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FORMULATION AND EVALUATION OF NANOSUSPENSION OF ROSIGLITAZONE

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ABSTRACT

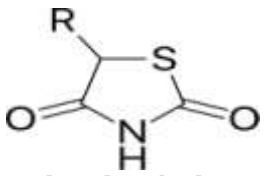
Diabetes mellitus (DM) is a metabolic disorder characterized by hyperglycaemia, glycosuria, hyperlipidaemia, negative nitrogen balance and sometimes ketonemia. Diabetes can be treated with number of drugs like metformin, glibenclamide and thiazolidnedione derivatives like pioglitazone, rosiglitazone, lobeglitazone and rosiglitazone. Number of conventional dosage forms is available to cure the diabetes. In the present research work rosiglitazone was formulated as nanosuspension. The prepared nanosuspensions were evaluated for drug content, FTIR,DSC, Zeta potential, Particle size analysis and in-vitro drug dissolution studies. Drug content of nanosuspension was in the range of 90.91 ±1.0 to 90.01 ±0.2. FTIR and DSC show that there is no incompatability between the drug and the polymer. Zetapotential shows that the prepared nanosuspension was stable. The particle size is in nano range and the in-vitro drug release shows that the S2 formulation shows highest amount of drug release of 98.1% in 2 hours.

INTRODUCTION: Diabetes mellitus (DM) is a metabolic disorder characterized by hyperglycaemia, glycosuria, hyperlipidaemia, negative nitrogen balance and sometimes ketonemia. The high blood sugar produces the symptoms of frequent urination, increased thirst, and increased hungry. Untreated, diabetes can cause many complications. Acute complications include diabetic ketoacidosis and non ketotichyperosmolarcoma. Serious long-term complications include heart disease, stroke, kidney failure, foot ulcers and damage to eyes. Diabetes is due to either the pancreas not producing enough insulin, or the cells of the body not responding properly to the insulin produced. In people with diabetes, blood sugar levels remain high. This may be Due to insulin is not being produced at all, is not made at sufficient levels, or is not as effective as it should be. The most common forms of diabetes are type 1 diabetes (5%), which is an autoimmune disorder and type2diabetes (95%), which is associated with obesity. Gestational diabetes is a form of Diabetes that occurs in pregnancy, and other forms of diabetes are very rare and are caused by single genemutation[1].

Classification:

Thiazolidinedione:

The thiazolidinediones, abbreviated as TZD, also known as after the glitziness Topical drug pioglitazone, are a class of heterocyclic compounds consisting of a five-membered C3NS ring. The term usually refers to a family of drugs used in the treatment of diabetes mellitus type 2 that



were introduced in the late 1990s.

Fig .1: Thiazolidinedione (Functional group)

Chemically, the members of this class are derivatives of the parent compound

Pioglitazone (Actos) France and Germany have suspended its sale after a study suggested the drug could raise the risk of bladder cancer.

Rosiglitazone (Avandia), which was put underselling restrictions in the US and withdrawn from the market in Europe due to some studies suggesting an increased risk of cardiovascular events. Upon re-evaluation of new data in2013, the FDA lifted the restrictions.

Lobeglitazone (Davie), approved for use in Korea Experimental, failed and non-marketed agents include: Pioglitazone, Englitazone

Rosiglitazone:

Rosiglitazone is an antidiabetic drug in thiazolidinedione class. It works as an insulin sensitizer, by binding to the PPAR in fat cells and making the cells more responsive to insulin. It is marketed by the pharmaceutical company GlaxoSmithKline (GSK) as a stand-alone drug or for use in combination with metformin or with glimepiride. First released in 1999, annual sales peaked at approximately $2.5-billion in 2006;however, following a meta-analysis in 2007 that linked the drug's use to an increased risk of heart attack, sales Plummeted to just $9.5-million in 2012. The drug's patent expired in 2012.

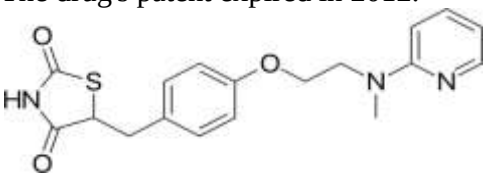


Fig.2: STRUCTURE OF ROSIGLITAZONE

It was patented in 1987and approved for medical use in 1999. Despite rosiglitazone's effectiveness at decreasing blood sugar in type 2 diabetes mellitus, its use decreased dramatically as studies showed apparent associations with increased risks of heart attacks and death. Adverse effects alleged to be caused by rosiglitazone were the subject of over 13,000 lawsuits against GSK, as of July2010, GSK had agreed to settlements on more than 11,500ofthesesuits[2].

Contraindications

Due to its mechanism of action, Rosiglitazone maleate is active only in the presence of endogenous insulin. Therefore, Rosiglitazone maleate should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis. The co administration of Rosiglitazone maleate and insulin is not recommended. The use of Rosiglitazone maleate with nitrates is not recommended.

Nano based drug delivery systems:

Recently, there have been enormous developments in the field of delivery systems to provide therapeutic agents or natural based active compounds to its target location for treatment of various ailments. There are a number of drug delivery systems successfully employed in the recent times, however there are still certain challenges that need to be addresses and an advanced technology need to be developed for successful delivery of drugs to its target sites. Hence the Nanobased drug delivery systems are currently been studied that will facilitate the advanced system of drug delivery.

Nanotechnology:

Nanotechnology can be defined as the science and engineering involved in the design, synthesis, characterization, and application of materials and devices whose smallest functional organization, in at least one dimension, is on the nanometre scale or one billionth of a meter. At these scales, consideration of individual molecules and interacting groups of molecules in relation to the bulk macroscopic properties of the material or device becomes important, as it has a control over the fundamental molecular structure, which allows control over the macroscopic chemical and physical properties. Nanotechnology is the study of extremely small structures. The

prefix–Nano‖ is a Greek word which means–dwarf‖.The word–Nano‖means very small or miniature size. Nanotechnology is the treatment of individual atoms, molecules, or compounds into structures to produce materials and devices with special properties. Nanotechnology involves work from top down i.e. reducing the size of large structures to smallest structure. Nanotechnology deals with materials in the size of 0.1 to 100 nm; however it is also inherent that these materials should display different properties such as electrical conductance chemical reactivity, magnetism, optical effects and physical strength, from bulk materials as a result of their small size. Nanotechnology works on matter at dimensions in the nanometre scale length (1-100 nm), and thus can be used for a broad range of applications and the creation of various types of Nanomaterials and Nanodevices. The history and development of nanotechnology was first started in1985.

Nanosuspensions:

Nanosuspensions are colloidal dispersions of Nano sized drug particles stabilized by surfactants. They can also be defined as a biphasic system consisting of puredrug particles dispersed in an aqueous vehicle in which the diameter of the suspended particle is less than 1μmin size. Reduction of drug particles to nanometer range leads to an enhanced dissolution rate not only because of increased surface area but also because of saturation solubility. The increase in the saturation solubility and solution velocity of nanoparticle is due to increase of vapour pressure of the particles[3].

Advantages of Nanosuspension Drug Delivery System:

- Generally applicable to most drugs& simplicity
- Improvement in biological performance due to high dissolution rate & saturation solubility of the drugs.
- Can be applied for poorly water-soluble drugs.
- Can be given by any route
- Reduced tissue irritation in case of subcutaneous/intramuscular administration.
- Rapid dissolution & tissue targeting by IV route of administration.
- Oral administration provides rapid onset, reduced fed/fasted ratio& improved bioavailability.
- Ocular administration& inhalation delivery provides higher bioavailability& more consistent dosing.
- Due to reduced particle size of Nanosuspension, the absorption form absorption window can be enhanced.
- Long-term physical stability (due to absence of Ostwald ripening).
- Nanosuspension can be
- incorporated in tablets, pellets,
- hydrogel& suppositories are suitable for various routes of administration.
- Increasing the amorphous fraction in the particles leading to a potential change in the crystalline structure& higher solubility.
- Surface-modification of Nanosuspension possible, for site specific delivery.

Disadvantages of Nanosuspension Drug Delivery systems

Physical stability, sedimentation &compaction can cause problems.

It is bulky sufficient care must be taken during handling &transport.

Improper dose.

Materials: Rosiglitazone was purchased from CIL Laboratory Pvt Ltd, Hyderabad, Polyethylene glycol, potassium dihydrogen phosphate, HCl, ethanol, sodium hydroxide pellets was purchased from Hi-media.

METHODOLOGIES

Formulation of Nanosuspension of rosiglitazone:

Accurately weighed quantities of Rosiglitazone, NaOH and potassium dihydrogen phosphate was taken and then triturated in mortar and pestle to reduce the size of the particles. Then it was added to dispersion medium i.e., methanol and water in different ratios and then wetting agent poly ethanol glycol was added and stirred well using mechanical stirrer for half an hour. The nanosuspension formed was stored well for further studies[4].

Characterization of nanosuspension:

Drug content: Accurately weighed amount of each preparation dissolved in required amount of methanol and diluted suitably in ph 6.8 phosphate buffers. The drug content was determined spectrophotometrically at required

Fourier transforms infrared spectroscopy (FTIR):

FTIR analysis can be carried out for the assessment of drug excipient interaction, polymerization, cross linking as well as drug loading in the formulation. It is also used for identifying the functional groups with their means of attachment and the fingerprint of the molecule. At low temperature a molecule exists in ground state and on absorbing the radiant energy, they get excited to higher energy states. IR spectroscopy is based on determining this energy difference (ΔE) between the excited and ground states ofthemolecule[5]

Differential scanning calorimetry (DSC):

DSC can be used to determine the compatibility between the drug and excipients and also used to evaluate the crystalline state of drug especially when converted to Nano emulsion. Thermal characteristics of the same materials that examined in FTIR study were determined by an automatic thermal analyser system(Shimadzu,DSC60,andJapan).Accurately weighed samples(5mg) were placed in non-thematically aluminium pans and heated at the rate of 10 ºC/minute against an empty aluminium pan as a reference covering a temperature range of 40 ºC to 300 ºC[6].

Zeta potential (-mV):

Zeta potential is measured by an instrument known as Zeta PALS. It is used to measure the charge on the surface of droplet in Nano emulsion. Emulsifiers not only act as a mechanical barrier but also through the formation of surface charges. Zeta potential can produce repulsive electrical forces among approaching oil droplets and this hinders coalescence. Zeta potential values lowerthan-30Mv generally indicates a highdegree of physical stability. Malvern Zeta sizer is based on dynamic light scattering and measures Zeta potential[7].

Particle size analysis: Generally, in case of Nano emulsion, dynamic light scattering (DLS) method is used for the measurement of particle size and their distribution.

In-vitro dissolution studies:

The invitro dissolution study for the rosiglitazone tablets were carried out in USP dissolution test apparatus using 900 ml of 0.1N HCL as dissolution medium at 50 rpm and temperature 37±0.5°c. at predetermined time interval's, 5 ml of the sample was withdrawn by means of a syringe fitted with a pre filter, the volume withdrawn at each interval was replaced with same quantity of fresh dissolution medium .the resultant samples were analysed for the presence of the drug released by measuring the absorbance at 318nm using uvvisible spectrophotometer after suitable dilutions. The determinations were performed in triplicate[8]. From the above table it was noted that increase in concentration of drug results in increase in drug content. All the formulations drug content was found to be in the range of 90.91± 1.1 to 90.01±0.2. The solubility of the drug sample was 1.895(mg/ml). The solubility of the drug sample was carried out in different solvents. Solubility can be determined by saturating the drug with different solvents used in solubility studies in a while. Then the vial was tightly closed, agitated at constant temperature for 24hrs in rotator mechanical shaker. The amount of drug in solution is determined periodically by filtering samples through whattman filterpaper and assayed by using U.V–visible spectrophotometer at 256nm

Table. 1: Composition of Nanosuspension of rosiglitazone

INGREDIENTS	F1	F2	F3
Rosiglitazone	5 mg	5 mg	5 mg
NaOH	10 ml	----	-----
Potassium dihydrogen sulfate	1gm	1gm	1gm
Polyethyleneglycol	1gm	1gm	1gm
Methanol	5 ml	10 ml	5 ml
Water	5 ml	5 ml	10 ml

Table. 2: Drug content of rosiglitazone

S.no	Sample code	Drug content
1.	S1	91.02±1.0
2.	S2	91.00±1.1
3 .	S3	89.15±1.0
4.	S4	92.50±0.95

Table 3: Solubility Studies Solubility studies for solvents

S.NO	MEDIUM	SOLUBILITY	SOLUBILITY(mg/ml)
1.	Normal Ph water	Partially soluble	0.89(mg/ml)
2.	0.1N HCl	Soluble	0.95(mg/ml)
3.	1N NaOH	Soluble	0.85(mg/ml)
4.	Ethanol	Soluble	1.10(mg/ml)

Table 4: Dissolution Profile of rosiglitazone

S.No	Time intervals	S1	S2	S3
1.	10	86.8	74.8	58.6
2.	20	85.2	68.3	63.2
3.	30	87.1	65.2	62.8
4.	40	90.3	84.3	84.3
5.	50	94.6	86.4	85.6
6.	60	97.2	80.4	86.3
7.	70	96.8	92.8	87.9
8.	80	97.4	94.6	89.3
9.	90	98.3	96.3	90.2
10.	100	97.9	95.4	94.3
11.	110	94.3	97.6	95.6
12.	120	97.4	98.1	97.8

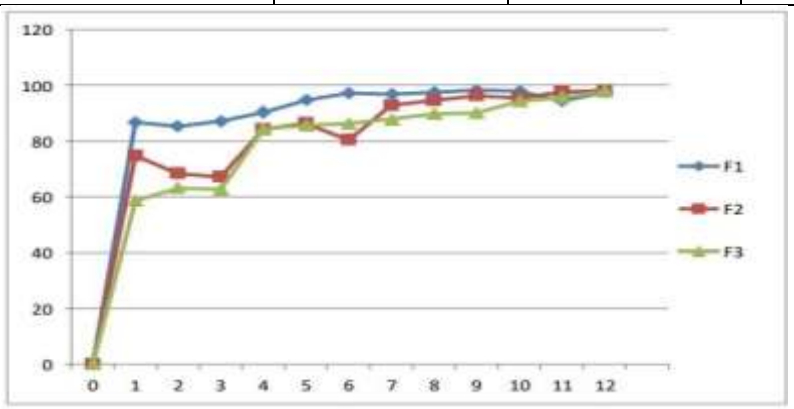


Fig: 3 Dissolution profiles of formulations F1–F3 of rosiglitazone

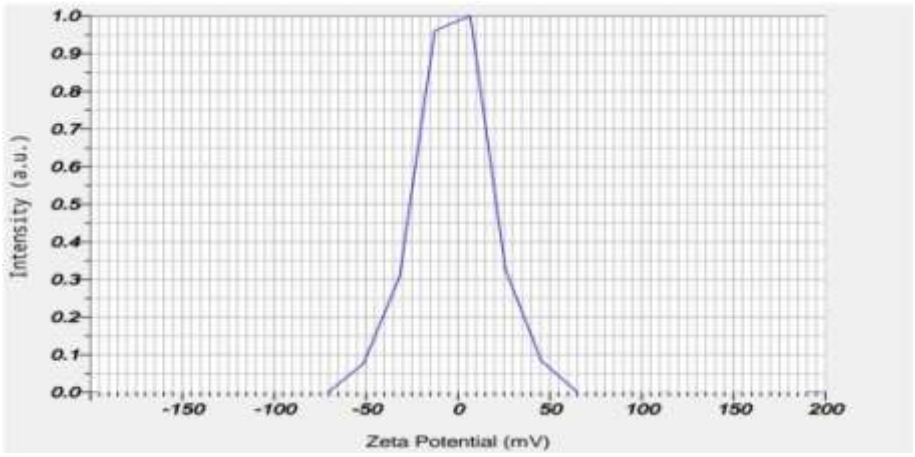


Figure 5: Zetapotential of rosiglitazone Nanosuspension

Table. 5: Zeta potential of rosiglitazone

Peak number	Zetapotential	Electrophoretic mobility
1.	-2.3mv	-0.000018cm²/vs
2.	Not obtained	Not obtained
3.	Not obtained	Not obtained

Table. 6: Particle size of rosiglitazone

Peaknumber	**s.parearatio**	**Mean**	**S.D**	**MODE**
1.	**1.00**	**79.3 nm**	**284.7 nm**	**15.9 nm**
2.	Not obtained	Not obtained	Not obtained	Not obtained
3.	Not obtained	Not obtained	Not obtained	Not obtained
Total	1.00	79.3 nm	284.7 nm	15.9 nm

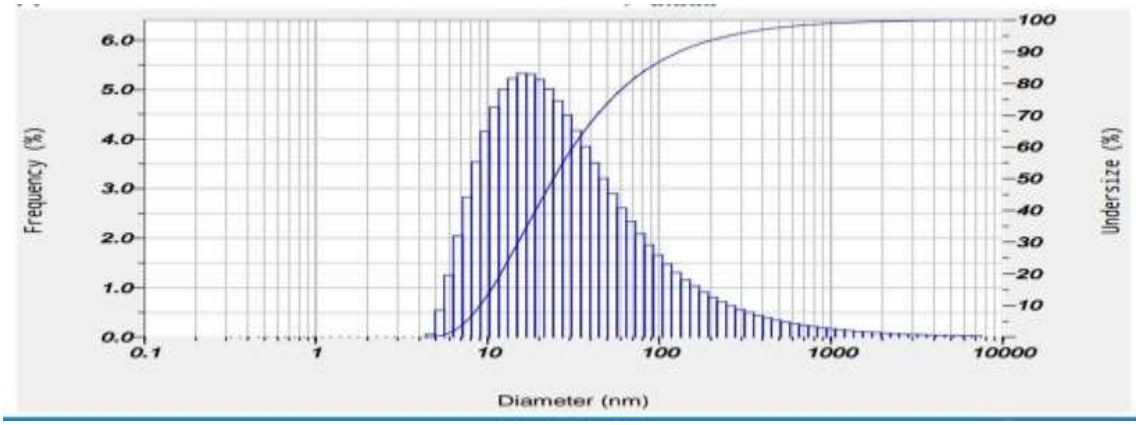


Figure. 6: Particle size Fourier Transform infrared spectroscopy

Functional groups	**Wavenumberof Rosiglitazone(Nm)**	**Wave Number of SLN's of Rosiglitazone(Nm)**
C-H	3114.83	3014.38
C=O	1689.25	1589.53
C-S	1346.07	1324.86
C-O	2491.13	2481.51

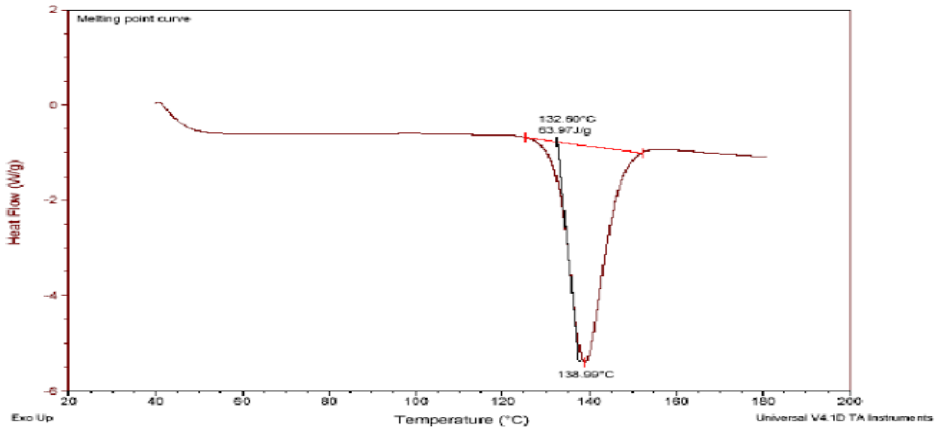


Fig 7 DSC for Rosiglitazone

IN-VITRO DISSOLUTION STUDIES

The *In vitro* dissolution study for the rosiglitazone tablets were carried out in US dissolution test apparatus using 900 ml of 0.1N HCL as dissolution medium at 50rpm and temperature 37±0.5°c. at predetermined time interval's, 5 ml of the sample was withdrawn by means of a syringe fitted with a pre filter, the volume withdrawn at each interval was replaced with same quantity of fresh dissolution medium. The resultant samples were analyzed for the presence of the drug released by measuring the absorbance at 318nm using UV visible spectrophotometer after suitable dilutions. The determinations were performed in triplicate.

DISCUSSION:

Drug content for rosiglitazone was obtained in range of 90.91±1.1to90.01±0.2. Particlesizeforrosiglitazonewasobtainedin79.3 nm. Zetapotential for rosiglitazone was obtained in -2.3mv. DSC is used to check the melting point analysis of drug and the excipient .here we mentioned that there is no interaction between the drug and excipient within the following limits from 120°cto155°c. FTIR is used to perform infrared spectroscopy analysis and there is no interaction between drug and excipient compatability studies. So there is no compatability between the pure drug and following excipient. Dissolution cumulative percentage drug release of rosiglitazone nanosuspension was 96.6 %with in15mins.

ZETAPOTENTIAL: Measurement results, Sample name: RST drug, Measurement type: zeta potential, Temperature of the holder: 25.2°C , Dispersion medium, viscosity:0.892mPa.s, Conductivity:12.852 ms/cm, Electrode voltage: 1.3v, Particle size Nanosuspensions Zetapotential (mean):- 2.3mv, Electrophoretic mobility (mean):- 0.000018cm²/vs.

CONCLUSION: Drug content for the rosiglitazone nanosuspension obtained in the range of 90.91±1.1 to 90.01±0.2, FTIR was studied and there is no incompatibility between drug and excipients, In case of DSC no change in melting point and no incompatibility between drug and excipients, Zeta potential for this nanosuspension obtained was–2.3mv,particlesize of nanosuspension was79.3nm and dissolution cumulative percentage drug release of rosiglitazone nanosuspension was 96.6% within 15mins.Finally, it can be concluded from the results of present study that nanosuspensions improved the solubility and site specificity of the drug rosiglitazone. Nanosuspensions create a new opportunity for the low soluble drugs.

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