metformin in terms of change from baseline in HbA1c after 6-8 months weeks of therapy.

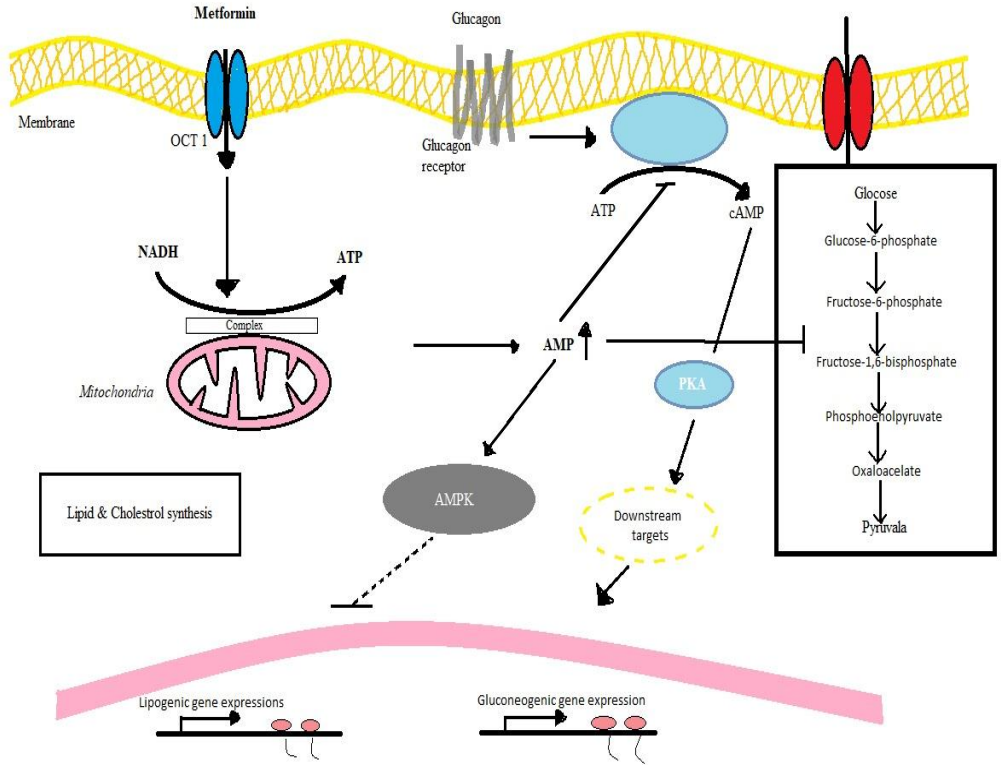
According to the outcomes of 24 weeks tests, the inclusion of vildagliptin 50mg twice per day to vildagliptin or pioglitazone 50mg once a day to glimepiride enhanced HbA1c noticeably more than glimepiride or thiazolidinedione individually in patients with NIDDM, whose disease was poorly controlled. (27)

5.) Insulin glargine and metformin

FPGs averaged 5.750.02 and 5.960.03 mmol/l (p0.001) over the previous 12 weeks, and insulin dosages were 685 and 706 IU/day (0.690.05 and 0.660.04kg-1 day 1,NS) in thr MET +G and MET+NPH groups, respectively. The means of HbA1c at 36 weeks was 7.140.12 and 7.160.14%respectively(NS).Symptomatic but not verified sympatomatichypoglycemia was substantially lower in the G+MET group (4.10.08episides/patients year) than in the NPH+MET group(9.02.03 episodes /patient-years,p0.05)during the first3 months, but not statically different thereafter, Throughout the nine months of research, glucose levels before the dinner were higher in the NPH+MET group(10.10.3mmol/l) than in the G+MET group (8.60.3mmol/l,p+0.002). there was no change in the baseline parameters such as beginning glycemia or C-peptide in those who have adequate glycaemic control (HbA1c 7.0%)and those who did not. There were differences across investigation centres, weight increase throughout the run-in phase and insulin treatment, and FPG during last 3 months.(28)

FUNCTIONS AND MECHANISM OF ACTION OF METFORMIN

Metformin, for example, is chemically constituted of coupled guanidine groups bonded together with the elimination of ammonia. Several, but not all, guanidine-containing drugs have been shown to have anti-hyperglycemic properties. These consequences are distinct from toxicity in the case of metformin. Prior to biguanides, researchers concentrated on guanidine(29), which was too poisonous to be used clinically, and then on diguanides(30), which are composed of coupled guanidines linked by an alkyl chain of variable length. Coupled synthalin A and B, diguanides, were employed in interventional studies, but significant toxicity, which could not be distinguished from therapeutic benefits, was immediately seen(31,32). By the end of the 1950s, metformin and two other biguanides, metformin has the best safety profile. This is mostly due to the increased risk of lactic acidosis, which can be deadly, with phenformin or buformin therapy(33)



Because of the large doses of medicines required for pharmacological advantages, early researchers hypothesized that it might not be relaint on a single distinct and specific protein target. Hypoglycaemia was reported with impaired oxygen utilization in early diguanide

physiological investigation. (30) Following the investigation, it was shown that guanidine (35,36) diguanide (36) and phenformin (37,38) reduce mitochondrial respiration expenditure, indicating that this organ site is a key target for guanidine-based therapeutics. Several models have been devised to account for these effects. The original notion was based on finding that biguanides and other derivatives may influence charge distribution.

Our findings suggest that the medication may block protons and other cations from transversing membranes. (39) However, the magnitude of these effects did not align well with anti-hyperglycemic efficacy, with certain ineffective medications interacting with membranes significantly easier than phenformin or metformin. (40) Furthermore, although phenformin is water loving medicine that is unlikely to interact substantially with membranes. Consequently, metformin is assumed to be transported via transporters. Another suggestion made during the time was that guanidine containing substances induce anti-hyperglycaemic effects by altering calcium from proteins like pyruvate kinase, (41) but these effects were only visible at very high concentrations, and hydrophobocity was required for potency to be determined. As a result, the IC50 for phenformin was 2.5 mmol/l but metformin corresponding value was 275mmol/l far higher than non-specific cation tetramethylammonium. (42) As result calcium mobilizing activities described above are unlikely to contribute to metformin therapeutic effect. It has not been thoroughly investigated whether calcium mobilizing or lipid modifying effects contribute to the toxicity of guanidine like phenformin. it was recently postulated that metformin actions on mitochondrial are dependent on a third non protein effect, direct metal targeting (43) via a planner ring with a unique electron delocalized structure in which square planner geometry substitute more normal tetragonal shape (44). The compelling proof for metformin immediate attachment to metal ions, includes extensive crystallographic (45) and spectroscopic investigations (44,46), which contrasts with the paucity of data supporting metformin direct binding to recognized metformin-regulated proteins. More study is required to understand how metformin metal binding properties enable it to induce mitochondrial repression.

Decreased gluconeogenesis is a prominent subsequent physiological response to biguanides over time, studies on guanidine derivatives began to correlate lower mitochondrial activity to reduces gluconeogenesis. Although as prior researched indicated, the sufficient correlation of the magnitudes of these effects for some pharmacological molecules led others to believe that mitochondrial effects, rather than therapeutic consequence, were more inclined to lead to side symptoms that included lactic acidosis. In the case of metformin, for example, even at doses considerably beyond those expected in vivo, there is typically no effect on cellular ATP levels. These concerns les to the hypothesis that anti-hyperglycaemic benefits might be the result of drug-specific mitochondrial effects superimposed on previously established generic mitochondrial reactions to guanide- containing drugs. Metformin has a particular effects revealed in studying its influence on the transport of electrons, the mitochondrial oxygen-dependent process that connects the citric acid cycle to ATP synthesis, giving most cell energy. Metformin suppression of complex I in the mitochondrial electron transport chain is followed by a reduction in hepatic glucose synthesis, according to experiments utilizing hepatocytes, mitochondria, and freeze-clamped livers, metformin lowered glutamate and malate mitochondrial oxidation more effectively than succinate, which may bypass complex I inhibition as a complex II substrate. Similar findings have previously been made with other guanidine-containing drugs, but our knowledge of the metabolism of mitochondria was likely inadequate at the time to allow this is explanation of the result. The result presented here gives compelling evidence of a connection between electron transport blockage and glucose generation. However genetic studies have yet to show whether complex I is the only mitochondrial target of metformin. Newer studies for, example, this have revealed that metformin's effect on mitochondrial respiration varied amongst cells, although further studies is needed to comprehend the underlying causes of the differences. (47)

CONCLUSION

Metformin is a widely used oral medication for the treatment of diabetes mellitus. It works by decreasing the amount of glucose produced by the liver and improves the body's response to insulin. Sustained-release metformin is a modified form of the medication that controls its release rate, which means that it is released slowly and gradually over several hours. Regular metformin, on the other hand, is released quickly and absorbed rapidly. The SR form of metformin renders with several advantages over the regular form.

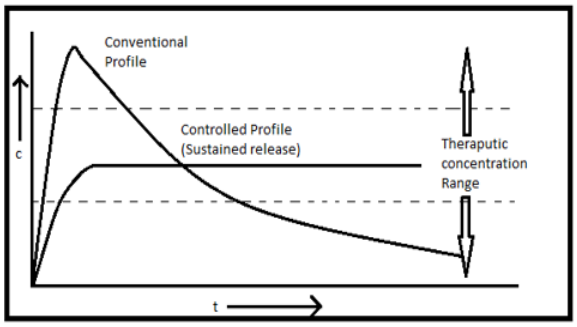


Fig. Comparative Therapeutic Index of regular and SR metformin

- Fewer side effects: The slow and gradual release of sustained-release metformin means that the medication is absorbed more gently and there is less chance of experiencing ADR such as gastrointestinal effects like constipation etc.
- Improved tolerability: As sustained-release metformin is released over longer periods, it is easier for patients to tolerate higher doses of the medication, which can enhance the effectiveness of the treatment.
- Better glycemic control: SR metformin has been shown to help patients maintain the stable sugar level the entire day, contributing to a better glycemic control.
- Reduced Dosing Frequency: SR metformin needs to be taken only once a day or two, which is more convenient for patients and can increase compliance with the regimen.

In summary, SR metformin can provide benefits in terms of tolerability, side effects, and glycemic control. However, it is important to always consult with the healthcare provider before switching from regular to the SR on, as the experience and ADR can vary individual to individual

REFERENCE

1. Zimmet, P. Z., Magliano, D. J., Herman, W. H., & Shaw, J. E. (2014). Diabetes: a 21st century challenge. The lancet Diabetes & endocrinology, 2(1), 56-64.https://doi.org/10.1016/S2213-8587(13)70112-8
2. Chen, L., Magliano, D. &Zimmet, P. The worldwide epidemiology of type 2 diabetes mellitus—present and future perspectives. Nat Rev Endocrinol **8**, 228–236 (2012). https://doi.org/10.1038/nrendo.2011.183
3. Chen, L., Magliano, D. &Zimmet, P. The worldwide epidemiology of type 2 diabetes mellitus—present and future perspectives. Nat Rev Endocrinol **8**, 228–236 (2012). https://doi.org/10.1038/nrendo.2011.183
4. American Diabetes Association. Economic costs of diabetes in the U.S. in 2012. Diabetes Care 2013; 36: 1033–46.
5. Wang W, McGreevey WP, Fu C, Zhan S, Luan R, Chen W, Xu B. Type 2 diabetes mellitus in China: a preventable economic burden. Am J Manag Care. 2009 Sep;15(9):593-601. PMID: 19747024.
6. American Diabetes Association. Economic costs of diabetes in the U.S. in 2012. Diabetes Care 2013; 36: 1033–46.
7. Pradeepa, R., Mohan, V., Epidemiology of type 2 diabetes in India. Indian J Ophthalmol. 2021 Nov;69(11):2932-2938. doi: 10.4103/ijo.IJO_1627_21. PMID: 34708726; PMCID: PMC8725109.
8. Ramachandran A, Jali MV, Mohan V, Snehalatha C, Viswanathan M. High prevalence of diabetes in an urban population in south India. BMJ 1988; 297 : 587-90, DOI: 10.1007/s001250100627
9. Rao PV, Ushabala P, Seshaiah V, Ahuja MMS, Mather HM. The Eluru survey: prevalence of known diabetes in a rural Indian population. Diabetes Res Clin Pract 1989; 7 : 29-31. DOI: 10.1016/0168-8227(89)90041-7
10. Ramachandran, A., Snehalatha, C., Kapur, A. et al. High prevalence of diabetes and impaired glucose tolerance in India: National Urban Diabetes Survey. Diabetologia **44**, 1094–1101 (2001). https://doi.org/10.1007/s001250100627
11. Vasilios G. Athyros, Emmanuel S. Ganotakis, Moses Elisaf& Dimitri P. Mikhailidis (2005) The prevalence of the metabolic syndrome using the National Cholesterol Educational Program and International Diabetes Federation definitions, Current Medical Research and Opinion, 21:8, 1157-1159, DOI: 10.1185/030079905X53333
12. Diabetes-related health expenditure: Total diabetes-related health expenditure, USD million. (n.d.). International Diabetes Federation. https://diabetesatlas.org/data/en/indicators/17
13. Witters, L. A., Journal of Clinical Investigation.,2001,108(8), pp. 1105-1107. doi: 10.1172/jci14178.
14. Bailey, C. and Day, C., Practical Diabetes International,. 2004, 21(3), pp. 115-117. doi: 10.1002/pdi.606.
15. Ratnaparkhi, M. P., Gupta, J. P., Sustained Release Oral Drug Delivery System - An Overview Terminology, 2013 3(4), 10-22270.

16. B Mamidala, R. K., Ramana, V., G, S., Lingam, M., Gannu, R., Yamsani, M. R., Factor Influencing the Design and Performance of Oral Sustained/Controlled Release Dosage Forms, Int. journal of pharmaceutical science and nanotechnology. 2009; 2:583.
17. Conaghey OM, Corish J, Corrigan OI. Iontophoretically assisted in vitro membrane transport of nicotine from a hydrogel containing ion exchange resin. Int. J. Pharm. 1998; 170:225.
18. Gupta S, Singh RP, Sharma R, Kalyanwat R, Lokwani P. Osmotic pumps: A review. Int. journal of comprehensive pharmacy. 2011; 6:1-8.
19. Lapidus H, Lordi NG. Studies on controlled release formulations. Journal of Pharmaceutical sciences. 1968; 57:1292- 1301.
20. Martin, A., Philadelphia, P. A., Micromeritics: Physical Pharmacy.,2001, pp. 423–54.
21. Wells, J., Pharmaceutical preformulationPharmaceutics the science of dosage form design. London: Churchill Livingstone., 2002, p. 247.
22. Higuchi, T., J Pharm Sci. 1963,52:1145–9. DOI: 10.1002/jps.2600521210
23. Korsmeyer, R.W., Gurny, R., Peppas, N. A., Int J Pharm. 1983,15:25–35. https://doi.org/10.1016/0378-5173(83)90064-9
24. Costa, P., Sousa Lobo, J.M., Eur J Pharm Sci. 2001,13:123–33.
25. Gohel, M. C, Panchal, M. K., Drug Dev Ind Pharm. 2002,28:77–87.doi: 10.1208/s12249-008-9174-1
26. Nauck, M.A., Meininger, G., Sheng, D., Terranella, L., Stein, P.P Diabetes ObesMetab 2007, 9(2): 194-205. DOI: 10.1111/j.1463-1326.2006.00704.x
27. Neumiller, J. J, Wood L., Campbell R. K. Pharmacotherapy, 2010 30(5): 463–84. DOI: 10.1592/phco.30.5.463
28. Pugh, J. A., Wagner, M.L., Sawyer, J., Ramirez, G., Tuley, M., Friedberg, S. J, Diabetes Care,2002 15:953–959. DOI: 10.2337/diacare.15.8.953
29. Riddle, M.C., Rosenstock, J., Gerich, J. E., I Diabetes Care 26:3080–3086. DOI: 10.2337/diacare.26.11.3080
30. Watanabe, C. K., J Biol Chem,1913 33:253–265.doi.org/10.1016/S0021-9258(18)86579-6
31. Bischoff, F., Sahyun, M., Long, M. L.,Guanidine structure and hypoglycemia. J Biol Chem,1929 81:325–349.
32. Blatherwick, N.R., Sahyun, M., Hill, E.,JBiol Chem,1927 75:671–683. https://doi.org/10.1016/S0021-9258(18)84136-9
33. Luft, D., Schilling, R.M., Eggstein, Diabetologia, 1978 14:75–87. https://doi.org/10.1007/BF01263444
34. Bodo, R., Marks, H.P., J Physiol,1928 65:83–99.doi: 10.1113/jphysiol.1928.sp002463
35. Chance, B., Hollunger, G., (1963). J Biol Chem 238:432–438. https://doi.org/10.1016/S0021-9258(19)84014-0
36. Pressman, B.C., J Biol Chem,1963 238:401–409.https://doi.org/10.1016/S0021-9258(19)84012-7
37. Davidoff ,F., J Biol Chem.1971 246:4017–4027. PMID: 5561472.
38. Davidoff, F., J Clin Invest,1968 47:2331–2343. DOI: 10.1172/JCI105918
39. Schafer, G., Pergamon Press, New York,1981 pp 165–185. https://doi.org/10.1016/0163-7258(80)90049-2
40. Schafer ,G., Biochem Pharm,1976 25:2005–2014.https://doi.org/10.1016/0006-2952(76)90423-8
41. Davidoff, F., N Engl J Med,1973 289:141–146. DOI: 10.1056/NEJM197307192890308
42. Davidoff, F, Carr , S., Proc Natl Acad Sci,1972 69:1957–1961. https://doi.org/10.1073/pnas.69.7.1957
43. Logie ,L., Harthill, J., Patel, K., Cellular responses to the metal-binding properties of metformin. Diabetes, 2012 61:1423–1433.https://doi.org/10.2337/db11-0961
44. Sen, D., J Chem Soc A,1969 2900–2903.https://doi.org/10.1039/J19690002900
45. Zhu, M., Lu, L., Yang, P., Jin, X., Bis(1,1-dimethylbiguanido)copper(II) octahydrate. Acta Cryst E58:m217–m219. https://doi.org/10.1107/S1600536802007092
46. Ray, R.K., Kauffman, G. B.,Metal and non-metal biguanide complexes. New Age International Publishers,1999 New Delhi.
47. Ray, R. K., Kauffman, G. B., InorgChim Acta,1990 174:257–262. https://doi.org/10.1016/S0020-1693(00)80309-6.