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In-vivo Study for Evaluation of Novel Formulated Bi-layered Tablet of Alpha Lipoic Acid and Metformin for Antidiabetic Activity

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ABSTRACT: Bilayer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances and also for sustained release tablet in which one layer is immediate release as initial dose and second layer is maintenance dose. Bilayer tablet is improved beneficial technology to overcome the shortcoming of the single layered tablet.The study was aimed to determine whether treatment with novel combination of alpha lipoic acid with metformin formulated as bilayered tablet dosage form could modulate hyperglycemia related to type 2 diabetes mellitus in Sprague–Dawley (SD) rats. Oral glucose test tolerance (OGTT) was performed on the overnight fasting normal rats Group I served as control received vehicle only (Tween 80 in distill water). Group II served as standard group first and received Metformin (500 mg/kg) suspended in vehicle, Group III standard group second and receive alphalipoic acid (200 mg/kg) suspended in vehicle. Group IV Test group bilayered tablet crushed containing Metformin and Alpha Lipolic acid 500mg/kg and 200 mg/kg respectively. All animals were loaded with glucose (2 g/kg, p.o.) 30 min after the drug administration. The blood samples were collected by snipping tail with surgically sterilized needle. Blood glucose was determined just prior to glucose administration (0h) and 1, 2, 3 and 6h after glucose administration. Blood glucose concentration was estimated by the glucose oxidase enzymatic method, using Accu-chek Active TM Test strips in Accu-chek Active TM Test meter.

Keywords: In-vivo; Anti-diabetic; Metformin; Alpha lipoic acid and Bilayered tablet.

INTRODUCTION: Solid oral dosage forms are the most advantageous and habitually used route to deliver drugs due to ease of administration and flexibility of the design. Compressed tablets are one of the most popular and acceptable dosage forms. Furthermore, controlled release oral dosage forms are increasingly popular.[1] They contribute to a better patient compliance, maintaining uniform dose levels and reducing dose frequency, as well as side effects. In some pathological conditions, immediate release of the dose must be achieved to provide a rapid onset of action, followed by extended drug release to maintain the therapeutic effect. In order to execute the dual drug release concept, one solution is a multi-layer tablet preparation. Over the past years, multi-layer tablets, whether as an oral immediate- or a controlled-release system, have, hence, become increasingly popular. The multi-layer tablet is a delivery system that aims to deliver two or more drugs at different rates or simultaneously release two or more drugs with desired release rate. What is more, two or more incompatible drugs may be formed into a multi-layer tablet. Multi-layer tablets are favored due to the controlled release profiles of the active ingredients.[2]

Modified/ controlled release formulations offer more benefits than immediate release dosage forms with the same active sub- stance. Products with modified/controlled drug release are designed to optimize the treatment regimens and provide greater patient convenience and compliance. The basic aim of controlled release systems is to maintain the drug delivery at a constant level. Throughout the years of research aimed to develop new dosage form of zero order or nearly zero order kinetic, a variety of oral dosage forms have come about.[3] These hold modified release properties, and include such forms as film coated capsules, pellets or tablets, compression-coated tablets, systems using electrostatic deposition, osmotic or ion controlled systems, technology three dimensional (3D) printing dosage forms. Miscellaneous release profiles e.g. delayed release, pulsatile or multimodal delivery profiles, may be attained using changes in the composition, combination of layers or the geometry of

multi-layer tablets. Bilayer tablet is new era for the successful development of controlled release formulation along with various features to provide a way of successful drug delivery system. Controlled release dosage forms have been extensively used to improve therapy with several important drugs. Use of bilayer tablet is a very different aspect for anti-inflammatory, analgesic especially anti-diabetic activity. Bilayer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances and also for sustained release tablet in which one layer is immediate release as initial dose and second layer is maintenance dose. Bilayer tablet is improved beneficial technology to overcome the shortcoming of the single layered tablet. Over the past 30 years greater attention has been focused on development of sustained or controlled release drug delivery systems. The development of combination of two or more active pharmaceutical ingredients (API) in a single dosage form has increased in the pharmaceutical industry, promoting patient convenience and compliance.[4-16]

Type 2 diabetes is a progressive disorder and most patients will need more than two oral agents to maintain sufficient glucose control. Shifting from one drug to another in a patient with poorly controlled glycemia or increasing the dose of an existing drug is not helpful always. Existing regimen needs to be modified by adding medications from different groups for glycemic control effectively. Several of the available oral agents have been studied in combination and have been shown to further improve glycemic control when compared with monotherapy.[17]

Metformin hydrochloride is an orally administered drug, which is widely used in the management of type 2 diabetes, a common disease that combines defects of both insulin secretion and insulin action. Alpha Lipoic acid responsible for oxidative glucose metabolism and cellular energy production.[18, 19] Metformin and Alpha Lipoic acid combination is used for diabetic polyneuropathy, Type 2 diabetes, weight loss and other conditions. Side effects and the frequency of administration (two or three times per day) when larger doses are required can decrease patient compliance. Sustained release products are needed for metformin to prolong its duration of action and to improve patient compliance. Moreover, the broad spectrum effects of Alpha lipoic acid make the combination of metformin and alpha Lipoic acid a promising treatment option not only for optimizing management of glycemic control but also for prevention of the cardiovascular complication. Fixed-dose formulation Metformin and Alpha lipoic acid offers an effective option for the management of patients with type 2 diabetes when monotherapy fails in the achievement of the recommended standards of care. Hence, the present research was undertaken to formulate bilayer tablet of alpha lipoic acid (immediate release) and metformin hydrochloride (sustained release) using 3^2 factorial designs.[20-21]

MATERIALS AND METHODS: Oral glucose test tolerance (OGTT) was performed according to the method reported by Jun-bo Wang, 2019.[22] Overnight fasting normal rats were divided into four groups of six animalsper group (n=6) table 1. Group I served as control received vehicle only (Tween 80 in distill water). Group II served as standard group first and received Metformin (500 mg/kg) suspended in vehicle, Group III standard group second and receive alphalipolic acid (200 mg/kg) suspended in vehicle. Group IV Test group bilayered tablet crushed containing Metformin and Alpha Lipolic acid 500mg/kg and 200 mg/kg respectively. All animals were loaded with glucose (2 g/kg, p.o.) 30 min after the drug administration. The blood samples were collected by snipping tail with surgically sterilized needle. Blood glucose was determined just prior to glucose administration (0h) and 1, 2, 3 and 6h after glucose administration. Blood glucose concentration was estimated by the glucose oxidase enzymatic method, using Accu-chek Active TM Test strips in Accu-chek Active TM Test meter.[22-24]

Table 1: Details of Group of rats.

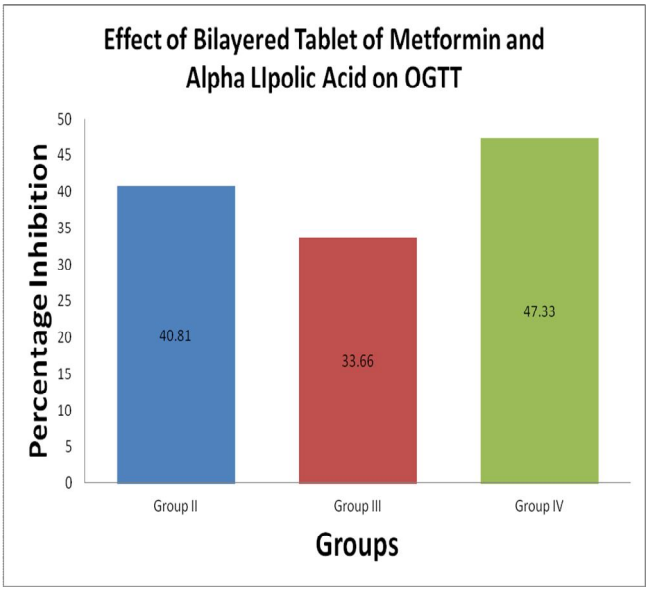
Groups (n=6)	**Treatment**
Group I	Receive vehicle only (Control)
Group II	Metformin (500 mg/kg)
Group III	Alpha lipolic acid (200 mg/kg)
Group IV	Test Group {Metformin (500 mg/kg)+ Alpha lipolic acid (200 mg/kg)}

RESULTS AND DISCUSSION: The blood glucose level (BGL) of bilayered tablets of Metformin (500 mg/kg)+ Alpha lipolic acid (200 mg/kg), both standard and vehicle treated albino rats after oral administration of glucose (2g/kg) are summarized in table 2 and figure 1. The blood glucose level of normoglycaemic rats acquired peak after 1 hr of oral administration of glucose and gradually decreases to the preglucose load level. Both standard prevented the severe increase in glucose level 1 hr after glucose loading and reduced blood glucose level of animals even below the normal values in 3rd and 6th hr. Test induced a potent reduction in glycaemia with maximum fall of (47.33%) may be due to increase in insulin concentration in glucose loaded rats.

Table 2 Oral Glucose Tolerance Test.

Groups	Blood Glucose level (mg/dl)					
	0hrs.	1 hrs	2 hrs	3 hrs	4hrs	6 hrs
Group -I Normal Group (Glucose 2 g/kg)	88.56 ± 5.33	142.64 ± 3.36	132.27 ± 5.26	116.26 ± 4.35	104.23 ± 1.26	99.32 ± 2.54
Group-II Positive Control I [Glucose 1.5g/kg + Metformin (500 mg/kg)]	86.83 ± 1.32	114.45 ± 4.31	104.63 ± 3.56 (20.90%)	86.33 ± 2.45 (25.74%)	65.22 ± 2.31 (37.42%)	58.78 ± 4.12 (40.81%)
Group-III+ Positive Control II Glucose 1.5g/kg + Alpha Lipolic Acid (200 mg/kg)]	84.56 ± 5.71	116.67 ± 6.36	112.77 ± 4.78 (14.74%)	88.25 ± 3.66 (24.09%)	69.54 ± 1.23 (33.28%)	65.88 ± 3.42 (33.66%)
Group-IV Test Group (Glucose 1.5g/kg + formulation)	89.32 ± 3.12	112.32 ± 4.31	100.73 ± 4.44 (23.85%)	80.84± 2.61 (30.46%)	60.26 ± 2.46 (44.10%)	53.31 ± 3.11 (47.33%)

Tabular values are mean ± SEM, n = 6; significant difference from control, c p < 0.05, b p < 0.01; a p < 0.001 (OGTT was observed in the 0th , 1st, 2nd, 3rd, 4th& 6th hr), data were analyzed by ANOVA followed by Dunnett test.



Error! No text of specified style in document.**1: Effect of Bi-layered Tablet of Metformin and Alpha LIpolic Acid on OGTT.**

CONCLUSION: Previously we have reported formulation, evaluation and UV spectrometric method intended to formulate stable and effective bi-layered tablet for the novel combination of alpha lipoic acid with metformin for the evaluation of anti-diabetic activity of these combination. In the present study we have reported In-vivo study of novel bi-layered tablet of alpha lipoic acid with metformin. It was found that novel combination of alpha lipoic acid with metformin incorporated in bi-layered tablet shows synergistic effect as compare to individual drugs, hence, this combination is consider as future treatment for type 2 diabetes.

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