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HYPOGLYCEMIC POTENTIAL OF TABLET METFORMIN 500 MG (GLUCOPHAGE® & METPHAGE®): A PHARMACOLOGICAL END POINT EVALUATION

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ABSTRACT

Quantitative determination of pharmacological response or clinical end point study is essential for successful evaluation of clinical pharmacology and Bioavailability/ Bioequivalence issues. Stride has been made for proper selection of a quality drug product from the various available therapeutic, which is the prime responsibility of Health care provider and specially pharmacist. Study was conducted in respect to investigate the Pharmacodynamics response, differences and individual variation of oral, Metphage (Metformin 500 mg tablet) as a test formulation manufactured by Efroze Chemical Industries (Pvt.) Ltd. and Glucophage (Metformin 500 mg tablet) as a reference formulation manufactured by Merck Marker. Blood glucose levels/hypoglycemic effect produced by both formulation were studied under cross over trial with respect to placebo/control treatment and result were discussed accordingly. There were no hypoglycemic episodes requiring medical intervention and/or pharmacologic therapy so the patients can easily manage it. Results of the study clearly suggest that formulation manufactured by Efroze Chemical Industries (Pvt.) Ltd. is near to the standard formulation and produced comparable results. No significant differences in pharmacodynamics was observed, however, minor differences might relate with inter individual variation in human volunteers and in different formulation as well as different pharmaceutical unit. Although this data assure the ultimate quality of Metformin 500 mg tablet manufactured by Efroze Chemical Industries (Pvt.) Ltd. but every Generic equivalent should be studied for assurance of safety and efficacy because life of patient is a matter of concern. Such type of study would provide better evaluation of the performance of a drug from a dosage form.

INTRODUCTION

Metformin:

Metformin is an oral medication designed to help control elevated blood sugar levels in NIDDM (non-insulin-dependant diabetes mellitus). It is believed to work by inhibiting hepatic glucose production and increasing the sensitivity of peripheral tissues to insulin. Metformin's brand name is Glucophage and it has been used clinically in Europe continually since 1970. However, in America in 1977 the drug was removed from the U.S market amid safety concerns about the related drug Phenformin. This was seen to occasionally promote lactic acidosis, a potentially fatal build-up of lactic acid in the blood. The medicine does not increase how much insulin the pancreas makes but acts on the liver preventing it from producing excess sugar and stopping hyperglycemia (high blood sugar). Metformin is primarily suited for the treatment of subjects with non-insulin-dependent diabetes mellitus (Type II diabetes). Compared to other

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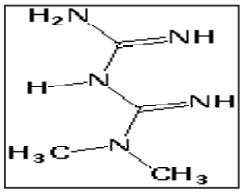
antidiabetic agents, it has the advantages of lowering rather than increasing body weight, of not causing hypoglycemia, and of entailing a reduction of triglycerides and LDL-cholesterol levels. Metformin is therefore recommended in single drug therapy especially for obese subjects. In the majority of the treated subjects a lowering of blood glucose levels by at least 25% is achieved (i.e. almost identical results as with sulphonylureas at the beginning of treatment). Metformin also helps lower the fatty blood components triglycerides and cholesterol that are often high in people with Type II diabetes. In December 1994, the U.S. Food and Drug Administration (FDA) approved the use of metformin for the treatment of Type 2 diabetes. Metformin was approved for use either alone or with sulphonylureas, a commonly used group of diabetes medicines. Metformin's brand name is Glucophage.



Metformin can also be combined with other antidiabetic agents. It can thus e.g. be used when there is secondary failure with sulfonylureas. Occasionally a small dose of metformin combined with a sulfonylurea is sufficient to restore an adequate diabetic control. In carefully selected cases, a combination with insulin can also be sensible - particularly for obese subjects with relative insulin resistance. Metformin quite frequently (5 to 20%) causes gastrointestinal problems such as nausea, stomach pain, bloating, diarrhea and malabsorption of vitamin B12 and folic acid. These side effects usually go away soon after the metformin is started and occur less often if metformin is taken with food. Another possible problem with metformin is a rare but serious condition called lactic acidosis, when your tissues do not get enough oxygen to survive. To avoid this problem, metformin should not be given to people with kidney or liver disease, severe heart failure, or a history of alcohol abuse. Skin rashes are rare. The platelet inhibition hardly has any clinical disadvantages. Metformin very rarely causes a dangerous lactic acidosis (roughly one case on every 10,000 patient years, mortality rate about 40%). Most cases affect individuals with risk factors, especially impaired renal functions. Other biguanides cause lactic acidoses (e.g. buformin) more often. The risk of a lactic acidosis under metformin is no greater than the risk of a severe hypoglycemia under sulfonylureas.

Bioavailability:

The property of a dosage form that delivers the active ingredient to its site of action in an amount sufficient to elicit the desired pharmacological response is referred to as its physiologic availability, biologic availability or bioavailability. (Blanchard and Sawchuk, 1979) Bio-availability is defined more precisely in The Code of Federal Regulations (21 CFR 320.1) as "the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action." According to this definition, a drug administered by the intravenous (IV) route is 100% bioavailable due to the absence of an absorption phase. Bioavailability of drugs administered by all the other parenteral and extravascular routes is incomplete and variable. Bioavailability (Table 1) of a drug is usually estimated by its concentration in body fluids, pharmacologic response, clinical response, and the rate and extent of excretion (Code of Federal Regulations 2000, FDA-CDER October 200). Which is a measure of the fraction of drug reaching the systemic circulation, is a function of the drug product, the patient’s physiology, and environmental factors such as ingested food or other drugs. Such products that produce similar blood or plasma levels are said to be bioequivalent. Bioequivalence goes beyond comparable bioavailability; it also implies that the absorption rate of the drug is

similar. Thus, bioequivalence is a function of both rate and extent of absorption. The extent of absorption is measured by the bioavailability, or fraction of dose absorbed measured by the area under the concentration-time profile (AUC), whereas the rate of absorption is roughly assessed by measuring the maximum plasma or blood level, C_{max}, of a compound (Mangione, 1998). Although C_{max} is a function of both the rate and extent of absorption, and some have argued that T_{max} would be a more pure measure of the rate of absorption, C_{max} is a clinically relevant parameter in most cases.

Absolute Bioavailability:

Absolute bioavailability of a drug usually involves a comparison of areas under the plasma concentration vs. time curve (AUC) obtained following extra vascular and IV administration of the drug Fig. 1A.

Table 1
Methods to Assess Bioavailability (Ritschel WA, GLK 1999)

Sequence of events after administration of a drug product	**Method of evaluation**	**Example**
Dissolution at administration or absorption site	Dissolution rate	*In vitro*: water, buffer, artificial gastric fluid, artificial intestinal fluid, artificial saliva, artificial rectal fluid
Free drug in systemic circulation	Blood level time profile Peak blood level Time to reach peak Area under blood level time curve	*In vivo*: whole blood, plasma, serum
Pharmacologic effect	Onset of effect Duration of effect Intensity of effect	*In vivo*: discriminate measurement of pharmacologic effect (blood pressure, blood sugar, blood coagulation time)
Clinical response	Controlled clinical blind or double-blind study Observed clinical success or failure	*In vivo*: evaluation of clinical responses
Elimination	Cumulative amount of drug excreted Maximum excretion rate Peak time for excretion	*In vivo*: urine

Relative Bioavailability:

Relative (comparative) bioavailability is obtained by comparing the AUCs when like or unlike dosage forms of the same drug are administered by same or different routes Fig. 1B.

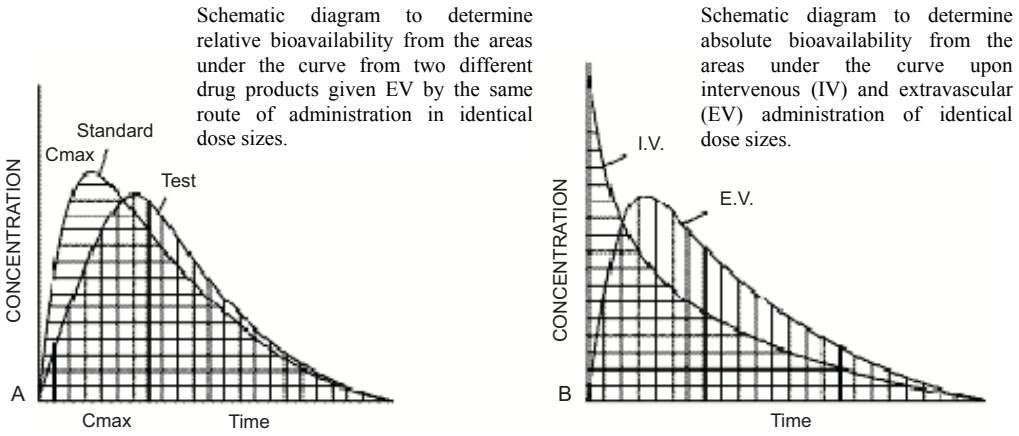


Fig. 1: Absolute vs. Relative Bioavailability

Bioequivalence (BE):

When the patent on a standard drug formulation ends, other companies are allowed to market generic formulations of the drug if they can prove bioequivalency (FDA 1992).

Bioequivalence is defined as the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes at the site of drug action when administered at the same molar dose under similar condition in an appropriate design study (FDA-CDER, 2000). Two or more chemically or generic equivalent products of the same preparation can be said to be bioequivalent, if they do not differ (<20%) significantly in their bioavailability characteristics. This bioequivalent drug is assumed that they will be therapeutically equivalent and can be use interchangeably (F.D.A., 1997, Draft Guidance for Industry).

Pharmaceutical Equivalency:

Two preparations are required to contain the same drug compound, in the same dose, amount and form usually, excipients (fillers or colours) are ignored if they do not have likely adverse effects in patients who are expected to use the drug.

Therapeutic Equivalency / Therapeutic Alternatives:

Drug products which when administered to the same individual in the same dosage regimen will provide, essentially the same efficacy (i.e. clinical result) and / or toxicity.

Chemical Equivalency:

Those products, which contain the same quantity and purity of the same therapeutically active ingredient in the same dosage, form. The term chemical equivalency, in general, only used in relation to the active ingredients different formulations may be of differing size, shape, colour, or taste and their binders, diluents, excipients and preservatives.

Pharmaceutical Alternatives:

Drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form, or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other

applicable standard of identity, strength, quality, and purity including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates.

Significance of Bioequivalency rather than Dissolution in Regulatory Affairs:

An active ingredient in a solid dosage form must undergo dissolution before it is available for absorption. Therefore, rate of dissolution may influence the onset, rate and extent of absorption and could affect the pharmacologic activity of a drug. Under regulatory bodies BE is required to ensure therapeutic equivalence between a pharmaceutically equivalent test drug product and a reference listed drug. Which is become an essential requirement for the registration of drug product and also contributes in ensuring the safety and efficacy of drug products (Table 2).

Historical Perspectives and Regulatory Guidelines:

Bioavailability concepts were formally embraced about 1885 when Dr. W.E. (Stubbs, 1975). Upjohn patented the 'friable' pill (a pill that is easily crumbled or pulverized). Blanchard and Sawchuk (1979) Reported that the awareness of bioavailability was significantly recognized during the 1960s due to the introduction of a new science of 'biopharmaceutics'. The development of the discipline of biopharmaceutics provided impetus for the passage of the Kefauver-Harris Amendment (Drug Amendments Act, 1962), requiring drug manufacturers to submit evidence of proof of efficacy as well as safety prior to marketing a new drug product. This shifted the emphasis from a concern that the dosage form contained the identical active ingredients to a greater regard for product formulation and the details of the manufacturing process.

Formulation and Dosage Forms:

Formulation and dosage forms can have a significant effect on the onset, duration and intensity of the pharmacological action of a drug. A pharmaceutical dosage form controls the rate at which the drug is released into the biological fluids. This release rate affects its intrinsic absorption pattern and therefore, the bioavailability of the drug. The absorption rate of a drug may also influence the frequency and severity of local and systemic reactions or toxic effects. A high peak concentration of some CNS drugs (Rosmurgy *et al.,* 1995) leads to undesirable systemic reactions. In such cases, it may be preferable to use a dosage form with a slower release pattern or to modify the dose. Drugs such as spironolactone (Tyrer *et al.,* 1970) have demonstrated a 50-fold difference in peak plasma metabolite concentrations when different formulations of this drug were compared.

Formulations for Oral Administration:

Different formulations for oral administration includes solutions, suspensions, capsules, compressed tablets, coated medications and controlled release dosage forms. The availability of a drug for absorption is maximum in solutions and decreases in descending order with suspensions, capsules, compressed tablets, and coated tablets, respectively.

Formulation excipients can also alter the absorption of a drug from the dosage form. For instance, a buffer can affect the absorption of a drug when the drug has acid degradation limited absorption. A study by Pilbrant and Cederberg (1985), showed that a non-buffered oral dosage form of omeprazole had a low systemic bioavailability when compared to a buffered oral formulation due to preabsorptive degradation of omeprazole in the stomach.

Pharmacokinetics:

(The dynamics of drug absorption, distribution and elimination)

Pharmacokinetic is the study of drug movement in the body over the time during the drug's absorption, distribution and elimination (excretion and biotransformation) (Leon Shargel, 1992).

Table 2
Selection of Standard for Bioavailability Testing (Ritschel WA, GLK. 1999)

Category	**Parameters to be Determined**	**Standard**	**Route of Administration for Standard**
New drug in any drug product	Extent and rate of absorption; elimination of half life, rate of metabolism and/or excretion; dose proportionality after single and multiple dosing	Solution or suspension of drug in single dose study	Same as drug product unless drug is poorly absorbed. In the latter case additional IV route
New formulation of marketed product	Extent and rate of absorption; pharmacokinetic parameters of new formulation	Current batch of approved drug product on the market in single dose study	Same as drug product
Controlled-release formulation	Extent and rate of bioavailability; pharmacokinetic performance of dosage forms	Solution or suspension of drug and/or currently marketed non-controlled release and/or controlled release product in single and multiple dosing study	Same as drug product
Combination drug product	Rate of extent of absorption of one, more or all active drugs	Two or more single ingredient drug products in single dose study	Same as drug product
Any drug product for which drug concentration is not determined in biological fluid	Pharmacologic effect or clinical response	Placebo in single or multiple dost study	Same as drug product

Significance of Pharmacodynamics:

Preventing medication-related problems in different persons requires an understanding of the differences between individuals, what these differences mean for the way medications prescribes and monitor their use, what these differences mean for the way to develop drugs, and what these differences mean for the way to monitor new medications after they are out in the marketplace. Now that medical and pharmacy profession have a sense and sufficient not enough knowledge of the complexity and extent of medication-related problems in individual persons, knowledge of

pharmacology, pharmacokinetics, and pharmacodynamics; medication appropriateness guidelines; and any other information available to fashion interventions to improve prescribing should use in order to rationalize (effective and safe) therapy.

Human Diversity Issues in PK & PD:

The goal of rational drug therapy is to produce a desired pharmacological response in an acceptable and predictable manner while minimizing the occurrence of undesired events. At present, there is significant interest in understanding how pharmacogenetics and pharmacogenomics may contribute in understanding of individual variability in the clinical responses to therapeutic agents. In the context of pharmacotherapy, genetic and environmental determinants of variability are superimposed on a changing background of development and maturation to add further complexity to optimal medication use (David *et al.,* 1999).

Influence of Disease on PK & PD:

Pharmacokinetics and pharmacodynamics of oral analgesics are different in subjects with severe pain as compared to those with mild pain. More recent data suggest that pharmacokinetic observation may not necessarily reflect pharmacodynamic outcomes. Many pathological conditions e.g. asthma, inflammation, infection etc. are likely to contribute intra-subject variability in both pharmacokinetics and pharmacodynamics observations. Factors contributing in pharmacokinetics and pharmacodynamics observations must be given consideration in designing studies / clinical trials (David *et al.,* 1999).

Age Issue in PK & PD:

There are reasonable evidences for important changes in both pharmacokinetic and pharmacodynamic parameters due to body composition changes even in the absence of diseases. Evidences suggest that in order to optimize drug therapy, due attention should be given at the time of designing pharmacodynamic or pharmacokinetic studies regarding age (David *et al.,* 1999).

PK-PD Relation:

During the past 30 years, clinicians have become very familiar with the science of pharmacokinetics, which is a very useful tool for describing how drugs behave in the human host, but it does not promote an understanding of a drug's desired or undesired pharmacologic effects. Pharmacodynamics has the potential to provide clinicians with the missing tools required to make prescribing more objectives and to expand our understanding of the interaction between disease and drug (Fig. 2).

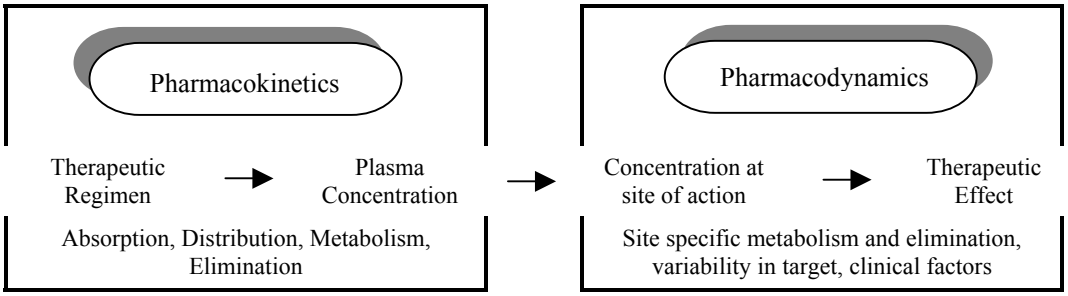


Fig. 2: Relationship between pharmacokinetics and pharmacodynamics parameters and their influence on therapeutic effects.

The pharmacokinetics and pharmacodynamics interactions affect drug action in a qualitative way, either through enhancing effects (synergistic or additive action) or antagonizing effects.

Pharmacodynamic Studies:

In those instances where a PK approach is not possible, suitable validated pharmacodynamic method can be use to demonstrate the BE.

Pharmacological / Clinical End Point (Comparative Clinical Trial):

When the measurement of the rate and extent of absorption of the drugs in biological fluids cannot be achieved or is unrelated to drug action, a pharmacological end-point (i.e. drug induced physiological changes which is related to approve indication for use) study may be conducted. If drug concentration in blood (or fluids or tissues) are not measurable or an inappropriate, and there are no appropriate pharmacological effects that can be monitored, then a comparative clinical end-point study can be conducted using positive (reference) and negative (placebo) controls.

In vitro Studies:

Dissolution testing is also used to assess batch-to-batch conformity/quality and may likely to measure relative bioavailability in some products. In research and development, dissolution test are often used to assist in the formulation development and may be used as a prognostic / economical tool for oral drug absorption, where applicable.

MATERIALS AND METHODS

- Reference drug Metphage (Table 3)
- Test drug Glucophage (Table 3)
- Glucometer Bayer Limited

Table 3
Label information of Tab. Gliclazide 80 mg different brands used in the pharmacokinetics and pharmacodynamics study

Batch No.	Name	Status
B-131	Metphage	T_1
894	Glucophage	R_2
T= Test		R= Reference

Human Study Protocol:

Cross over two treatment three-occasion study was performed as a single dose two treatment and one placebo occasion with adequate washout period of one weeks.

Volunteers

The ten healthy male subjects participated in the study. The panel of human subjects consisted of ten human, healthy, adults, male young volunteers.

Health/Safety Evaluation:

The panel members were given a general medical examination to establish good health. The following selection criteria were used for this purpose.

- No congenital disease

- No underline hypertension
- No diabetic history in family

Response of the following were checked and got normal:

- Hepatic
- Gastrointestinal tract
- Cardiovascular
- Respiratory tract
- Hematological
- Neurological
- Psychiatric

No history of hypersensitivity to sulfonylurea, Metformin and to any other ingredient used in the formulation of test or reference drug. Neither treatment taken nor any drug used for at least a month prior to the study.

In order to assure the safety/selection based on this criteria physical examination by a consulting physician and biochemical/hematological tests were performed pre and post study and also each subject was observed throughout the study for possible adverse event and shortly monitored the blood glucose level. The consulting physician continued physical examination during the study regarding vital signs.

Exclusion Criteria:

Subjects with any current or past medical condition that might significantly affect their pharmacokinetics and pharmacodynamics response to the administered drug were the limiting factors in the study. All volunteers were thoroughly informed about the aims and objectives of the study, the drug to be tested, and the hazards/side effects of the drug Metformin and also their rights to separate themselves from the study at any stage without mentioning any reason. Informed consent was also obtained from each subject to participate in the study.

Restrictions:

No volunteer was allowed to take any prescription or OTC drug one week prior to dosing and during the study period, in order to avoid interference with the hypoglycemic potential of Metformin in the body. The volunteers were instructed to report the investigator about the illness/side effects and the treatment undertaken. No volunteer took any drug for at least one month prior to and during the study.

Study Design:

Study was designed according to described objectives and conducted on a triple occasion, with an interval of one week between the first & second and second & third. The first one was the control study to monitor the blood glucose level patterns in volunteers after control breakfast and lunch. No drug was given on first occasion. This study was preliminary to evaluate the blood sugar level patterns in volunteers in normal (control) state volunteers were divided into two equal groups A and B. Tab Glucophage and Metphage 500 mg were administered to Group A and B respectively on second occasion, while Tab Glucophage and Metphage 500 mg were administered to Group B and A respectively on third occasion in order to comply the requirement of cross over trial. Blood glucose levels were monitored on different intervals under the described method. The exactly same diet in quantity and quality was provided to the volunteers on both occasions as was provided in the control study.

Bioequivalence and Pharmacodynamics Calculation:

To evaluate the therapeutic equivalence of the studied formulations the blood glucose levels were monitored at serial intervals. To compute the hypoglycemia produced by the test formulation BGL after the use of drug were subtracted from levels, which were obtained in the same subject on first occasion (control trial). The statistical technique employed in calculation of representative mean of hypoglycemia for test/ reference formulation.

Data Quality Assurance:

Data obtained throughout the study was recorded on the subjects' in-process control sheet by Research Coordinator and crosschecked by other Research Coordinator. Steps taken to assure accurate and reliable data included selection of research associate review of protocol procedure and report with the principle investigator and associated personnel at an investigator meeting.

RESULTS AND DISCUSSION

Pharmacological End Points:

The Pharmacological end points/pharmacodynamics were observed by monitoring of blood glucose levels as shown in Table (RT 1) and Fig. RF 1. The lowering of blood glucose level (hypoglycemia) by the drug is measured by subtracting the glucose level after the use of drug from those observed without drug in the control state.

Table RT-1

Blood glucose level after drug administration to healthy human, male, adult volunteers

VOL	Rx	0	30	60	90	150	180	210	270	330	390	450
PLACEBO/ CONTROL												
1	P	75	54	69	65	104	89	77	75	91	85	91
2	P	75	72	69	72	106	73	88	80	102	92	105
3	P	64	65	60	62	117	65	88	108	77	96	98
4	P	76	73	70	73	140	115	115	96	86	109	92
5	P	74	74	76	77	111	84	103	110	107	104	73
6	P	78	79	75	72	90	74	85	83	89	96	133
7	P	79	90	83	86	89	75	77	92	89	104	90
8	P	66	72	63	63	78	102	110	85	99	90	89
9	P	66	69	64	63	92	85	73	69	93	110	85
10	P	61	62	57	66	174	155	113	83	110	105	110
11	P	76	70	72	75	109	95	74	66	102	119	115
Mean		71.82	70.91	68.91	70.36	110	92	91.18	86.09	95	100.9	98.27
±SEM		1.897	2.782	2.291	2.234	8.141	7.648	4.885	4.329	2.985	3.032	4.983

Table continued ...

Table contd.

METPHAGE 500 mg TABLET												
1	T	73	68	69	67	63	74	90	78	65	90	89
2	T	80	76	74	76	93	86	100	98	97	125	107
3	T	77	78	58	70	73	77	67	88	98	103	86
4	T	73	74	77	72	78	84	93	105	74	96	87
5	T	76	72	72	74	89	87	75	80	91	101	88
6	T	80	75	78	73	79	86	80	92	82	121	73
7	T	77	99	99	89	83	85	79	81	100	78	83
8	T	73	71	66	69	92	77	91	81	86	90	109
9	T	61	62	59	61	85	69	79	87	93	85	87
10	T	71	70	72	62	106	87	80	73	77	66	113
11	T	72	64	67	64	101	76	102	69	81	80	79
Mean		73.91	73.55	71.91	70.64	85.64	80.73	85.09	84.73	85.82	94.09	91
±SEM		1.593	2.944	3.343	2.36	3.741	1.898	3.283	3.214	3.36	5.372	3.892
GLUCOPHAGE 500 mg TABLET												
1	R	76	70	69	70	112	96	87	76	91	84	105
2	R	78	68	76	74	98	87	93	84	87	80	102
3	R	77	71	65	62	80	72	77	100	77	140	103
4	R	71	76	70	65	105	117	124	114	119	86	105
5	R	86	77	86	71	98	92	79	80	89	107	103
6	R	78	77	76	75	87	86	87	97	94	100	117
7	R	84	88	87	85	87	83	81	88	102	92	91
8	R	77	76	81	73	80	91	82	95	96	88	72
9	R	71	64	65	66	87	90	73	75	93	71	75
10	R	65	67	65	67	106	87	106	64	81	83	85
11	R	78	73	73	74	84	76	86	97	110	92	86
Mean		76.45	73.36	73.91	71.09	93.09	88.82	88.64	88.18	94.45	93	94.91
± SEM		1.776	1.974	2.44	1.89	3.373	3.514	4.431	4.264	3.68	5.531	4.251

VOL = Volunteer Identity, R_X = Drug, P = Placebo, T = Test, R = Reference

Blood glucose level and hypoglycemia caused by test drug is almost equal to the hypoglycemia produced by reference drug. The blood glucose level (BGL) of every observation was comparable to each other (reference versus standard) with insignificant difference. Maximum hypoglycemia was observed after 90 minutes (probably it is T_{max} and may be C_{max}) of drug administration and also in placebo trial. It was observed that hypoglycemia produced by drug was lower than placebo trial during first 90 minutes of the study which may correlate with unknown

defensive mechanism or sensitivity/resistance of the body towards drug. Blood glucose level sharply raised after the breakfast but drug administration significantly resist in our study as compare to the control i.e. 12.26% by Glucophage and 19.81% by Metphage. Blood glucose level was again dropped markedly on second and third occasion whereas placebo blood glucose level result was higher before lunch.

The study was designed in such a way that pattern of hypoglycemia can easily be observed and compared to each other. The whole data revealed that blood glucose level caused by metformin does not drop below 70mg/dl of blood and raise up-to 95mg/dl. Although blood glucose level of both drugs shows competing to each other but there is no significant difference between them. Minor differences might relate with inter individual variation in human volunteers and in different formulation as well as different pharmaceutical unit. Although this data assure the ultimate quality of both metformin 500 mg tablet but every formulation should be studied for assurance of safety and efficacy because life of patient is a matter of concern.

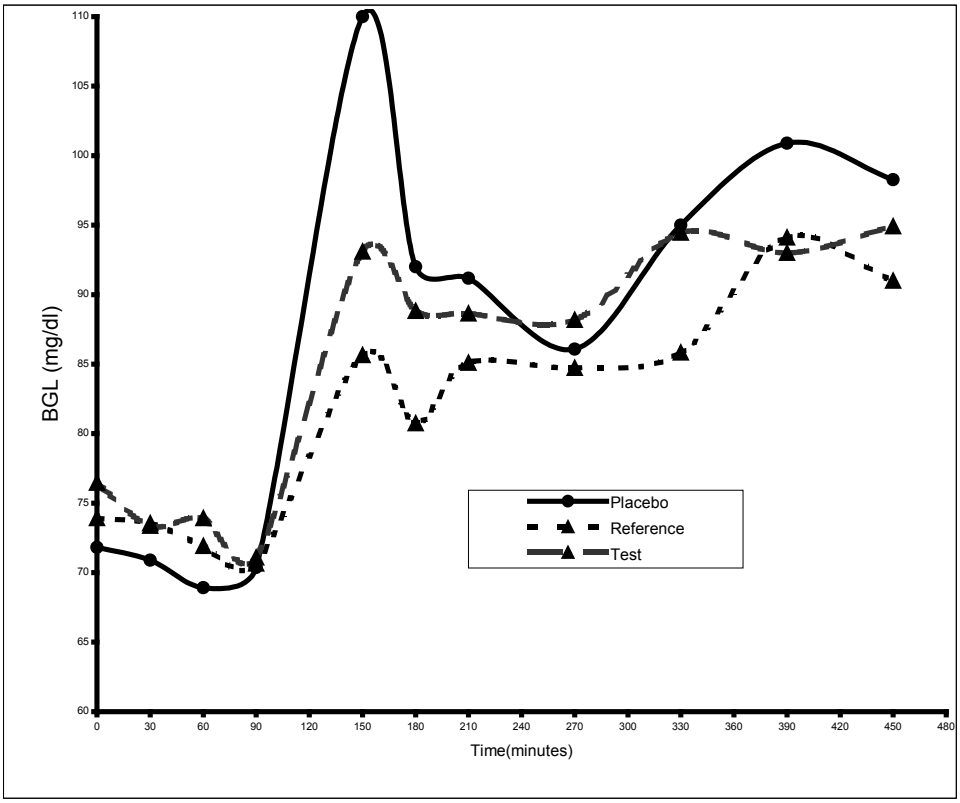


Fig. R-1: Blood Glucose pattern after administration of placebo, reference and test formulations of Metformin 500 mg per oral tablet in healthy, human volunteers.

CONCLUSION

Pharmacodynamics response of any drug may help in assessment of any new molecule as well as formulation. Ultimate quality of any drug can only be assessed by end response of the drug to the body, which can be done by measuring the body behaviour toward drugs. Difference in price and quality of same formulations of different companies can be seen and observed but ultimate

quality assessment can not be achieved without pharmacokinetics and pharmacodynamics studies. It is also not necessary that costly drug is more effective, until it is not proved. The out come of the said study suggests that all formulations were found almost equivalent regarding pharmacokinetics and pharmacodynamics evaluation inspite of having different excipients, concentration of excipients, sources of raw material, manufacturing process, machinery, resources and also inter individual variation of the study.

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