Advance Research in Pharmaceuticals and Biologicals

(A Peer Reviewed International Journal for Pharmaceutical and Allied Research)

ISSN 2250-0774 USA CODEN: ARPBGZ

ANTIDIABETIC DRUG AND COMBINATION THERAPY

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Received on 11/04/2013 **Revised on 01/05/2013** **Accepted on 12/05/2013**

ABSTRACT:
Diabetes is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction,and failure of different organs, especially the eyes, kidneys, nerves, heart, and blood vessel. Diet remains the mainstay of treatment. If diet alone is unsuccessful then, for most patients, short-acting sulphonylurea agents are the treatment of choice. Second line agents include the biguanide, or an α-glucosidase inhibitor. As Diabetes mellitus is concerned with other complications so combined therapy is beneficial as Combination therapy has various advantages over monotherapy. voglibose is an alpha-glucosidase inhibitor which reduces intestinal absorption of starch, dextrin, and disaccharides by inhibiting the action of á-glucosidase in the intestinal brush border. Metformin lowers both basal and postprandial blood glucose. Metformin decreases hepatic glucose production, decrease intestinal absorption of glucose and improves peripheral glucose uptake and utilization. Metformin is the first-line drug of choice for the treatment of type 2 diabetes, particularly in overweight and obese people and those with normal kidney function. Bi-layered tablets increases patient compliance and also allows for designing and modulating the dissolution and release characteristics and they are prepared with one layer of drug for immediate release while second layer designed to release drug latter in sustained release manner.

Keywords: Bilayer tablet, diabetes, Antidiabetic drugs classification, Combination therapy.

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INTRODUCTION

Diabetes is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of different organs, especially the eyes, kidneys, nerves, heart and blood vessels[1]. Diabetes medications can make your pancreas release more insulin, help your liver to make less sugar, make your muscles take in more sugar, or slow the breakdown of starches into sugar. In general, diabetic medications will help control high blood sugar in people with diabetes. However, these medications work best when used with meal planning and exercise. Although most people find that their blood sugar levels decrease when they begin taking their medication, the blood sugar still may not reach the normal range[2]. Diabetes be of any kind is still one of the major threat to world in 21st century. People who have type 2 Diabetes may need to take medicine to help lower their blood glucose, in addition to being active & choosing healthy foods. The longer a person has type 2 diabetes, the more effort it takes to control it. It is typical to start on one type of medicine and add a second, third, or fourth type of medicine as time goes on. The management of hyperglycaemia in type 2 diabetes often requires a combination of two or more glucose-lowering therapies[3,4].. These can be used to improve glycaemic control by addressing different pathophysiological aspects of the disease, such as insulin resistance, b-cell dysfunction, a-cell dysfunction and defects of nutrient metabolism affecting liver, muscle and adipose tissue[5,6].

DIABETES IN INDIA

The prevalence of diabetes is rising all over the world due to population growth, aging, urbanisation and an increase of obesity and physical inactivity. Unlike in the West, where older persons are most affected, diabetes in Asian countries is disproportionately high in young to middle-aged adults. This could have long-lasting adverse effects on a nation's health and economy, especially for developing countries[7]. The International Diabetes Federation (IDF) estimates the total number of people in India with diabetes to be around 50.8 million in 2010, rising to 87.0 million by 2030[8]. Ramachandran et al. reported that age-standardised prevalence of diabetes and impaired glucose tolerance (IGT) in urban India in 2000 were 12.1% and 14.0%, respectively, with no gender difference[9]. The "Top 10" countries in the world, in terms of the number of people with diabetes, for 2010 and 2030, are shown in Table. At both time points, the three countries with the largest number of people with diabetes are India, China and the U.S[10].

According to the World Health Organization (WHO) criteria, the prevalence of known diabetes was 5.6% and 2.7% among urban and rural areas, respectively. Diabetes showed positive and independent associations with age, body mass index (BMI), waist-to-hip ratio, an family history of diabetes, monthly income and sedentary physical activity. Age, BMI and a family history of diabetes showed associations with IGT. More recent reports from various parts of India showed further increases in diabetes prevalence in urban areas Moreover, the prevalence of diabetes was also found to be increasing rapidly in rural areas, as a result of the recent socioeconomic transitions[12].

Table no 1:- Top 5 countries for estimated numbers of adults with diabetes, 2010 and 2030.[11]

Sr. No	Country/ Territory	2010 (millions)	Country/ Territory	**2030 (millions)**
1	India	50.8	India	87.0
2	China	43.2	China	62.6
3	U.S.A.	26.8	U.S.A.	36.0
4	Russia	9.6	Russia	13.8
5	Brazil	7.6	Brazil	12.7

Table 2 : Prevalence of diabetes in urban India.[12]

Region	**Year**	**Age (years)**	**Prevalence (%)**		
			Diabetes	**IGT**	**IFG**
National Ramachandran et al	2000	> 20	12.1	14.0	--
Northern India Ramachandran et al	2000	> 20	11.6	8.6	--
Southern India Ramachandran et al	2000	> 20	13.5	16.8	--
Reddy et al.	2003	20-69	8.4	--	6.4
Mohan et al	2004	> 20	14.3	10.2	--

MANAGEMENT OF DIABETES:

For managing Diabetes drugs are being categorized as:-

- Oral medicines
- Combination medicine

Oral medicines[13]:- The list of oral medicines given in Table No. 3

Combination medicines (bilayer tablet):- Combination medicines are the one which include two different medicines

- Voglibose and Metformin- volix
- Metformin and Glipizide-Metaglip
- Saxagliptin and Metformin ER- Kombiglyze XR
- Sitagliptin and Metformin- Janumet®
- Vidagliptin and Metformin-Galvumet®
- Metformin and Rosiglitazone- Avandamet®
- Glimepride and Metformin- Diapred-m2

TYPE OF TABLETS:-

One may have had difficulty controlling your blood glucose (sugar) simply by eating more healthily and increasing your level of exercise. The next step for many people is to start taking tablets to help lower blood glucose levels. As diabetes mellitus needs combination of effective oral agents from different chemical classes to maintain adequate blood glucose level. Design, development and optimization of various tablet types become a rational approach for the treatment of type-II Diabetes mellitus.There are lot of different types of tablets,[14] and they suit people with different needs. Usually single tablets are used for the treatment of diabetes, they are categorized as follows:-

Immediate release tablets:-

1. Sulphonylureas:

Gliclazide:-Glyade, Mellihexal, Nidem
GenrxGliclazide.
Glibenclamide:-Daonil,Glimel
GilmepirideSandoz
Glipizide:-Melizide, Minidiab

2. Biguanides:-

Metformin:-Diabex, Diaformin
Glucohexal, Glucomet®,Glucophage
Metformin, Genepharm metformin

Extended release tablets:-

1. Sulphonylureas:-

Gliclazide:-Diamicron MR, Glyade MR, Oziclide MR

2. Biguanides:-

Metformin:-Diabex,Diaformin XR, Metex XR,
Glucophage,Glumetza, Comet XR 500.

Bilayer Tablets:-

Two layers in tablet containing two drugs:-
Metafort G853:- Each uncoated bilayer tablet contains: Glimepride USP 3mg Metformin Hydrochloride IP 850mg (in Sustained Release Form.

Metafort G852:- Each uncoated bilayer tablet contains: Glimepride USP 2mg Metformin Hydrochloride IP 850mg (in Sustained Release Form).
Metafort G853:- Each uncoated bilayer tablet contains: Glimepride USP 3mg Metformin Hydrochloride IP 850mg (in Sustained Release Form).
Glimisave M1forte:- Each uncoated bilayer tablet contains: Glimepiride 1mg Metformin Hydrohloride 1000mg (in Sustained Release Form).
Glimisave M1:- Each uncoated bilayer tablet contains: Glimepiride USP 1mg Metformin Hydrohloride IP 500mg (in Extended Release Form).
Glimisave M2CP:-Each uncoated bilayer tablet contains: Glimepiride USP 2mg MetforminHydrohloride IP 500 mg (in Extended Release Form).

- **Multidrugs two layers in single tablet**:-Examples

Triglimisave 1HS:-Each uncoated bilayer tablet contains: Metformin Hydrochloride IP 850mg (in extended releaseForm) Pioglitazone 15mg Glimepiride 1mg.
Triglimisave1:-Each uncoated bilayer tablet contains:MetforminHydrochloride IP 500mg (in extended releaseForm) Pioglitazone 15mg Glimepiride 1mg .
Triglimisave 2HS:-Each uncoated bilayer tablet contains: Metformin Hydrochloride IP 850mg (in extended releaseForm) Pioglitazone 15mg Glimepiride 2mg
In bilayer tablet the combination therapy has various advantages over monotherapy such as less dose dependent side effects. Also low dose combination of two different drugs minimizes the clinical and metabolic effects that occur with maximal dosage of individual component of the combined tablet and thus dosage of the single component can be reduced. Hence Bi-layered tablets are prepared for treating two different diseases with one unit dosage form. This dosage form has the advantage of separating two incompatible drugs with inert barrier between them. Incompatible drugs can be separated by formulating them in separate layers as a two layer tablets or separating the two layers by a third layer of an inert substance as a barrier below the two[15]. Bi-layered tablets allows for designing and modulating the dissolution and release characteristics and they are prepared with one layer of drug for immediate release while second layer designed to release drug latter, either as second dose or in an sustained release manner.[16]
In bilayer tablet contain two layers

1. Immediate release
2. Sustained release

Immediate release:-Immediate release layer : Contains loading dose.
Immediate release layer of the dosage form containing the loading dose that delivers the entirely of its drug content at once after administration for the purpose of providing a rapid rise of drug concentration in the blood stream.[17]
Sustained release:-The advantages of administering a single dose of a drug that is released over an extended period of time, instead of numerous doses, have been obvious to the Pharmaceutical industry for some time. Sustained Release is also providing promising way to decrease the side effect of drug by preventing the fluctuation of the therapeutic concentration of the drug in the body.[17]
Layer Tablets[18] are composed of two or three layers of granulation compressed together. These are usually consisting of two and sometimes three layers. They have appearance of sandwich because the edges of each layer are exposed.
Classification of Layered Tablets

- Bilayer tablets of one immediate release and other sustained release.
- Bilayer tablets of both immediate release.
- Bilayer tablets of one sustained and other inert layer as supporting.
- Bilayer tablets of one sustained release and other inert layer as protective.

Advantages of Bilayer Tablets
Two or more drugs having different having different pharmacological action can be given in single dose.

- Two or more drugs having different mechanism of action have been given in single dose.
- Increase in patient compliance.
- Decrease resistance of drug especially in case of antibiotics.
- Cost effective.
- Synergistic effect of two drugs.

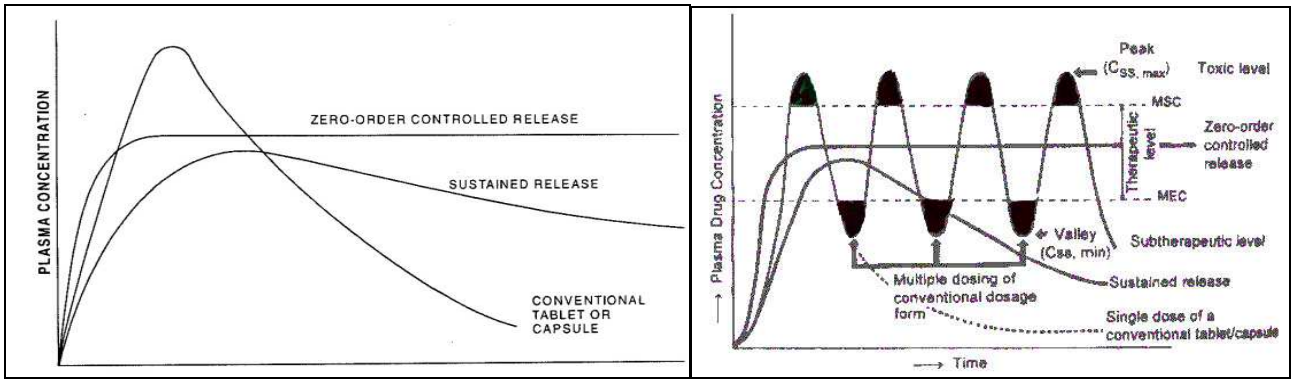
Disadvantages of Bilayer Tablets

- Labour cost is high.
- Producion reduces to less than half.
- Proper weight adjustment of each layer is difficult during running of batch.

Kinetic Pattern of Drug Release Required for Ideal Bilayer Tablets
It is assumed that the drug which is to be incorporated in to an ideal bilayer tablet dosage form confers upon the body, the characteristics of a one compartment open model. Two further conditions must be fulfilled in order to ensure that the therapeutic concentration of drug in the body remains constant. The zero order rate of release of the drug from the maintenance dose must be

rate determining with respect to the rate at which the released drug subsequently absorbed in to the body. The kinetic of absorption of the maintenance dose will be characterized by the same zero order release rate constant.

Class, Generic Name(Brand Name)	Comments/Cautions
Alpha-Glucosidase Inhibitors (AGIs): acarbose (Precose®) miglitol (Glyset®)	Take with the fi rst bite of each meal. Advantages: Acarbose and miglitol normally do not cause weight gain. Common side effects: Gas, bloating and diarrhea. Cautions: Because these medications work directly in the intestines, people with inflamatory bowel disease, other intestinal diseases, or obstructions should not take them. Hypoglycemia: Acarbose and miglitol don't cause low blood glucose (hypoglycemia) when usedalone. When used with certain other diabetes medications, low blood glucose can occur. In thesecases, treat hypoglycemia with pure glucose, such as glucose tablets or glucose gels, or fruit juice.
Biguanides metformin (Glucophage®) metformin, long-acting (Glucophage® XR, Glumetza®, others) metformin, liquid (Riomet®)	Metformin is usually taken with a meal. Advantages: Metformin does not cause weight gain and may improve cholesterol levels. It does notcause low blood glucose (hypoglycemia) when used alone. Common side effects: Nausea, diarrhea, or loss of appetite, but these should subside within a fewweeks. To minimize these side effects, take with meals. Lactic acidosis is a very rare, but seriousside effect.Metformin may not be right for you if you have kidney problems or severe respiratory problems, are80 or older, are taking medication for heart failure, have a history of liver disease, drink alcoholexcessively, or are hospitalized.
DPP-4 Inhibitors sitagliptin (Januvia®)	Advantages: Does not cause weight gain. Common side effects: May occasionally cause stomach discomfort and diarrhea. Cautions: If you have kidney problems, your doctor may prescribe lower dos
Meglitinides nateglinide (Starlix®) repaglinide (Prandin®)	Take at start of meals. Skip the dose if you skip a meal. Common side effects: Can cause low blood glucose
Sulfonylureas glimepiride (Amaryl®) glipizide (Glucotrol®) glipizide, long-acting (Glucotrol® XL) glyburide (DiaBeta®, Micronase®) glyburide, micronized (Glynase® PresTab)	These medications are generally taken once or twice daily. Common side effects: These drugs can cause low blood glucose and weight gain.
Thiazolidinediones (TZDs): pioglitazone (Actos®) rosiglitazone (Avandia®)	It typically takes 4 to 6 weeks to see an effect on your blood glucose. These drugs are typicallytaken once daily. Common side effects: Can cause weight gain and fluid retention. Heart failure: These drugs can cause heart failure. Call your doctor right away if you have any signsof heart failure, such as rapid weight gain, shortness of breath, edema (fluid retention in ankles,legs, or hands), or fatigue. People with heart failure should not take these drugs. Liver tests: Your doctor should check your liver function prior to starting these medications andperiodically throughout your treatment. Call your doctor right away if you have any symptoms of liverdamage, such as nausea, vomiting, abdominal pain, fatigue, loss of appetite, or dark urine.



(a) **(b)**

Figure 1 Plasma drug concentration profiles for (a) conventional tablet or capsule formulation, a sustained release formulation and a zero order controlled release formulation. (b) Hypothetical plasma concentration time profile from conventional multiple dosing and single dose of sustained and sustained delivery formulations.[18]

CONCLUSION:

Bi-layer tablet quality and GMP-requirements can vary widely. This explains why many different types of presses are being used to produce bi-layer tablets, ranging from simple single-sided presses to highly sophisticated machines such as the Courtoy-R292F. Compression Force-controlled presses are clearly limited when a quality bi-layer tablet needs to be produced in conjunction with accurate weight control of both layers. Low pre-compression forces are necessary to secure interlayer bonding. Such problems become even more apparent when the tableting speed is high or increased. Whenever high-quality bi-layer tablets need to be produced at high speed, the use of an 'air compensator' in combination with displacement control appears to be the best solution. The sensitivity of the displacement-based control system increases as pre-compression force decreases, resulting in a higher accuracy. As explained, this is particularly important with regard to bi-layer compression. Accurate individual layer weight monitoring/control at high speed and in combination with reduced layer-separation risk can be achieved with the Courtoy-R292F. In addition, the increased dwell time provided by the 'pneumatic compensator' and the special attention to reduced interlayer cross-contamination risk make the Courtoy- R292F an excellent bi-layer tablet press.

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