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Research article ***Pharmaceutics***

Formulation development and invitro characterization of rutin nanoparticles

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ABSTRACT

Nanoparticles represent a promising drug delivery system of controlled and targeted drug release. They are specially designed to release the drug in the vicinity of target tissue. The aim of this study was to prepare and evaluate Carbopol p934 nanoparticles containing Rutin in different drug to polymer ratio. SEM indicated that nanoparticles have a discrete spherical structure. FT-IR studies indicated that there was no chemical interaction between drug and polymer and stability of drug. The *in vitro* release behavior from all the drug loaded batches was found to be first order release and provided sustained release over a period of 12 h. The developed formulation overcome and alleviates the drawbacks and limitations of Rutin sustained release formulations and could possibility be advantageous in terms of increased bioavailability of Saxagliptin.

Keywords: Nanoparticles, PLGA, Carbopol p934, Eudragit RL and Rutin.

INTRODUCTION

Nanotechnology has gained huge attention over time. The fundamental component of nanotechnology is the nanoparticles. Nanoparticles are particles between 1 and 100 nanometres in size and are made up of carbon, metal, metal oxides or organic matter [1]. The nanoparticles exhibit a unique physical, chemical and biological properties at nanoscale compared to their respective particles at higher scales. This phenomena is due to a relatively larger surface area to the volume, increased reactivity or stability in a chemical process, enhanced mechanical strength, etc.[2]. These properties of nanoparticles have led to its use various applications. The nanoparticles differ from various dimensions, to shapes and sizes apart from their material [3]. A nanoparticle can be either a zero dimensional where the length, breadth and height is fixed at a single point for example nano dots, one dimensional where it can possess only one parameter for example graphene, two dimensional where it has length and breadth for example carbon nanotubes or three dimensional where it has all the parameters such as length, breadth and height for example gold nanoparticles.
The nanoparticles are of different shape, size and structure. It be spherical, cylindrical, tubular, conical, hollow core, spiral, flat, etc. or irregular and differ from 1 nm to 100 nm in size. The surface can be a uniform or irregular with surface variations. Some nanoparticles are crystalline or amorphous with single or multi crystal solids either loose or agglomerated. Numerous synthesis methods are either being developed or improved to enhance the properties and reduce the production costs. Some methods are modified to achieve process specific nanoparticles to increase their optical, mechanical, physical and chemical properties. A vast development in the instrumentation has led to an improved nanoparticle characterisation and subsequent application. The nanoparticles are now used in every objects like from cooking vessel, electronics to renewable energy and aerospace industry. Nanotechnology is the key for a clean and sustainable future.[4]

Advantages of nanoparticles

Nanoparticles offer numerous advantages in drug delivery system. These advantages include, but are not limited:

- Nanoparticles have many significant advantage over conventional and traditional drug delivery system.
- Nanoparticles are control and sustain release form at the site of localization, they alter organ distribution of

drug compound. They enhance drug circulation in blood, bioavailability, therapeutic efficacy and reduce

- Nanoparticles can be administer by various routes including oral, nasal, parenteral, intra-ocular etc.
- In the tiny areas of body nanoparticles shows better drug delivery as compare to other dosage form and target to a particular cell type or receptor.
- Due to small particle size nanoparticles overcome resistance by physiological barriers in the body and easily penetrates to cell walls, blood vessels, stomach epithelium and blood–brain barrier.
- Nanoparticle enhance the aqueous solubility of poorly soluble drug, which improves bioavailability of drug.
- As a targeted drug carrier nanoparticles reduce drug toxicity and enhance efficient drug distribution.
- By using polymers drug release form nanoparticles can be modified which makes polymeric nanoparticle an ideal drug delivery system for cancer therapy, vaccines, contraceptives and antibiotics.
- Useful to diagnose various diseases
- Enhanced stability of ingredients
- Prolonged shelf life
- Used in dental surgery also as filling the tiny holes in teeth.
- Change the method of drug delivery to improve customer acceptance or reduce manufacturing costs.[5-8]

Limitations of Nanoparticles

a) Small size and large surface area can lead to particleparticle aggregation, making physical handling of nanoparticles difficult in liquid and dry forms.

b) In addition, small particles size and large surface area readily result in limited drug loading and burst release. These practical problems have to be overcome before nanoparticles can be used clinically or made commercially available.[9,10]

Classification Of Nanoparticles

The nanoparticles are generally classified into the organic, inorganic and carbon based.

Organic nanoparticles

Dendrimers, micelles, liposomes and ferritin, etc. are commonly knows the organic nanoparticles or polymers. These nanoparticles are biodegradable, non-toxic, and some particles such as micelles and liposomes has a hollow core (Figure1), also known as nanocapsules and are sensitive to thermal and electromagnetic radiation such as heat and light. These unique characteristics makes them an ideal choice for drug delivery. The drug carrying capacity, its stability and delivery systems, either entrapped drug or adsorbed drug system determines their field of applications and their efficiency apart from their normal characteristics such as the size, composition, surface morphology, etc. The organic nanoparticles are most widely used in the biomedical field for example drug delivery system as they are efficient and also can be injected on specific parts of the body that is also known as targeted drug delivery.

Inorganic nanoparticles

Inorganic nanoparticles are particles that are not made up of carbon. Metal and metal oxide based nanoparticles are generally categorised as inorganic nanoparticles

Metal based. Nanoparticles that are synthesised from metals to nanometric sizes either by destructive or constructive methods are metal based nanoparticles. Almost all the metals can be synthesised into their nanoparticles. The commonly used metals for nanoparticle synthesis are aluminium (Al), cadmium (Cd), cobalt (Co), copper (Cu), gold (Au), iron (Fe), lead (Pb), silver (Ag) and zinc (Zn). The nanoparticles have distinctive properties such sizes as low as 10 to 100nm, surface characteristics like high surface area to volume ratio, pore size, surface charge and surface charge density, crystalline and amorphous structures, shapes like spherical and cylindrical and colour, reactivity and sensitivity to environmental factors such as air, moisture, heat and sunlight etc.

Metal oxides based. The metal oxide based nanoparticles are synthesised to modify the properties of their respective metal based nanoparticles, for example nanoparticles of iron (Fe) instantly oxidises to iron oxide (Fe2O3) in the presence of oxygen at room temperature that increases its reactivity compared to iron nanoparticles. Metal oxide nanoparticles are synthesised mainly due to their increased reactivity and efficiency. The commonly synthesised are Aluminium oxide (Al2O3), Cerium oxide (CeO2), Iron oxide (Fe2O3), Magnetite (Fe3O4), Silicon dioxide (SiO2), Titanium oxide (TiO2), Zinc oxide (ZnO). These nanoparticles have possess an exceptional properties when compared to their metal counterparts.

Carbon based. The nanoparticles made completely of carbon are knows as carbon based. They can be classified into fullerenes, graphene, carbon nano tubes (CNT), carbon nanofibers and carbon black and sometimes activated carbon in nano size.

Fullerenes. Fullerenes (C60) is a carbon molecule that is spherical in shape and made up of carbon atoms held together by sp2 hybridization. About 28 to 1500 carbon atoms forms the spherical structure with diameters up to 8.2 nm for a single layer and 4 to 36 nm for multi-layered fullerenes.

Graphene. Graphene is an allotrope of carbon. Graphene is a hexagonal network of honeycomb lattice made up of carbon atoms in a two dimensional planar surface. Generally the thickness of the graphene sheet is around 1 nm.

Carbon Nano Tubes (CNT). Carbon Nano Tubes (CNT), a graphene nanofoil with a honeycomb lattice of carbon atoms is wound into hollow cylinders to form nanotubes of diameters as low as 0.7 nm for a single layered and 100 nm for multi-layered CNT and length varying from a few micrometres to several millimetres. The ends can either be hollow or closed by a half fullerene molecule.

Carbon Nanofiber. The same graphene nanofoils are used to produce carbon nanofiber as CNT but wound into a cone or cup shape instead of a regular cylindrical tubes.

Carbon black. An amorphous material made up of carbon, generally spherical in shape with diameters from 20 to 70 nm. The interaction between the particles is so high that they bound in aggregates and around 500 nm agglomerates are formed.[11-14]

MATERIALS

Rutin Provided by SURA LABS, Dilsukhnagar, Hyderabad. PLGA from Lactel, Durect corporation Birmingham Division. Carbopol p934 from Eastman company, UK. Eudragit RL from SRL,Span 60 (mL) from Himedia, Distilled water (ml) from Rankem,

Dichloromethane (ml) from Rankem, Methanol from Rankem.

METHODOLOGY

Analytical method Development

Determination of absorption maxima

Absorption maxima are the wavelength at which maximum absorption takes place. For accurate analytical work, it is important to determine the absorption maxima of the substance under study.

Procedure

For the preparation of calibration curve stock solution was prepared by dissolving 100 mg of accurately weighed drug in 100ml of Methanol (1mg/ml). Further 1ml of the stock solution was pipette out into a 100 ml volumetric flask and volume was made up with phosphate buffer (pH 6.8). From this stock solution pipette out 1ml and dilute to 10 ml with phosphate buffer and subject for UV scanning in the range of 200-400 nm using double beam UV spectrophotometer. The absorption maxima were obtained at 367 nm with a characteristic peak.

Preparation of calibration curve

It is soluble in Methanol; hence Methanol was used for solubilizing the drug. Stock solution (1 mg/mL) of Rutin was prepared in Methanol and subsequent working standards (2, 4, 6, 8 and 10 µg/mL) were prepared by dilution with phosphate buffer of pH-6.8. These solutions were used for the estimation Rutin by UV method. The whole procedure was repeated three times and average peak area was calculated. Calibration plot was drawn between concentrations and peak area. Calibration equation and R^2 value are reported.

Preparation of nanoparticles

Preparation of Rutin loaded nanoparticles

Rutin loaded Nanoparticle was prepared by previously reported emulsification sonication method. Rutin was dissolved in organic solvent (20 ml, methanol and DCM 30ml). Polymers in different concentrations were dissolved in water. The organic phase was added drop wise into the polymeric solution for emulsification. Then the dispersion was sonicated (20 min) with the application of ultra-probe sonication (60 W/cm^3, Hielscher, Ultra-sonics, Germany). The formulation was stirred at 1500 rpm for 6 h using a magnetic stirrer to evaporate the organic solvent. The prepared NPs were centrifuged at 15,000 rpm for 20 min at 25 °C (Remi, Mumbai, India). NPs were separated and lyophilized using cryoprotectant (Mannitol 0.2%) and stored for further evaluation.

Table1: Composition of nanoparticles formulations (F1 to F9)

Excipients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Rutin	450	450	450	450	450	450	450	450	450
PLGA	200	400	600	-	-	-	-	-	-
Carbopol p934	-	-	-	200	400	600	-	-	-
Eudragit RL	-	-	-	-	-	-	200	400	600
Span 60 (mL)	2	4	6	2	4	6	2	4	6
Distilled water (ml)	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Dichloromethane (ml)	30	30	30	30	30	30	30	30	30
Methanol	20	20	20	20	20	20	20	20	20

All the quantities were in mg

RESULTS AND DISCUSSION

Preparation of Standard Graph

a. Determination of absorption maxima

The standard curve is based on the spectrophotometry. The maximum absorption was observed at 367 nm.

b. Calibration curve

Graphs of Rutin was taken in 6.8 Phosphate buffer

Table 2: Calibration curve data for Rutin at 367 nm

Concentrations [µg/mL]	Absorbance
0	0
2	0.128
4	0.234
6	0.347
8	0.448
10	0.573

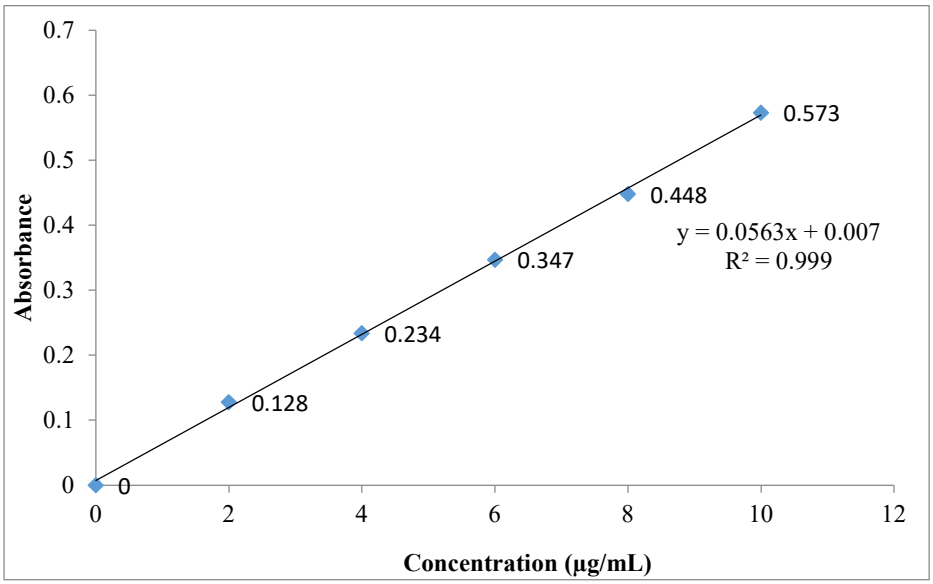

Fig 1: Standard curve of Ciprofloxacin HCL

Evaluation of rutinloaded nanoparticles

Table 3: Evaluation of Nanoparticles

Batch No	Mean Particle size(nm)	%Yield	Drug Content	Drug encapsulation efficiency	PDI	Zeta Potential (mV)
F1	286.12 ± 18	65.92	94.27	65.23	0.668	-27.25 ± 1.2
F2	292.22 ± 19	74.09	96.16	73.41	1.268	-29.05 ± 1.5
F3	305.19 ± 16	78.25	97.06	81.06	1.153	-31.92 ± 1.0
F4	267.22 ± 20	72.17	92.54	77.91	0.868	-28.05 ± 2.2
F5	278.56± 18	80.61	95.82	83.26	0.577	-29.29± 1.4
F6	281.72± 23	87.97	97.84	88.28	0.309	-33.56± 2.9
F7	351.72± 23	75.39	94.14	64.79	0.498	-26.95± 2.7
F8	368.32± 42	79.24	95.14	72.30	0.385	-27.63± 2.5
F9	371.52± 32	84.73	96.82	77.98	0.325	-28.05± 2.1

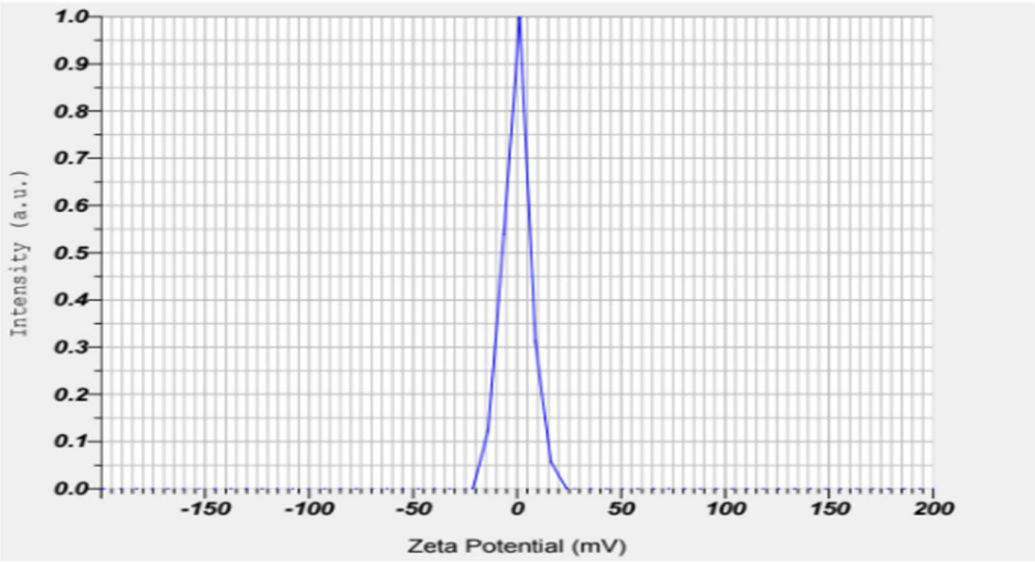

Fig 2: Zeta Potential of F6 Formulation

In Vitro Drug Release Studies

Table 4: *In vitro* Drug release studies of Rutin

TIME (hr)	CUMULATIVE PERCENT OF DRUG RELEASED								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	29.25	26.69	20.41	26.06	31.85	23.08	18.92	17.92	14.01
2	35.90	32.09	27.69	42.12	36.76	30.56	32.36	22.65	20.08
3	48.10	44.16	38.34	49.56	40.50	36.12	40.61	33.89	31.51
4	57.06	55.65	44.61	61.93	47.11	58.14	51.53	44.32	43.98
5	68.79	65.19	50.08	67.76	51.78	69.05	60.88	52.87	50.31
6	79.91	72.67	68.39	79.88	66.89	76.39	73.46	65.90	62.57
7	86.26	80.76	74.56	88.14	73.43	84.22	83.87	73.36	67.04
8	97.34	86.54	81.98	97.06	87.14	92.81	87.29	79.77	75.91
10	98.11	91.34	90.18		92.09	95.35	96.14	90.53	83.09
12		95.54	94.14			99.19		96.91	94.91

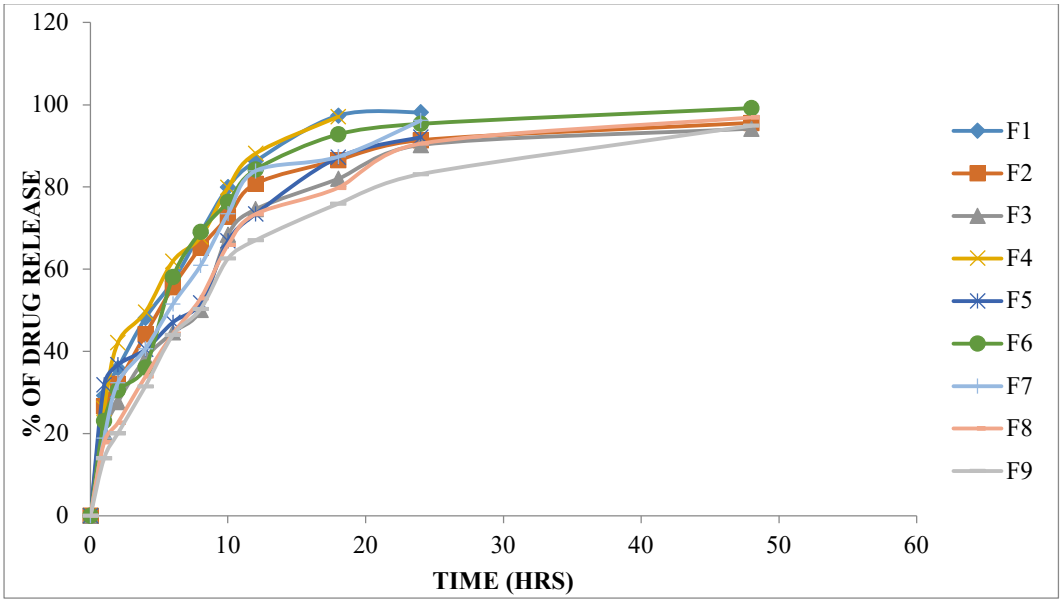

Fig 3: Dissolution study of Rutin Nanoparticles

Table 5: Release Kinetics

CUMULATIVE (%) RELEASE Q	TIME (T)	ROOT (T)	LOG(%) RELEASE	LOG (T)	LOG (%) REMAIN	RELEASE RATE (CUMULATIVE % RELEASE / t)	1/CUM% RELEASE	PEPPAS log Q/100	% Drug Remaining	Q01/3	Qt1/3	Q01/3-Qt1/3
0	0	0			2.000				100	4.642	4.642	0.000
23.08	1	1.000	1.363	0.000	1.886	23.080	0.0433	-0.637	76.92	4.642	4.253	0.389
30.56	2	1.414	1.485	0.301	1.842	15.280	0.0327	-0.515	69.44	4.642	4.110	0.531
36.12	3	1.732	1.558	0.477	1.805	12.040	0.0277	-0.442	63.88	4.642	3.997	0.644
58.14	4	2.000	1.764	0.602	1.622	14.535	0.0172	-0.236	41.86	4.642	3.472	1.169
69.05	5	2.236	1.839	0.699	1.491	13.810	0.0145	-0.161	30.95	4.642	3.140	1.502
76.39	6	2.449	1.883	0.778	1.373	12.732	0.0131	-0.117	23.61	4.642	2.869	1.773

84.22	7	2.646	1.925	0.845	1.198	12.031	0.0119	-0.075	15.78	4.642	2.508	2.133
92.81	8	2.828	1.968	0.903	0.857	11.601	0.0108	-0.032	7.19	4.642	1.930	2.712
95.35	10	3.162	1.979	1.000	0.667	9.535	0.0105	-0.021	4.65	4.642	1.669	2.972
99.19	12	3.464	1.996	1.079	-0.092	8.266	0.0101	-0.004	0.81	4.642	0.932	3.709

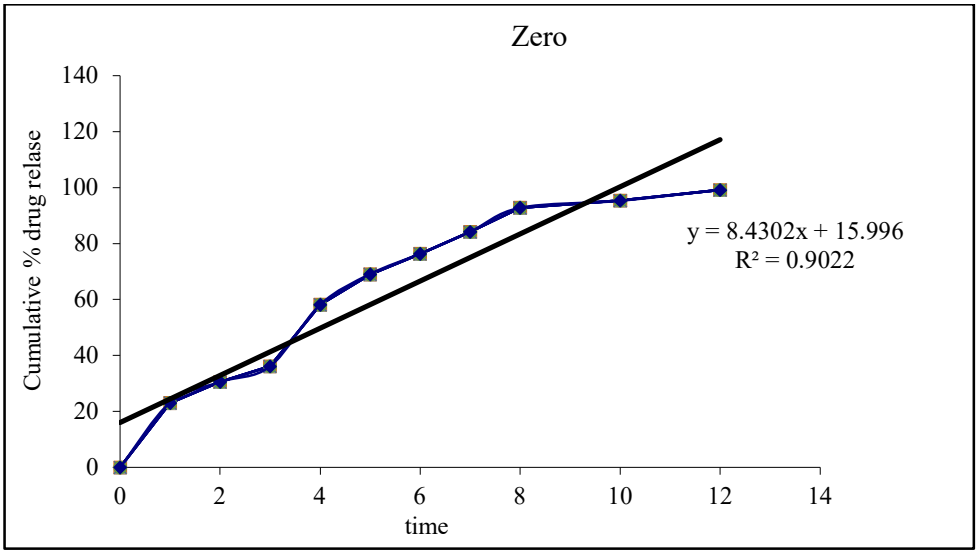

Fig 4: Zero order release kinetics

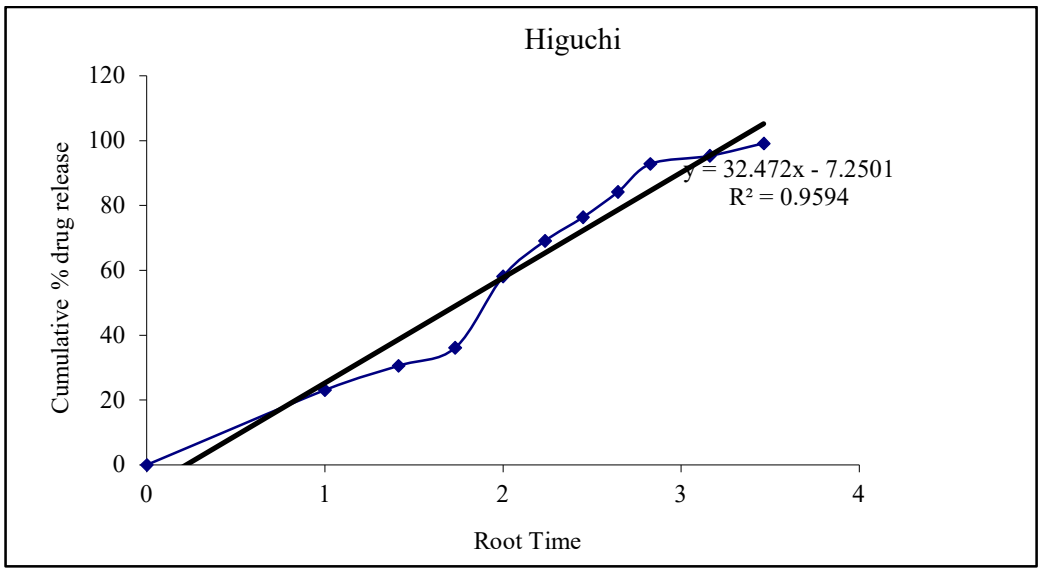

Fig 5: Higuchi release kinetics

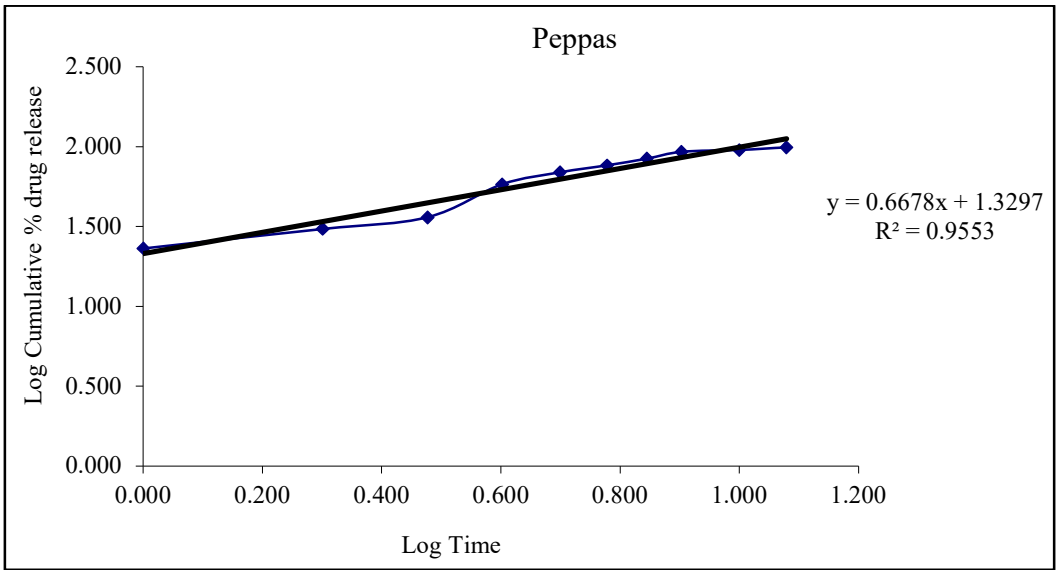

Fig 6: Kors mayer peppas release kinetics

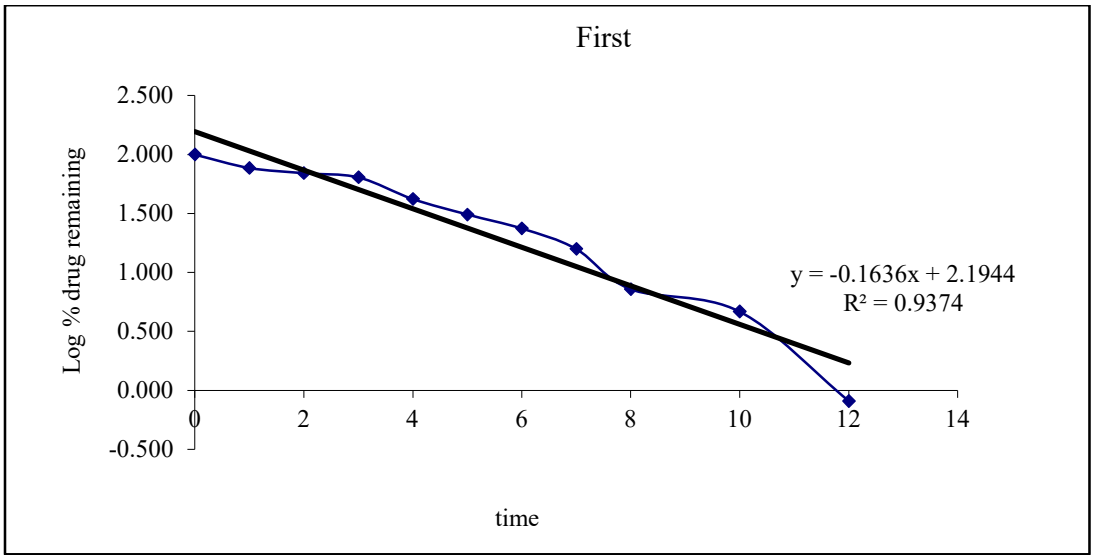

Fig 7: First order release kinetics

Drug – Excipient compatibility studies

Fourier Transform-Infrared Spectroscopy

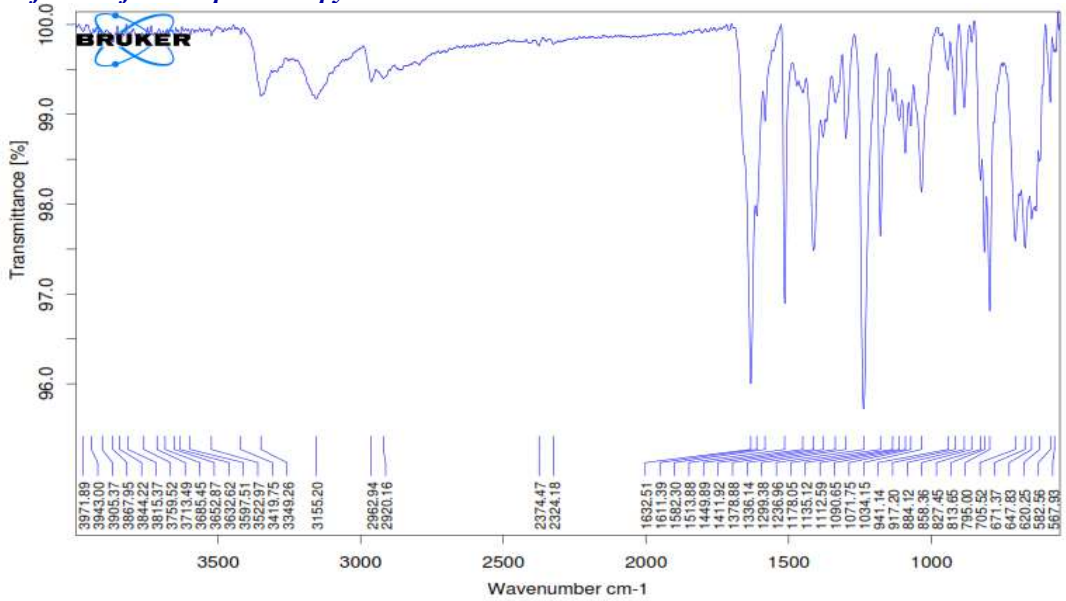

Fig 8: FTIR Spectrum of pure drug

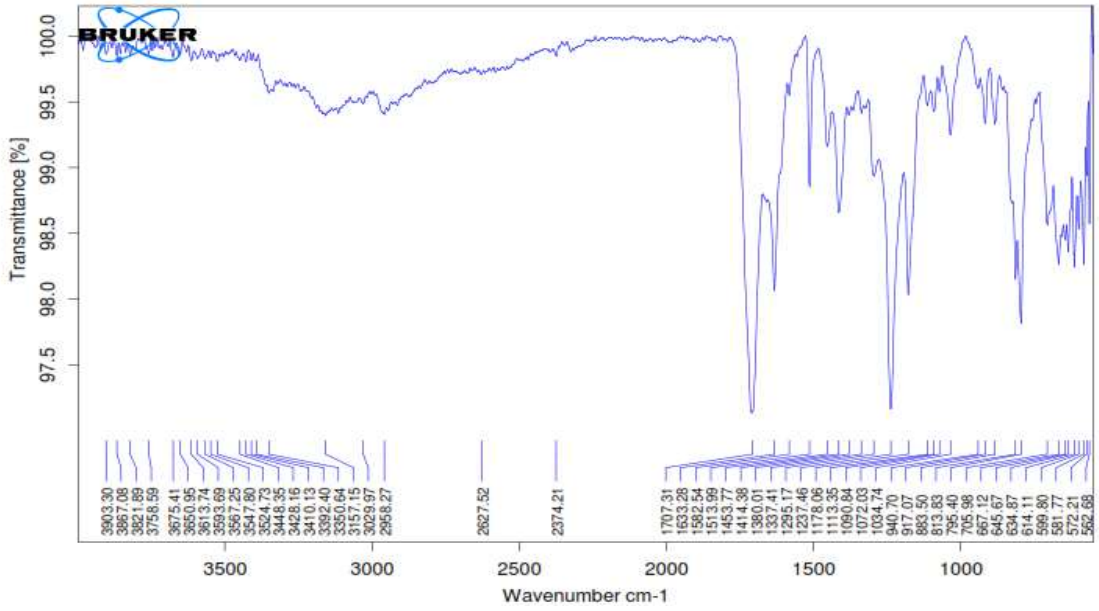

Fig 9: FTIR Spectrum of optimised formulation

CONCLUSION

Nanoparticles have a special place in nanoscience and nanotechnology, not only because of their particular properties resulting from their reduced dimensions, but also because they are promising building blocks for more complex nanostructures.

In our current work, we have prepared Rutin nanoparticles. Emulsification sonication method is a simple, fast and reproducible method which is widely used for the preparation of both nanospheres and nanocapsules and its superior advantage is obtaining small particles size and narrow size distribution. The optimized Rutin loaded Carbopol p934 nanoparticles formulations (F6) were in nano size range (281.72±23nm) with high drug release (99.19%) adequate encapsulating efficiency exhibiting a homogenous, stable and effective.

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