Abstract:

A novel cocrystals of Metformin and oleoylethanolamide with other anti-diabetic agents. The invention discloses novel synergistic pharmaceutical co-crystals which disclose improved residence time thereby increasing the bioavailability and efficacy, as anti-diabetic agents. The invention further discloses a pharmaceutical composition comprised of co-crystals of Metformin or its pharmaceutically acceptable salts and oleoylethanolamide with other anti-diabetic agents.

Inventors:

Anand Arapu Satyanarayana, Gopakumar Nair Associates, 3rd Floor, 'Shivamgali', Near Big Bazaar, Akurli Road, Kandivali (East), Mumbai 400 101, Maharashtra (IN).

Applicant:

NUTRACRYST THERAPEUTICS PRIVATE LIMITED [IN/IN]; C-71, Sector -63, Noida 200130, UP (IN).

Agents:

P. ARUNA SREE; Patent & Trademark Attorney, Gopakumar Nair Associates, 3rd Floor, 'Shivamgali', Near Big Bazaar, Akurli Road, Kandivali (East), Mumbai 400 101, Maharashtra (IN).
"NOVEL COCRYSTALS / MOLECULAR SALTS OF METFORMIN WITH OLEOYLETHANOLAMIDE AS AN EFFECTIVE ANTI-DIABETIC + ANTI-OBESETY AGENT"

FIELD OF INVENTION:

The present invention relates to novel co-crystals of Metformin or its pharmaceutically acceptable salts. More particularly, it relates to synergistic co-crystals of Metformin with Oleoylthanolamide with improved residence time, thereby increasing bioavailability and efficacy, as an anti-diabetic in lower dosages. The invention further relates to pharmaceutical composition consisting of co-crystals of metformin and Oleoylthanolamide with other antidiabetic agents.

BACKGROUND AND PRIOR ART:

The utility of pharmaceutical co-crystals in solving stability, solubility, bioavailability, filtration, hydration, and tableting, etc. issues has been well documented recently. Co-crystals are potentially attractive for improving properties while leaving an API unaltered. They are defined as hydrogen bonded complexes between an active pharmaceutical ingredient (API) and a coformer (CCF, benign partner molecule), usually having a fixed API: CCF stoichiometry. These co-crystals have utility in imparting desirable physical properties and stability, which are otherwise not achievable for the pure active agent or in combination as a simple formulation using the excipients incorporated with the active agent.

Metformin, originally sold as Glucophage is an oral anti-diabetic drug. It 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. It is also known for its efficacy in gestational diabetes, although safety concerns still preclude its widespread use in this setting. It is also used in the treatment of polycystic ovary syndrome and has been investigated for other diseases where insulin resistance may be an important factor.

When prescribed appropriately, Metformin causes few adverse effects and is not known to cause hypoglycemia if used alone. Metformin helps reduce LDL cholesterol and
triglyceride levels and is not associated with weight gain, and is the only anti-diabetic
drug that has been conclusively shown to prevent the cardiovascular complications of
diabetes. As of 2009, Metformin is one of only two oral anti-diabetics in the World
Health Organization Model List of Essential Medicines. Metformin improves
hyperglycemia primarily through its suppression of hepatic glucose production (hepatic
 gluconeogenesis).

In addition to suppressing hepatic glucose production, Metformin increases insulin
sensitivity, enhances peripheral glucose uptake, increases fatty acid oxidation, and
decreases absorption of glucose from the gastrointestinal tract. Increased peripheral
utilization of glucose may be due to improved insulin binding to insulin receptors.

Oleoylethanolamide (OEA) is an endogenous peroxisome proliferator-activated receptor
alpha (PPAR-α) agonist. It is a naturally-occurring lipid derivative that regulates feeding
and body weight in vertebrates ranging from mice to pythons. OEA is the
monounsaturated analogue of the endocannabinoid anandamide, but unlike anandamide it
acts independently of the cannabinoid pathway, regulating PPAR-α activity to stimulate
lipolysis.

OEA is produced by the small intestine following feeding in two steps. First an N-acyl
transferase (NAT) activity joins the free amino terminus of phosphatidylethanolamine
(PE) to the oleoyl group (one variety of acyl group) derived from sn-1-oleoyl-
phosphatidylcholine, which contains the fatty acid oleic acid at the sn-1 position.
(illustration). This produces an N-acylphosphatidylethanolamine, which is then split
(hydrolyzed) by N-acyl phosphatidylethanolamine-specific phospholipase D (NAPE-
PLD) into phosphatidic acid and OEA. OEA has recently been demonstrated to bind to
the novel cannabinoid receptor GPR119. OEA has been suggested to be the receptor's
endogenous ligand.

OEA decreases neutral lipid content in hepatocytes, as assessed by Oil red O staining, as
well as serum cholesterol and triglyceride levels. The results suggest that OEA regulates
lipid metabolism and that this effect may contribute to its anti-obesity properties.
Peroxisome proliferator-activated receptor-alpha (PPAR\(\alpha\)) belongs to the nuclear receptor (NR.) family of transcription factors and regulates lipid and glucose metabolism. Like other NRs, the regulation of gene expression by PPAR\(\alpha\) depends on cofactor recruitment to the transcription complex and multiple protein-protein interactions.

Peroxisome proliferator-activated receptor-\(\alpha\) (PPAR\(\alpha\)) regulates the expression of fatty acid (FA) oxidation genes in liver and heart. Metabolic alterations in hearts from PPAR\(\alpha\)-treated diabetic mice most likely reflect indirect mechanisms related to improvement in diabetic status in vivo according to Asum Ellen; Cooper Marie etal., in Canadian Journal of Physiology and Pharmacology, Volume 83, Number 2, 1 February 2005 , pp. 183-190(8).

Oral absorption of metformin is variable and incomplete and has an oral bioavailability of 50-60% under fasting conditions, and is absorbed slowly. Peak plasma concentrations (Cmax) are reached within one to three hours of taking immediate-release Metformin and four to eight hours with extended-release formulations. The plasma protein binding of Metformin is negligible, as reflected by its very high apparent volume of distribution (300-1000 L after a single dose). Steady state is usually reached in one or two days. Metformin is not metabolized. It is cleared from the body by tubular secretion and excreted unchanged in the urine; Metformin is undetectable in blood plasma within 24 hours of a single oral dose. The average elimination half-life in plasma is 6.2 hours. Metformin is distributed to (and appears to accumulate in) red blood cells, with a much longer elimination half-life: 17.6 hours (reported as ranging from 18.5 to 31.5 hours in a single-dose study of non-diabetic people).

Since the Bioavailability / blood plasma binding of Metformin being poor, one objective of the present research was to improve the lipophilicity and, consequently, enhance the oral absorption of this highly water-soluble drug.

The present inventors therefore felt a need to develop novel co-crystals of Metformin as these co-crystals would enhance the plasma binding ability of Metformin, thereby improving the efficacy, and synergistic effect as well as lowering the dose of Metformin.
OBJECT OF THE INVENTION:

The object of the invention is to prepare novel co-crystals of Metformin with Oleoylethanolamide leading to an enhancement of anti-diabetic effect.

Another object of the invention is to increase the bioavailability of the Metformin preparation which will enhance its efficacy and lower the dose.

Yet another object of the invention is to provide alternate synergistic bioavailable dosage form of Metformin in the form of co-crystals that would enhance the residence time of Metformin in the blood and prove to be a potent anti-hyperglycemic agent.

Yet another object of the invention is to treat related metabolic syndrome associated with diabetic patients such as obesity, elevated triglyceride and cholesterol levels through known and unknown mechanisms of actions of OEA and Metformin.

The other object of the invention is to provide a pharmaceutical composition consisting of Metformin with Oleoylethanolamide along with other antidiabetic agents.

SUMMARY OF THE INVENTION:

In accordance with the above objectives, the present invention provides novel co-crystals of Metformin with Oleoylethanolamide in 1:1 ratio.

The novel co-crystal of Metformin with Oleoylethanolamide has enhanced bioavailability and additional anti-obesity action.

In an aspect of the present invention, Metformin free base (synthesized from Metformin hydrochloride in house) or its pharmaceutically acceptable salts and Oleoylethanolamide (Synthesized) in a 1:1 ratio are neatly grinded by solvent drop grinding method in presence of solvent such as acetonitrile (3 drops) for 5 min to yield the novel co-crystal of Metformin with oleoylethanolamide.
In another aspect, the novel co-crystals comprising of Metformin or its pharmaceutically acceptable salts as API along with Oleoylethanolamide is used as medically valuable compounds having synergistic effect. Accordingly, the novel cocrystal is used as an improved anti-diabetic agent.

In yet another aspect, the novel cocrystals comprising of Metformin or its pharmaceutically acceptable salts as API along with Oleoylethanolamide is used to treat related metabolic syndrome associated with diabetic patients such as obesity, elevated triglyceride and cholesterol levels through known and unknown mechanisms of actions of OEA and Metformin.

In yet another aspect, the invention relates to a pharmaceutical composition consisting of Metformin with Oleoylethanolamide along with other antidiabetic agents selected from DPP-IV inhibitors, sulfonylureas of first and second generation, thiazolidinediones and alpha-glucosidase inhibitors.

DESCRIPTION OF FIGURES:

Fig 1 depicts Infrared spectrum of Metformin free base
Fig 2 depicts Infrared spectrum of Oleoylethanolamide
Fig 3 depicts Infrared spectrum of Metformin Oleoylethanolamide Cocrystal
Fig 4 depicts PXRD of Metformin free base
Fig 5 depicts PXRD of Oleoylethanolamide
Fig 6 depicts PXRD of Metformin Oleoylethanolamide Cocrystal
Fig 7 depicts DSC Analysis of Metformin free base
Fig 8 depicts DSC Analysis of Oleoylethanolamide
Fig 9 depicts DSC Analysis of Metformin Oleoylethanolamide Cocrystal

DETAILED DESCRIPTION OF THE INVENTION:

The invention will now be described in detail in connection with certain preferred and optional embodiments, so that various aspects thereof may be more fully understood and appreciated.
Accordingly, the present invention relates to novel synergistic co-crystals of metformin or its pharmaceutically acceptable salts as API along with oleoylethanolamide (OEA) in fixed stoichiometric ratio with improved residence time, increased bioavailability and efficacy, as an anti-diabetic in lower dosages.

The stoichiometric ratio of metformin or its pharmaceutically acceptable salts as API along with oleoylethanolamide (OEA) is in molar ratio 1:1.

Metformin improves hyperglycemia primarily through its suppression of hepatic glucose production (hepatic gluconeogenesis).

Metformin is concurrently marketed in the U.S. in the form of its hydrochloride salt (Glucophage). Various organic or inorganic salts of metformin which can be used in the co-crystal formation are as follows:

- as phosphates, sulfates, hydrobromides, salicylates, maleates, benzoates, succinates, ethanesulfonates, fumarates and glycolate salts of metformin;
- as p-chlorophenoxyacetic acid salt of metformin;
- as pamoate salt of metformin;
- as orotate salt of metformin;
- as (4-chlorophenoxy) isobutyrate salt of metformin;
- as clofibrate salt of metformin;
- as acetylsalicylate salt of metformin;
- as theophyllin-7-acetate salt of metformin;
- as nicotinic acid salt of metformin;
- as adamantoate salt of metformin;
- as zinc-chlorophyllin salt of metformin;
- as hydroxy acid salts of metformin, including salts of hydroxy aliphatic dicarboxylic acids such as mesotartaric acid, tartaric acid, mesoxalic acids, and oxidized maleates;
- as tannic acid salt of metformin;
- as 3-methyl-pyrazole-5-carboxylic acid (or other 5-members heterocycle carboxylic acid) salt of metformin;
• as sulfamido aryloxyalkyl carboxylic acid salts of metformin;
• as trimethoxy benzoic acid salt of metformin;
• as dichloroacetic acid salt of metformin;
• as metformin salts of dibasic acids (2:1 molar ratio), preferably metformin (2:1) fumarate and metformin (2:1) succinate; preferably its hydrochloride salt.

Oleoylethanolamide (OEA) is an endogenous peroxisome proliferator-activated receptor alpha (PPAR-a) agonist. OEA is the monounsaturated analogue of the endocannabinoid anandamide, but unlike anandamide it acts independently of the cannabinoid pathway, regulating PPAR-a activity to stimulate lipolysis.

PPARs have been an extremely active target for the drug industry for decades. Despite the fervent interest in PPARs, the only PPAR modulators marketed in the U.S. are the relatively PPAR-gamma-selective agonists, rosiglitazone and pioglitazone for treatment of hyperglycemia in type 2 diabetes, and the relatively PPAR-alpha-selective agonist fibrates (e.g. fenofibrate, gemfibrozil), which are used to lower triglycerides and raise HDL-C in dyslipidemia to reduce risk of cardiovascular events.

PPARα agonist, ureido-fibrate-5 (UF-5), ~200-fold more potent than fenofibric acid, exerts TG-lowering effects (37%) in fat-fed hamsters.

In an aspect, intake of novel co-crystals of metformin or its pharmaceutically acceptable salts with OEA increases the production of GLP-1 (Glucagon-like peptide-1) due to endogenous stimulation. This results in an additive anti-diabetic effect due to GLP-1 secretion which inhibits glucagon secretion, promotes insulin secretion and decreases glucose levels. Inhibiting the enzymatic degradation of GLP-1 has been the main mechanism of action of Dipeptidyl peptidase -IV (DPP-IV) inhibitors like sitagliptin and vildagliptin. GLP-1 secretion is a more natural way of glucose homeostasis after food intake and therefore provides a better non-toxic option unlike DPP-4 inhibitors which cause numerous side effects. However, there could be possible complimentary and synergistic action if the metformin co-crystal of OEA is combined with DPP-4 inhibitors like sitagliptin, vildagliptin, dutaglititin ,saxagliptin, linagliptin, gemigliptin and alogliptin.
Multiple dosing regimens together, along with large doses, dose dependent absorption, poor bioavailability are not preferred since it leads to patient non-compliance, potential side effects & danger of overdosing. It is therefore imperative to shift from multiple dosing to a new and ideal once-a-day or twice-a-day dosing regimens. The invention further provides a novel patient-convenient, cost effective pharmaceutical dosage form to improve the quality of treatment.

Thus, in a further aspect the present invention relates to pharmaceutical dosage form to provide the advantages already described herein and to improve the treatment of the diseases.

In an aspect, the combination is in the form of a fixed combination dosage form e.g. the three active ingredients are in the same formulation as described below.

Accordingly, the present invention provides a fixed dose pharmaceutical composition comprising of co-crystal of metformin- Oleoylethanolamide (OEA) with other antidiabetic agents such as DPP-IV inhibitors selected from sitagliptin, vildagliptin, dutogluptin ,saxagliptin, linagliptin, gemigliptin and alogliptin.

In yet another aspect, the present invention provides a fixed dose pharmaceutical composition comprising of co-crystal of metformin- Oleoylethanolamide (OEA) with sulfonylureas of first generation such as carbutamide, acetohexamide, chlorpropamide, tolbutamide, tolazamide and second generation sulfonyl ureas selected from glipizide, gliclazide, glibenclamide, gliquidone, glycopyramide and glimepiride.

In yet another aspect, the present invention provides a fixed dose pharmaceutical composition of co-crystal of metformin- Oleoylethanolamide (OEA) with thiazolidinediones such as rosiglitazone and pioglitazone.

In another aspect, the present invention provides a fixed dose pharmaceutical composition comprising of co-crystal of metformin- Oleoylethanolamide (OEA) with alpha-glucosidase inhibitors like acrabo etc.

The dosage form is preferably a solid pharmaceutical dosage form for oral administration.
The dosage form may be tablets or capsules. The tablet is in the form of a multi-layered or bilayered tablet. The tablet may include a coating.

The capsules may include one or more of pellets, beads, granules, multiparticulates, tablets and powder.

The dosage form can comprise an extended release core of metformin and an immediate release layer of a PPAR antidiabetic and a DDP-IV inhibitor.

The dosage form can be a capsule comprising immediate release granules (or pellets or multiparticulates etc. as described below) of a PPAR ANTIDIABETIC and a DDP-IV inhibitor (in the same or in separate granules, pellets or multiparticulates) and extended release granules (or pellets or multiparticulates etc. as described below) of metformin.

The dosage form can be a tablet comprising an immediate release layer containing a PPAR ANTIDIABETIC and a DDP-IV inhibitor, and an extended release layer containing metformin-OEA co-crystal. The dosage form can also be a tablet comprising an immediate release layer containing a PPAR ANTIDIABETIC a second immediate release layer containing a DDP-IV inhibitor and an extended release layer containing metformin.

The extended release layer may be a core and the immediate release layer may cover at least a portion of the core. The dosage form may be a multi-layered or bilayered dosage form. The core may be a matrix and the matrix may be a uniform mixture of metformin and one or more rate controlling polymers and may further include one or more pharmaceutically acceptable excipients. The immediate release outer layer may further include film-forming polymers and; optionally other pharmaceutically acceptable excipients. The film-forming polymers may be water-soluble polymers. The pharmaceutically acceptable excipients may be one or more of plasticizers, opacifiers and colorants.

After oral administration metformin may be released over a period of about 4 to about 36 hours and, more particularly, over a period of about 8 to about 24 hours.
Extended release formulations comprise pharmaceutically acceptable excipients (used in extended release layers or granules or tablets) and are well known in the art and are e.g. described in the herein cited prior art documents. Extended release layer may be a matrix and the matrix may have a uniform mixture of the metformin and one or more rate controlling polymers. The one or more rate-controlling polymers may be hydrophilic polymers, hydrophobic polymers, or a combination thereof. The matrix may further include one or more pharmaceutically acceptable excipients. The pharmaceutically acceptable excipients may be one or more of diluents, lubricants, disintegrants, binders, glidants, coloring and flavoring agents. Preferably the formulation e.g. in the form of granules containing metformin is capable of being effectively compressed into a single tablet system exhibiting pH independent prolonged release of metformin.

Immediate release formulations comprise pharmaceutically acceptable excipients (used in extended release layers or granules or tablets) and are well known in the art. However an immediate release formulation can be limited only to the active ingredient or ingredients without the addition of a further pharmaceutically acceptable excipient.

The term 'bilayered' as used herein is meant to encompass solid dosage forms in which there are two separate drug layers, with only one surface in contact with each other. These may be prepared, for example, by compressing additional granulation on a previously compressed granulation or alternatively by feeding previously compressed tablets into a machine and compressing another granulation layer around the preformed tablets.

An example of a bi-layer tablet manufacturing method includes: (1) blending a quantity of a PPAR ANTIDIABETIC and DPP-IV inhibitor with various excipients, colorants, and/or other pharmaceutically acceptable excipients and additives to form an immediate release formulation, (2) blending a quantity of metformin with a rate-controlling polymer, and various excipients, colorants, and/or other pharmaceutical additives to form an extended release formulation, and (3) compressing a quantity of the immediate release formulation of the PPAR ANTIDIABETIC and DPP-IV inhibitor with a quantity of the extended release formulation of metformin to form a bi-layer tablet.

The manufacturing process can also involve the separate preparation of specially formulated granules containing Metformin, the PPAR ANTIDIABETIC and the DPP-IV
inhibitor and then compressing them (the three separate granules) into multilayered tablets exhibiting prolonged (preferably pH independent in-vitro) release of Metformin and immediate release of the PPAR ANTIDIABETIC and DPP-IV inhibitor. Preferably pH independent in-vitro release of Metformin up to a period of 8-12 hours.

In another aspect, the co-crystals of metformin with OEA decrease bodyweight in obese diabetics through known and unknown mechanisms of action of OEA and Metformin.

In yet another aspect, the novel co-crystals of metformin with OEA decrease the triglyceride and cholesterol levels through known and unknown mechanisms of OEA thus addressing the metabolic syndrome comprising of diabetes, obesity, elevated triglyceride and cholesterol levels in combination with metformin thereby reducing glucose levels as well as reduces obesity through known and unknown mechanisms.

In another aspect, the present invention relates to a process for the preparation of novel co-crystals of Metformin along with Oleoyl ethanolamide (OEA) as an improved anti-diabetic and anti-obesity agent.

Metformin free base is obtained from Metformin hydrochloride by neutralization of Metformin hydrochloride with a base in alcoholic solvent. The base is selected from alkali and alkaline metal hydroxides, carbonates such as sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate etc. The alcohol is selected from Cl-C4 alcohols. The resultant product was confirmed as metformin using IR, NMR studies and melting point (111°C).

Oleoyl ethanolamide (OEA) is synthesized from oleic acid and ethanol amide in a solvent at 0°C. The solvent is selected from lower boiling polar aprotic solvents such as dichloromethane, THF, ethylacetate, acetone etc. The product was confirmed by NMR and Mass spectroscopy.

Accordingly, Metformin free base and Oleoyl ethanolamide (synthesized) in a 1:1 ratio are neatly grinded by solvent drop grinding method in presence of solvent such as
acetonitrile (3 drops) for 5 min to yield the novel co-crystal of Metformin with oleoylethanolamide.

The formation of these co-crystals or salt was confirmed by powder X-ray diffractometry, IR spectrometry, DSC and TGA.

The physical characteristics of the co-crystals of Metformin or its pharmaceutically acceptable salts with Oleoylethanolamide prepared according to the current invention are as tabulated below.

**Table 1: Comparative infrared frequencies**

From Infrared spectrum [Table 1] it is clear that the O-H Stretching in Oleoylethanolamide (OEA) has disappeared and also the there is a corresponding shift in metformin-N-C=N peaks from 1577 to 1567 cm⁻¹ indicating that this moiety would be interacting with OEA. 1° & 2° N-H Stretching frequencies are slightly shifted indicating that those moieties also might interact with OEA.

<table>
<thead>
<tr>
<th>Metformin (cm⁻¹)</th>
<th>Oleoylethanolamide (cm⁻¹)</th>
<th>Cocrystal (cm⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1°-N-H (Asym str)</td>
<td>-3368</td>
<td>N-H (Broad)</td>
</tr>
<tr>
<td>-N-H (sym str)</td>
<td>-3368</td>
<td>C=O (Str)</td>
</tr>
<tr>
<td>2°-N-H</td>
<td>-3180</td>
<td>C=C (Str)</td>
</tr>
<tr>
<td>-C=N (Str)</td>
<td>-1635</td>
<td>O-H (str)</td>
</tr>
<tr>
<td>N-H Deformation</td>
<td>-1620</td>
<td>C-0</td>
</tr>
<tr>
<td>-N-C=N (Asym str)</td>
<td>-1577</td>
<td></td>
</tr>
<tr>
<td>CH₃-Asym Deformation</td>
<td>-1470</td>
<td></td>
</tr>
<tr>
<td>Sym deformation</td>
<td>-1440</td>
<td>-C=O (Str)</td>
</tr>
<tr>
<td>C-N (Strech)</td>
<td>-1060</td>
<td>N-C=N (Asym str)</td>
</tr>
<tr>
<td>CH₃streach</td>
<td>-940</td>
<td>C-N (Stretch)</td>
</tr>
</tbody>
</table>
Table 2: Comparative PXRD ANALYSIS

The PXRD pattern shows that the co-crystal is a different crystalline form as compared to the two individual components (Table 2).

<table>
<thead>
<tr>
<th>Metformin(2theta)</th>
<th>Oleoylethanolamide</th>
<th>Cocrystal</th>
</tr>
</thead>
<tbody>
<tr>
<td>15.74,16.29,17.7,18</td>
<td>5.06,6.86,10.5,20.9,21.2</td>
<td>16.2,16.6,17.9,24.6,</td>
</tr>
<tr>
<td>.26,25.89, 29.2</td>
<td>.22,2,23.2</td>
<td>28.4,29.0</td>
</tr>
</tbody>
</table>

DSC ANALYSIS:

While the Metformin shows an endotherm at 111°C and OEA at 55°C, in the case of co-crystal two endotherms are observed at 123°C & 205°C.

TGA ANALYSIS:

In metformin the weight loss observed at 147°C is around 46 mass which roughly corresponds to the NH2-C=NH moiety. Also, its shift in the IR for co-crystal might indicate that it is susceptible for cleavage under the conditions. In OEA there is no considerable weight loss was observed below 350°C .In co-crystal at 99.73°C one water molecule weight loss was observed and at 264.84°C ,221 weight loss observed.

The said novel co-crystal of Metformin with Oleoylethanolamide has good anti-diabetic activity with enhanced anti-obesity action. The product is an improved Metformin with enhanced bioavailability and additional anti-obesity action.

In a further aspect, the invention provides pharmaceutical compositions comprising a therapeutically effective amount of Metformin - Oleoylethanolamide co-crystals of the current invention in association with one or more pharmaceutical carriers/excipients. The co-crystals of the invention have the same pharmaceutical activity as its API. Further, the pharmaceutical composition of the invention may be any pharmaceutical form which maintains the crystalline form of a co-crystal of the invention.

The carriers/ excipients are added to the composition for variety of purposes. Dosage forms include solid dosage forms such as tablets, powders, capsules, liquid dosage forms as well as parenteral dosage forms. The dosage forms can also be prepared as sustained, controlled, modified and immediate dosage forms. The active ingredient(s) and excipients
can be formulated into compositions and dosage forms according to methods known in
the art.

The pharmaceutical composition of the instant invention may be prepared in the form of
raw powders or granules dispersed in a suitable aqueous or non-aqueous liquid(s), pellets,
beads, micro or nano particles, micro or a solvated powders, sachets, semisolids, an
Injectable preparations, a tablets, a capsules or a suitable specific two- or three-
dimensional matrix compositions. Preferably, the composition pharmaceutical
composition is a single layer or a bilayer tablet.

The composition may be prepared by the techniques of dry granulation, wet granulation
and / or direct compression using aqueous / Non aqueous solvent further fabricate into the
single layer, bilayer, and multilayer and / or multicoated tablet dosage forms. The
composition is prepared by the techniques of homogenization, emulsification comprising
o/w, w/o or multiple emulsion (s), hot-melt fusion, lyophilization and/or precipitation.

The pharmaceutical composition of the instant invention may be extended to the
development of micelle, emulsion and liposome formulation including small molecules,
peptides, nucleic acids etc.

In another aspect, the invention relates to use of novel co-crystal of Metformin-
Oleylethanolamide for treating metabolic disorders such as diabetes, obesity, elevated
triglyceride and cholesterol levels. This use is provided in the form of a medicament or a
pharmaceutical composition according to the invention as described above.

In an embodiment, a daily dosage of 250, 500, 750, 1000, 1500, 2000mg of metformin or
its pharmaceutically acceptable salt is administered.
A daily dosage of 2550 mg of metformin or a salt thereof is administered, and divided in
3 administrations of 850 mg a day preferably before each meal.
A daily dosage of 2000 mg of metformin or a salt thereof is administered, and divided in
2 administrations of 1000 mg a day.
A daily dosage of 1500 mg of metformin or a salt thereof is administered, and divided in 2 administrations of 750 mg a day, or 3 administrations of 500 mg a day.

A daily dosage of 1000 mg of metformin or a salt thereof is administered, once a day or divided in 2 administrations of 500 mg a day.

A daily dosage of 750 mg of metformin or a salt thereof is administered, once a day, or divided in 3 administrations of 250 mg a day.

A daily dosage of 500 mg of metformin or a salt thereof is administered, once a day, or divided in 2 administrations of 250 mg a day.

A daily dosage of 15 or 30 mg of thiazolidinediones is administered.

A daily dosage of 50 mg or 100 mg of DPP-IV is administered.

In yet another aspect, the invention provides a method for the treatment of metabolic disorders such as diabetes, obesity, elevated triglyceride and cholesterol levels by administering an effective amount of the 'composition of invention' to the subject suffering from said disease. Accordingly, Metformin-Oleylethanolamide cocrystals and pharmaceutical compositions containing them may be administered using any amount, any form of pharmaceutical composition via any route of administration effective for the treatment. After formulation with an appropriate pharmaceutically acceptable carrier in a desired dosage, as known by those of skill in the art, the pharmaceutical compositions of this invention can be administered by any means that delivers the active pharmaceutical ingredient(s) to the site of the body whereby it can exert a therapeutic effect on the patient.

The invention provides a method for treating diabetes, obesity, elevated triglyceride and cholesterol levels comprising administering an effective amount of the pharmaceutical composition to the subject, preferably human suffering from said disease.

Examples of further embodiments of the disclosure described herein are indicated below without, however, being limiting in nature.
Example 1: Preparation of metformin from metformin hydrochloride:

1:1 molar ratio of metformin hydrochloride and sodium hydroxide was dissolved in 2-propanol. The suspension was stirred for 3 hours at 313K, filtered and the filtrate evaporated to yield a white solid free of chloride ion (checked with 0.1M AgNO3 solution).

Example 2: Preparation of Oleoylethanolamide from oleic acid:

Oleic acid (1m mole) was taken in Dichloromethane at 0°C and stirred for 10 minutes followed by addition of SOCl2 (1m mole) drop wise in a round-bottom flask and refluxed for 1 hour, and finally ethanol amine (1m mole) was added to obtain the desired product.

Example 3: Preparation of co-crystal of Metformin-Oleoylethanolamide (OEA):

To the Metformin free base and Oleoylethanolamide (synthesized as in example 1 and 2) in a 1:1 ratio was added 3 drops of acetonitrile and neatly grinded for 5 min to yield the novel co-crystal of Metformin with oleoylethanolamide.
We Claim,

1. Novel synergistic pharmaceutical co-crystals of Metformin or its pharmaceutically acceptable salts as API with oleylethanolamide in fixed stoichiometric ratio, at lower dosage, with improved residence time, increased bioavailability and efficacy, as anti-diabetic agent.

2. Novel synergistic pharmaceutical co-crystals of Metformin or its pharmaceutically acceptable salts and oleylethanolamide as claimed in claim 1, wherein metformin and the oleylethanolamide present in a molar ratio 1:1.

3. Novel synergistic pharmaceutical co-crystals of Metformin or its pharmaceutically acceptable salts and oleylethanolamide as claimed in claim 1, wherein the pharmaceutically acceptable salts of metformin comprises organic or inorganic salts.

4. Novel synergistic pharmaceutical co-crystals of Metformin or its pharmaceutically acceptable salts and oleylethanolamide as claimed in claim 3, wherein the inorganic or organic salts selected from phosphates, sulfates, hydrobromides, salicylates, maleates, benzoates, succinates, ethanesulfonates, fumarates, glycolate salts of metformin; p-chlorophenoxyacetic acid salt, pamoate, orotate, (4-chlorophenoxy) isobutyrate, clofibrate, acetylsalicylate, theophyllin-7-acetate, nicotinic acid, adamantoate, zinc-chlorophyll in, hydroxy acid salts such as salts of hydroxy aliphatic dicarboxylic acids selected from mesotartaric acid, tartaric acid, mesoxalic acids, and oxidized maleates; tannic acid, 3-methyl-pyrazole-5-carboxylic acids or other 5-member heterocycle carboxylic acids, as sulfamido aryloxyalkyl carboxylic acid, trimethoxy benzoic acid, dichloroacetic acid, salts of dibasic acids (2:1 molar ratio), preferably metformin (2:1) fumarate and metformin (2:1) succinate.
5. Novel synergistic pharmaceutical co-crystals of Metformin or its pharmaceutically acceptable salts and oleylethanolamide as claimed in claim 1, having characteristic peaks in a powder X-ray diffraction pattern at 16.2, 16.6, 17.9, 24.6, 28.4, 29.0.

6. Novel synergistic pharmaceutical co-crystals of Metformin or its pharmaceutically acceptable salts and oleylethanolamide as claimed in claim 1, having characteristic peaks in IR at 3296 cm⁻¹, 3365 cm⁻¹, 3176 cm⁻¹, 1644 cm⁻¹, 1567 cm⁻¹, 1059 cm⁻¹.

7. Novel synergistic pharmaceutical co-crystals of Metformin or its pharmaceutically acceptable salts and oleylethanolamide as claimed in claim 1, exhibit DSC endotherm at 123°C and 205°C.

8. A fixed dose pharmaceutical composition comprising co-crystals of Metformin or its pharmaceutically acceptable salts and oleylethanolamide with other antidiabetic agents.

9. The fixed dose pharmaceutical composition as claimed in claim 8, wherein the antidiabetic agents selected from DPP-IV inhibitors, sulfonylureas, thiazolidinediones and alpha-glucosidase inhibitors.

10. The fixed dose pharmaceutical composition as claimed in claim 8, wherein DPP-4 inhibitors selected from sitagliptin, vildagliptin, dutogliptin, saxagliptin, linagliptin, gemigliptin and alogliptin.

11. The fixed dose pharmaceutical composition as claimed in claim 8, wherein sulfonylureas of first generation selected from carbutamide, acetohexamide, chlorpropamide, tolbutamide, toiazamide and second generation sulfonylureas selected from glipizide, gliclazide, glibenclamide, gliquidone, glycopyramide and glimepiride.
12. The fixed dose pharmaceutical composition as claimed in claim 8, wherein the thiazolidinediones selected from rosiglitazone and pioglitazone.

13. The fixed dose pharmaceutical composition as claimed in claim 8, wherein alpha-glucosidase inhibitors selected from acarbose.

14. A pharmaceutical composition comprising novel synergistic co-crystal of Metformin or its pharmaceutically acceptable salts and oleylethanolamide as claimed in claim 1, in association with one or more pharmaceutically acceptable carriers/excipients.

15. The pharmaceutical composition as claimed in claim 16, wherein said pharmaceutical composition may be formulated in oral dosage form such as tablets, powders, capsules, liquid dosage forms as well as parenteral dosage forms.

16. The pharmaceutical composition as claimed in claim 16, wherein said pharmaceutical composition may be administered as sustained, controlled, modified and immediate dosage forms.

17. Novel synergistic pharmaceutical co-crystals of Metformin or its pharmaceutically acceptable salts and oleylethanolamide as claimed in claim 1, for the treatment of metabolic syndrome such as diabetes, obesity, elevated triglyceride and cholesterol levels.

18. Novel synergistic pharmaceutical co-crystals of Metformin or its pharmaceutically acceptable salts and oleylethanolamide as claimed in claim 1, wherein said pharmaceutical composition is prepared in the form of raw powders or granules dispersed in a suitable aqueous or non-aqueous liquid(s), pellets, beads, micro or nano particles, micro or a solvated powders, sachets, semisolids, an Injectable preparations, a tablets, a capsules or a suitable specific two- or three-dimensional matrix compositions.
19. Novel synergistic pharmaceutical co-crystals of Metformin or its pharmaceutically acceptable salts and oleylethanolamide as claimed in claim 1, wherein said pharmaceutical composition is a single layer or a bilayer tablet.

20. Novel synergistic pharmaceutical co-crystals of Metformin or its pharmaceutically acceptable salts and oleylethanolamide as claimed in claim 1, wherein said composition is prepared by dry granulation, wet granulation and/or direct compression using aqueous/Non aqueous solvent further fabricated into the single layer, bilayer, and multilayer and/or multicoated tablet dosage forms.

21. Novel synergistic pharmaceutical co-crystals of Metformin or its pharmaceutically acceptable salts and oleylethanolamide as claimed in claim 1, wherein said composition is prepared by homogenization, emulsification comprising o/w, w/o or multiple emulsion(s), hot-melt fusion, lyophilization and/or precipitation.

22. Use of novel synergistic pharmaceutical co-crystals of Metformin or its pharmaceutically acceptable salts and oleylethanolamide for reducing diabetes, obesity, elevated triglyceride and cholesterol levels.

23. A method for treating diabetes, obesity, elevated triglyceride and cholesterol levels comprising administering an effective amount of the pharmaceutical composition to the subject suffering from said disease.
<table>
<thead>
<tr>
<th>No.</th>
<th>Peak No.</th>
<th>Position</th>
<th>Intensity</th>
<th>No.</th>
<th>Peak No.</th>
<th>Position</th>
<th>Intensity</th>
<th>No.</th>
<th>Peak No.</th>
<th>Position</th>
<th>Intensity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>19,680</td>
<td>19,681</td>
<td>19,683</td>
<td>5</td>
<td>19,681</td>
<td>19,683</td>
<td>19,685</td>
<td>4</td>
<td>19,681</td>
<td>19,683</td>
<td>19,685</td>
</tr>
<tr>
<td>2</td>
<td>29,181</td>
<td>29,181</td>
<td>29,184</td>
<td>9</td>
<td>29,181</td>
<td>29,184</td>
<td>29,185</td>
<td>8</td>
<td>29,181</td>
<td>29,184</td>
<td>29,185</td>
</tr>
<tr>
<td>16</td>
<td>49,681</td>
<td>49,681</td>
<td>49,684</td>
<td>16</td>
<td>49,681</td>
<td>49,684</td>
<td>49,685</td>
<td>14</td>
<td>49,681</td>
<td>49,684</td>
<td>49,685</td>
</tr>
<tr>
<td>27</td>
<td>69,681</td>
<td>69,681</td>
<td>69,684</td>
<td>27</td>
<td>69,681</td>
<td>69,684</td>
<td>69,685</td>
<td>26</td>
<td>69,681</td>
<td>69,684</td>
<td>69,685</td>
</tr>
<tr>
<td>37</td>
<td>89,681</td>
<td>89,681</td>
<td>89,684</td>
<td>37</td>
<td>89,681</td>
<td>89,684</td>
<td>89,685</td>
<td>36</td>
<td>89,681</td>
<td>89,684</td>
<td>89,685</td>
</tr>
</tbody>
</table>

Fig. 1
**INSTITUTE OF LIFE SCIENCES**

Sample Code: ILS-JSR-1-139-1KBr

Analyst: J.S.N

---

**Result of Peak Picking**

<table>
<thead>
<tr>
<th>No.</th>
<th>Position</th>
<th>Intensity</th>
<th>No.</th>
<th>Position</th>
<th>Intensity</th>
<th>No.</th>
<th>Position</th>
<th>Intensity</th>
<th>No.</th>
<th>Position</th>
<th>Intensity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3286.64</td>
<td>18.2477</td>
<td>2</td>
<td>2347.54</td>
<td>33.7857</td>
<td>3</td>
<td>3089.4</td>
<td>43.0284</td>
<td>4</td>
<td>3004.55</td>
<td>38.1701</td>
</tr>
<tr>
<td>6</td>
<td>2850.27</td>
<td>17.0946</td>
<td>7</td>
<td>2669</td>
<td>73.393</td>
<td>8</td>
<td>2577.4</td>
<td>78.9869</td>
<td>9</td>
<td>2953.32</td>
<td>92.7137</td>
</tr>
<tr>
<td>11</td>
<td>1644.02</td>
<td>12.1986</td>
<td>12</td>
<td>1561.09</td>
<td>20.5529</td>
<td>13</td>
<td>1465.63</td>
<td>27.7052</td>
<td>14</td>
<td>1446.55</td>
<td>33.6474</td>
</tr>
<tr>
<td>16</td>
<td>1339.32</td>
<td>55.0573</td>
<td>17</td>
<td>1306.54</td>
<td>52.8336</td>
<td>18</td>
<td>1265.07</td>
<td>41.6432</td>
<td>19</td>
<td>1232.29</td>
<td>48.6041</td>
</tr>
<tr>
<td>21</td>
<td>1121.4</td>
<td>57.0911</td>
<td>22</td>
<td>1058.73</td>
<td>31.0692</td>
<td>23</td>
<td>1038.55</td>
<td>34.1204</td>
<td>24</td>
<td>923.736</td>
<td>64.7578</td>
</tr>
<tr>
<td>26</td>
<td>882.025</td>
<td>91.3956</td>
<td>27</td>
<td>792.6</td>
<td>69.7451</td>
<td>28</td>
<td>721.247</td>
<td>35.6129</td>
<td>29</td>
<td>704.855</td>
<td>39.6227</td>
</tr>
<tr>
<td>31</td>
<td>654.715</td>
<td>53.4758</td>
<td>32</td>
<td>644.108</td>
<td>58.221</td>
<td>33</td>
<td>624.623</td>
<td>66.5978</td>
<td>34</td>
<td>610.36</td>
<td>75.7934</td>
</tr>
</tbody>
</table>

---

**Fig. 2**
Fig. 3
### Table 1

<table>
<thead>
<tr>
<th>Sample</th>
<th>1.5-2012-1-119-12</th>
<th>X-ray</th>
<th>Cu Kα, Al Kα, Fe Kα / 50 kV / 30 mA</th>
<th>Counter</th>
</tr>
</thead>
<tbody>
<tr>
<td>File</td>
<td>PXA010000714X04</td>
<td>Gen.</td>
<td>R1N200 K with angle generator</td>
<td></td>
</tr>
<tr>
<td>Comment</td>
<td>WEPEC D2-AN</td>
<td>Align.</td>
<td>Standard Sample = slice</td>
<td></td>
</tr>
<tr>
<td>Date</td>
<td>20 Mar 02 16 46</td>
<td>Filter</td>
<td>Not installed</td>
<td></td>
</tr>
<tr>
<td>Operator</td>
<td>[Signature]</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Diagram

![Graph](image_url)

**Fig. 4**
Fig. 5
### Raw Data

- **Sample**: ILS-J3R-113-4
- **File**: 0415003_217.8733
- **Goniometer**: RINT2000 Wide angle goniometer
- **Attenuation**: Standard Sample Holder
- **Date**: 2010-04-20 18:20
- **Operator**: S. N. Novoselov
- **Filter**: Not installed
- **Counter**: Scintillation counter

#### Parameters
- **Scan mode**: Continuous
- **Scan speed**: 3 deg/min
- **Scan step**: 0.02 deg
- **Scan axis**: 2 Theta / Theta
- **Scan range**: 1 -> 45 deg
- **Theta offset**: 0 deg
- **Sample rotation**: 0 deg

### Graph

![Graph](image_url)

**Fig. 6**
Fig. 8
Fig. 9