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Preparation and Evaluation of Pirfenidone Loaded Microspheres

Dr. K. Mangulal[*1], Pankarla Divya[1], Pavani[1], Pawar Varsha[1], Pedda Kurva Vasantha[1], Pinnamwar Vaishnavi[1], Dr. Kantlam[1]

[1]*Department of Pharmaceutics, Brilliant Grammar School Educational Society's Group of Institutions (Engineering And Pharmacy), Abdullapur (V), Abdullapurmet (M), Rangareddy (D), Hyderabad*

*Corresponding Author: **Dr. K. Mangulal***
Email: mangupharmacist@gmail.com.

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Abstract: The present study was aimed at the preparation and evaluation of Pirfenidone-loaded microspheres for sustained drug delivery. Pirfenidone is an antifibrotic agent used in the treatment of idiopathic pulmonary fibrosis, and the development of a controlled-release formulation can improve therapeutic efficacy and patient compliance. Microspheres were prepared using an appropriate microencapsulation technique and evaluated for their physicochemical characteristics and drug release behaviour.

A series of formulations (F1–F9) were developed by varying the polymer concentrations. The prepared microspheres were subjected to pre-compression and post-compression evaluation tests, including bulk density, tapped density, angle of repose, Carr's index, Hausner's ratio, particle size analysis, drug content, entrapment efficiency, and in vitro drug release studies. The results revealed that all pre-compression and post-compression parameters were within the acceptable limits prescribed by the Indian Pharmacopoeia (IP), indicating good flow properties, uniformity, and overall quality of the formulations.

Among all the formulations, F5 was identified as the optimized formulation based on its superior performance in drug release studies. The optimized formulation exhibited a cumulative drug release of 99.72% over a period of 12 hours, which was higher than that of the other formulations and demonstrated an effective sustained-release profile.

Keywords: Pirfenidone-loaded microspheres

1. INTRODUCTION

Oral route drug administration is by far the most preferable route for taking medications. However, their short circulating half life and restricted absorption via a defined segment of intestine limits the therapeutic potential of many drugs. Such a pharmacokinetic limitation leads in many cases to frequent dosing of medication to achieve therapeutic effect. Rational approach to enhance bioavailability aSnd improve pharmacokinetic and pharmacodynamics profile is to release the drug in a controlled manner and site specific manner. Microspheres are small spherical particles, with diameters 1 µm to 1000 µm. They are spherical free flowing particles consisting of proteins or synthetic polymers which are biodegradable in nature. There are two types of microspheres; microcapsules and micromatrices, which are described as, Microcapsules are those in which entrapped substance is distinctly surrounded by distinct capsule wall. and micromatrices in which entrapped substance is dispersed throughout the matrix. Microspheres are sometimes referred to as microparticles. Microspheres can be manufactured from various natural and synthetic materials. Microsphere play an important role to improve bioavailability of conventional drugs and minimizing side effects. Ideal characteristics of microspheres: [1,2,3,4,5]

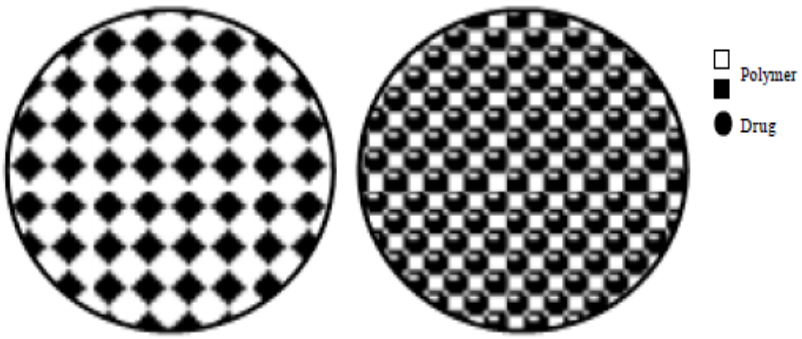


Fig 1.1: Structure of Microspheres

Ideal characteristics of microspheres: [6]

- The ability to incorporate reasonably high concentrations of the drug.
- Stability of the preparation after synthesis with clinically acceptable shelf life.
- Controlled particle size and dispersability in aqueous vehicles for injection.
- Release of active reagent with a good control over a wide time scale.
- Biocompatibility with a controllable biodegradability.
- Susceptibility to chemical modification.

Advantages of microspheres:

1. Particle size reduction for enhancing solubility of the poorly soluble drug.
2. provide constant and prolonged therapeutic effect.
3. provide constant drug concentration in blood there by increasing patent compliance,
4. Decrease dose and toxicity.
5. Protect the drug from enzymatic and photolytic cleavage hence found to be best for drug delivery of protein.
6. Reduce the dosing frequency and thereby improve the patient compliance
7. Better drug utilization will improve the bioavailability and reduce the incidence or intensity of adverse effects.
8. Microsphere morphology allows a controllable variability in degradation and drug release.
9. Convert liquid to solid form & to mask the bitter taste.
10. Protects the GIT from irritant effects of the drug.
11. Biodegradable microspheres have the advantage over large polymer implants in that they do not require surgical procedures for implantation and removal.
12. Controlled release delivery biodegradable microspheres are used to control drug release rates thereby decreasing toxic side effects, and eliminating the inconvenience of repeated injections.

Limitation:

Some of the disadvantages were found to be as follows

1. The costs of the materials and processing of the controlled release preparation, are substantially higher than those of standard formulations.
2. The fate of polymer matrix and its effect on the environment.
3. The fate of polymer additives such as plasticizers, stabilizers, antioxidants and fillers.
4. Reproducibility is less.
5. Process conditions like change in temperature, pH, solvent addition, and evaporation/agitation may influence the stability of core particles to be encapsulated.
6. The environmental impact of the degradation products of the polymer matrix produced in response to heat, hydrolysis, oxidation, solar radiation or biological agents.

Types of microspheres:

1. Bioadhesive microspheres
2. Magnetic microspheres
3. Floating microspheres
4. Radioactive microspheres
5. Polymeric microspheres

i) Biodegradable polymeric microspheres
ii) Synthetic polymeric microspheres

METHODOLOGY

PREPARATION OF 0.1N HCl (pH 1.2):

Take 8.5 ml of HCl in a 1000ml volumetric flask and make up the volume with distilled water

Preparation of Standard Calibration Curve of Pirfenidone:

- 10 mg of Pirfenidone was accurately weighed and dissolved in 10ml of methanol (Stock Solution –I) to get a concentration of 1000 µg/ml.
- From the stock solution-I, 1ml of aliquots was taken and suitably diluted with 0.1N HCl (Stock Solution-II) to get concentrations of 100µg/ml.
- From the stock solution-II, aliquots were taken and suitably diluted with 0.1N HCl (pH 1.2) to get concentrations in the range of 2 to 10µg/ml. The absorbance of these samples was analyzed by using UV-Visible Spectrophotometer at 312nm against reference solution 0.1N HCl (pH 1.2). The procedure repeated to pH 6.8 phosphate buffer and pH 7.4 phosphate buffer.

METHOD OF PREPARATION

Pirfenidone microspheres were prepared using Eudragit, Carbopol 934p and HPMC K4M and distilled water as continuous phase by solvent evaporation technique. Initially dichloromethane (DCM) and methanol was mixed uniformly at room temperature, then Eudragit, Carbopol 934p and HPMC K4M in various proportions was dissolved in the above solution. To this mixture, a drug solution corresponding was added and mixed thoroughly and injected drop wise in to the continuous phase consisting of 100mL of 0.2% (w/v) SLS (Sodium Lauryl sulphate) at 250 rpm. The microspheres obtained was washed for 2-3 times with distilled water and dried at room temperature. Different concentrations and ratios of polymers used in the formulation of microspheres are mentioned in Table.

Table 7.1: Formulation chart

INGREDIENTS (MG)	FORMULATIONS								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Pirfenidone	300	300	300	300	300	300	300	300	300
Eudragit	0.25 %	0.5 %	0.75 %	-	-	-	-	-	-
Carbopol 934p	-	-	-	0.25 %	0.5 %	0.75 %	-	-	-
HPMC K4M	-	-	-	-	-	-	0.25 %	0.5 %	0.75 %
Dichloromethane (mL)	20	20	20	20	20	20	20	20	20
Methanol (mL)	30	30	30	30	30	30	30	30	30
Sodium lauryl sulphate (mg)	25	25	25	25	25	25	25	25	25

CHARACTERIZATION OF MICROSPHERES:

Micromeritic properties

The microspheres were characterized by their micromeritic properties such as Particle size, Bulk density, Tapped density, Compressibility index, Hausner’s ratio and Angle of repose.

Bulk density

$$\text{Bulk density} = \frac{\text{Mass of microspheres}}{\text{Bulk volume}}$$

In this method floating microspheres are transferred to a measuring cylinder and is tapped manually till a constant volume is obtained. This volume is bulk volume and it includes true volume of the powder and the void space among the microspheres.

Tapped density

In this method floating microspheres were transferred to a measuring cylinder & tapped for 100 times. After tapping volume of microspheres was visually examined. The ratio of mass of microspheres to volume of microspheres after tapping gives tapped density floating microspheres.

Percent Compressibility index was determined by using the formula,

Carr's Index = (tapped density – bulk density) x 100 / tapped density

Hausner's ratio

Hausner's ratio of microspheres was determined by comparing tapped density to bulk density using the equation

Hausner ratio = tapped density / bulk density

Angle of repose

Angle of repose (θ) of the microspheres, which measures the resistance to particle flow, was determined by a fixed funnel method4. The height of the funnel was adjusted in such a way that the tip of the funnel just touches the heap of the blends. Accurately weighed microspheres were allowed to pass through the funnel freely on to the surface. The height and radius of the powder cone was measured and angle of repose was calculated using the following equation.

$$\theta = \tan^{-1} h / r$$

Here,

θ - Angle of repose

h - Height of granules above the flat surface

r - Radius of the circle formed by the granule heap.

Percentage yield

The percentage of production yield was calculated from the weight of dried microsphere-res recovered from each batch and the sum of the initial weight of starting materials. The percentage yield was calculated using the following formula:

$$\% \text{ Yield} = \frac{\text{Practical mass (Microspheres)}}{\text{Theoretical mass (Polymer + Drug)}} \times 100$$

Drug entrapment efficiency:

Weighed amount of microspheres (100 mg) with phosphate buffer pH 7.4 (10 ml) was added in a vial. The solution was stirred vigorously for 24 hours with mechanical stirrer. Supernatant was collected by centrifugation and drug content in supernatant was determined by using UV spectrophotometer at wavelength 312nm. The amount of drug entrapped in the microspheres was calculated by the following formula,

$$\% \text{ Drug Entrapment Efficiency} = \frac{\text{Experimental Drug Content}}{\text{Theoretical Drug Content}} \times 100$$

Swelling study:

Swelling ratio of different dried microspheres were determined gravimetrically in simulated gastric fluid pH 1.2. The microspheres were removed periodically from the solution, blotted to remove excess surface liquid and weighed on balance. Swelling ratio (% w/v) was determined from the following relationship:

$$(Wt – W0)$$

$$\text{Swelling ratio} = \frac{\text{---------- } \times 100}{(W0)}$$

Where W0 &Wt are initial weight and Final weight of microspheres respectively

In vitro drug release study:

The dissolution studies were performed in a fully calibrated eight station dissolution test apparatus (37 ± 0.5^0C, 50 rpm) using the USP type – I rotating basket method in simulated gastric fluid pH 1.2 (900ml) for 2 hours then replace the media with pH 6.8 phosphate buffer for 3 hours, then replace the media with pH 7.4 Phosphate buffer. A quantity of accurately weighed microspheres equivalent to 100mg Pirfenidone each formulation was employed in all dissolution studies. Aliquots of sample were withdrawn at predetermined intervals of time and analyzed for drug release by measuring the absorbance at 312nm. At the same time the volume withdrawn at each time intervals were replenished immediately with the same volume of fresh pre-warmed simulated gastric fluid pH 1.2 maintaining sink conditions throughout the experiment.

In Vitro drug release kinetics

The release data obtained was fitted into various mathematical models. The parameters 'n' and time component 'k', the release rate constant and 'R', the regression coefficient was determined by Korsmeyer-Peppas equation to understand the release mechanism.

To examine the release mechanism of Pirfenidone from the microspheres, the release data was fitted into Peppa's equation,

$$Mt / M\infty = Ktn$$

Where, Mt / M∞ is the fractional release of drug, 't' denotes the release time, 'K' repr-esents a constant incorporating structural and geometrical characteristics of the device, 'n' is the diffusional exponent and characterize the type of release mechanism during the release process.

Table 7.2: *In-Vitro* drug release kinetics

Release exponent (n)	Drug transport mechanism	Rate as a function of time
0.5	Fickian diffusion	$t^{-0.5}$
0.5<n<1.0	Anomalous transport or non-Fickian	t^{n-1}
1.0	Case-II transport	Zero-order release
Higher than 1.0	Super Case-II transport	t^{n-1}

If n < 0.5, the polymer relaxation does not affect the molecular transport, hence diffus-ion is Fickian.
If n > 0.5, the solid transport will be non-fickian and will be relaxation controlled.
Other equations to study the drug release kinetics from dosage forms

a. Zero Order

% R = kt

This model represents an ideal release in order to achieve prolonged pharmacological action. This is applicable to dosage forms like transdermal systems, coated forms, osmotic systems, as well as Matrix tablets containing low soluble drugs.

b. First Order

Log (fraction unreleased) = kt/2.303

The modelis applicableto hydrolysiskinetics andto studythe release profiles of pharmaceutical dosageforms such as those containing water soluble drugs in porous matrices.

c. Matrix (Higuchi Matrix)

% R = kt 0.5

This model is applicable to systems with drug dispersed in uniform swellable polymer matrix as in case of matrix tablets with water soluble drug.

d. Peppas Korsmeyer Equation

% R = kt n

log % R = logk + nlogt

This model is widely used when release mechanism is well known or when more than one type of release phenomenon could be involved. The 'n' values could be used to characterize different release mechanisms as.

Fourier Transform Infrared (FTIR) spectroscopy:

The physical properties of the physical mixture were compared with those of plain drug. Samples were mixed thoroughly with 100mg potassium bromide IR powder and compacted under vacuum at a pressure of about 12 psi for 3 minutes. The resultant disc was mounted in a suitable holder in Agilent spectrophotometer and the IR spectrum was recorded from 4000 cm-1 to 500 cm-1. The resultant spectrum was compared for any spectrum changes.

SEM (Scanning Electron Microscope) studies:

The surface morphology of the layered sample was examined by using SEM (JEOL Ltd.,Japan). The small amount of powder was manually dispersed onto a carbon tab (double adhesive carbon coated tape) adhered to an aluminum stubs were coated with a thin layer (300A) of gold by employing POLARON - E 3000 sputter coater. The samples were examined by SEM with direct data capture of the images on to a computer.

Powder X-ray Diffraction (PXRD) Studies

The prepared mixtures were also analyzed using X-ray powder diffractometer (PXRD) which confirms the formation of the new solid phases. The difference in the 2 theta lines confirms the formation of the new solid phases as no two solids have same 2 theta lines, thus revealing the formation of new solid phases. It also reveals the informationabout thecrystal structure, chemical composition, andphysical propertiesof thematerial andalso helpsin structural characterization. This technique detectschanges inthe crystal lattice and istherefore apowerful toolfor studyingpolymorphism, pharmaceuticalsalts, andcocrystalline phases. Spectra of PXRD were taken on a sample stage Spinner PW3064. The samples wereexposed tonickel filtrateCukœ radiations (40 KV, 30 mA) and were scanned from 10° to 40° , 2Θ ata stepsize of 0.045° andstep timeof 0.5 s.

DIFFERENTIAL SCANNING CALORIMETRY (DSC):

The possibility of any interaction between the drug and the polymer during preparation of tablets was assessed by carrying out thermal analysis of drug and polymer alone as well as physical mixture. 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.

Zeta Potential:

Zeta capability becomes anticipated on the premise of electrophoretic mobility under an electric powered field, the use of zeta Sizer Nano ZS (Malvern Instruments, UK). For the Zeta ability measurement, Samples have been diluted as 1:40 ratio with filtered water (v/v) before analysis. zeta potential has been then measured in triplicate.

RESULTS AND DISCUSSION

8.1. PREFORMULATION STUDIES

8.1.1. SPECTROSCOPIC STUDIES

Determination of λmax

A solution of 10µg/ml of Pirfenidone was scanned in the range of 200 to 400nm. The drug exhibited a λmax at 312 nm in simulated gastric fluid pH 1.2 and pH 7.4 phosphate buffer respectively. Correlation between the concentration and absorbance was found to be near to 0.998, with a slope of 0.0711 and intercept of 0.004.

Calibration curve of Pirfenidone in simulated gastric fluid pH 1.2

Table 8.1 shows the calibration curve data of Pirfenidone in simulated gastric fluid pH 1.2 at 312 nm Fig.8.1 shows the standard calibration curve with a regression value of 0.997, slope of 0.071 and intercept of 0.0159 in simulated gastric fluid pH 1.2. The curve was found to be linear in the concentration range of 2-10µg/ml.

Table 8.1: Calibration curve data for Pirfenidone in simulated gastric fluidpH 1.2

CONCENTRATION (µg /ml)	ABSORBANCE
0	0
2	0.167
4	0.306
6	0.459
8	0.579
10	0.718

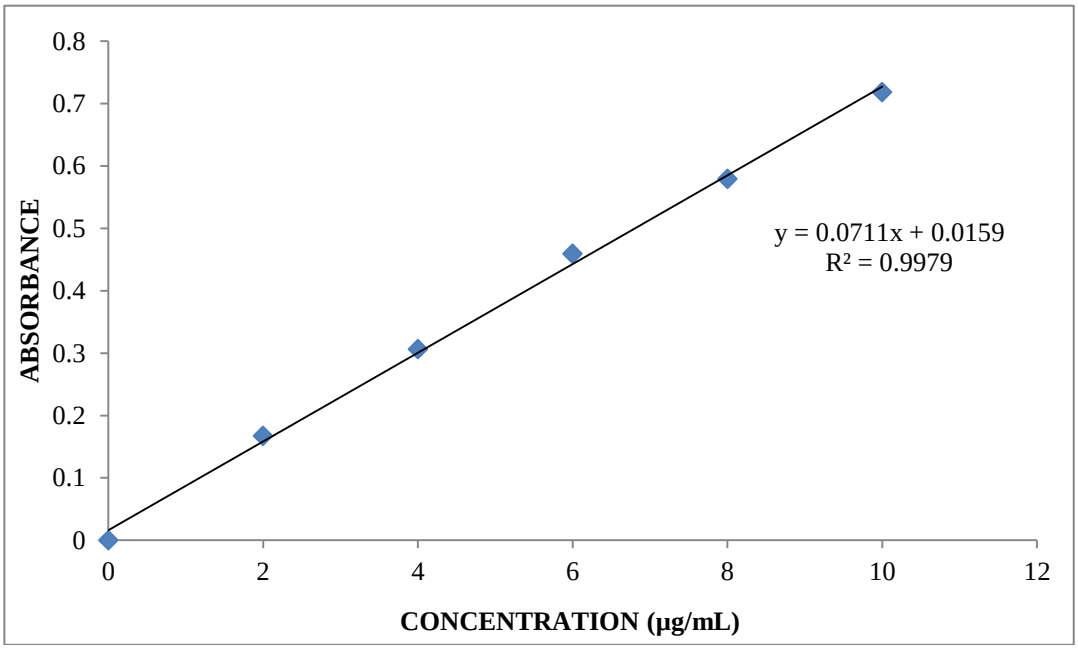


Fig 8.1: Standard graph of Pirfenidone in simulated gastric fluid pH 1.2

Calibration curve of Pirfenidone in pH 7.4 phosphate buffer

Table 8.2 shows the calibration curve data of Pirfenidone in pH 7.4 phosphate buffer at 232nm. Fig. 8.2 shows the standard calibration curve with a regression value of 0.998, slope of 0.075 and intercept of 0.015 in simulated gastric fluid pH 1.2. The curve was found to be linear in the concentration range of 2-10µg/ml.

Table 8.2: Calibration curve data for Pirfenidone in pH 7.4 phosphate buffer

CONCENTRATION (µg /ml)	ABSORBANCE
0	0
2	0.185
4	0.319
6	0.471
8	0.622
10	0.769

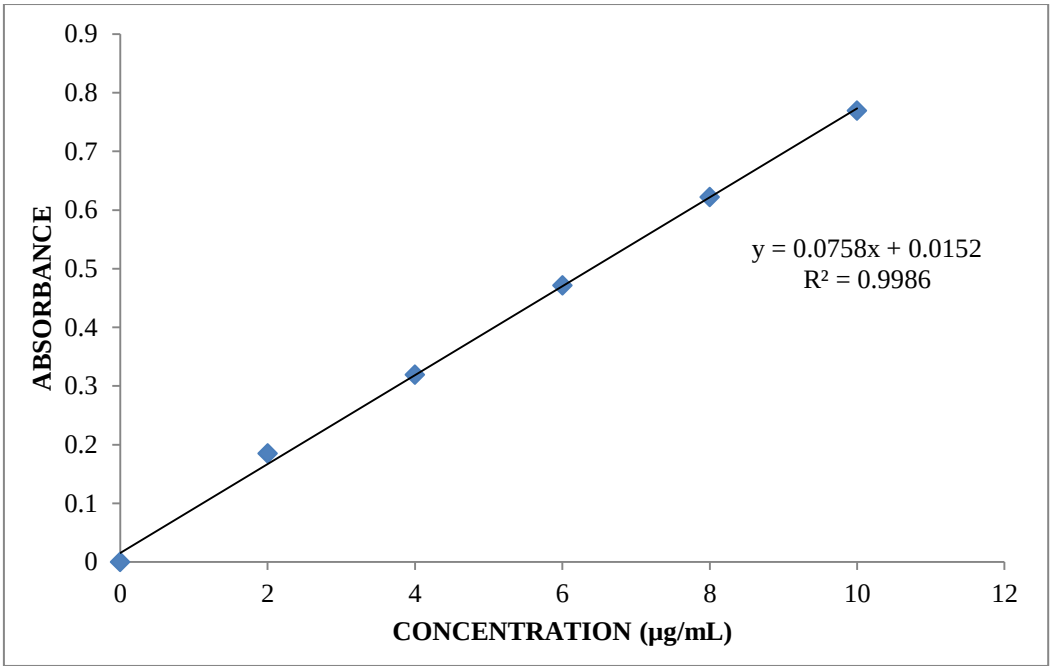


Fig 8.2: Standard graph of Pirfenidone in pH 7.4 phosphate buffer

Evaluation and characterization of microspheres

Micrometric Properties

The mean size increased with increasing polymer concentration which is due to a significant optimum in the viscosity, thus leading to an increased droplet size and finally a higher microspheres size. Microspheres containing Eudragit as a polymer had a size range of 125±0.01 µm to 187±0.05 µm. Microspheres containing Carbopol 934p as polymer exhibited a size range between 137±0.08 µm to 191±0.09 µm.

Microspheres containing HPMC K4M as polymer exhibited a size range between 152±0.04 µm to 191±0.01µm.

The particle size data is presented in Tables 8.3 and displayed in Figures. The effect of drug to polymer ratio on particle size is displayed in Figure. The particle size as well as % drug entrapment efficiency of the microspheres increased with increase in the polymer concentration.

The bulk density of formulation F1 to F9 containing Eudragit, Carbopol 934p and HPMC K4M formulation was in the range of 0.50 to 0.59 gm./cm^3 (as shown in table 8.3), tapped density 0.50 to 0.59 and hausners ratio 1.135 to 1.237.

The carr's index of formulation F1 to F9 containing different grades of Eudragit, Carbopol 934p and HPMC K4M 11.86 to 19.18 respectively. The angle of repose of formulation F1 to F9 containing Eudragit, Carbopol 934p and HPMC formulation was in the range <31.45 respectively (as shown in table 8.3) The values of carr's index and angle of repose indicate good flow properties.

Table 8.3: Micromeritic property of microspheres of Pirfenidone

Formulation code	Mean partical size	Bulk density (gm./cm^3)	Tapped density (gm./cm^3)	Hausener's ratio	Carr's index	Angle of repose
F1	125±0.01	0.59	0.73	1.237	19.18	31.45
F2	171±0.06	0.58	0.71	1.224	18.31	30.64
F3	187±0.05	0.58	0.70	1.207	17.14	30.05
F4	191±0.09	0.50	0.57	1.140	12.28	23.49
F5	166±0.02	0.52	0.59	1.135	11.86	23.82
F6	137±0.08	0.53	0.62	1.170	14.52	24.50
F7	152±0.04	0.55	0.64	1.164	14.06	24.68
F8	185±0.07	0.56	0.67	1.196	16.42	25.07
F9	191±0.01	0.54	0.65	1.194	16.40	25.05

Percentage yield

It was observed that as the polymer ratio in the formulation increases, the product yield also increases. The low percentage yield in some formulations may be due to blocking of needle andwastage of the drug-polymer solution, adhesion ofpolymer solution tothe magnetic bead and microspheres lost during the washing process. The percentage yield was found to be in the range.

Drug entrapment efficiency

Percentage Drug entrapment efficiency of Pirfenidone ranged from 72.90 to 90.45 % for microspheres containing Eudragit, Carbopol 934p and HPMC polymer, the drug entrapment efficiency of the prepared microspheres increased progressively with an increase in proportion of the respective polymers. Increase in the polymer concentration increases the viscosity of the dispersed phase. The particle size increases exponentially with viscosity. The higher viscosity of the polymer solution at the highest polymer concentration would be expected to decrease the diffusion of the drug into the external phase which would result in higher entrapment efficiency. The % drug entrapment efficiency of the prepared microspheres is displayed in Table 8.4, and displayed in Figures.

Table 8.4: Percentage yield and percentage drug entrapment efficiency of the prepared microspheres

Formulation code	% Yield	Drug Content (mg)	% Drug entrapment efficiency	Zeta Potential (mV)
F1	96.25	96.14	72.90	-22.12
F2	86.21	98.39	84.63	-25.81
F3	90.14	98.50	90.25	-25.52
F4	94.31	97.19	82.70	-24.25
F5	97.35	99.24	89.12	-38.55
F6	97.51	98.76	90.45	-22.83
F7	87.64	95.81	82.63	-27.59
F8	92.32	98.63	86.81	-31.11
F9	94.14	97.58	89.69	-30.80

Swelling studies

The swelling ratio is expressed as the percentage of water in the hydrogel at any instant during swelling. Swell ability is an important characteristic as it affects mucoadhesion as well as drug release profiles of polymeric drug delivery systems. Swellability is an indicative parameter for rapid availability of drug solution for diffusion with greater flux. Swellability data revealed that amount of polymer plays an important role in solvent transfer. It can be concluded from the data shown in Table 8.5 that with an increase in polymer concentration, the percentage of swelling also increases. Thus, we can say that amount of polymer directly affects the swelling ratio. As the polymer to drug ratio increased, the percentage of swelling increased from 12.33 to 34.26 % for microspheres containing Eudragit as polymer, 15.53 to 38.8 % for microspheres containing Carbopol 934p as polymer. The percentage of swelling of the prepared microspheres is displayed in Figures. The effect of drug to polymer ratio on percentage swelling is displayed in

Table 8.5: Swelling studies

S.NO.	FORMULATION CODE	INITIAL (Wt)	FINAL (Wt)	PERCENTAGE SWELLING
1	F1	15	16.85	12.33
2	F2	15	18.92	16.13
3	F3	15	20.14	34.26
4	F4	15	17.33	15.53
5	F5	15	18.24	21.6
6	F6	15	20.82	38.8
7	F7	15	23.41	56.06
8	F8	15	27.92	86.13
9	F9	15	26.34	85.61

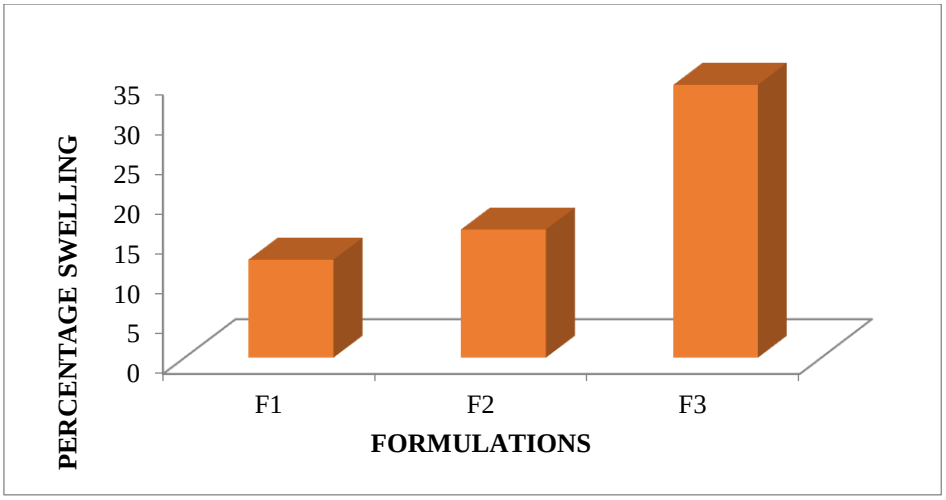


Fig 8.3: Percentage swelling of microspheres containing Eudragit

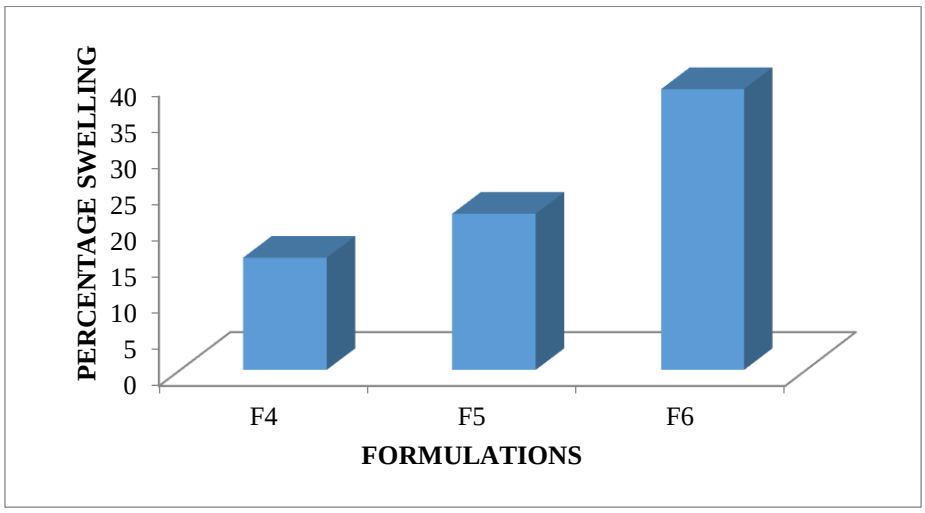


Fig 8.4: Percentage swelling of microspheres containing Carbopol 934p

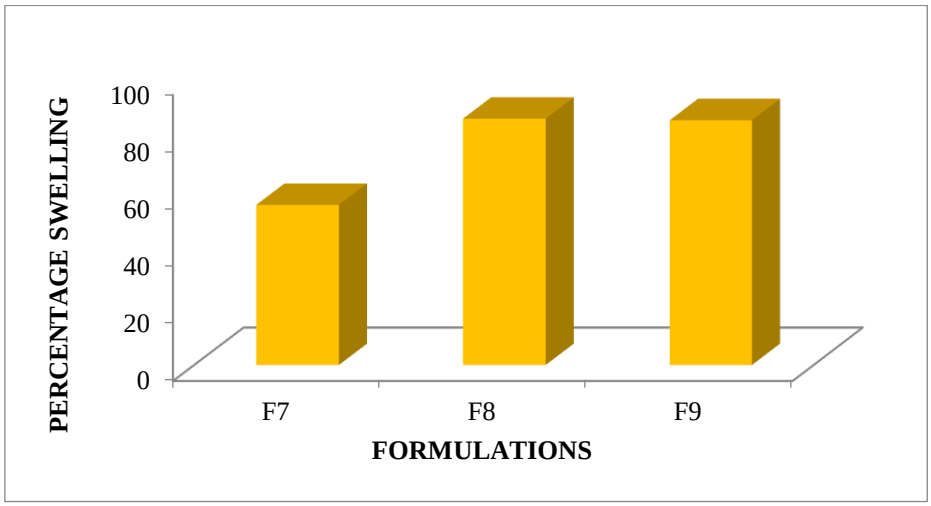


Fig 8.5: Percentage swelling of microspheres containing HPMC K4M

IN VITRO MUCOADHESION TEST

As the polymer to drug ratio increased, microspheres containing Eudragit, Carbopol 934p and HPMC exhibited % mucoadhesion ranging from 72.75 to 96.25 %, the results of *in-vitro* mucoadhesion test are compiled in Table 8.6.

Table 8.6: *In Vitro* Mucoadhesion Test of all Formulations

S.NO.	FORMULATION CODE	No. OF MICROSPHERES		PERCENTAGE MUCOADHESION
		INITIAL	FINAL	
1	F1	20	14.55	72.75
2	F2	20	16.12	80.60
3	F3	20	18.14	90.7
4	F4	20	18.92	94.60
5	F5	20	19.25	96.25
6	F6	20	15.72	78.60
7	F7	20	17.32	86.6
8	F8	20	17.86	89.3
9	F9	20	17.89	90.01

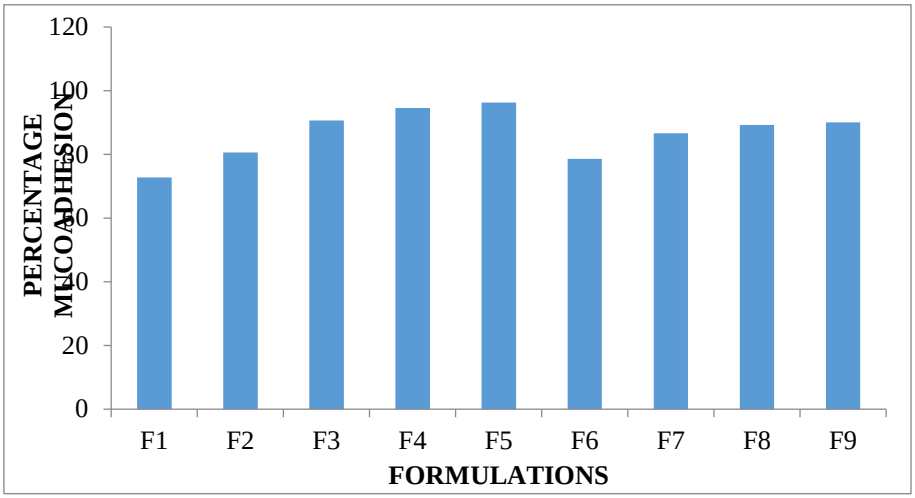


Fig 8.6: Percentage mucoadhesion of microspheres

IN-VITRO DRUG RELEASE STUDIES

Dissolution studies of all the formulations were carried out using dissolution apparatus USP type I. The dissolution studies were conducted by using dissolution media, pH 1.2. The results of the *in-vitro* dissolution studies of formulations F1 to F9 are shown in below table. The plots of Cumulative percentage drug release Vs Time.

The formulations F1, F2, and F3 containing Eudragit showed a maximum release of79.70 % at 12 hours, 87.91 % after 12 hours, 91.53% 12 hoursrespectively.

The formulations F4, F5, and F6 containing Carbopol 934p showed a maximum release of97.29 % at 12 hours, 99.72 % after 12 hours, 86.14% 12 hoursrespectively.

The formulations F7, F8, and F9 containing HPMC K4M polymershowed a maximum release of80.15% 12 hours, 76.94 % after 12 hours, 73.04% after 12 hours respectively.

Table 8.7: *In-Vitro* drug release data of Pirfenidone microspheres

TIME (h)	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	12.85	15.75	10.57	12.62	7.82	10.12	15.34	12.31	10.02
2	17.36	20.11	16.31	17.17	13.29	16.72	21.51	17.42	15.36
3	25.17	28.90	20.69	25.34	18.34	21.63	29.86	25.69	23.61
4	30.28	34.71	26.14	32.23	23.71	27.72	35.11	31.34	30.65
5	34.20	40.67	31.52	37.60	27.62	31.34	39.82	36.29	34.92
6	41.63	45.29	37.43	42.57	35.78	37.21	43.51	41.14	40.52
7	47.71	53.75	45.92	47.82	41.83	42.26	49.22	45.28	42.95
8	52.89	59.97	53.21	56.71	56.90	46.33	53.32	56.95	51.82

9	57.40	62.76	60.82	62.22	63.14	52.82	57.81	61.24	56.74
10	65.71	67.34	79.29	77.99	79.57	67.34	61.12	67.32	62.58
11	68.43	74.82	86.32	89.18	86.25	72.21	75.23	71.41	69.25
12	79.30	87.91	91.53	97.29	99.72	86.14	80.15	76.94	73.04

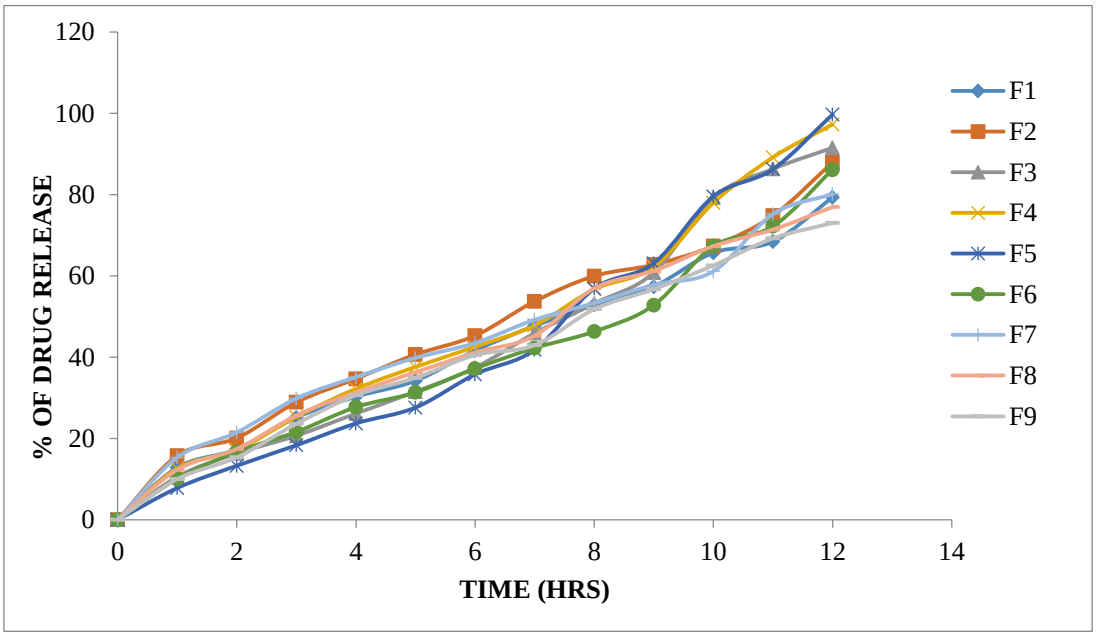


Fig 8.7 : *In-Vitro* drug release profile of Pirfenidone microspheres

Invitro drug release from all the formulation was found to be slow and sustained over the period of 12 hours, among other formulation F5 showed better sustained release pattern and the cumulative percentage release at the end of 12 hours was found to be 99.72 %.

In-vitro drug release kinetics

For understanding the mechanism of drug release and release rate kinetics of the drug from dosage form, the *in-vitro* drug dissolution data obtained was fitted to various mathematical models such as zero order, First order, Higuchi matrix, and Krosmeyer-Peppas model. The values are compiled in Table 8.9. The coefficient of determination (R^2) was used as an indicator of the best fitting for each of the models considered. The kinetic data analysis of all the formulations reached higher coefficient of determination with the peppas release kinetics whereas release exponent value (n) ranged from 0.970. From the coefficient of determination and release exponent values, it can be suggested that the mechanism of drug release follows peppas release kinetics along with non-Fickian diffusion mechanism which leading to the conclusion that a release mechanism of drug followed combination of diffusion and spheres erosion.

Table 8.8: Release kinetics studies of the optimized formulation (F5)

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	Q0 1/3	Qt 1/3	Q0 1/3-Qt1 /3
0	0	0			2.000				100	4.642	4.642	0.000
7.82	1	1.000	0.893	0.000	1.965	7.820	0.1279	-1.107	92.18	4.642	4.517	0.124
13.29	2	1.414	1.124	0.301	1.938	6.645	0.0752	-0.876	86.71	4.642	4.426	0.215
18.34	3	1.732	1.263	0.477	1.912	6.113	0.0545	-0.737	81.66	4.642	4.338	0.303
23.71	4	2.00	1.375	0.602	1.882	5.928	0.0422	-	76.29	4.6	4.2	0.40

		0						0.625		42	41	0
27.62	5	2.236	1.441	0.699	1.860	5.524	0.0362	-0.559	72.38	4.642	4.167	0.474
35.78	6	2.449	1.554	0.778	1.808	5.963	0.0279	-0.446	64.22	4.642	4.005	0.637
41.83	7	2.646	1.621	0.845	1.765	5.976	0.0239	-0.379	58.17	4.642	3.875	0.767
56.9	8	2.828	1.755	0.903	1.634	7.113	0.0176	-0.245	43.1	4.642	3.506	1.135
63.14	9	3.000	1.800	0.954	1.567	7.016	0.0158	-0.200	36.86	4.642	3.328	1.314
79.57	10	3.162	1.901	1.000	1.310	7.957	0.0126	-0.099	20.43	4.642	2.734	1.908
86.25	11	3.317	1.936	1.041	1.138	7.841	0.0116	-0.064	13.75	4.642	2.396	2.246
99.72	12	3.464	1.999	1.079	-0.553	8.310	0.0100	-0.001	0.28	4.642	0.654	3.987

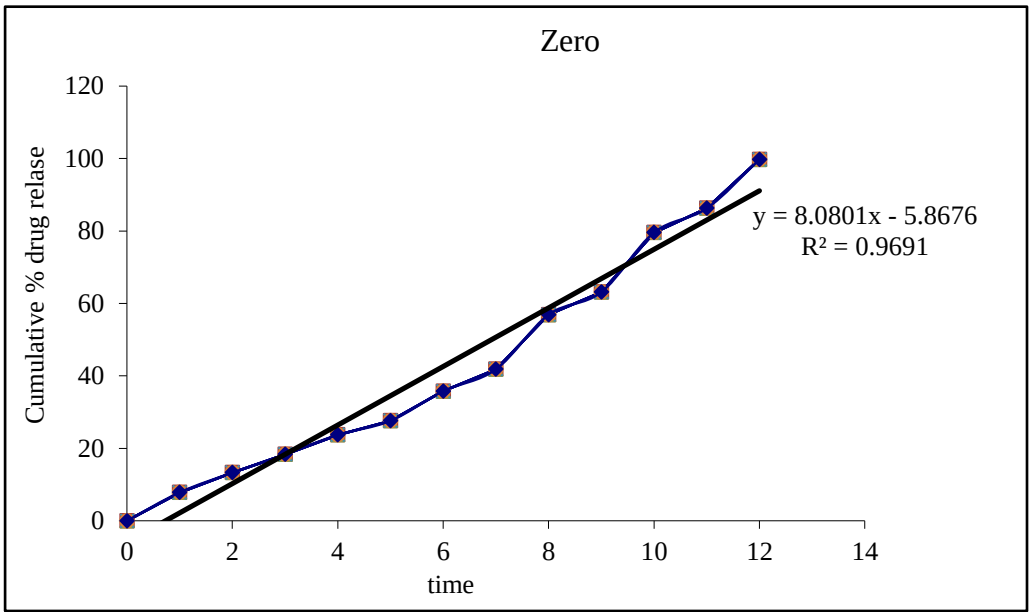


Fig:8.8: Graph of zero order release kinetics of optimized formula

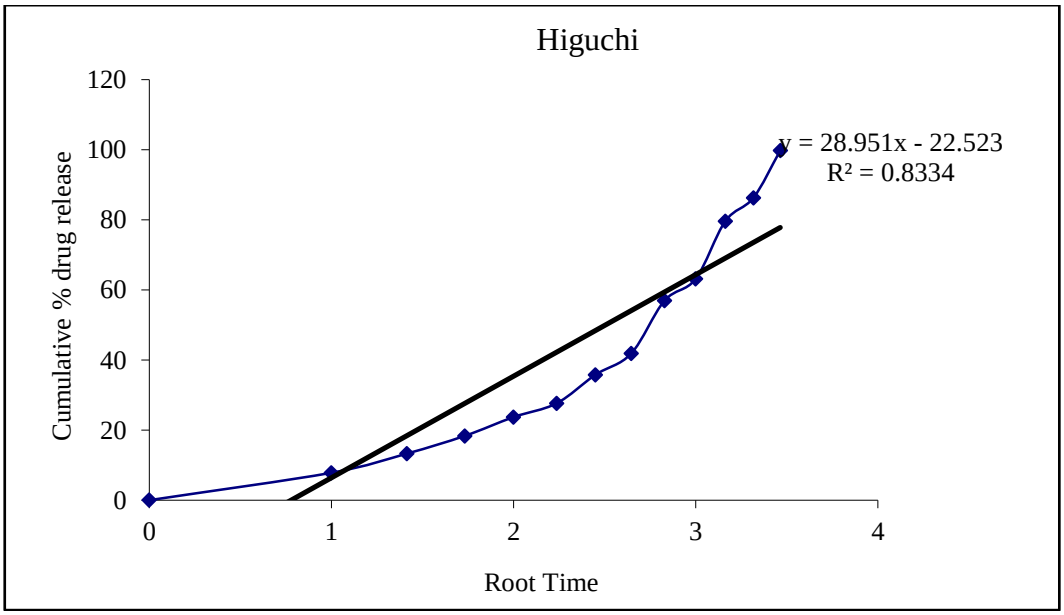


Fig 8.9: Graph of higuchi release kinetics of optimized formula

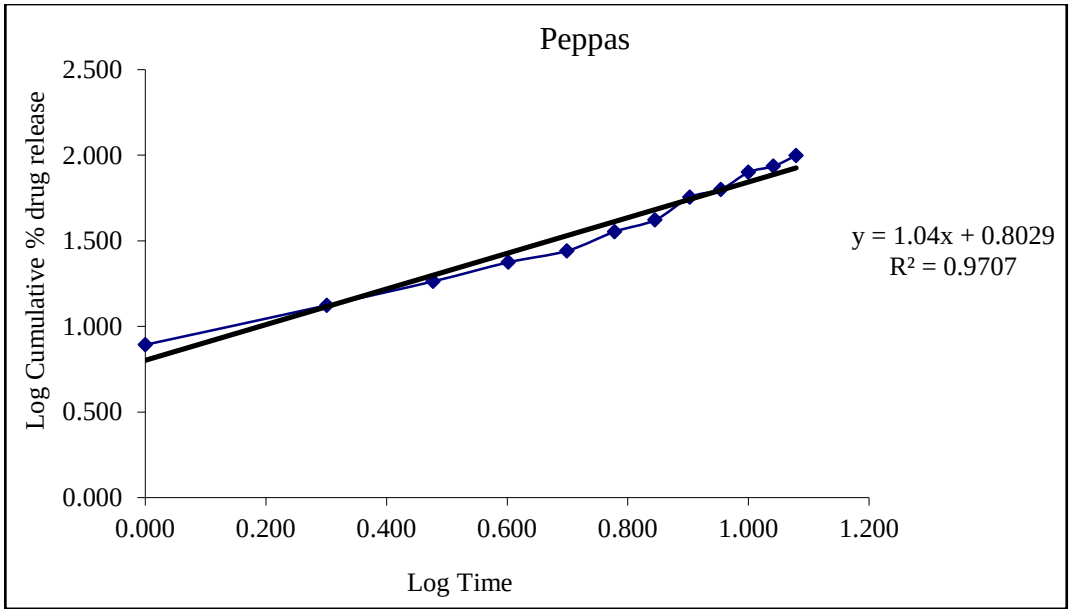


Fig :8.10: Graph of peppas drug release kinetics of optimized formula

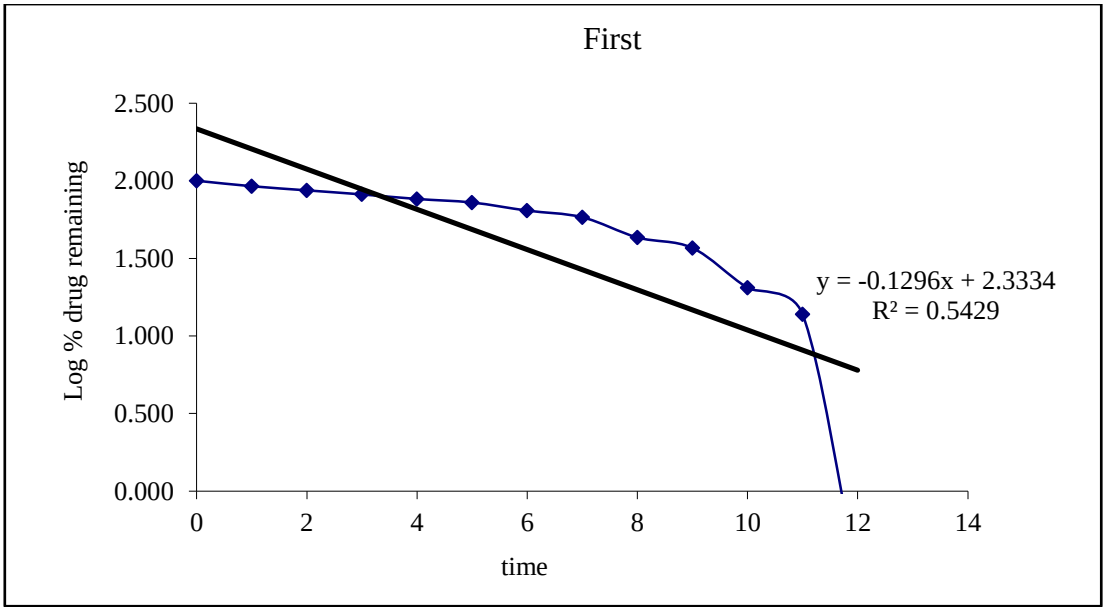


Fig:8.11: Graph of first order release kinetics of optimized formula

Optimized formulation F5 was kept for release kinetic studies. From the above graphs it was evident that the formulation F5 was followed peppas drug release kinetics.

COMPATIBILITY STUDIES

Drug polymer compatibility studies were carried out using Fourier Transform Infra Red spectroscopy to establish any possible interaction of Drug with the polymers used in the formulation. The FT-IR spectra of the formulations were compared with the FTIR spectra of the pure drug.

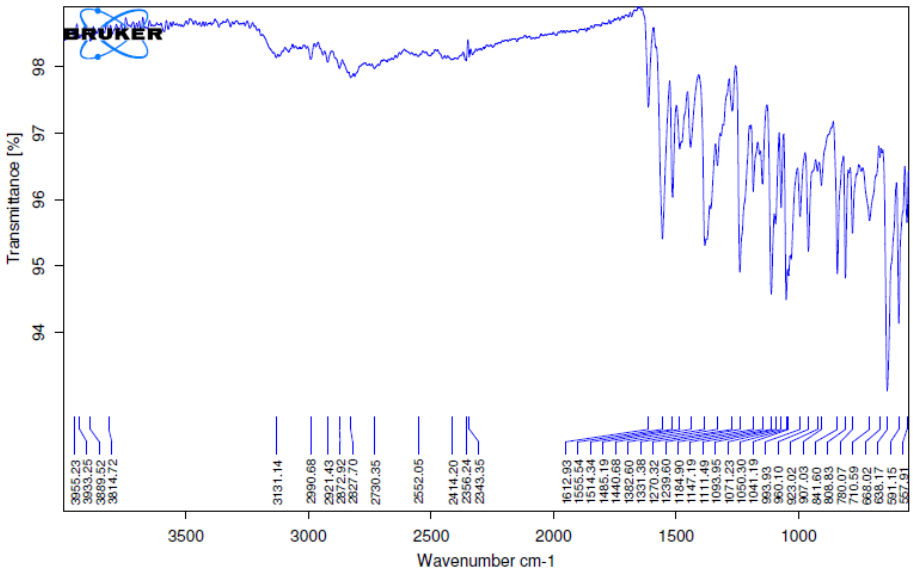


Fig 8.12: FT-IR spectra of Pure drug

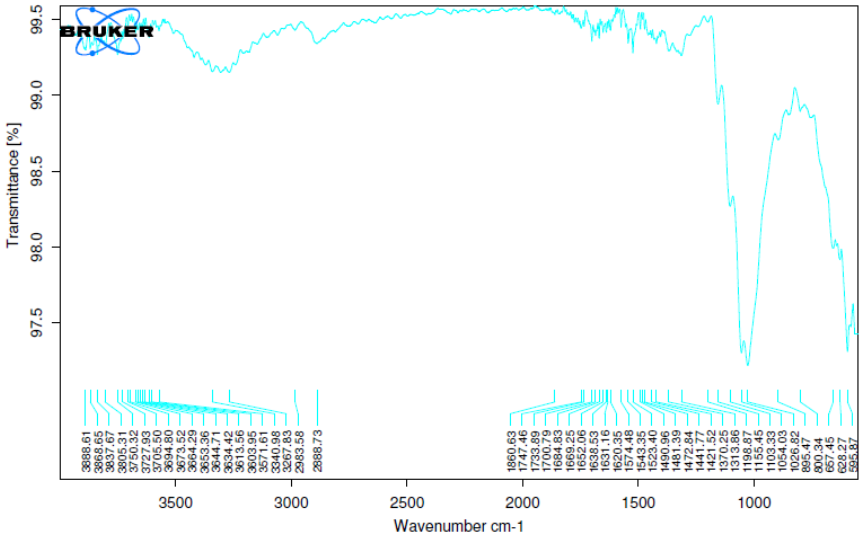


Fig 8.13: FT-IR spectra of Optimised formulation

SEM:

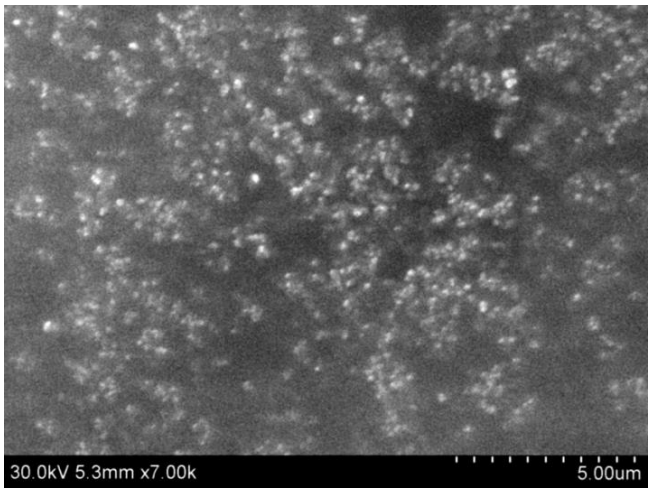


Fig 8.14: SEM of Optimised formulation

SEM was used to examine the morphologies and surfaces of the Pirfenidone (Fig). The surface morphology of the microspheres was found in plain Pirfenidone powder made up of irregularly shaped crystals with rough surface. The particles of formulation F5 appeared a numerous uniform spherically shaped particles 166±0.02 µm with smooth surfaces of drug-loaded microspheres could be seen with the solvent evaporation technique similar findings have been reported.XRD:

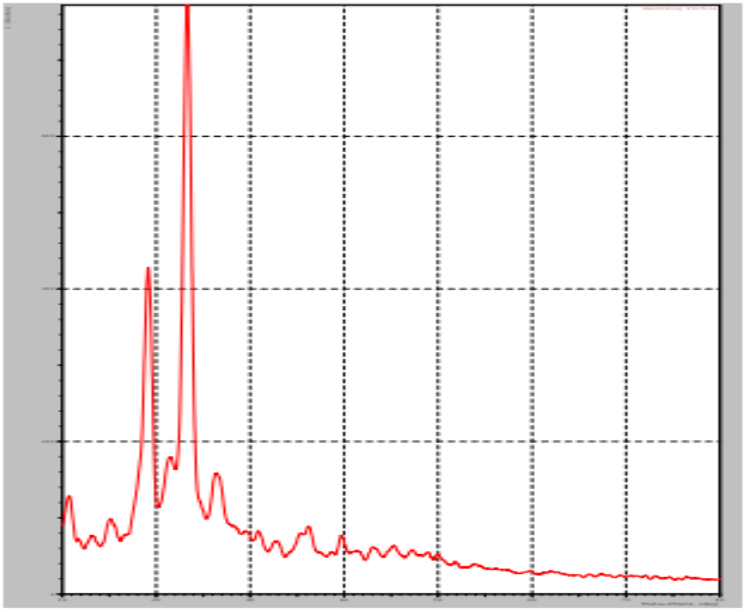


Fig 8.15: Graph: XRD graph of optimized formulations

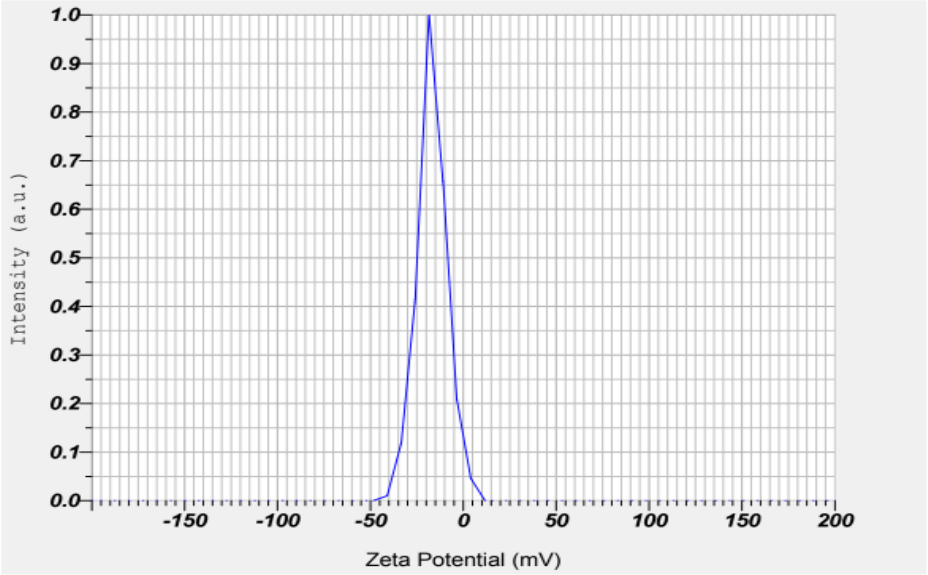
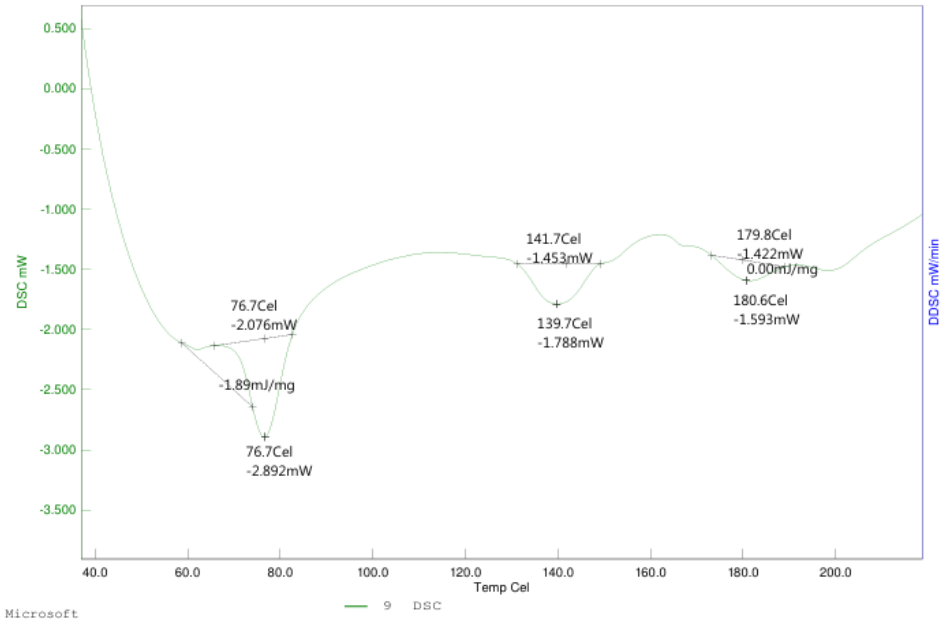


Fig 8.16: Zeta potential of optimized Formulation

The assessment of the zeta potential values (properly related to the double electric layer on the surface of colloidal particles) of a microsphere. Stronger repulsive forces are produced by extreme positive or negative zeta potential values, although repulsion between particles with similar electric charges prevents particle agglomeration and hence simple redispersion. A minimum zeta potential of -38.55 mV is required for simultaneous electrostatic and steric stabilization. The zeta potential study of microsphere formulations F5 were found to be in the range of -38.55 mV) respectively, the zeta potential measurement indicates negatively charged due to double layer repulsion between the droplets and also it depends upon the pH and concentration, which indicates good physical stability of microspheres.



Graph 8.17: DSC graph of pure drug

Upon analysis of the drug Excipient mixture for their physical characteristics no Colour change was observed. Based on the chemical evaluation it was found that there was no significant change observed indicating that the drug is compatible with the added ingredients.

9. CONCLUSION

Pirfenidone-loaded microspheres were successfully prepared and evaluated using suitable formulation and processing techniques. The prepared microspheres exhibited satisfactory physicochemical characteristics and demonstrated good formulation performance. Evaluation of the pre-compression parameters indicated acceptable flow properties and compressibility, while the post-compression parameters were found to comply with the limits specified by the Indian Pharmacopoeia (IP), confirming the quality and uniformity of the formulation.

The microspheres showed appropriate particle size distribution, drug entrapment efficiency, and drug release behavior, indicating their potential as a controlled drug delivery system. Overall, the study demonstrates that the developed Pirfenidone-loaded microspheres possess desirable pharmaceutical properties and can serve as an effective approach for improving drug delivery and therapeutic efficacy.

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