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Research Article

Formulation and evaluation of Rosiglitazone nanosuspension

K.Hemalatha, S.Rajashekar

CMR of Pharmacy, Kandlakoya Hyderabad, Telangana

Corresponding Author: K.Hemalatha

Email: hemasweety.latha903@gmail.com

ABSTRACT

The main aim of this study is to formulate and evaluate Rosiglitazone Nano suspension. Nano suspensions are colloidal dispersion of Nano sized drug particles stabilized by surfactants. They can also be defined as a biphasic system consisting of pure drug particles dispersed in an aqueous vehicle in which the diameter of the suspended particle is less than 1micro meter in size. Rosiglitazone is an oral rapid and short –acting anti-diabetic drug from the sulfonylurea class. It is classified as a second generation sulfonylurea, which means that it undergoes enter hepatic circulation. Rosiglitazone Nano suspension was prepared by precipitation technique. After preparation of Nano suspension various characterization studies were done such as drug content, %yield, FTIR, DSC, TEM, and Invitro drug release.PVPK30,polaxomer are used as stabilizers. From the dissolution study F4 formulation which containts PVPK30 as stabilizer was considered as optimized formulation. It showed maximum drug release at 30min.FTIR and DSC studies revealed that good stability in dispersion.

INTRODUCTION

Oral drug delivery system

Oral dosage form is the physical form of a dose of a chemical compound used as a drug or medication intended for administration or consumption by oral route. Oral drug delivery is the most desirable and preferred method of administering therapeutic agents for their systemic effects. In addition, the oral medication is generally considered as the first avenue investigated in the discovery and development of new drug entities, pharmaceutical formulations, mainly because of patient acceptance and convenience in administration. Of drugs that are administered orally, solid dosage forms represent the preferred class of product.

Advantages

- Oral route of drug administration have wide acceptance up to 50-60% of total dosage forms
- Ease of administration
- Solid dosage forms represent unit dosage forms in which one usual dose of the drug has been accurately placed
- Self-medication
- Avoidance of pain
- Patient compliance

Disadvantages:

- Action of drugs is slower
- Unpalatable drugs are difficult
- May cause nausea and vomiting

Importance of drug solubility

Solubility is one of the important parameter in Biopharmaceutical classification system (BCS), and dissolution rate is the most essential factor controlling the bioavailability of drugs. Poorly water soluble drugs often require high doses in order to reach therapeutic plasma concentrations after oral administration. Low aqueous solubility is the major problem encountered with formulation development of new chemical entities as well as generic development. A compound with solubility of less than 1 part per 10,000 part of water is categorized as poorly water soluble drug (sanjeev K, et al. 2009) [1].

Approaches for enhancement of solubility and dissolution rate

Solubility behavior of a drug is one of the key determinants of its oral bioavailability. Noyes-Whitney equation provides some hints as to how the dissolution rate of even very poorly soluble compounds might be improved to minimize the limitations to oral availability.

dc/dt = AD (Cs-C)/h

Where, dC/dt = rate of dissolution

A = surface area available for dissolution

D =diffusion coefficient of the compound

Cs= solubility of the compound in the dissolution medium

C =concentration of drug in the medium at time t

h =thickness of the diffusion boundary layer adjacent to the surface of the dissolving compound.

To increase the dissolution rate from equation the following approaches are available.

1. To increases the surface area available for dissolution by
   - Decreasing the particle size of drug.
   - Optimizing the wetting characteristics of compound surface.
2. To decrease the boundary layer thickness.
3. Ensure sink condition for dissolution.
4. Improving apparent solubility of drug under physiologically relevant conditions.

Methods for enhancement of bioavailability:

(Pinnamaneni S, et al. 2002) [2]

There are numerous techniques to enhance bioavailability, which involves:

Physical modification

Physical modification often aims to increase the surface area, solubility and wet ability of the powder particles and is therefore focused on particle size reduction or generation of amorphous states. The various approaches under this method are:

i. Particle size reduction:
   - Micronization
   - Nanosuspension

ii. Modifications of the crystal habit:
   - Polymorphs.
   - Pseudo polymorphs (including solvates)

iii. Complexation / solubilization:
   - Use of cyclodextrines
   - Use of surfactants

iv. Drug dispersion in carriers:
   - Solid dispersions
   - Eutectic mixtures
   - Solid solutions

Chemical modification

Chemical modification aim at altering the drug chemically by various methods in order to produce a water soluble compound. The widely used approaches under this category are:

- Formation of soluble prodrugs
- Formation of salts of the compound
- Preparation of covalent polymer drug conjugates.

Nanosuspension

Nanosuspension is favoured for compounds that are insoluble in water (but are soluble in oil) with high log P value, high melting point and high doses. Nanosuspension technology can also be used for drugs which are insoluble in both water and organic solvents. Hydrophobic drugs such as Atorvastatin, 13 Famotidine, 14 Simvastatin, 15 Revaprazan, 16 Aceclofenac, 17 are formulated as Nanosuspension. Nanosuspensions are colloidal dispersions of nanosized drug particles stabilized by surfactants. They can also be defined as a biphasic system consisting of pure drug particles dispersed in an aqueous vehicle in which the diameter of the suspended particle is less than 1µm

in size. The Nanosuspensions can also be lyophilized or spray dried and the nanoparticles of a Nanosuspension can also be incorporated in a solid matrix.(Banavath H, et al. 2010) [3]

Nano is a Greek word, which means 'dwarf'. Nano means it is the factor of 10^{-9}or one billionth. Some comparisons of nanoscale are given below,

0.1 nm = Diameter of one Hydrogen atom.

2.5 nm = Width of a DNA molecule

1micron = 1000 nm.

1 nm = 10^{-9} m = 10^{-7} cm = 10^{-6} mm.

Micron = 10^{-6} m= 10^{-4} cm = 10^{-3} mm 4.

For a long duration of time micronization of poorly soluble drugs by colloid mills or jet mills was preferred. The overall particle size distribution ranges from 0.1µm to approximately 25µm, only negligible amount being below 1µm in the nanometer range.

Rationale for nanosuspension

- Preparing nano suspensions is preferred for the compounds that are insoluble in water (but are soluble in oil) with high log P value.
- Conventionally the drugs that are insoluble in water but soluble in oil phase system are formulated in liposome, emulsion systems but these lipidic
- Formulation approaches are not applicable to all drugs. In these cases nano suspensions are preferred.
- In case of drugs that are insoluble in both water and in organic media instead of using lipidic systems Nano suspensions are used as a formulation approach.
- Nano suspension formulation approach is most suitable for the compounds with high log P value, high melting point and high dose.(Mohanty S, et al.2010) [4]

Benefits of nanosuspension technology for poorly soluble drugs

- Reduced particle size, increased drug dissolution rate, increased rate and extent of absorption, increased bioavailability of drug, area under plasma versus time curve, onset time, peak drug level, reduced variability, reduced fed/fasted effects.
- Nanosuspensions can be used for compounds that are water insoluble but which are soluble in oil. On the other hand, Nanosuspensions can be used in contrast with lipidic systems, successfully formulate compounds that are insoluble in both water and oils.
- Nanoparticles can adhere to the gastrointestinal mucosa, prolonging the contact time of the drug and thereby enhancing its absorption.
- A pronounced advantage of Nanosuspension is that there are many administration routes for Nanosuspensions, such as oral, parenteral, pulmonary, dermal and ocular.
- Nanosuspension of nanoparticles (NPs) offers various advantages over conventional ocular dosage forms, including reduction in the amount of dose, maintenance of drug release over a prolonged period of time, reduction in systemic toxicity of drug, enhanced drug absorption due to longer residence time of nanoparticles on the corneal surface, higher drug concentrations in the infected tissue, suitability for poorly water-soluble drugs and smaller particles are better tolerated by patients than larger particles, therefore nanoparticles may represent auspicious drug carriers for ophthalmic applications.
- Nanosuspension has low incidence of side effects by the excipients.
- Nanosuspensions overcome delivery issues for the compounds by obviating the need to dissolve them, and by maintaining the drug in a preferred crystalline state of size sufficiently small for pharmaceutical acceptability.
- Increased resistance to hydrolysis and oxidation, increased physical stability to settling.
- Reduced administration volumes; essential for intramuscular, subcutaneous, ophthalmic use.
- Finally, Nanosuspensions can provide the passive targeting (.Nagare SK,et al.2012) [5]

PREPARATION OF NANO SUSPENSION

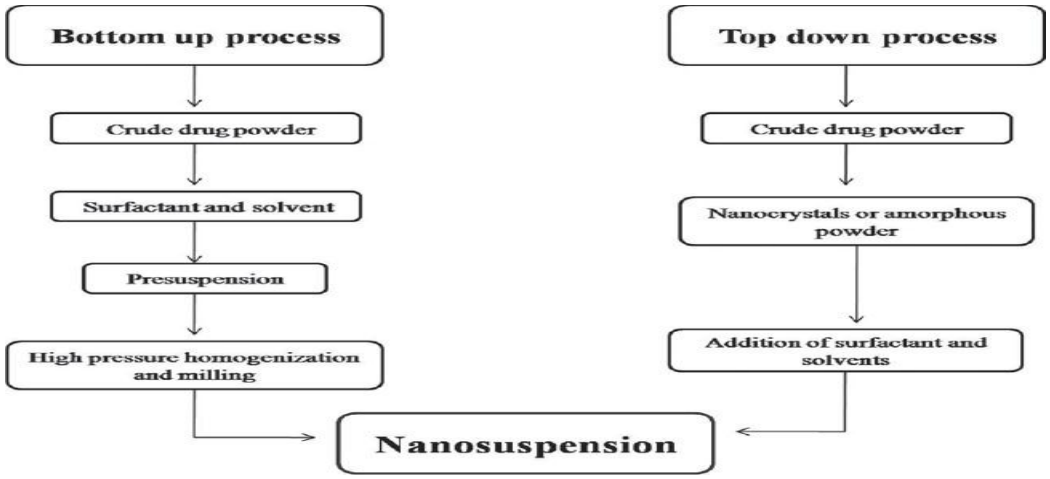


Figure no 1: Approaches for Preparation of Nano suspension

Precipitation method

Precipitation method is a general method used to prepare submicron particles of poorly soluble drugs. [Matteucci ME, et al.2007] [7] In this method, drug is dissolved in solvent and then solution is mixed with solvent to which drug is insoluble in the presence of surfactant. Rapid addition of solution to such solvent (generally water) leads to rapid supersaturation of drug in the solution, and formation of ultrafine amorphous or crystalline drug. This method involves nuclei formation and crystal growth which are mainly dependent on temperature. High nucleation rate and low crystal growth rate are primary requirements for preparing a stable suspension with minimum particle size. [Bodmeier R, et al.1998] [6]

High-pressure homogenization

This technique involve the following three steps: First, drug powders are dispersed in a stabilizer solution to form pre suspension; after that, pre suspension is homogenized by high pressure homogenizer at a low pressure sometimes for pre milling; and finally homogenized at a high pressure for 10 to 25 cycles until the nano suspension

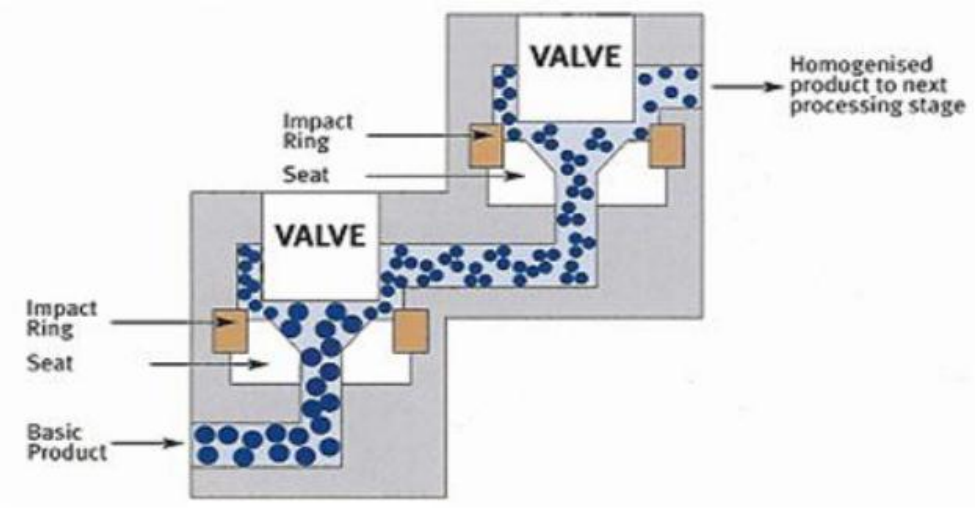


Figure no 2: High pressure homogenization

MATERIALS AND METHODS

Materials

The following materials available were used as supplied by the manufacturer without further purification or investigation

Table no 2: list of materials used in formulation

S.NO	INGREDIENTS	SPECIFICATION	RATIONALE	SOURCE
1	Rosiglitazone	USP	API	CHANDRA LABS
2	PVP	USP	polymer	STANDARD REAGENTS PVT LTD
3	UREA	USP	polymer	STANDARD REAGENTS PVT LTD
4	Polaxomer	USP	polymer	STANDARD REAGENTS PVT LTD
5	Potassium dihydrogen phosphate	USP	Buffer	STANDARD REAGENTS PVT LTD
6	HCL	USP		STANDARD REAGENTS PVT LTD
7	Sodium hydroxide pellets	USP		STANDARD REAGENTS PVT LTD

Formulation development

Preparation of Nano suspension by Microprecipitation

Nanoedge is a combination of microprecipitation techniques. The drug dissolved in suitable solvent. In another one beaker stabilizer and solvent which drug is insoluble. Drug and stabilizer different ratios were taken as shown in Table 6.

- Drug was dissolved in methanol
- Stabilizer dissolved in water

Table 3: Drug and Excipients ratio for Nanosuspesion

INGREDIENTS	F1	F2	F3	F4	F5	F6	F7	F8	F9
Drug (mg)	500	500	500	500	500	500	500	500	500
PVP K 30 (mg)	250	500	750	-	-	-	-	-	-
Polaxomer 188 (mg)	-	-	-	250	500	750	-	-	-
Urea(mg)	-	-	-	-	-	-	250	500	750
Methanol(ml)	10	10	10	10	10	10	10	10	10
Water(ml)	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

Characterisation 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 wavelength. Calculation was done using following formula:

$$\% \text{ Drug content} = \frac{\text{Obtained Amount of Drug}}{\text{Theoratical Amount of Drug}} \text{ X } 100$$

Determination of Nanosuspension particle yield

The nanosuspension production yield was calculated by gravimetry. Fixed volumes of nanoparticles suspension were centrifuged (15,000×g, 30 min, 15ºC) and sediments were dried. The percentage yield was calculated as follows:

$$\% \text{ Percentage Yield} = \frac{\text{Nano suspension Weight}}{\text{Total Solids Weight}} \text{ X } 100$$

Micromeritic properties of Nanosuspension

Bulk Density (D_b)

It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weight powder (passed through standard sieve # 20) into a measuring cylinder and initial weight was noted. This initial volume is called the bulk volume. From this the bulk density is calculated according to the formula mentioned below. It is expressed in g/ml and is given by,

$D_b = M / V_b$

Where, M is the mass of powder

V_b is the bulk volume of the powder.

Tapped Density (D_t)

It is the ratio of total mass of the powder to the tapped volume of the powder. Volume was measured by tapping the powder for 750 times and the tapped volume was noted if the difference between these two volumes is less than 2%. If it is more than 2%, tapping is continued for 1250 times and tapped volume was noted. Tapping was continued until the difference between successive volumes is less than 2 % (in a bulk density apparatus). It is expressed in g/ml and is given by,

$D_t = M / V_t$

Where,

M is the mass of powder

V_t is the tapped volume of the powder.

Angle of Repose (Ɵ)

The friction forces in a loose powder can be measured by the angle of repose (q). It is an indicative of the flow properties of the powder. It is defined as maximum angle possible between the surface of the pile of powder and the horizontal plane

$\text{Ɵ} = \tan^{-1} (h / r)$

Where,

Ɵ is the angle of repose.

h is the height in cm

r is the radius in cm

The powder mixture was allowed to flow through the funnel fixed to a stand at definite height (h). The angle of repose was then calculated by measuring the height and radius of the heap of powder formed. Care was taken to see that the powder particles slip and roll over each other through the sides of the funnel. Relationship between angle of repose and powder flow property.

Table 4: Angle of Repose as an Indication of Powder Flow Properties

Sr. No.	Angle of Repose(^{0})	Type of Flow
1	<20	Excellent
2	20-30	Good
3	30-34	Passable
4	>34	Very Poor

Carr's index (or) % compressibility

It indicates powder flow properties. It is expressed in percentage and is give by,

$$I = \frac{D_t - D_b}{D_t} \times 100$$

Where,
Dt is the tapped density of the powder and
Db is the bulk density of the powder

Table 5: Relationship between % compressibility and flow ability

s no.	% Compressibility	Flow ability
1	5-12	Excellent
2	12-16	Good
3	18-21	Fair Passable
4	23-35	Poor
5	33-38	Very Poor
6	<40	Very Very Poor

Hausners ratio

Hausner ratio is an indirect index of ease of powder flow. It is calculated by the following formula.

$$\text{Hausner ratio} = \frac{D_t}{D_b}$$

Where, D_t is the tapped density, D_b is the bulk density.
Lower Hausners ratio (<1.25) indicates better flow properties than higher ones (>1.25).

Invitro drug release studies

Dissolution test was carried out in USP rotating basket dissolution apparatus. Employing the stirrer speed at 100 rpm and Phosphate buffer pH 6.8 as dissolution medium (900ml), at fixed time intervals 5 ml of the aliquot was withdrawn and same quantity was replaced by fresh buffer. The withdrawn samples were spectrophotometrically analyzed at respective wavelength on Lab India UV3000+.

The results of *invitro* release pro files obtained for the BDDS formulations were fitted into four models of data treatment as follows:

1. Cumulative percent drug released versus time (zero order kinetic model).
2. Log cumulative percent drug remaining versus time (first- order kinetic model).

Fourier transform Infrared spectroscopy (FTIR)

Fourier transform infrared (FTIR) spectroscopy was employed to characterize further the possible interactions between the drug and the carrier in the solid state on a FTIR spectrophotometer by the ATR (attenuated total reflectance) technique. For this technique ZnSe crystal was used to know the wavelength of those drug and carriers. The spectra were scanned over a frequency range 4000-550 cm-1.

H) Differential Scanning Calorimetry (DSC)

The possibility of any interaction between the drug and the carriers during preparation of solid dispersion was assessed by carrying out thermal analysis of drug and polymer alone as well as physical mixture and solid dispersion using DSC. DSC analysis was performed using Hitachi DSC 7020, on 5 to 15 mg samples. Samples were heated in sealed aluminum pan at a rate of 10°C/min

conducted over a temperature range of 30 to 350°C under a nitrogen flow of 50 mL/min.

Scanning Electron Microscopy (SEM)

The surface morphology of the raw materials and of the ternary systems was examined by means of JSM-6400 (Jeol, Japan) scanning electron microscope. The samples were previously fixed on a brass stub using double-sided adhesive tape and were then made electrically conductive by coating with a thin layer of gold and palladium alloy (180-200 Å) using a fine coat ion sputter (JEOL, fine coat ion sputter JFC-1100). The pictures were taken at an excitation voltage of 20 kV and magnification in the range of 118 to 245X.

Zeta potential

The stability of dispersion of Nanosuspension was examined by using HORIBA SZ 100 Nano partical series. The samples were taken by Electrode cell (Carbon, 6mm) and measured at 25.1^{o}C. The picture was taken at electrode voltage 3.9V and conductivity 0.092 mS/cm.

Table no 7 : Stability behaviour by zeta potential

Zeta potential [mV]	Stability behavior of the colloid
From 0 to ±5,	Rapid coagulation or flocculation
From ±10 to ±30	Incipient instability
From ±30 to ±40	Moderate stability
From ±40 to ±60	Good stability
More than ±61	Excellent stability

Particle Size analysis

The Particle size of Nanosuspension was examined by using HORIBA SZ 100 Nano partica series.

Spray drying of Nanosuspension

Spray drying was carried out to get the dry nano size powder. An optimized batch of aqueous nanosuspension was transferred into nano size powder by a lab spray dryer LU-222 lab ultima. Spray dried powder was directly collected after the process. In this process, the spray dryer was set to the conditions given in following table.

Table no 8 : Spray dryer Parameter

Inlet Temperature	105-110^{o}C
Outlet Temperature	100^{o}C
Cool Temperature	40^{o}C
Aspirator flow rate	45 nm^{3}/hr
Feed pump flow rate	3 ml/min
Cycle time	70 min

RESULTS AND DISCUSSIONS

Melting point

Drug: Rosiglitazone

Limit: 153 - 155^{0}C

Observed: 154^{0}C

Characterization of Nanosuspension

Table no 11: Drug content and % Yield of Nanosuspension

Formulation Code	Drug content	% Yield	Solubility (mg/ml)
F1	91.75±0.46	86.62±0.48	0.78
F2	91.02±1.20	90.80±0.88	0.84
F3	93.51±0.66	93.68±0.90	0.94
F4	94.80±0.65	98.05±1.05	1.20
F5	95.83±0.82	98.67±1.17	1.26
F6	88.58±1.50	90.80±0.72	1.24
F7	89.33±1.17	89.24±1.45	0.68
F8	92.33±0.86	93.75±1.40	0.72
F9	91.16±1.32	92.46±0.70	0.85

Drug content

From the table 7.2, it was noted that increase the concentration of stabilizer obtaining more drug content. All the formulations drug content was found to be in the range of 88.50±1.50 to 95.83±0.82.

Percentage Yield

From the table 7.2, it was noted that increase the concentration of stabilizer obtaining more yield. The entire formulations percentage yield was found to be in the range of 86.62±0.48 to 98.67±1.17.

Solubility studies

From the table 7.2, it was noted that, all the formulations solubility was found to be in the range of 0.68 to 1.26 mg/ml.

Drug – Excipient compatibility studies

Fourier transform-infrared spectroscopy

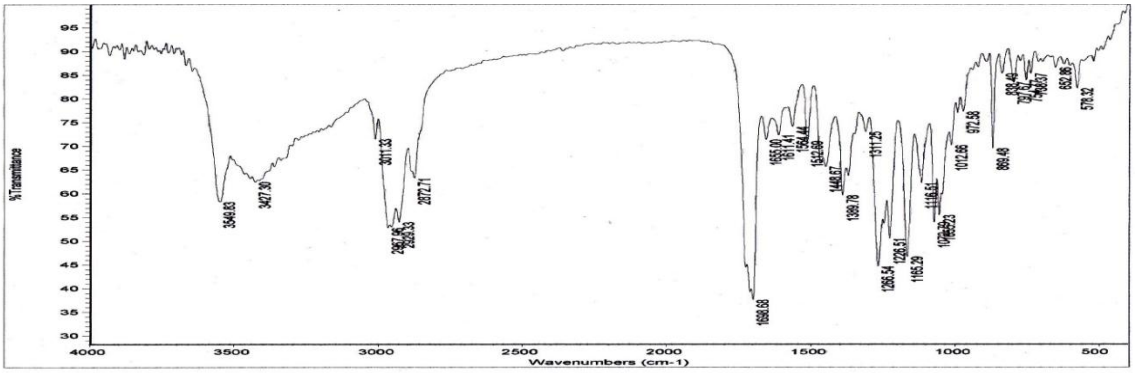


Fig No: 12 FT-IR Spectrum of Rosiglitazone pure drug.

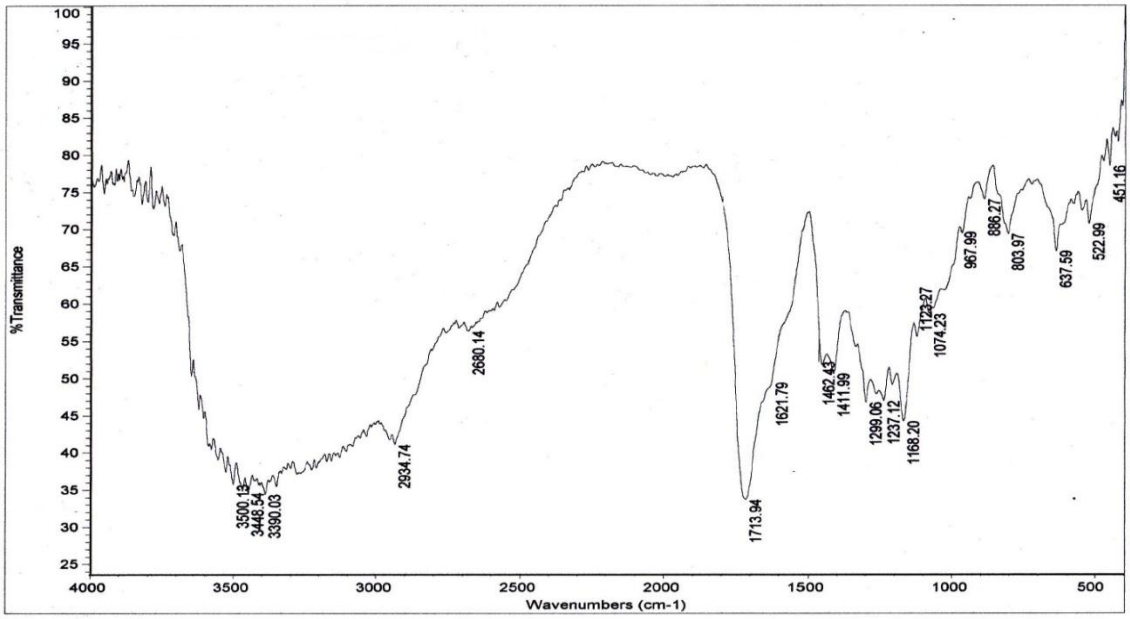


Figure no 13: FT-IR Spectrum of Optimised

DSC studies

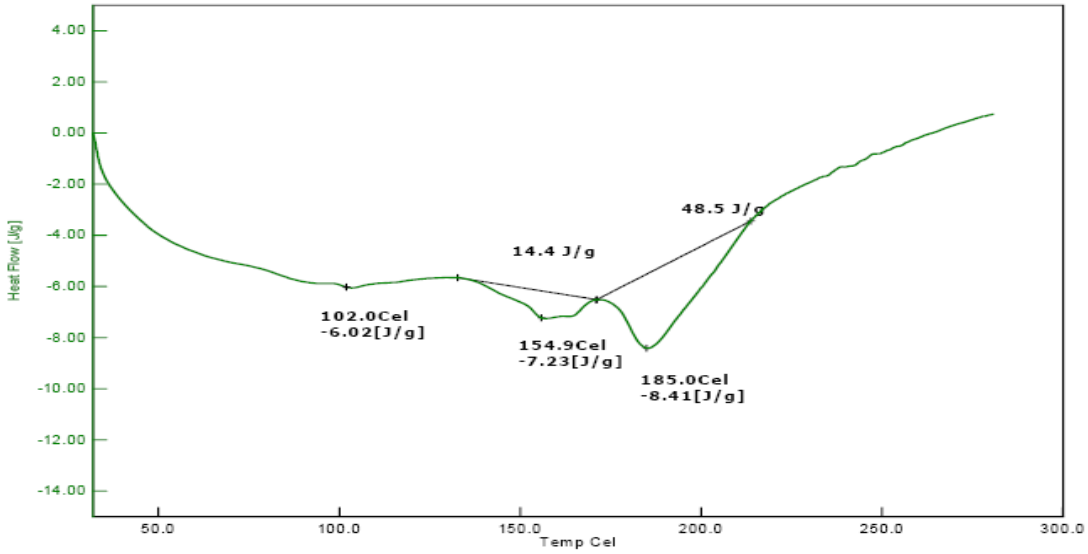


Figure no 14: DSC Spectrum of Rosiglitazone pure drug.

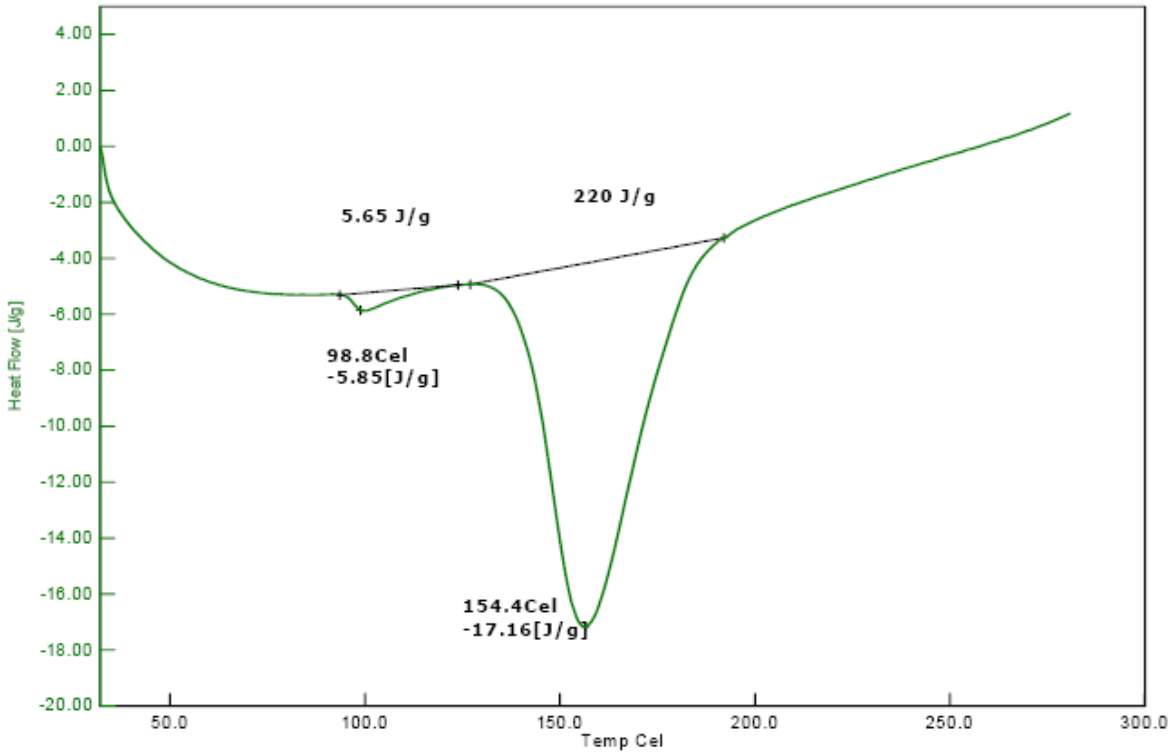


Figure no 15: DSC Spectrum of Optimised

Particle size analysis

Transmission electron microscopy

The nanosuspension appeared dark and with bright surroundings and a positive image (Fig. 2). The droplet size ranged between 30 and 50nm and was in agreement with the droplet size distribution measured using photon correlation spectroscopy.

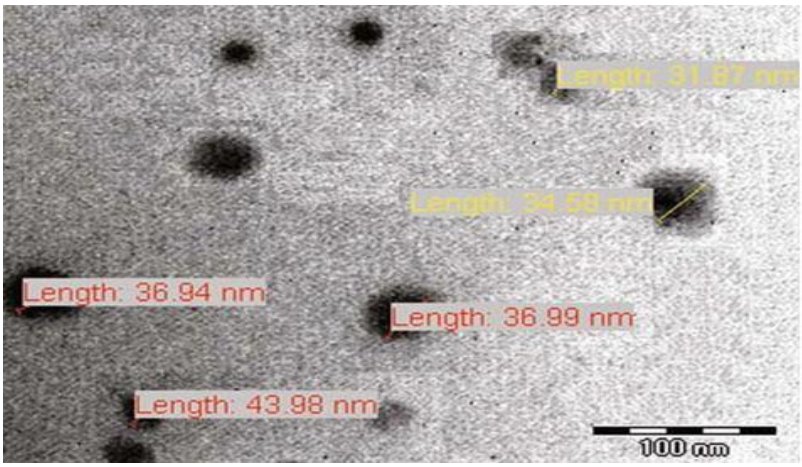
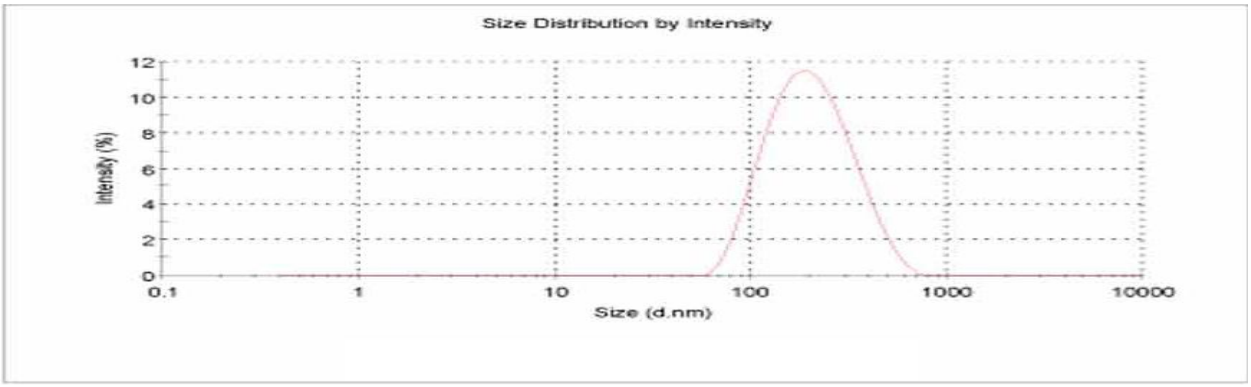


Fig 16: TEM image of Optimized formulation (F5)

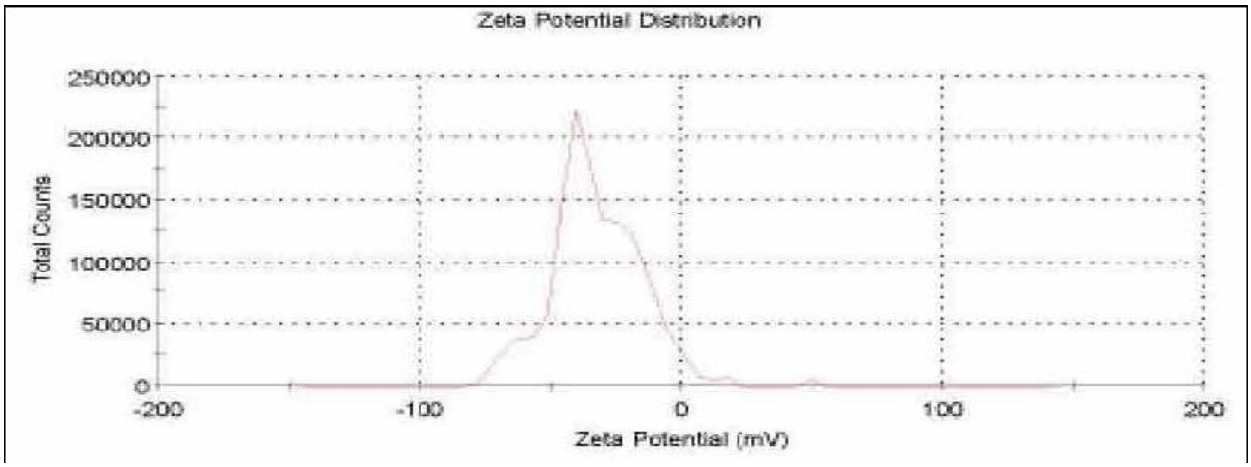
Zeta sizer

The Size of the nanosuspension droplet size was found to be 32.1nm in diameter with the help of zeta sizer with a zeta potential of -13.

Resultssize(d.nm):	%Intensity	Width(d.nm)		
Z- AVERAGE (D.NM): 32.1	Peak1: 38.4	100	106.8	
PdI: 0.168	Peak2:--	--	--	
Intercept: 0.96	Peak3:--	--	--	
Result quality:good				



Resultssize(d.nm):	%Intensity	Width(d.nm)		
Zeta Potential (mV): -13.61	Peak1: -13.1	98.5	16.4	
Conductivity (mS/cm): 1.24	Peak2:--	--	--	
Result quality: good	Peak3:--	--	--	



Accelerated stability studies

All the selected formulations were subjected to a stability testing for three months as perICH norms at a temperature of 40º ± 2º. All selected formulations were analysed for the change in appearance, pH or drug content by procedure stated earlier.

Sr.no.	Batches	Months	Appearance	pH	Drug content (%)	Dissolution at 30mins
01	F5	0	Clear	6.8	99.95	98.52
		1	Clear	6.8	98.60	98.20
		2	Clear	6.7	97.00	98.20
		3	Clear	6.6	96.20	97.62

Invitro drug release studies

Table no 12: Dissolution data of Nanosuspension

Time (Min)	F1	F2	F3	F4	F5	F6	F7	F8	F9	Pure Drug
0	0	0	0	0	0	0	0	0	0	**0**
5	12.24	13.16	8.24	15.21	20.87	10.15	10.25	12.50	12.2	2.56
10	30.72	25.52	20.79	23.33	36.8	21.87	24.23	25.23	24.11	8.95
15	57.18	49.47	35.93	45.92	51.23	45.23	48.21	48.23	37.31	18.58
20	79.68	64.16	52.29	67.29	78.23	61.23	69.23	66.23	50.33	36.54
30	84.89	73.02	72.29	79.02	98.23	71.34	76.77	78.12	63.29	48.52
45	94.68	82.70	75.41	99.11		80.23	82.28	86.32	77.60	62.35
60	97.5	93.12	85.52			99.23	89.23	92.16	94.99	78.84

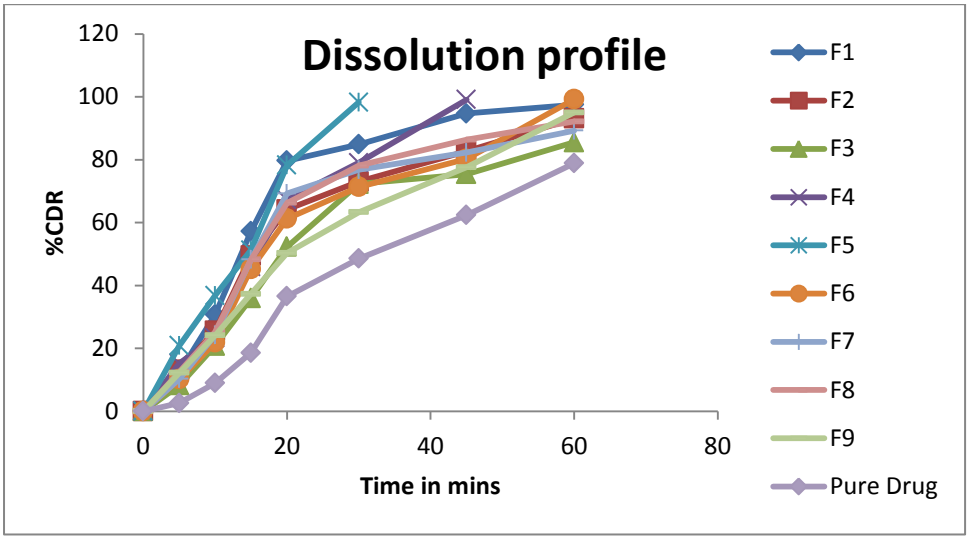


Figure no 17: invitro drug release studies for F1-F9

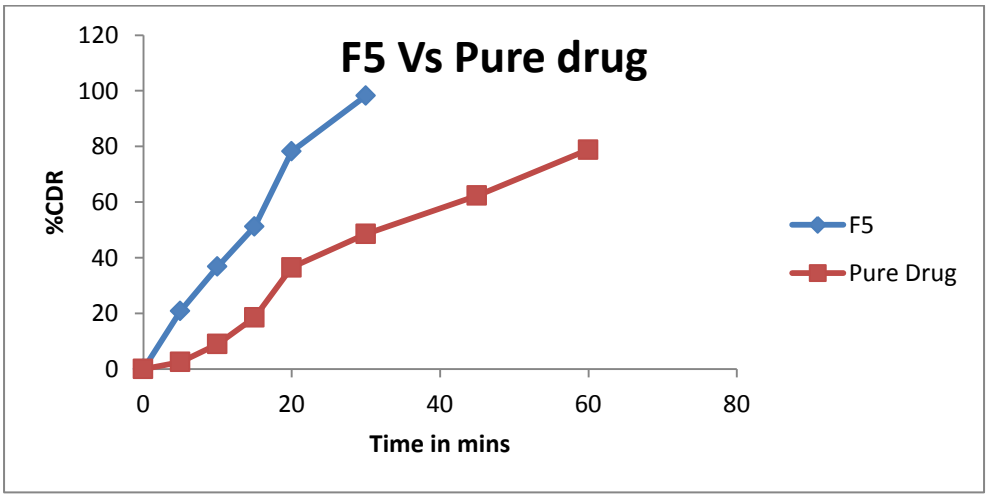


Figure no 18: Comparison of i*n vitro* drug release studies with pure drug

From the dissolution studies, it was evident that the formulations prepared with PVP K30 were shown good drug release at 60min in concentration of 250mg. Increase the concentration of stabilizer above 250mg retarded the release of drug [8].

Formulations prepared with Polaxomer 188 were shown good drug release at 30 min in the concentration of 500 mg of stabilizer. Among all formulations F5 formulation was considered as optimized formulation which was shown maximum drug release at 30 min [9]

CONCLUSION

Finally, it can be concluded from the results of present study that Nanosuspension improve the solubility, and improve the site specificity of the drug Rosiglitazone. Nanosuspension creates a new opportunity for the low soluble drugs [10-11]. The obtained nanosuspension was carried out for the following characterization:

Drug content

From the table 7 it was noted that increase the concentration of stabilizer obtaining more drug content.All formulations drug content was found to be in the range of 88.50+1.50to 95.83

Solubilitiy studies

From the table 7 it was noted that, All formulations solubility was found to be in the range of 0.68 to 1.28mg/ml.

Percentage Yield

From the table 7 it was noted that increase the concentration of stabilizer obtaining more yield. The entire formulations percentage yield was found to be in the range of 86.62+98.67.

Dissolution studies

The formulations prepared with PVPK30 were shown good drug release at 30min in concentration of 1000mg.Increase the concentration of stabilizer above 1000mg retards the release of drug.

Drug and Excipient Compatibility Studies

These studies were carried out using FTIR. There is good computability were found between drug and excipients.

TEM Studies

Optimized formulation has taken for TEM studies. It has shown that nano suspension particle size was ranged between 30 to 50 nm [12].

Zeta potential

Zeta potential studies were revealed that good stability in dispersion of optimized nano suspension [13].

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