Journal of Pharmacognosy and Phytochemistry

Available online at www.phytojournal.com

E-ISSN: 2278-4136
P-ISSN: 2349-8234
https://www.phytojournal.com
JPP 2024; 13(1): 341-359
Received: 19-12-2023
Accepted: 23-01-2024

Mohd. Adil Tahseen
Ph.D. Research Scholar, Shobit University, Saharanpur, Uttar Pradesh, India

Aqsa Shamsi
B. Pharm, Mohammad Ali Jauhar University, Rampur, Uttar Pradesh, India

Sabahat Khan
B. Pharm, Mohammad Ali Jauhar University, Rampur, Uttar Pradesh, India

Corresponding Author:
Mohd. Adil Tahseen
Ph.D. Research Scholar, Shobit University, Saharanpur, Uttar Pradesh, India

Formulation optimization for controlled release of acetaminophen in matrix tablets

Mohd. Adil Tahseen, Aqsa Shamsi and Sabahat Khan

DOI: https://doi.org/10.22271/phyto.2024.v13.i1e.14853

Abstract
The present study reports the influence of Poloxamer 407 polymer on the release kinetics of Acetaminophen (Paracetamol) in matrix tablets. The formulations were developed using excipients such as Poloxamer 407 and Lactose in different ratios. Characterization was carried out by Fourier Transform Infrared (FTIR) Spectroscopy ultraviolet (UV) Spectroscopy, and Differential scanning Colorimetry (DSC). The FTIR and UV studies suggested no bond formation occurred between the polymer and the drug. DSC results ruled out any interaction or complex formation between the drug and the polymer which released the drug over an extended period of more than eight hours. Sustained release tablets were prepared by dry Granulation method. The formulations were subjected to various evaluation parameters such as Drug Excipients compatibility studies, Angle of Repose, Bulk Density, Hardness, Friability, Drug content uniformity, Wetting time, *in vitro* dissolution studies, and Curve fitting analysis. All the formulations appeared good and showed better physical and mechanical properties. The results indicate that there is no chemical interaction between the polymer and the drug. Based on R-value Formulation follow the zero-order model and Korsmeyer Peppas model showing that the drug is poorly soluble in matrix dosage form. According to the calculation, the n value of all formulations is higher than 0.89. So, these formulations follow the super case II transport Mechanism of release.

Keywords: Matrix tablets, Paracetamol, Poloxamer 407, Lactose

Introduction
Among all drug delivery methods, oral drug delivery is still the most popular choice for administering different medications. By preventing the drug's therapeutic concentration in the body from fluctuating, sustained release is another promising method of lowering adverse effects. The fundamental idea behind a continuous drug delivery system is to optimize a medication's biopharmaceutical, pharmacokinetic, and pharmacodynamic characteristics to maximize its usefulness, minimize its adverse effects, and ultimately cure the patient. Reduced fluctuations in steady-state drug levels, maximum drug utilization, enhanced safety margin of potent drug, shortened treatment periods and improved therapy all contribute to improved patient compliance with sustained release drug delivery. The development of sustained release or controlled release drug delivery systems has received more attention as a result of the increased complexity and cost associated with marketing novel pharmacological entities. Sustained release is a common use case for matrix systems. The medicine that has dissolved or dispersed is released and its release is controlled and prolonged by the release system. A well-mixed combination of one or more medications with a gelling agent, such as hydrophilic polymers, is really what is referred to as a matrix. Reducing a drug's rate of release from the dosage form can lower its absorption rate, which is an intriguing finding in pharmaceutical research. The development of the matrix tablet as a sustained release (SR) has revolutionized the world of pharmaceutical science by creating a novel drug delivery system (NDDS). The kind and amount of polymer employed in the preparations primarily controls the drug release rate from the dosage form, and it does not include complicated production processes like coating and pelletization during manufacture. When creating an SR dosage form, hydrophilic polymer matrices are frequently employed. The development of sustained release or controlled release drug delivery systems has received more attention as a result of the increased complexity and cost associated with marketing novel pharmacological entities [1, 2].

Materials and Methods
1. Chemicals and Apparatus: Paracetamol, Poloxamer, Lactose, PVP K30, Isopropyl alcohol, Magnesium Stearate, Talc, Distilled Water, Electronic Balance, Monsanto Hardness tester, Friability Test Apparatus, Disintegration test apparatus, Dissolution Apparatus USP

XXIII, FTIR 200 Spectrometer, Hot Air Oven, Distillation Assembly, UV Spectrophotometer, Tablet punching machine, pH Meter.

2. UV analysis of drug

- **Preparation of 0.1N HCl solutions:** 8.1774 ml of 37.5% concentrated HCl is needed to prepare 0.1 N HCl.
- **Preparation of standard stock solution:** Accurately weighed 1 0 mg of Paracetamol HCl was dissolved in 100 ml of 0.1 N HCl which gives 100 µg/ml standard stock solutions. Determination of analytical wavelength (λmax). The standard stock solution of 100 µg/ml of Paracetamol HCl was estimated by UV-Visible Spectro photometric method and the absorption maxima were determined. The λmax of Paracetamol HCl was found to be 241 nm (≈246nm).

Standard calibration curve of Paracetamol HCl: From standard stock solution of 100 µg/ml, appropriate aliquots were taken into different volumetric flasks and volume was made up to 10 ml with 0.1 N HCl so as to get drug concentrations of 20, 30, 40, 50, 60, 60, 70, 80, 90 and 100 µg/ml. The absorbencies of these drug solutions were estimated at λmax 300 nm [3-5].

3. Drug excipients compatibility study: Drug: Excipients compatibility study was carried out for any interference of drug and excipients used for the formulation of gastro retentive floating tablet of Paracetamol HCl. It was carried out using Fourier Transformed Infrared Spectroscopy (FT-IR) and Differential Scanning Colorimetry (DSC) analysis. The infrared absorption spectra of pure drug, pure polymer and physical mixture of polymer and drug were performed for polymer drug interaction studies between 4000 cm^{-1} to 400 cm^{-1}. The DSC analysis of pure drug and physical mixture of polymer and drug were carried polymer drug interaction studies out between 50-250 ºC. [6].

4. Bulk density: The bulk density of a powder is the ratio of the mass of an untapped powder sample and its volume including the contribution of the interparticulate void volume.
Bulk density= m/V_o
Where m = weighed sample
V_o = Unsettled apparent volume

5. Tapped density: The tapped density is an increased bulk density attained after mechanically tapping a container containing the powder sample. Tapped density was measured by using formula.
Tapped density = m/V_F
Where V_F = The final tapped value
m= weighed of sample

6. Carr's index (compressibility): The Carr index (Carr's index or Carr's Compressibility Index) is an indication of the compressibility of a powder. The Carr index is calculated by the formula=100[ρT–ρB/ρB], where ρB is the freely settled bulk density of the powder, and ρT is the tapped bulk density of the powder after "tapping down".

1. **Hauser's ratio:** Another way to measure the flow of a powder is the Hausner ratio, which can be expressed as ρT/ρB
2. **Angle of repose:** It is defined as the maximum angle that can be obtained between the free standing of powder heap and horizontal plane.

$\theta = \tan^{-1} (h/r)$
Where, θ = Angle of repose h= Height of powder heap, r = Radius of the powder cone [7, 8].

Method used for preparation of paracetamol HCL
Wet granulation method is used for the preparation of Paracetamol Sustained tablet.
Method: All the ingredients, except lubricant, glident and binder, were accurately weighed and mixed geometrically. Alcoholic solution of PVP K-30 (5%w/w) is used as granulating agent. The granules were dried in conventional hot air oven. The dried granules were sieved through 40/60 meshes. Talc and magnesium stearate were added and granules were compressed using multiple rotatory punching machine. Punching was done using 9 mm punch [9].

Evaluation of the batches of tablets

1. **Weight variation:** Twenty tablets were taken randomly, weighed individually and average weight was determined. The individual tablet weight was compared with the average tablet weight.
2. **Hardness:** 3 tablets were randomly selected and hardness was measured in Monsanto hardness tester. The average was taken as the hardness of the tablet.
3. **Thickness:** 3 Tablets were selected randomly from individual formulations and thickness was measured by using the venire caliper scale, which permits accurate measurement.
4. **Friability:** 10 tablets were weighed (initial weight) and then transferred into the Roche friabilator. It was subjected to 100 revolutions in 4 min. The tablets were de-dusted and reweighed & calculated as follows

   % Friability = (Initial weight - Final weight) / (Initial weight) × 100

5. **Drug content uniformity:** Three tablets were individually weighed and crushed. A quantity of powder equivalent to the mass of one tablet (100 mg) was extracted in 100 ml of 0.1N HCl. The solution was filtered. The drug content was determined by UV spectroscopy at a wavelength of 300 nm after a suitable dilution with 0.1 N HCl.
6. ***In-vitro* dissolution study:** Dissolution profiles of the gastroretentive floating tablet were determined using the USP XXIII dissolution test apparatus II (Electro lab) with 50 rpm and the dissolution medium was 900 ml 0.1 N HCl. Samples (5 ml) were withdrawn with replacement at fixed time intervals and filtered. The filtered samples were then diluted with a dissolution medium (when necessary) and the absorbance was measured at 241 nm by Shimadzu UV spectrophotometer (Shimadzu-1800, Japan) [9].

Drug release kinetic study of optimized formulation

1. **Zero order equation:** A graph of the cumulative percentage drug released from matrix against time is plotted. Zero order release is linear in such a plot, indicating that the release rate is independent of concentration.

$Qt = k0.t$

Where, Qt is the percentage of drug release at time t and k0 is the release rate constant.

2. **First order equation:** A graph of Log cumulative% drug release against time is plotted.

   In (100 - Qt) = in 100 - kit
   Where, kid is release rate constant

3. **Higuchi's equation:** A graph of cumulative percentage of drug release against the square root of time is plotted.

   Qt = kH.t1/2
   Where, kH is higuchi release rate constant.

4. **Korsmeyer-Pappas:** A graph of Log cumulative percentage of drug release against Log time is plotted.

   Qt/Q∞ = kKP.tn
   Where Qt/Q∞ is the fraction of drug released at time t. KKP is constant and n is release exponent [10].

5. **Stability study of optimized formulation:** To determine the stability profile of the novel pharmacological substance, testing is crucial at specific intervals. The products with a six-month shelf life in the first year, months in the second, and years in the following years throughout the shelf-life projection. As for expedited stability studies, at least three intervals, such as three, six, and nine months. If the same product is to be evaluated but has variable strengths, sizes, etc. One option is to employ retained stability testing, which requires less points. The selection of storage conditions should be based on the climate zones where the product is intended for marketing. WHO, CPMP and ICH have all issued general recommendations about storage conditions. ICH guidelines were followed for the stability study. Short-term stability study i.e. accelerated stability study for one month is carried out with temperature 40ºC±2ºC, relative humidity 75% ± 5% RH [10-12].

Method of preparation
Composition of Paracetamol matrix tablet

	Ingredient (mg)	Formulation Codes (F1)	F2	F3	F4
1	Paracetamol	500 mg	500 mg	500 mg	500 mg
2	Poloxamer 407	50 m	100 mg	150 mg	50 mg
3	Lactose	20 mg	15 gm	10 mg	5 mg
4	PVP K30	40 mg	40 mg	40 mg	40 mg
5	Sodium bicarbonate	30 mg	30 mg	30 mg	30 mg
6	Mg Stearate	5 mg	5 mg	5 mg	5 mg
7	Talc	5 mg	5 mg	5 mg	5 mg

Preparation of Paracetamol Tablets
Sustained release tablets each containing 500 mg Paracetamol were prepared by direct compression technique using different polymers at various concentrations (150, 200, 250, 200 mg) and were accurately weighed and passed through sieve no. 45. The content was mixed thoroughly in a mixer for 10 minutes. The lubricant and glident were added to the above mixture and again mixed for 5 minutes. Then the mixture was directly compressed on a Rotary Tablet Machine (single punch) equipped with an 8 mm standard flat-faced punch and die set [13].

Standard Curve for Paracetamol with PVP K30 in Isopropyl alcohol: The standard curves for Paracetamol were prepared in distilled water. Accurately 500 mg of Paracetamol with Poloxamer-407 was dissolved in 7.5 ml PVP-K30 with Isopropyl alcohol of respectively which is called mg/ml solution. 1 ml of this solution was taken and diluted to 500 ml with PVP-K30 with Isopropyl alcohol respectively. Take 2ml, 4ml, 6ml, 8ml, and 10ml of the resulting stock solution and dilute to 10 ml with distilled water to give Paracetamol solution of 2, 4, 6, 8, 10 µg/ml concentration. The absorbance of prepared solutions of Paracetamol in distilled water was measured individually at λ_{max} 241 nm respectively, in UV spectrophotometer against the respective medium as blank (Distilled water). The absorbance data for standard curves are given on the screen of the UV Spectrophotometer and are noted down for the Standard curve following the Lambert-Beers Law in concentration range of 1-10 µg/ml [14].

Wet Granulation
- The active ingredient and excipients are weighed and mixed.
- The wet granulate is prepared by adding the liquid binder adhesive to the Powder blend and mixing thoroughly.
- Screening the damp mass through a mesh to form pellets or granules.
- Granules are dried by using a tray dryer or fluid bed dryer.
- After the granules are dried, they are passed through a screen to form uniform-sized granules.
- Lubricants and other excipients are added to the granules and mixed thoroughly.
- The granules are compressed into tablets [15].

Characterization and Evaluation of the Formulations
(a) Pre-compression parameters
(I) Drug excipients compatibilities studies: The compatibility of drugs and polymers under experimental conditions is an important prerequisite before formulation. It is therefore necessary to confirm that the drug does not react with the polymer and excipients under experimental conditions and should not affect the shelf life of the product. This is confirmed by Fourier Transform Infrared Spectroscopy (FTIR). It is a powerful technique for functional group identification of the drug molecules hence the chemical interaction of the drug with the other excipients. In the present study, the potassium bromide disc (pellet) of the drug and excipients were prepared for recording the FTIR spectra. The spectra were taken in the transmittance range of 4000-450 cm^{-1}. The pure drugs such as Ionized, and their formulations were subjected to IR studies. There are two techniques are used-
- Fourier Transform Infrared Spectroscopy (FTIR).
- Differential Scanning Colorimetry (DSC) [16].

Dissolution test for Paracetamol formulations: The following procedure was employed throughout the study to determine the *in vitro* dissolution rate for all the formulations.
- Dissolution medium: 900 ml of Distilled water for 8-10 hours.
- Temperature: 37 °C ± 1 °C
- Stirring speed: 50 rpm
- Tablet taken: One tablet (drug content known) in each basket
- Volume withdrawn: 10 ml every 1 hour.
- Volume made up to: 10 ml
- λ_{max}: 241 nm
- Beer's range: 1-20 mg/ml
- Dilution factor: 20ml

The various parameters related to dissolution which were evaluated in the present work are as follows: Drug release and Cumulative percentage drug release.

Results and Discussion

The wet-dry granulation method has been used for sustained release and any other type of tablet formulation development of Paracetamol and its combination with any other drug. The effect of various binders such as polymers (Poloxamer) was studied on various formulation parameters. The characterization of formulated tablets for various evaluation parameters was studied successfully.

Standard Calibration Curve of Paracetamol: Standard calibration curve of Paracetamol was obtained by plotting absorbance vs. concentration using UV spectroscopy. The λ_{max} of Paracetamol in Distilled water was determined to be 241nm respectively. The absorbance values are tabulated in Table 1. The curve is found to be linear in the Beer's range between 1-20 mg/ml.

Table 1: Absorbance values of Paracetamol

S. No.	Concentration µg/ml	Absorbance
1.	0	0
2.	2	0.124
3.	4	0.240
4.	6	0.360
5.	8	0.480
6.	10	0.590
7	12	0.680

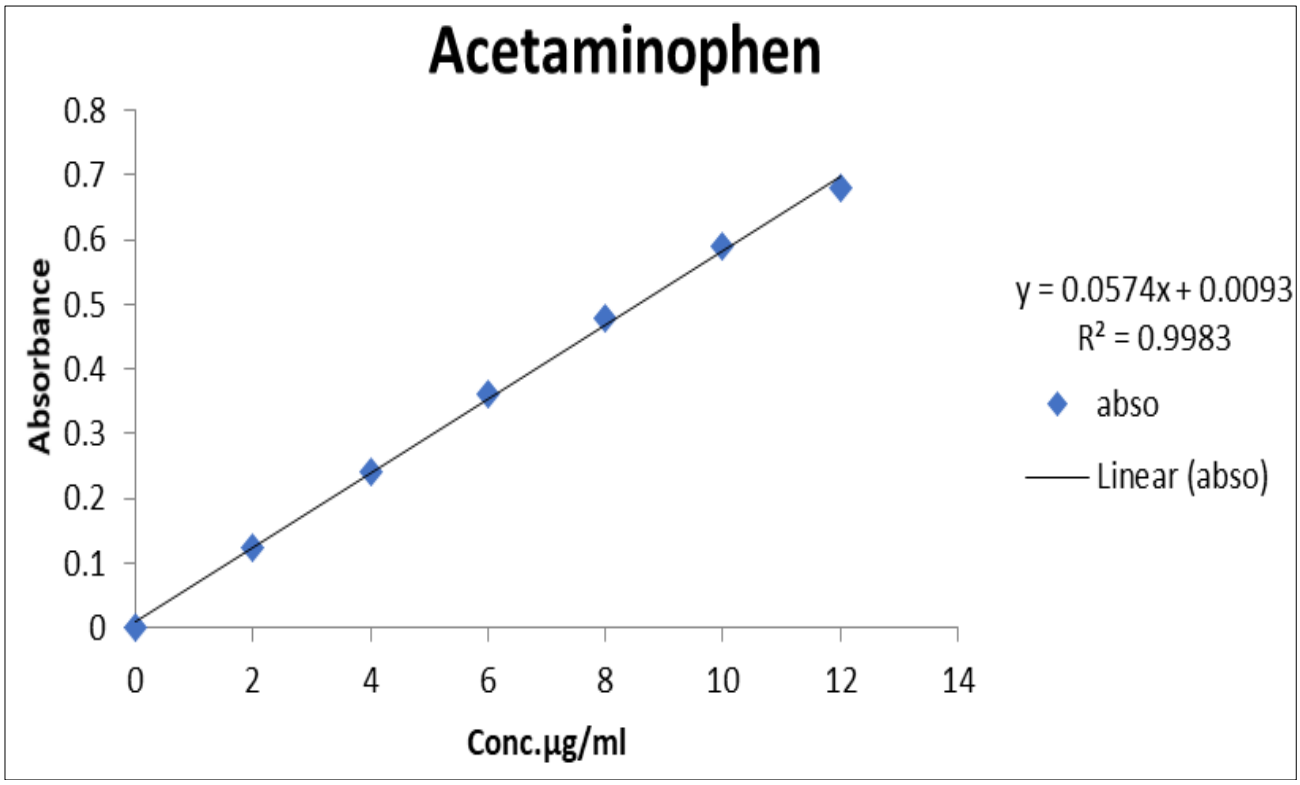

Fig 1: Standard calibration curve shown in the graph (Conc. V /S Abs)

Compatibility Study: Compatibility studies were performed using an FTIR spectrophotometer. The FTIR spectrum of pure drug and physical mixture of drug and polymer were studied. The characteristic absorption peaks of Paracetamol and polymer were obtained.

The FTIR spectra of pure Paracetamol indicated the characteristic absorption stretch for a Strong C=O Stretch band (Amide II) at 1560 cm^{-1} and broad band between 3300 and 3000 cm^{-1} for bonded N-H and C-H, stretch is obtained. The finger point region FTIR spectra showed a characteristic sharp peak at 1670 and 1610, 1500 cm^{-1} for C=O, ring C=C and C=N. In comparison with the pure Paracetamol, the absorption peak of the spectra for Paracetamol and polymer (Poloxamer407) showed no shift and no disappearance of characteristic peaks suggesting that there is no interaction between Paracetamol and other additives. No degradation of the Paracetamol molecule was observed during its formulation development; hence the drug-excipient combinations used in the formulation development were compatible under the given set of experiments.

Paracetamol matrix tablet formulations: Super binders represent a suitable material for formulating sustained-release tablets using traditional technology. The percent composition of the formulations is adjusted by varying the content of the excipients steadily to be compacted. Polymer Poloxamer 407 and lactose are used as the binders in the formulation, the PVP K30 and Isopropyl alcohol are the good binders and polymer poloxamer407 is the super binder. The talc and magnesium stearate are used in the formulation as lubricants. They help in the punching during tablet punching. They are allowing the tablet punching machine too freely. With the use of lubricants, the tablets are not stay in the machine it freely prepared. The distilled water was used as the solvent in the formulation. The mixture was prepared in the mortar and pestle for the preparation of the tablets, no special equipment was adopted to compact the physical mixtures of the tablets. Operative parameters were modulated to give the final tablets a satisfactory de-aggregation time, but at the same time, it was also necessary to maintain mechanical resistance during processing and handling both in case of formulation packing and its extraction from the container, before administration.

Sustained-release tablets are harder than fast-disintegration tablets. A hot air oven is used for the drying of granules before the punching of tablets, single unit punching machine. Store the prepared tablets in a well-closed container.

Evaluation of Tablets

(a) Pre-Compression Parameters

Drug Excipients Compatibilities Studies: The compatibility of the drug and polymers is important to confirm that the drug does not react with the polymer and excipients under experimental conditions. There are two parameters or testing used to know the drug, excipient compatibility studies.

Fourier Transform Infrared Spectroscopy (FTIR).

- Differential Scanning Colorimetry (DSC)

Fourier Transform Infrared Spectroscopy (FTIR): Some conditions are applied during the testing show in Table 2.

Table 2: Fourier Transform Infrared Spectroscopy

S. No.	Sample Name	Substance for Analysis	Analysis Conditions	Precautions	Required Parameter
1.	R-4	Pure Drug	400-4000 cm¯1	NA	FTIR
2.	R-5	Pure Polymer	400-4000 cm¯1	NA	FTIR
3.	R-6	Mixture of Drug and Polymer	400-4000 cm¯1	NA	FTIR

The result is show in graphically of the samples, R-4, R-5 and R-6.

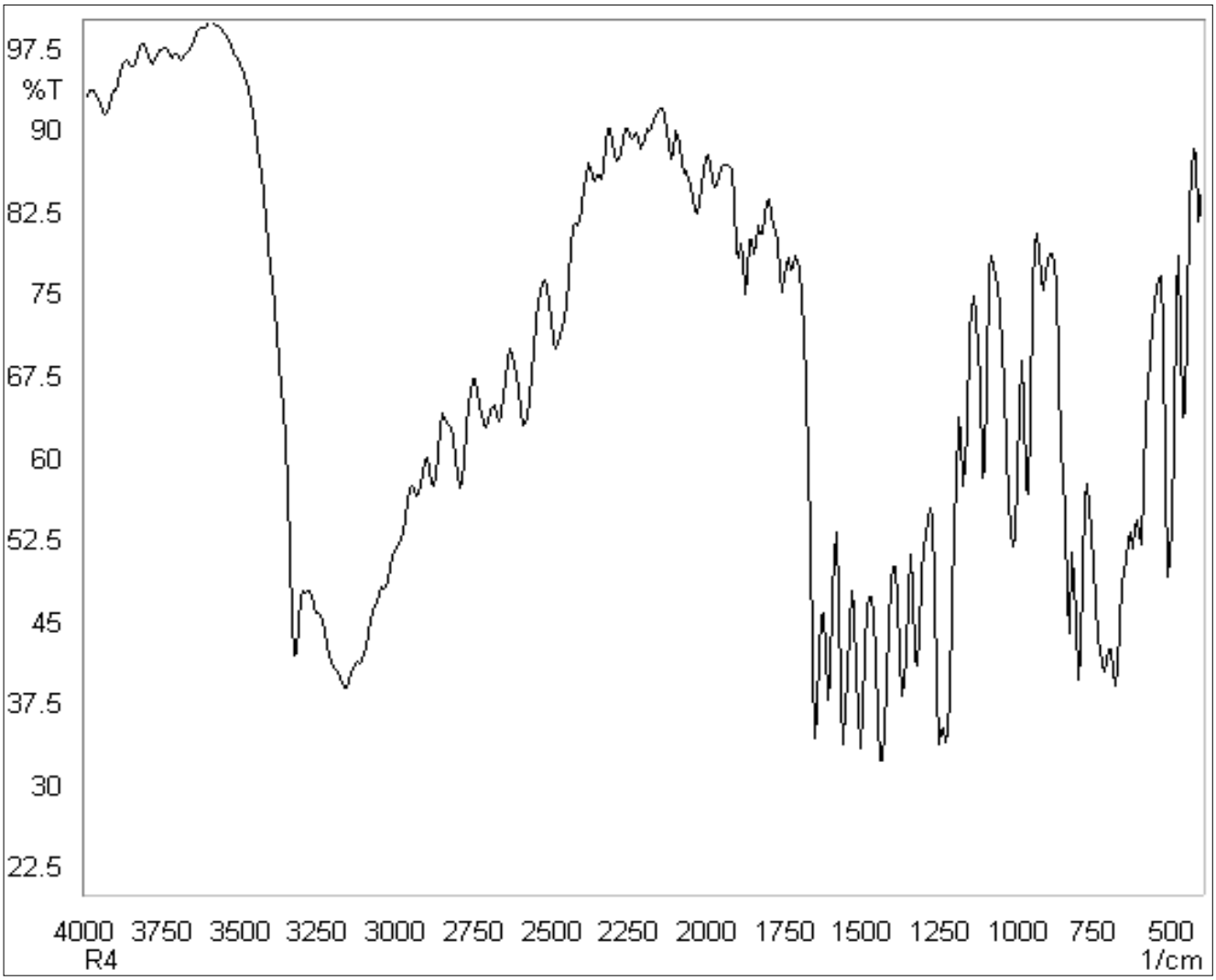

Fig 2: Fourier Transform Infrared Spectroscopy (FTIR) of Paracetamol

IR Characterization of Paracetamol: The FTIR spectra of Paracetamol (Fig 5) exhibited absorption bands at 3325, 3163, and 1651 cm^{-1} due to CH_2 stretch, C=C stretch, and Are C-C stretch. Absorption bands at 1501, 1503, and 1018 are attributed to C-O stretching vibrations.

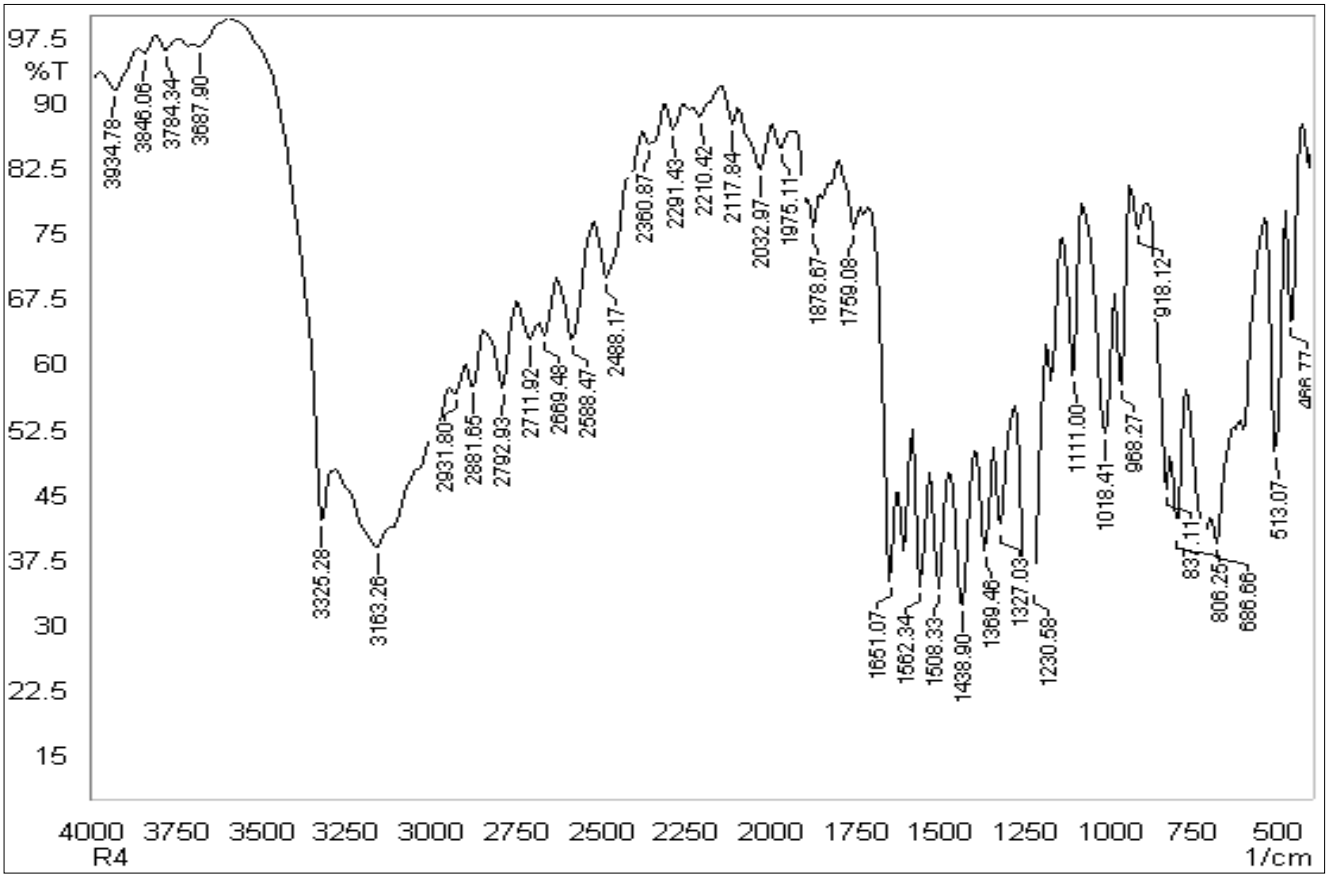

Fig 3: Fourier Transform Infrared Spectroscopy (FTIR) of Paracetamol with peak values

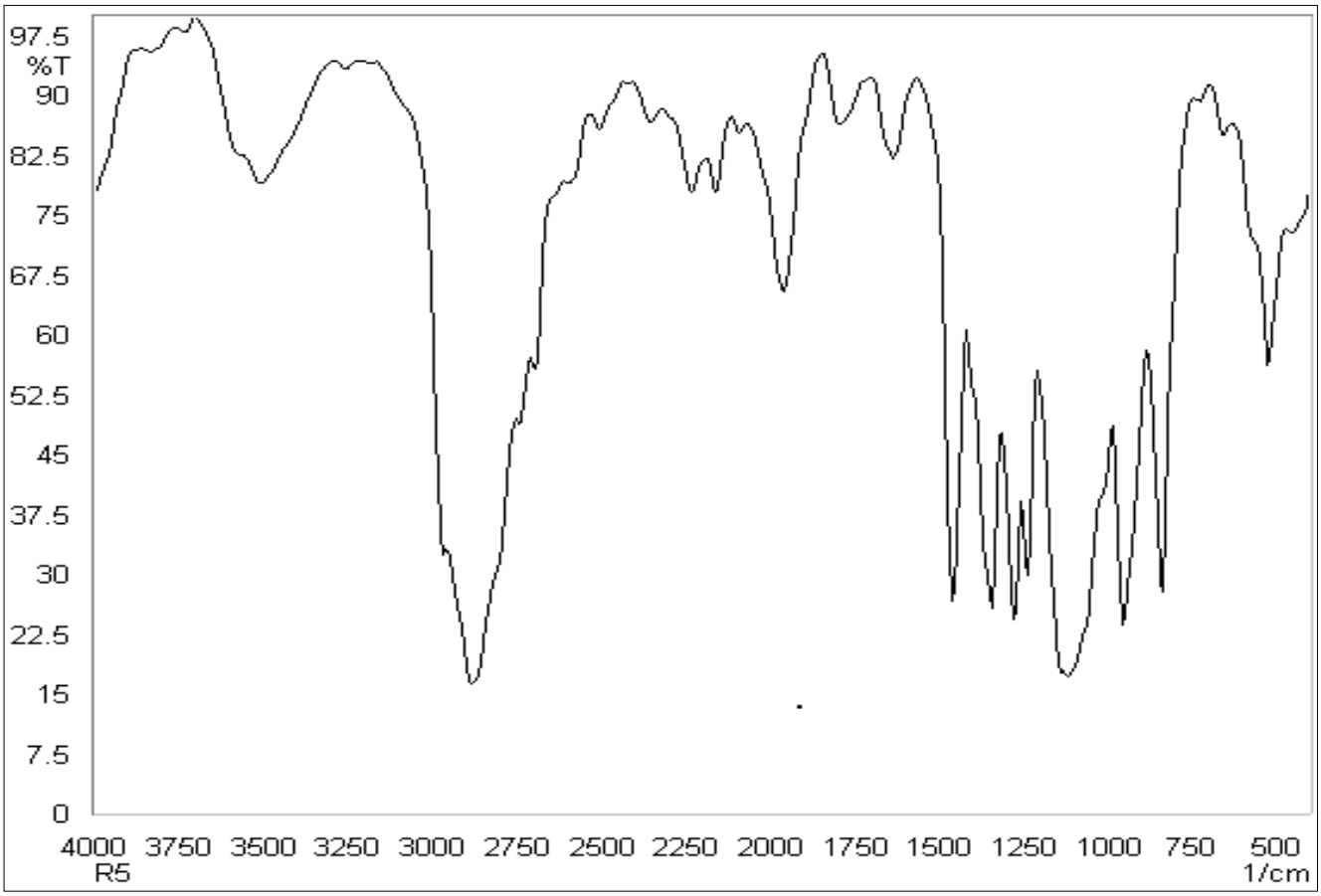

Fig 4: Fourier Transform Infrared Spectroscopy (FTIR) of Poloxamer 407

IR Characterization of Poloxamer 407: The FTIR spectra of Poloxamer 407 (Fig 5) exhibited absorption bands at 3508, 2885, and 2700 cm^{-1}. 1967 are due to CH_2 stretch, C=C stretch, and Are C-C stretch. Absorption bands at 1639, 1118 and are attributed to C-O stretching vibrations.

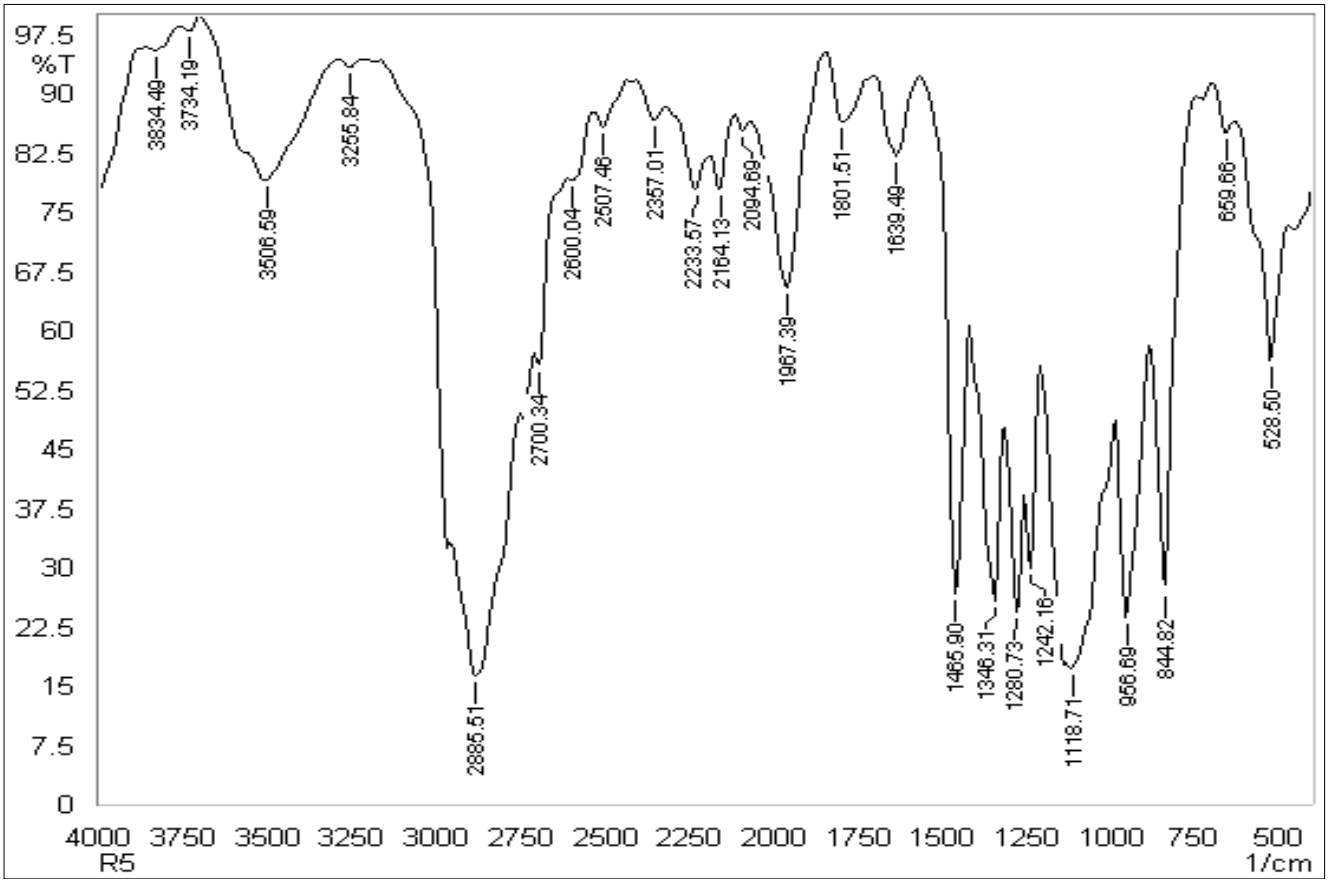

Fig 5: Fourier Transform Infrared Spectroscopy (FTIR) of Poloxamer 407 with peak values

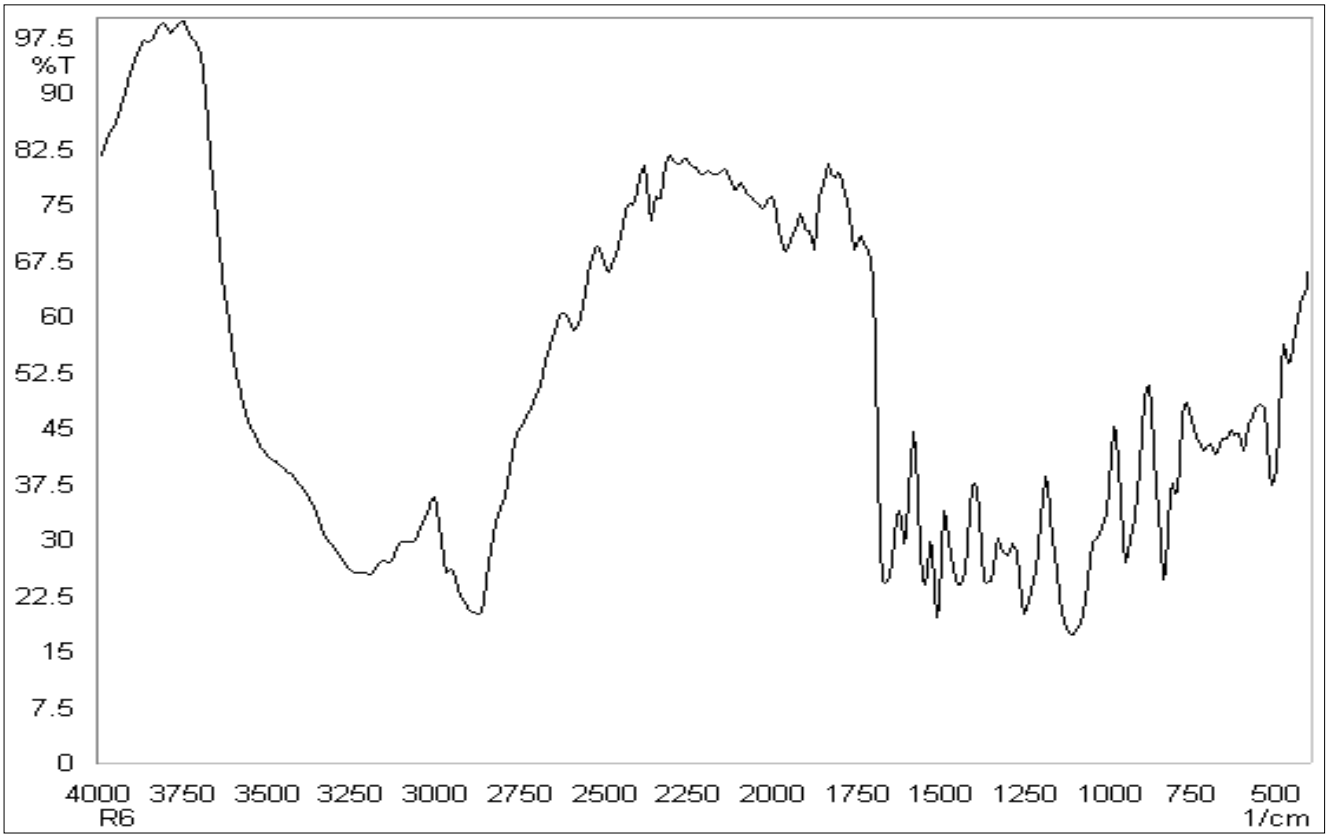

Fig 6: FTIR of Paracetamol with Poloxamer 407 polymer

IR Characterization of Paracetamol with Poloxamer 407: The FTIR spectra of Paracetamol with Poloxamer 407 (Fig 6) exhibited absorption bands at 3197, and 2837 cm^{-1} due to CH_2 stretch, C=C stretch, and C-C stretch. Absorption bands in 1967, 1878 and are attributed to C-O stretching vibrations. That shows no interaction was found between the drug and polymer.

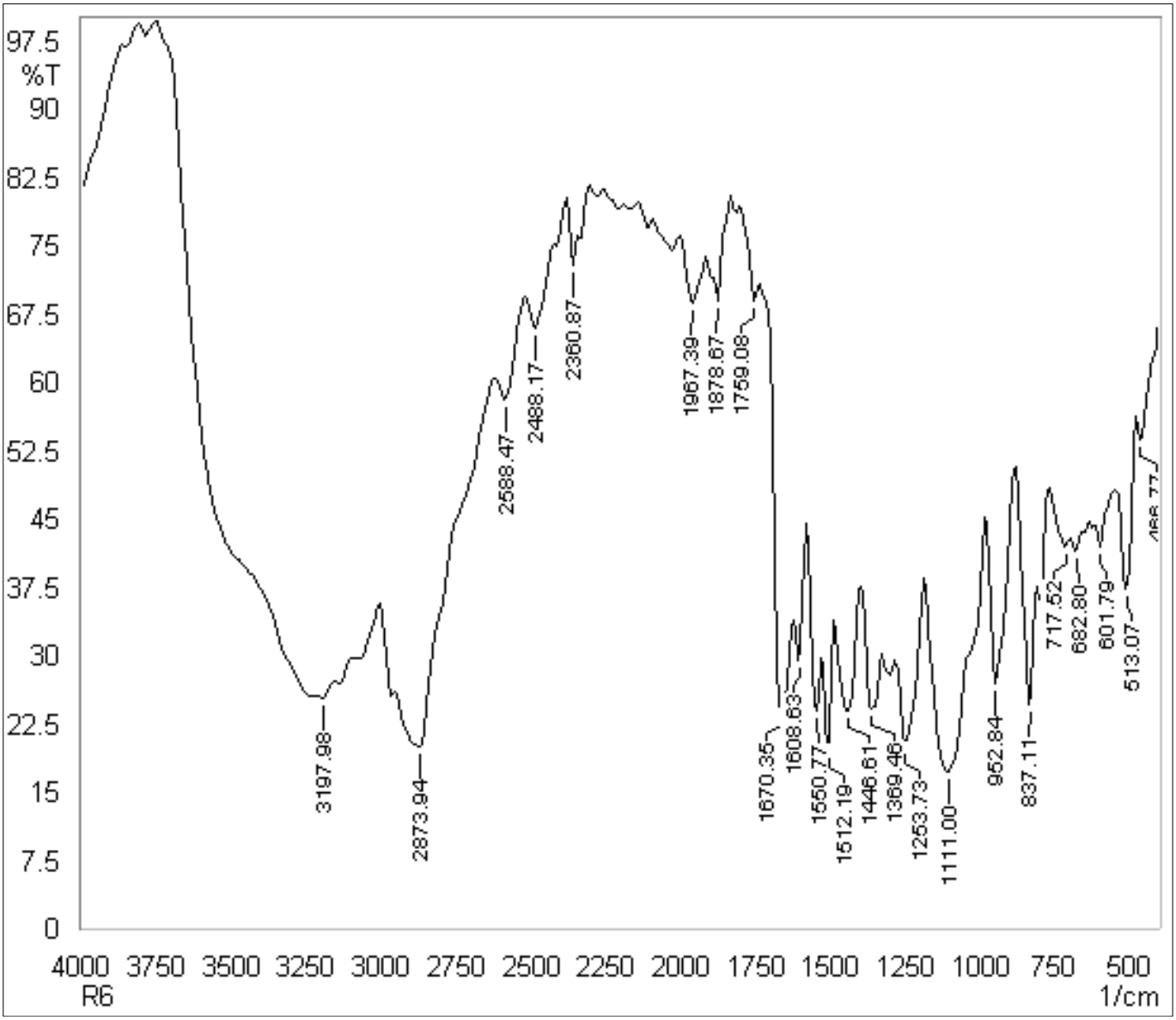

Fig 7: FTIR of Paracetamol with Poloxamer 407 polymer with peak values

Differential Scanning Colorimetry (DSC): Differential Scanning Colorimetry (DSC) is a thermo analytical technique in which the difference in the amount of heat required to increase the temperature of a sample and references is measured as a function of temperature.

Table 3: DSC same conditions are applied during the testing

S. No.	Sample Name	Substance for Analysis	Analysis Conditions	Precautions	Required Parameter	Melting Point	Deg. Temp.
1.	R-1	Pure Drug	40°C to 600°C	NA	DSC	170.66°C	Above 350°C
2.	R-2	Pure Polymer	40°C to 600°C	NA	DSC	55°C	Above 350°C
3.	R-3	Mixture of Drug and Polymer	40°C to 600°C	NA	DSC	150-250°C	Above 350°C

The result is show in graphically of the samples, R-1, R-2 and R-3.

DSC Study of Pure Paracetamol: The DSC thermo gram of low Paracetamol showed a broad endothermic peak at endothermic peak at 170.66 °C which indicate glass transition temperature of drug Paracetamol that is close to original melting point of 169 °C. Broad endothermic peak at 294.40 °C attributed to the slow degradation of the drug.

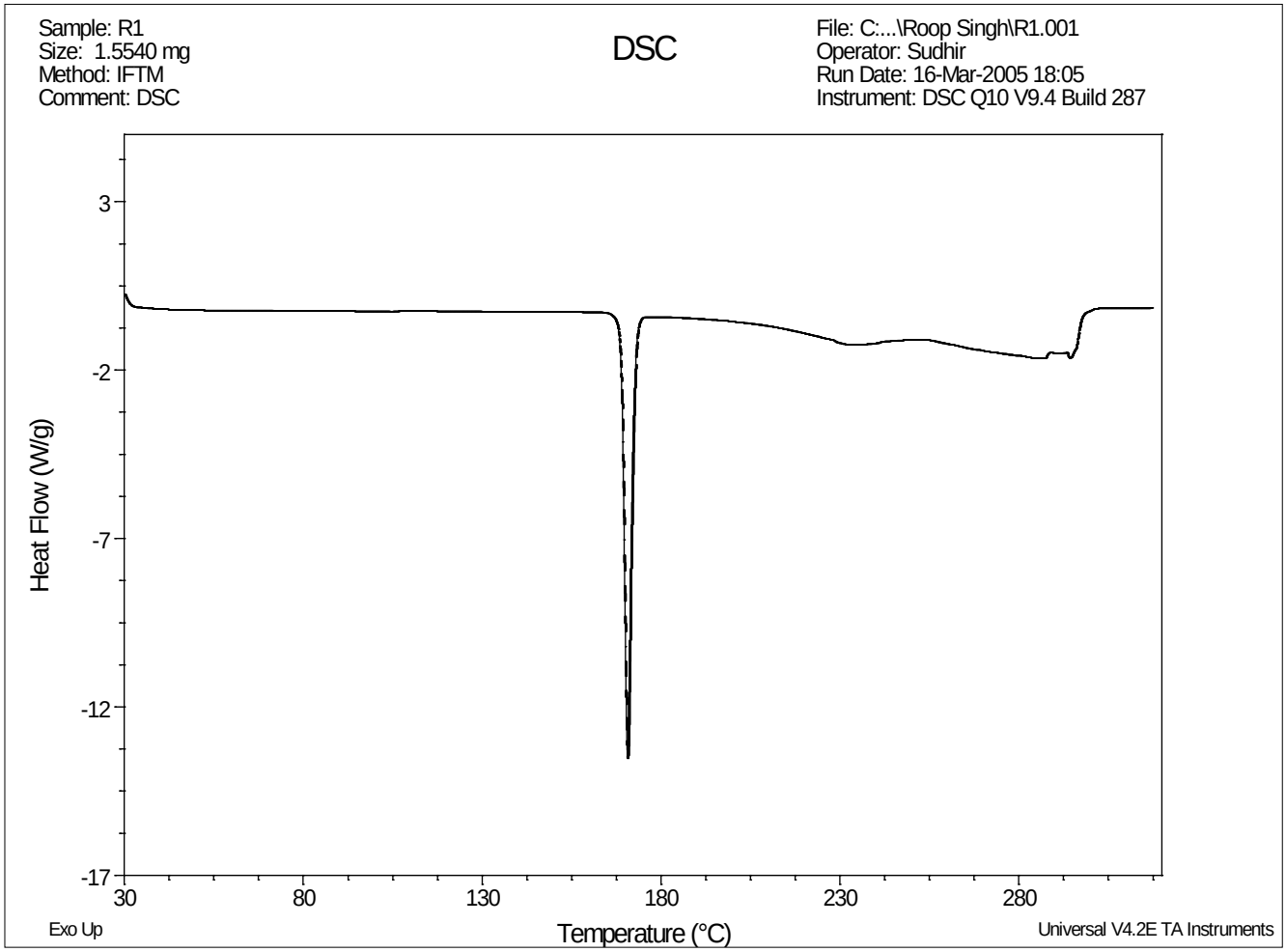

Fig 8: Differential Scanning Colorimetry (DSC) Paracetamol

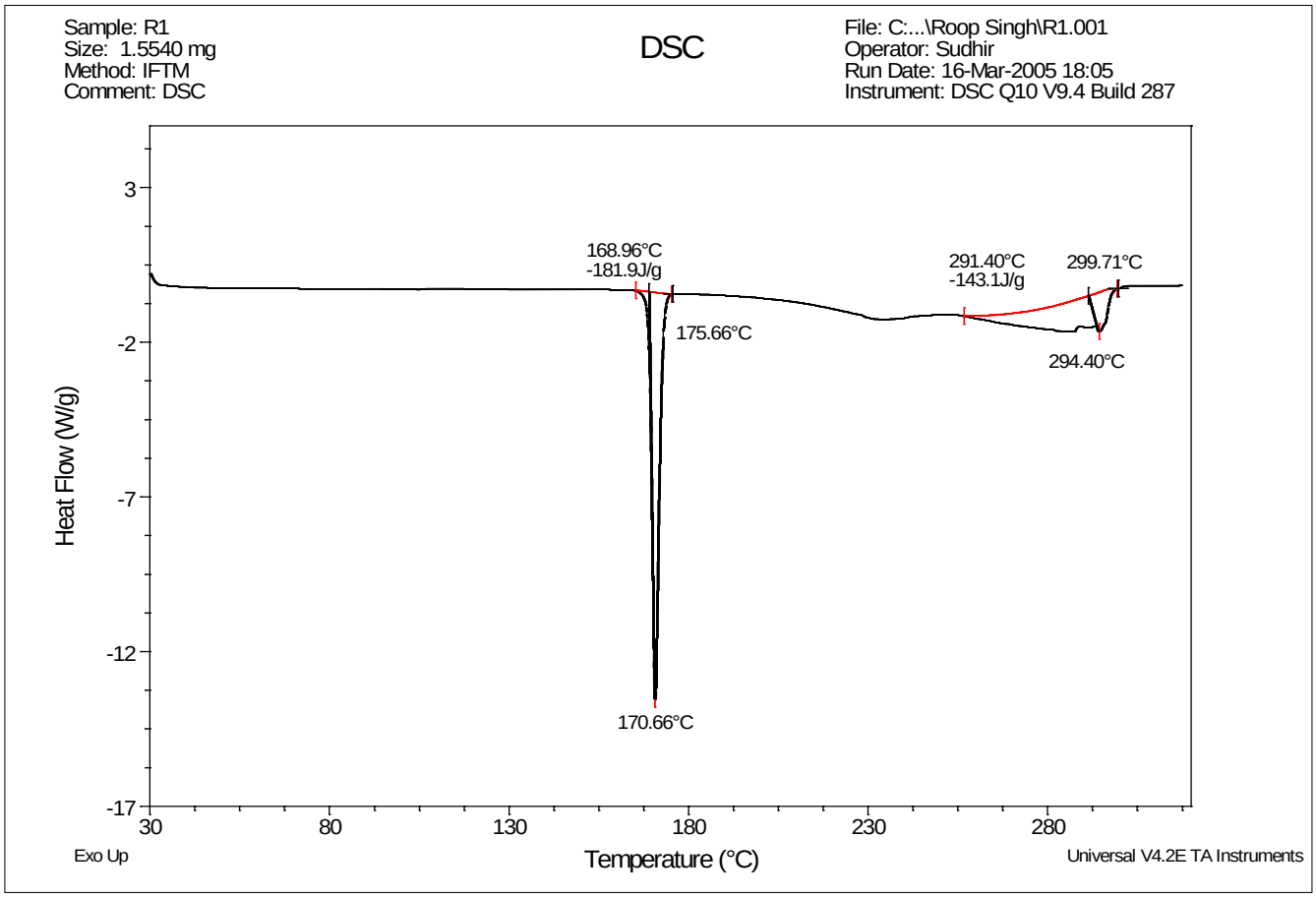

Fig 9: Differential Scanning Colorimetry (DSC) Paracetamol with peak values

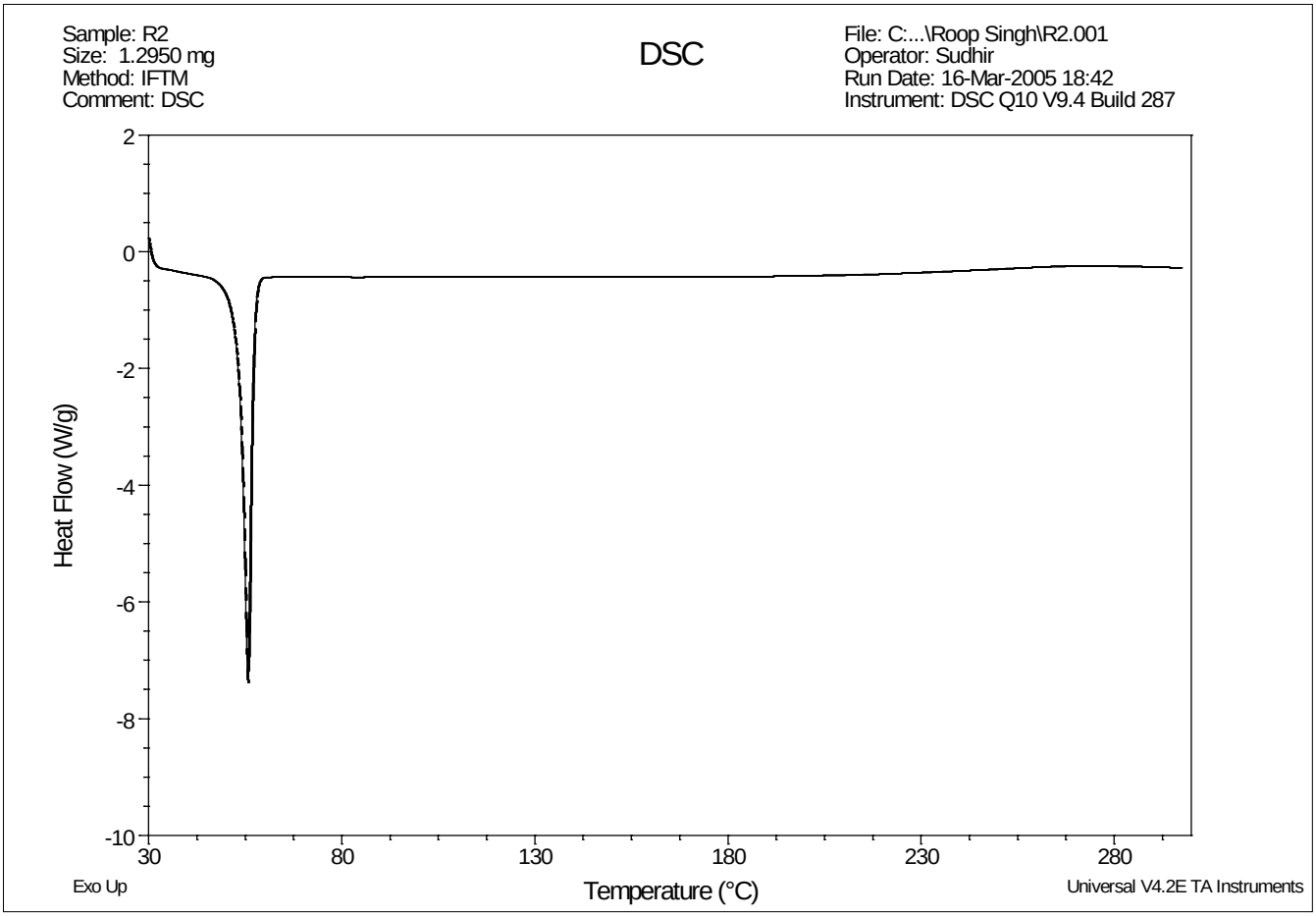

Fig 10: Differential Scanning Colorimetry (DSC) Poloxamer 407

DSC Study of Poloxamer 407: The DSC thermo gram of low Poloxamer 407 showed a broad endothermic peak at endothermic peak at 55.70 ºC which indicate glass transition temperature of polymer. Broad endothermic peak at 60.40C attributed to the slow degradation of the polymer.

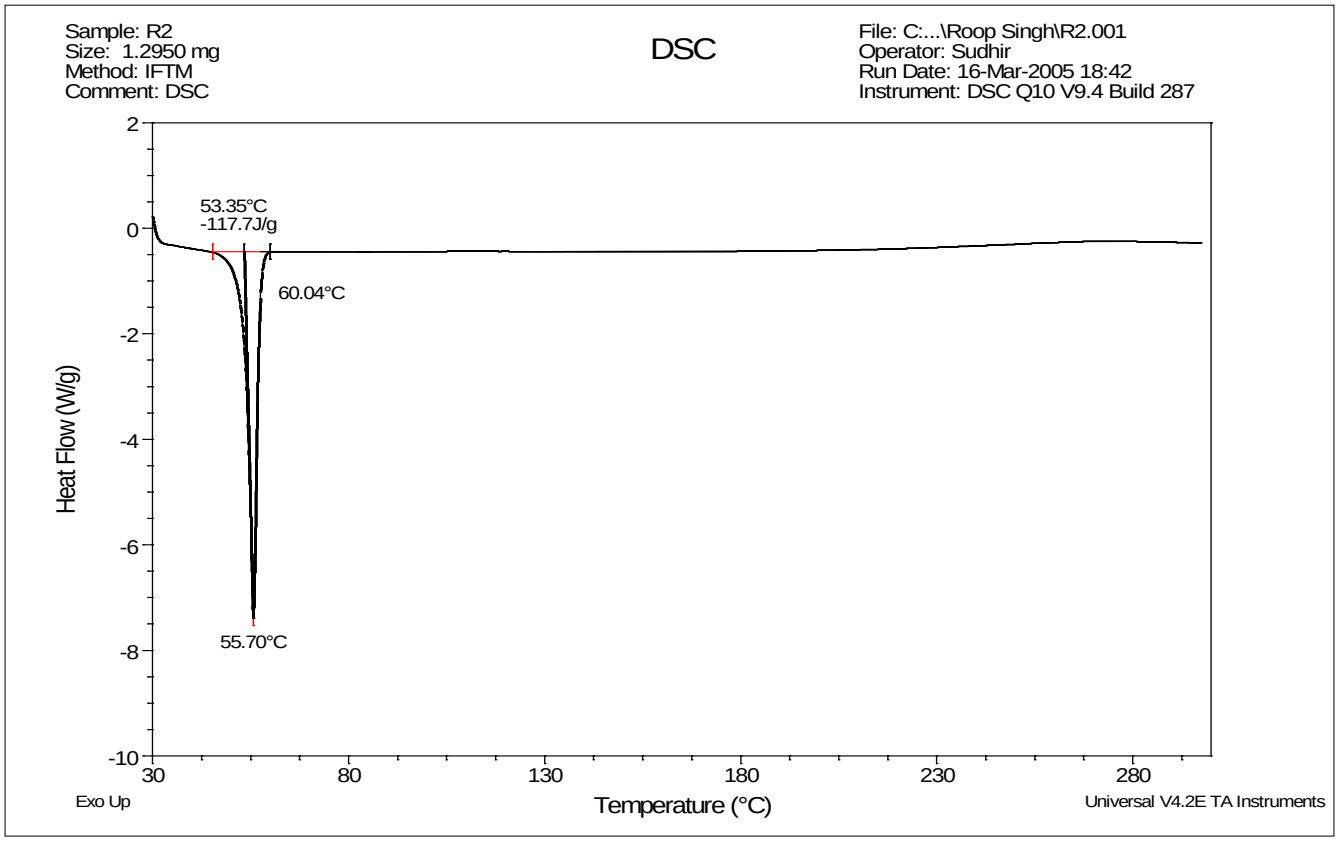

Fig 11: Differential Scanning Colorimetry (DSC) Poloxamer 407 with peak values

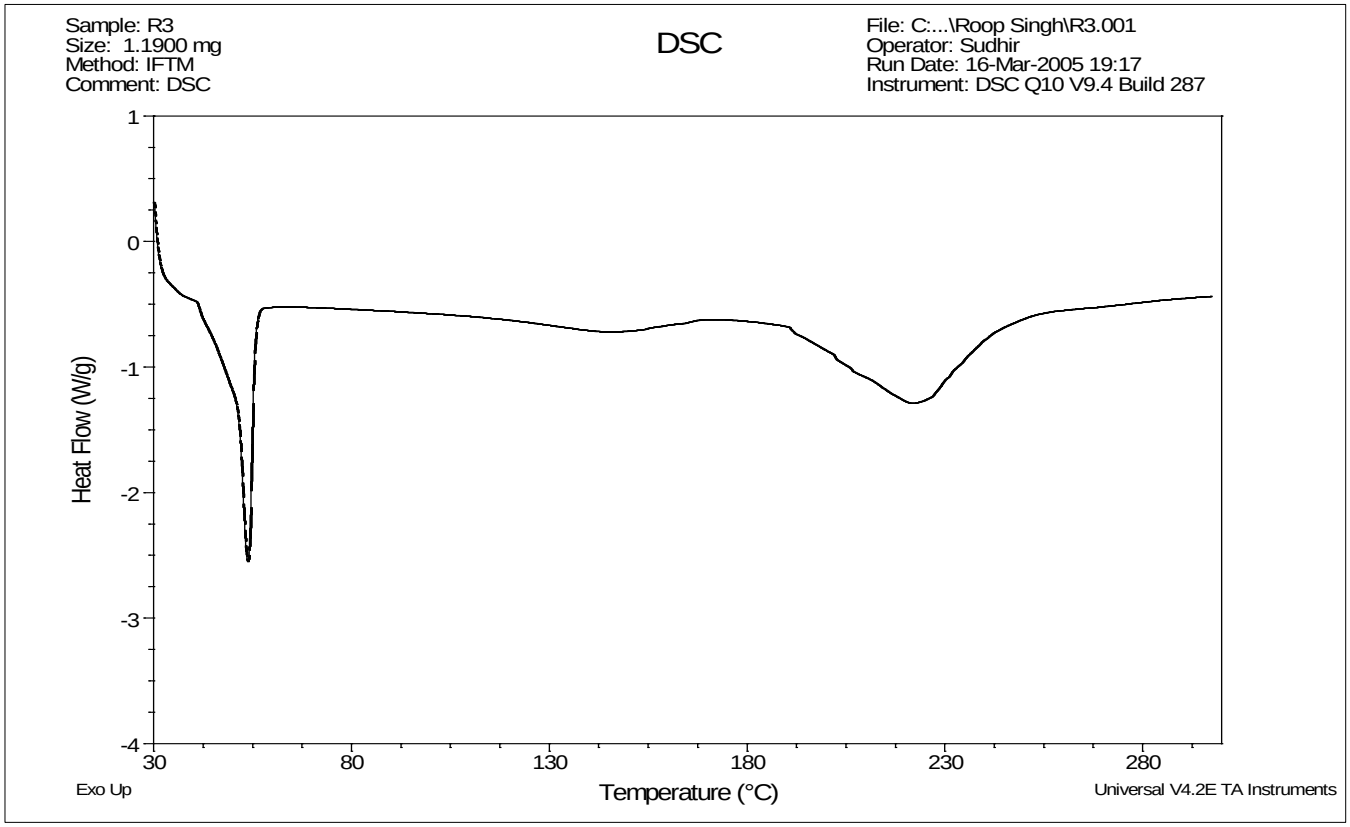

Fig 12: DSC Study of Paracetamol with Poloxamer 407

DSC Study of Paracetamol with Poloxamer 407: The DSC thermo gram of low Paracetamol Poloxamer 407 showed a broad endothermic peak at endothermic peak at 53.85ºC which indicate glass transition temperature of polymer. Broad endothermic peak at 53.85^{0}C and at 222.0 to 256.15^{0}C that attributes to the slow degradation the Paracetamol with polymer.

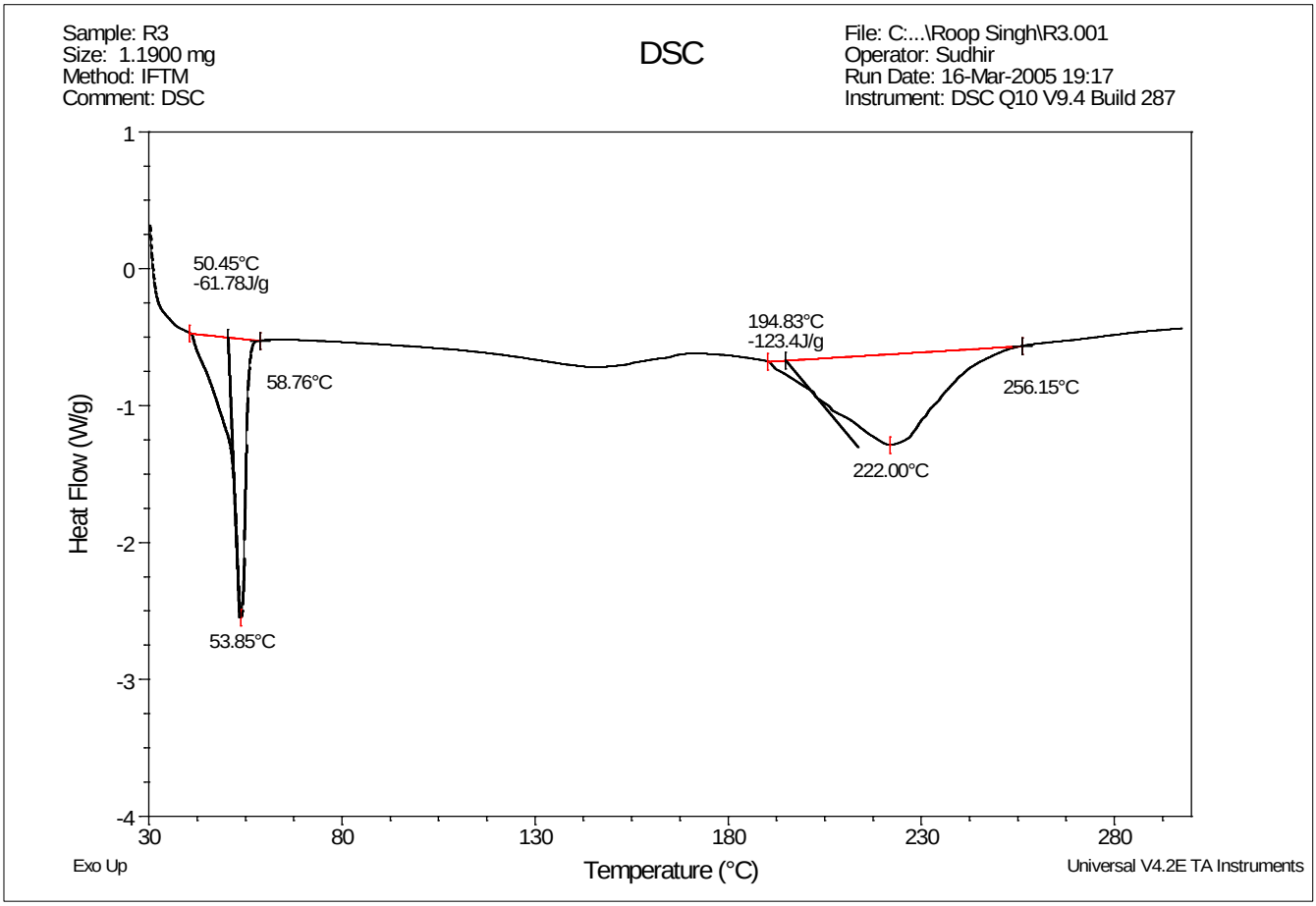

Fig 13: DSC Study of Paracetamol with Poloxamer 407 with peak values

Table 5: Pre-Compression Parameters and post compression parameters for evaluation of formulations

S. No.	Parameters	F-1	F-2	F-3	F4
1	Angle of repose	27°.16'±0.5°	28°.10'±0.6°	26°.0.2'±0.3°	28°.0.6'±0.3°
2	Loose Bulk Density (gm/cm^3)	0.55±0.08	0.59±0.1	0.52±0.05	0.58±0.05
3	Tapped Bulk Density (gm/cm^3)	0.68±0.09	0.75±0.12	0.63±0.08	0.65±0.08
4	Carr's index (%)	19.44±0.7	21.33±1.3	17.46±0.9	18.46±0.9
5	Hardness Test (kg/cm^2)	5.3±0.17	4.2±0.10	6.5±0.25	6.5±0.25
6	Friability Test	0.69±0.9	0.42±0.07	0.86±0.11	0.80±0.11
7	Weight Variation Test	2.66±0.89	4.11±0.65	2.99±0.52	2.50±0.52
8	Drug Content Uniformity	295.21±0.51	294.44±0.5	296.21±0.55	298.21±0.55
9	Wetting Time (min)	11±1.0	10±0.9	12±1.2	11±0.2
10	Hauser's Ratio	.80±83	0.79±83	0.75±80	0.80±90

Angle of repose: Angle of repose is indicative of flow behavior of the powders. Angle of repose was determined to find out the flow ability of drug and excipients combination. Shows the results obtained for angle of repose of all the formulations. The values were found to be in the range of 26°.16' to 30°.48'. All formulations showed angle of repose within 31° which indicates good flow of powder mixture.

Bulk Density: Both loose bulk density (LBD) and tapped bulk density (TBD) results were shown in Table 6.

Table 6: Loose bulk density and tapped density

S. No.	Parameter	Result
1.	Loose bulk density (LBD)	0.52 g/cm^3 to 0.59 g/cm^3
2.	Tapped bulk density (TBD)	0.63 gm/cm^3 to 0.75 gm/cm^3

The values obtained lies within the acceptable range and not large differences found between loose bulk density and tapped bulk density. This result helps in calculating the% compressibility of the powder.

Compressibility index: Percent compressibility of powder mix was determined by Carr's compressibility index. The percent compressibility for all the twelve formulations lies within the range of 13.23 to 17.46. All formulations showed good compressibility hence can be directly compressed.

Post-compression Parameters

- **Appearance:** Examination of tablets from each batch showed flat circular shape with no cracks and having white and reddish white color.
- **Thickness test:** The thickness of the tablets from each formulation was measured by using dial caliper by picking the three tablets randomly. The values are almost uniform in specific method. In direct compression method was found in the range from 3.05 mm to 3.65 mm.
- **Hardness Test:** Hardness test was performed by Monsanto tester. Hardness was maintained to be within 6.5 kg/cm^2 to 7.2 kg/cm^2. Since sustained release tablets are harder than fast disintegration. These tablets can therefore be fragile and need individual packaging. The lower standard deviation values indicated that the hardness of all the formulations were almost uniform in specific method and possess good mechanical strength with sufficient hardness. To obviate the difference in the hardness, we added super binder in the formulations. In fact, a sustained release tablet must release in the stomach.
- **Friability Test:** All formulations possess good mechanical strength. The study results were found well within the approved range (<1%) in all the formulation. Friability of the tablets, lower than 1% in most cases, indicates that the developed formulations can processed and handled without excessive care. Friability of tablets = 0.42% to 0.86% 5.8.5.
- **Weight Variation Test:** The percentage weight variations for all the formulation are calculated successfully. The average weight of the formulation was 830 mg. All the tablets passed weight variation test as the% weight variation was within the pharmacopoeia limits of ±7.5%.

  Standard value
  Weight of 1 tablet = 830mg
  Weight of 10 tablets = 8300 mg
  Practical value
  Weight of 10 tablets = 8000 mg
  Weight variation = 8300-8000 mg = 300 mg
  Percent weight variation (%) = 2.66%

  The weights of all the tablets were found to be uniform. The result indicates the formulation contains the appropriate amount of drug.

- **Drug Content Uniformity:** The content uniformity was performed for all formulations. Five trials from each formulation were analyzed using spectrophotometer. The mean value and standard deviation of all the formulations were calculated. The drug content of the tablets was found between 94.44 ± 0.5 mg to 96.21 ±0.55 mg for Paracetamol respectively. The results indicated that, in all the formulations the drug content was uniform. The cumulative percentage drug released by each tablet in the *in vitro* release studies were based on the mean content of the drug present in the respective tablet.

  Drug Content Uniformity = 94.44 ± 0.5mg to 96.21 ±0.55 mg

- **Wetting Time:** Wetting is closely related to inner structure of tablets. Tablet breakdown was affected by the wicking and swelling of the binders, and the wicking property would be closely related to the porosity. Both the porosity and average pore size of tablets in all formulation decreased with increase of the tablet hardness. The wicking property may also correlate to the wetting behavior of the tablet. Wetting time of the tablet containing (Poloxamer 407) and PVP K30 (Isopropyl alcohol) was 10-12 minutes.
  In the range of tablet hardness 2-5 kg, wetting time was not affected by tablet hardness the breakdown time of the formulation in the stomach increases with increase the wetting time. To long time of dissolution in the stomach

for the tablet, the addition of the binders having a property of slow PVP K30 in isopropyl alcohol uptake in the formulation is preferable. It was considered that the slow dissolution would be due to its wet ability. All super binders have low water absorption capacity and wicking property which lead to slower swelling of the binders. The tablet containing Poloxamer significantly slow swelled and closed the shape. It has been known that Poloxamer 407 absorbs a less amount of PVP K30 in Isopropyl alcohol, and slow dissolution. The wetting time of the tablet is directly affected to the dissolution of the tablet in the dissolution medium. We can call that dissolution time of the tablet is directly proposal to wetting time of tablet.

- ***In vitro* Dissolution Studies:** All the three formulations were subjected for *in vitro* dissolution studies using tablet dissolution tester USP XXIII. The samples were withdrawn at different time intervals and analyzed at 241nm respectively. Cumulative drug release and cumulative% drug release were calculated on the basis of mean amount of Paracetamol present in respective formulations. The results obtained in the *in vitro* drug release for the formulations F1, F2 and F3 tabulated in Table 7.

Table 7: The results obtained in the *in vitro* drug release for the formulations F1, F2 and F3 tabulated

S. No.	Time	Aborbance F1	Aborbance F2	Aborbance F3	Aborbance F4
1	15 min	0.116	0.154	0.144	0.190
2	30 min	0.160	0.201	0.270	0.270
3	1 Hrs	0.246	0.260	0.322	0.350
4	2 Hrs	0.320	0.322	0.390	0.413
5	3 Hrs	0.452	0.380	0.465	0.490
6	4 Hrs	0.580	0.412	0.480	0.576
7	5 Hrs	0.630	0.480	0.565	0.660
8	6 Hrs	0.740	0.570	0.620	0.698
9	7 Hrs	0.890	0.680	0.690	0.795
10	8 Hrs	0.962	0.723	0.779	0.856

Sustained release tablets are design to dissolve in the stomach or intestine (large or small) and usually release and allow the active agent to dissolve remarkably slowly in the gastric juice. Association between the drug and binders as in present case, introduces a control of the release differences between uncoated formulations, where the drug is associated only with a hydrophobic, and free drug were observed in preliminary tests while the formulation take more than 15 minutes to dissolve, the free drug reaches complete dissolution in more time. The control of the release is even more important for tablets, where Paracetamol release is affected only by the association with super binders. The release of Paracetamol from all the formulations containing the Poloxamer407 as super binder is <60-70% after 8 hours.

Calculation table for formulation-1

S. No.	Time	Absorbance	Concentration µg/ml	Amt. of drug release (mg)	% CDR
1	15min	0.116	1.87	33.66	6.73
2	30min	0.160	2.64	47.5	9.50
3	1 hrs	0.246	4.15	74.70	14.94
4	2hrs	0.320	5.45	98.10	19.62
5	3hrs	0.452	7.77	139.86	27.97
6	4hrs	0.580	10.01	180.80	36.03
7	5hrs	0.630	10.89	196.02	39.20
8	6hrs	0.740	12.82	230.76	46.15
9	7hrs	0.890	15.45	278.10	55.67
10	8hrs	0.962	16.71	300.78	60.15

Calculation table for formulation 2

S. No.	TIME	Absorbance	Concentration µg/ml	Amt. of drug release (mg)	Amt. of drug release (mg)
1	15min	0.154	2.54	45.72	9.14
2	30min	0.201	3.36	60.48	12.09
3	1 Hrs	0.260	4.40	79.20	15.84
4	2 Hrs	0.322	5.45	98.10	19.62
5	3 Hrs	0.380	6.50	11.7	23.40
6	4 Hrs	0.412	7.07	127.26	25.45
7	5 Hrs	0.480	8.26	148.64	29.73
8	6 Hrs	0.570	9.84	177.15	35.42
9	7 Hrs	0.680	11.71	211.86	42.37
10	8 Hrs	0.723	12.52	225.36	45.07

Calculation table for formulation 3

S. No.	Time	Absorbance	Concentration µg/ml	Amt. of drug release(mg)	Amt. of drug release(mg)
1	15min	0.144	2.36	42.63	8.49
2	30min	0.270	4.92	88.73	17.74
3	1 Hrs	0.322	5.49	98.84	19.76
4	2 Hrs	0.390	6.68	120.31	24.06
5	3 Hrs	0.465	8	144	28.80
6	4 Hrs	0.480	8.26	148.73	29.74
7	5 Hrs	0.565	9.75	175.57	35.11
8	6 Hrs	0.620	10.71	192.94	38.58
9	7 Hrs	0.690	11.94	215.05	43.01
10	8 Hrs	0.779	13.50	243.15	48.63

Calculation table for formulation 4

S. No.	Time	Absorbance	Concentration µg/ml	Amt. of drug release (mg)	Amt. of drug release (mg)
1	15min	0.190	2.54	45.78	4.15
2	30min	0.270	3.36	60.63	12.12
3	1 Hrs	0.350	4.40	79.26	15.85
4	2 Hrs	0.413	5.49	98.84	14.76
5	3 Hrs	0.490	6.50	117.15	23.43
6	4 Hrs	0.576	7.07	127.26	25.45
7	5 Hrs	0.660	8.26	148.68	29.61
8	6 Hrs	0.698	98.84	177.15	35.43
9	7 Hrs	0.795	11.77	211.89	42.37
10	8 Hrs	0.856	1.11	19.98	3.99

The presence of the Poloxamer-407 in the formulations F1produced tablets dissolving very slowly. These tablets can be defined as “Sustained Release”. It emerged also that the release appears to be governed by simultaneous diffusion/ erosion, since ‘n’ values are lower then 0.5, where the release is non-linearly related to the squire root of time (n=0.5) and diffusion appears the dominant mechanism of the release.

Finally, it is interesting to note that despite the presence of Poloxamer-407 as binder in the formulations, the pure Poloxamer-407 displays very slow dissolution. It was in fact reported that a close association between a drug and polymer enables the formation of a state suitable to improve the dissolution rate in the present case. The preliminary blend of the drug with polymer does not prevent any contact between the drug and polymer, when present in the formulation, promotion dissolution mechanism.

Curve Fitting Analysis

For formulation- 1: The results of dissolution data fitted to various drug release kinetic equations to determine the drug release order from the formulations. Release rates were subjected to kinetic treatment. The data were grouped according to two modes

- Cumulative percent drug released Vs. Time
- Log cumulative percent drug release Vs. Time.

Table 8: Calculated%CDR & log%CDR of formulations

S. No.	Time	%CDR				Log % CDR			
		F-1	F-2	F-3	F4	F-1	F-2	F-3	F4
1.	15min	6.73	9.14	8.49	1.41	0.82	0.96	0.92	0.14
2.	30min	9.50	12.09	17.74	17.05	0.97	1.08	1.24	1.23
3.	1 hrs.	14.94	15.84	19.76	21.52	1.17	1.19	1.29	1.33
4.	2 hrs.	19.62	19.62	24.06	25.51	1.29	1.29	1.38	1.40
5.	3 hrs.	27.97	23.40	28.80	30.37	1.44	1.36	1.43	1.48
6.	4 hrs.	36.03	25.45	29.74	35.81	1.55	1.40	1.47	1.55
7.	5 hrs.	39.20	29.73	35.11	41.11	1.59	1.47	1.54	1.61
8.	6 hrs.	46.15	35.37	38.58	43.51	1.66	1.54	1.58	1.63
9.	7 hrs.	55.67	42.37	43.01	49.64	1.74	1.62	1.63	1.69
10	8 hrs.	60.15	43.07	48.63	53.49	1.77	1.65	1.68	1.72

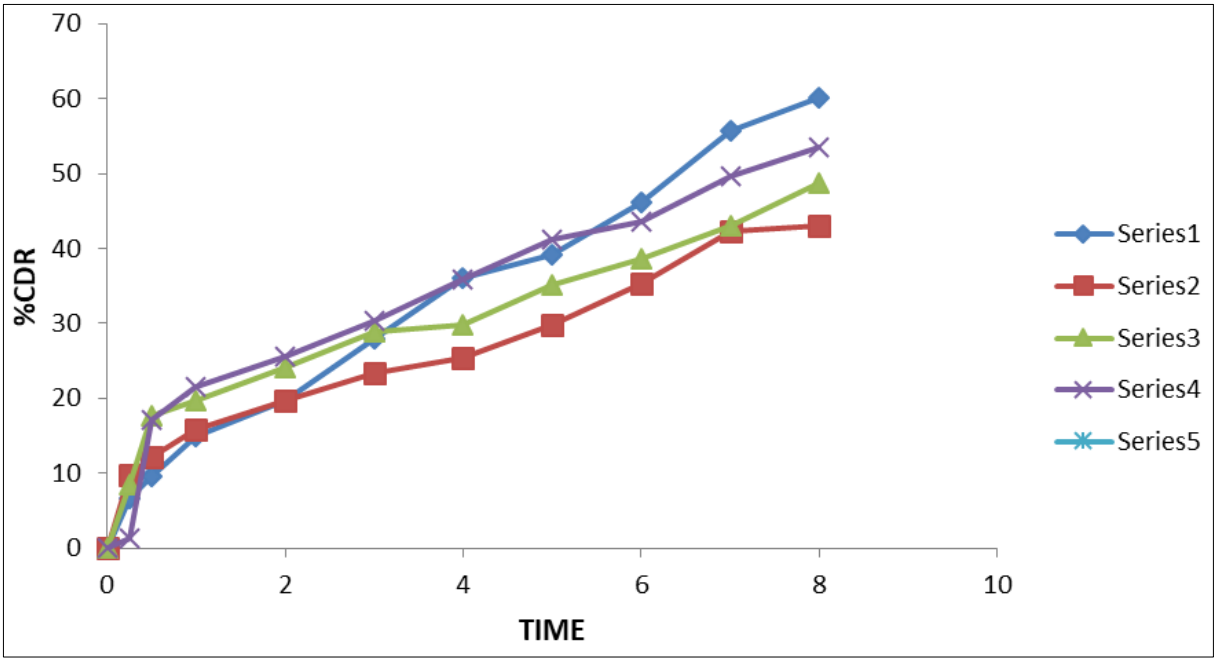

Fig 15: Graph: Cumulative percent drug released V/s. Time

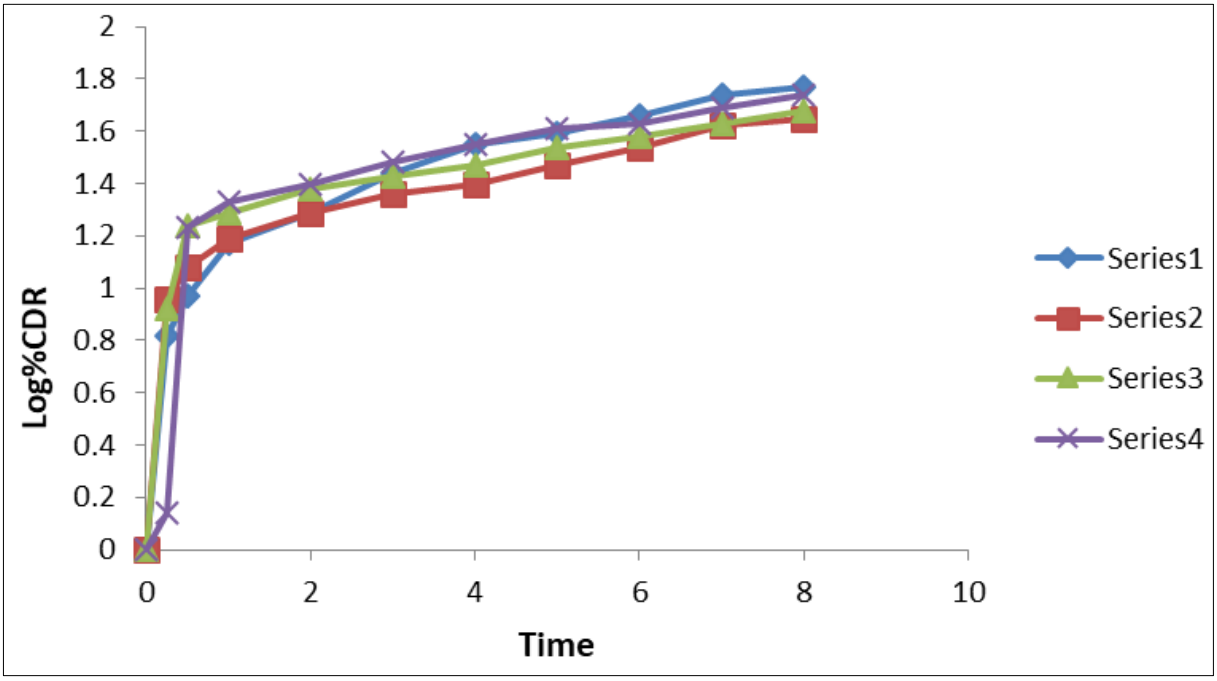

Fig 16: Graph of Log cumulative percent drug release Vs. Time

The mechanism of drugs released from the matrix system was studied by fitting the dissolution data in four did afferent models.

- Zero Order Equation
- First Order Equation
- Korsmeyer-Peppas Equation
- Higuchi Square Root Equation

The results were found to be linear for zero order release. It is concluded that release of drug from formulations F1 followed Zero order. The plots are represented in graphs.

Table 9: Calculated log%DR, Square root Time and log Time of formulations

S. No.	Time	Square root Time	Log Time	Log%DR			
				F1	F2	F3	F4
1	15min	0.5	0.60	0.82	0.96	0.92	0.14
2	30min	0.70	0.30	0.97	1.08	1.24	1.23
3	1	1	0	1.17	1.19	1.29	1.33
4	2	1.41	0.30	1.29	1.29	1.38	1.40
5	3	1.273	0.47	1.44	1.36	1.43	1.48
6	4	.2	0.60	1.55	1.40	1.47	1.55
7	5	2.23	0.69	1.59	1.47	1.54	1.61

8	6	2.244	0.77	1.66	1.54	1.58	1.63
9	7	2.64	0.84	1.74	1.62	1.63	1.69
10	8	2.82	0.90	1.77	1.65	1.68	1.72

Table 10: Formulation F1 Zero order, first order, higuchi and Korsemeyer-Peppas models

S. No.	Time	Amt. of drug release (mg)	Log% DR	% CDR	Log% CDR	Square root time	Log Time
1.	0 min.	0	0	0	0	0	0
2	15min	33.66	0.82	6.73	0.82	0.5	0.60
3	30 min.	47.5	0.97	9.50	0.97	0.70	0.30
4	1 hrs.	74.70	1.17	14.94	1.17	1	0
5	2 hrs.	98.10	1.29	19.62	1.29	1.41	0.30
6	3 hrs.	139.86	1.44	27.97	1.44	1.73	0.47
7	4 hrs.	180.80	1.55	36.03	1.55	2	0.60
8	5 hrs.	196.02	1.59	39.20	1.59	2.23	0.69
9	6 hrs.	230.76	1.66	46.15	1.66	2.44	0.77
10	7 hrs.	278.10	1.74	55.67	1.74	2.64	0.84
11	8 hrs.	300.78	1.77	60.15	1.77	2.82	0.90

Further, the models fitting of the release profiles were performed using Microsoft excel software to observe the release. The correlation coefficient values obtained for all four models. After comparing the data of all Pharmacokinetic models such as Zero order, first order, Higuchi and Korsemeyer-Peppas models, it is concluded that the release of drug from the formulations was governed by their its solubility and the particle size and they following these models as release models. It is observed that formulations F1 dissolution (release) of the drugs follows zero order.

Then value could be used to characterize different release mechanisms in the present study 'n' values were determined within 0.326 to 0.4461 for formulations-1. Drug release occurred via flicking diffusion mechanism as 'n' value range was found within 0 to 0.5.

Zero Order Equation: A chemical reaction in which the rate of reaction is constant and independent of the concentration of the reacting substances.

The rates of these Zero order reaction do not vary with increasing nor decreasing reactant concentration. This means that the rate of the reaction is equal to the rate constant of that reaction a constant amount of drug is eliminated per unit time of example 10 mg of drug may be eliminated per hour.

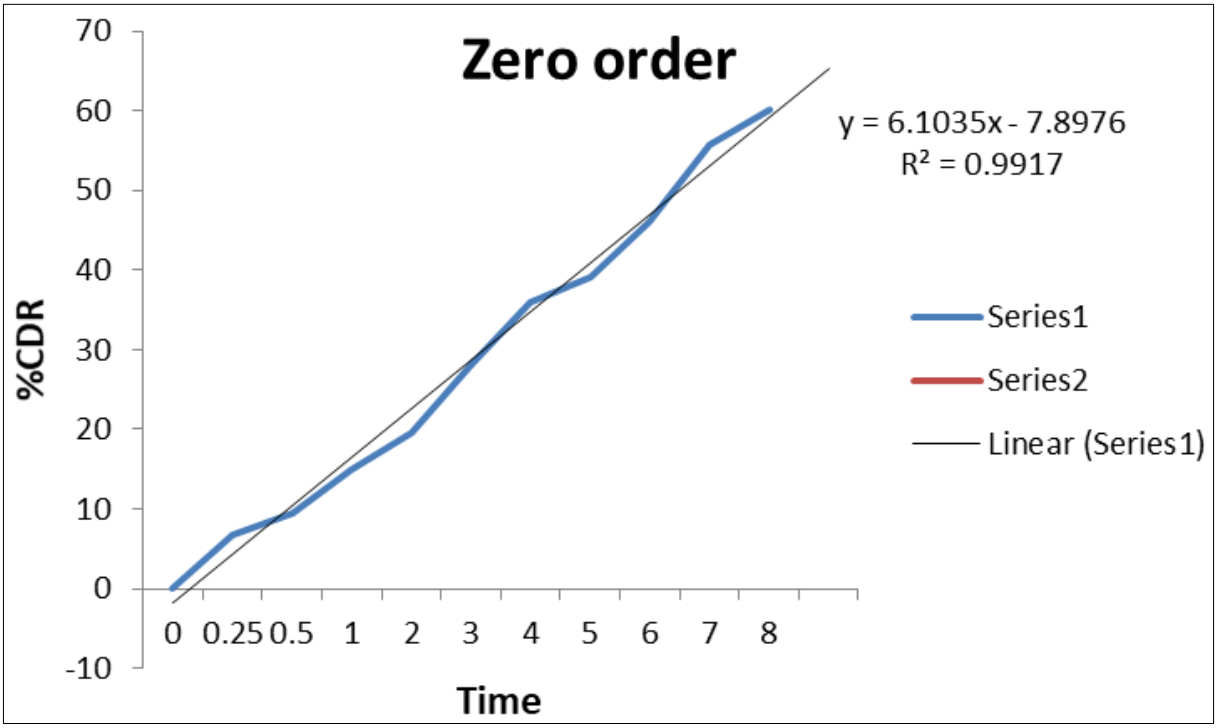

Fig 18: Zero Order Equation

First Order Equation: For the reaction to be of first order, the rate constant of a first order reaction has only time unit. It has no concentration unit. This means the numerical value of k for a first order reaction is independent of the unit in which concentration is expressed.

First order kinetics occurs when a constant proportion of the drug is eliminated per unit time. Rate of elimination is proportional to the amount of drug in the body. The higher the concentration, the greater the amount of drug eliminated per unit time.

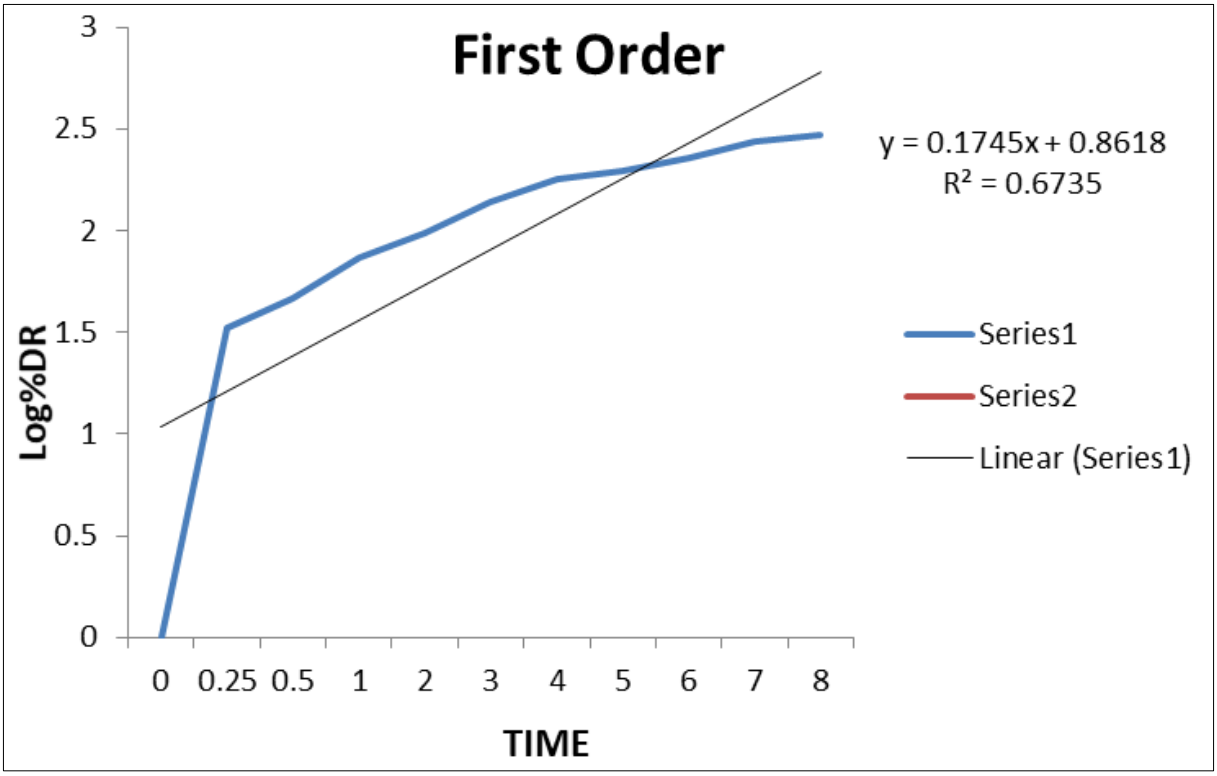

Fig 19: First Order Equation

Korsmeyer-Peppas Equation: The Korsmeyer-Peppas equation is piloted between log percent commutative drug release and log time.

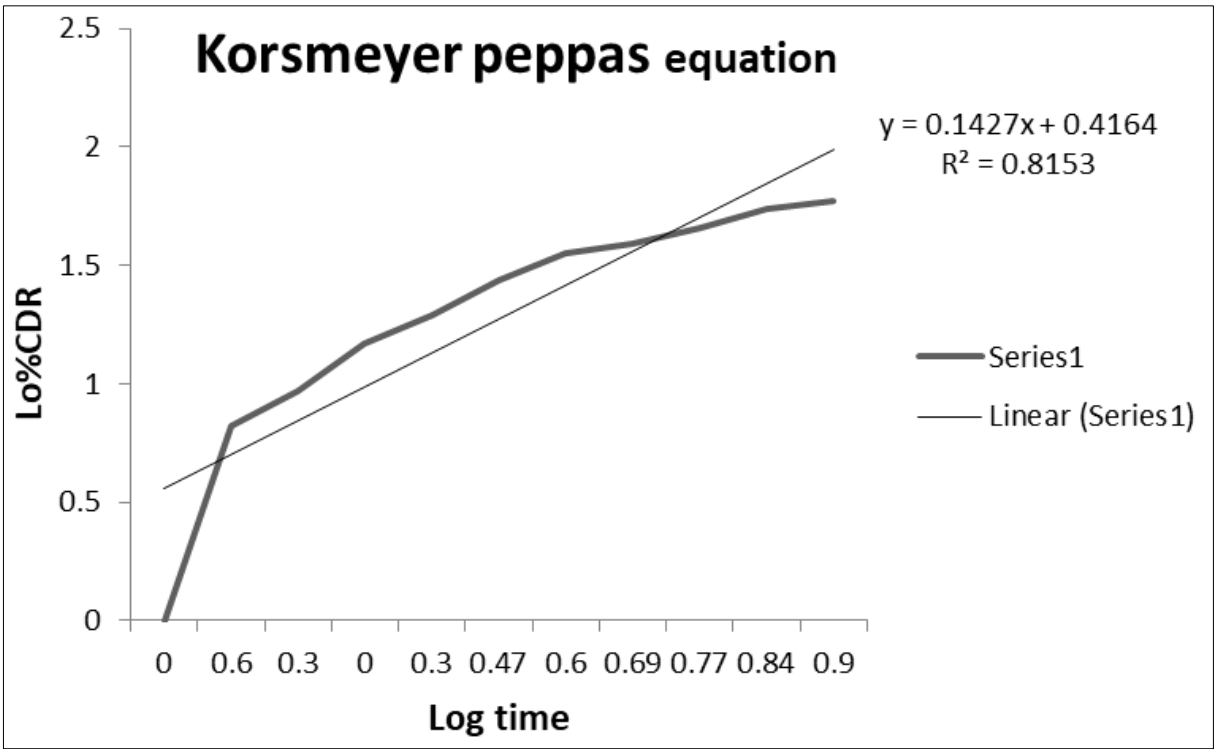

Fig 20: Korsmeyer-Peppas Equation

Higuchi Square Root Equation: For the Higuchi equation the graph is plated between percent cumulative drug release and square root of time.

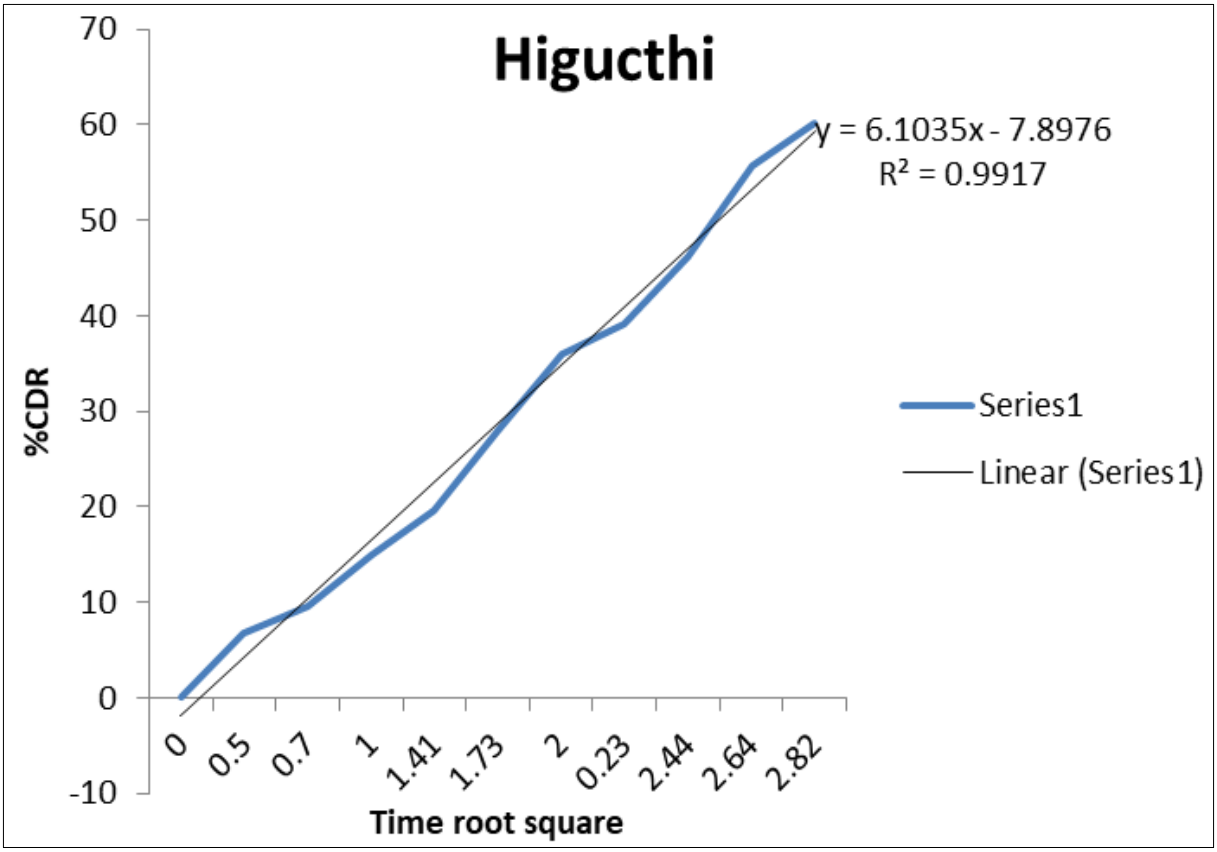

Fig 21: Higuchi Square Root Equation

Table 11: R^2 Values and n values of Models

Formulation	Zero Order Model	First Order Model	Higuchi Model	Korsmeyer poppas Model	
	R^2	R^2	R^2	R^2	N
F-1	**0.991**	0.673	0.815	**0.991**	0.142
F-2	0.985	0.989	0.978	0.953	0.074
F-3	0.958	0.807	0.595	0.580	0.113
F4	0.220	0.109	0.284	0.109	0.38

Stability Studies

The formulations F-1, F-2 -F3 and F-4 were selected for stability studies on the basis of their high cumulative% drug release and *in vitro* disintegration time, wetting time, *in vivo* disintegration time and *in vitro* dispersion studies. The stability studies were carried out at 25 °C/60% RH and 40 °C/75% RH for all the selected formulations up to 6 months. Formulations were analyzed at 1 month time interval for drug content and *in vitro* disintegration time. These formulations showed not much variation in any parameter. From the results it was concluded that, formulations F-1, F-2 -F3 and F-4 are stable and retained their original properties.

Shelf life (also referred to as expiration dating period)

The time period during which a drug product is expected to remain within the approved shelf life specification, provided that it is stored under the conditions defined on the container label. The combination of physical, chemical, biological, and microbiological tests and acceptance criteria that determine the suitability of a drug substance throughout its retest period, or that a drug product should meet throughout its shelf life. The shelf life of selected formulations F-1, F-2 F-3 and F4 were determined, average shelf life of Paracetamol sustained release tablets (F-1) was found to be 34.66 months, at storage condition of 25°C/60% RH.

Discussion

In present study, sustained release tablets of Paracetamol, formulations were successfully prepared using wet granulation method to improve bioavailability of drugs with slow dissolution of action by dissolved in stomach within 8-10 hours to achieve better patient compliance.

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