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Formulation and In vitro Evaluation of Mucoadhesive Buccal Tablets of Naproxen

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Abstract
The objective of this study is to develop and evaluate mucoadhesive buccal tablets containing naproxen. Naproxen is a drug with a long half-life of 12-17 hours, making it suitable for formulation into mucoadhesive buccal tablets. These tablets offer rapid and complete absorption from the gastrointestinal tract, providing a high bioavailability of 95%. The formulation of naproxen mucoadhesive buccal tablets was achieved using a direct compression technique. Various polymers such as sodium alginate, carbopol, and chitosan were incorporated to investigate their impact on key parameters including drug content, in- vitro swelling studies, and in-vitro disintegration. Compatibility studies were conducted using FTIR and DSC methods. The prepared mucoadhesive buccal tablets were subjected to extensive evaluation tests. The optimized formulation showcased promising results with regards to in-vitro swelling studies (3.10±1.76), in-vitro disintegration (238.63±3.89), and drug content (98.95±0.026). These tablets were further evaluated for thickness, hardness, friability, weight variation, surface pH, drug content, and disintegration time. The release exponent for the formulation indicated super case II transport with a cumulative drug release of 97.87%.

Keywords: Direct compression method, Naproxen, Carbopol, Sodium alginate, Chitosan, HPMC-K4M.

Introduction

The oral route of drug administration is widely preferred due to its convenience, self-medication capabilities, accurate dosage, flexible dosing schedules, and high patient compliance rates [1, 2]. However, this route of administration has certain drawbacks, including the first-pass effect, gastrointestinal enzymatic degradation, and slow onset of action [3]. To address these challenges, alternative drug delivery methods such as mucoadhesive and sublingual drug delivery have emerged as promising alternatives [4]. Mucoadhesive dosage forms have been specifically designed to adhere to the mucosal surface, enhancing drug retention at the site of application and providing controlled release for improved therapeutic outcomes [5]. Examples of mucoadhesive drug delivery systems include adhesive patches, gels, tablets, films, and discs [6]. Mucosal surfaces, such as those in the gastrointestinal (GI) tract, urogenital tract, ear, nasal route, and airways, are potential sites for the application of mucoadhesive drug delivery systems. These surfaces are lined by either a single-layered epithelium, as found in the GI tract, bronchi, and intestines, or a multilayered stratified epithelium, as found in the esophagus, vagina, and cornea [6, 7]. One such mucosal site with high vascularization and direct drainage of blood flow into the jugular vein is the buccal mucosa, which presents a promising option for drug absorption. Buccal drug delivery involves the absorption of medication through the mucosal lining of the buccal cavity. This approach offers advantages such as ease of drug administration, the possibility of promptly terminating drug delivery in case of unexpected side effects or emergencies, and the potential for incorporating enzyme inhibitors or permeation enhancers [9, 10]. Various mucoadhesive polymers, including natural, semi-synthetic, and synthetic ones, are utilized in mucoadhesive drug delivery systems. These polymers become adhesive upon hydration and can be used to target drugs to specific regions of the body. When the mucoadhesive product encounters the mucosal membrane, it swells and spreads, establishing deep contact with the mucosal layer. The mucoadhesive materials (polymers) are activated by moisture, resulting in slow drug release [11, 12].

Rheumatoid arthritis (RA) is an inflammatory disease characterized by severe pain, stiffness, and swelling in the peripheral joints. Inflammation is initiated through the interaction between antigen-presenting cells (APCs) and CD+T cells, leading to the activation of macrophages and the release of proinflammatory cytokines such as IL-1 and TNFα. These cytokines activate synovial fibroblasts and chondrocytes in the surrounding articular cartilage, which then release enzymes that degrade proteoglycans and collagen, causing tissue destruction. RA is more prevalent in women compared to men, affecting approximately 1- 2% of the global population. Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly prescribed to manage pain and inflammation associated with RA. Naproxen (NAP), belonging to the NSAIDs' propionic acid class, is widely used to treat pain, inflammation, and stiffness caused by conditions such as osteoarthritis, rheumatoid arthritis, tendinitis, bursitis, and psoriatic

arthritis. Developing a naproxen formulation with an improved controlled release pattern could potentially offer significant advantages in managing inflammatory and painful states within the body. Naproxen, classified under Biopharmaceutical Classification System (BCS) class II drugs, exhibits good membrane permeation but low solubility. The anti-inflammatory effects of naproxen are mediated through the inhibition of COX-1 and COX-2, which play a role in prostaglandin E2 production when activated by inflammatory mediators. The use of oral NSAIDs can lead to gastrointestinal complications such as peptic ulcers and hemorrhages. Like other NSAIDs, naproxen also poses the risk of gastric bleeding and ulceration after oral administration. These gastric damage events are primarily associated with increased gastric acid secretion, reduced mucus, and bicarbonate secretion, decreased mucosal cell proliferation, and compromised blood flow mediated by prostaglandins [13].
Considering the potential side effects associated with the oral route of naproxen administration, topical drug delivery via mucoadhesive buccal tablets offers an alternative with minimal side effects, including peptic ulcer disease and gastrointestinal hemorrhage. Therefore, the development of sustained-release formulations provides a favorable alternative for reducing dosing frequency, achieving prolonged drug effects with improved bioavailability, and enhancing the safety and efficacy of the medication. In this study, naproxen mucoadhesive buccal tablets were formulated using the direct compression technique. Sodium alginate, Carbopol, and chitosan were varied as polymers to investigate their impact on drug content, in-vitro swelling studies, and in-vitro disintegration. FTIR and DSC studies were conducted to assess compatibility. Mucoadhesive buccal tablets were prepared using the direct compression method, followed by various evaluation tests.

Materials and Methods

The materials used in this study included Naproxen (API) obtained from Navakar Biochemical, Gujarat. Bucco adhesive polymers used were Carbopol, Chitosan, Sodium alginate, and HPMC K4M, sourced from Loba Chemicals Pvt Ltd, Merck Limited, and Fisher Scientific. The penetration enhancer 36erosol came from Loba Chemicals Pvt Ltd. Sweetener mannitol, binder/diluent MCC (microcrystalline cellulose), glidant magnesium stearate, and lubricant talc were obtained from Merck Limited and SD Fine Chemicals. Instruments and equipment used included a digital balance from Infra, India, for accurate weighing, a 10-station rotary compression machine (Accura Punching Machine) for tablet compression, vernier calipers from Gogna for dimensional measurements, an analytical digital balance (Digisun Electronics) for precise weighing, a hardness tester, friability tester, and disintegration apparatus supplied by Electrolab, India. Fourier Transmission Infrared radiation (FTIR) analysis was performed using a Shimadzu IR-470 instrument from Tokyo, Japan. Dissolution testing was conducted using a dissolution apparatus from Lab India, and UV-visible Spectrophotometry was carried out using a Shimadzu instrument from Japan.

Methodology

Identification of Drug:
The following physical and chemical properties of the drug were tested in preliminary studies.
Organoleptic properties:
The drug's organoleptic properties, such as physical state, colour, odour, and so on, were reported using descriptive terminology. It helps with drug identification.
Determination of Melting point:
It is the simplest method of identifying the drug. Naproxen melting point was determined usinga laboratory melting point apparatus and the procedure outlined in the Indian Pharmacopoeia 2007 [14].
Solubility study:
Naproxen solubility in various solvents was determined using a micropipette to meet official standards. The drug's solubility was measured using various descriptive terminology from the Indian Pharmacopoeia, 2007 [14].
Calibration Curve Preparation:
To create a calibration curve for Naproxen, a stock solution was prepared by accurately dissolving 10 mg of the drug in 100 ml of phosphate buffer with a pH of 6.8. This resulted in a concentration of 100 µg/ml. From the stock solution, a series of standard dilutions were prepared using five 50 ml volumetric flasks. The dilutions were made to achieve concentrations of 2 µg/ml, 4 µg/ml, 8 µg/ml, 12 µg/ml, and 16 µg/ml, respectively. Each dilution was then analyzed using a UV-visible spectrophotometer at a wavelength of 331 nm. By plotting the concentration of Naproxen against the corresponding absorbance values obtained from the spectrophotometer, a calibration curve was generated. This curve allows for the determination of unknown concentrations of Naproxen in future samples based on their absorbance readings.

Drug-polymerCompatibility studies:
To investigate any possible interactions between the drug and the used bio adhesive polymers, infrared spectroscopy was adopted. The IR spectrum of pure drug, polymer as well as physical mixture of drug and polymer was taken, interpreted, and compared with each other. The IR spectra were carried out using Shimadzu

IR-470 spectrophotometer. The samples were prepared as potassium bromide discs compressed under a pressure of 6 tons. The scanning range was over 4000-400 cm^{-1} [15].

Table. 1: Formulation of mucoadhesive buccal tablets

S. No	Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Naproxen	250	250	250	250	250	250	250	250	250
2	Sodium alginate	25	25	25	-	-	-	-	-	-
3	Carbopol	-	-	-	25	25	25	-	-	-
4	Chitoson	-	-	-	-	-	-	25	25	25
5	HPMC K4M	25	50	75	25	50	75	25	50	75
6	Magnesium stearate	5	5	5	5	5	5	5	5	5
7	MCC	20	20	20	20	20	20	20	20	20
8	Mannitol	65	40	15	65	40	15	65	40	15
9	Talc	5	5	5	5	5	5	5	5	5
10	Aerosil	5	5	5	5	5	5	5	5	5
Grand total/tablet		400	400	400	400	400	400	400	400	400

Preparation of mucoadhesive buccal tablet:

The mucoadhesive buccal tablets containing Naproxen were prepared using the direct compression method. The formulations, as outlined in the designated table, incorporated chitosan, sodium alginate, Carbopol, and HPMC as the polymers. Before compression, all the ingredients, including the drug, polymers, and excipients, were passed through a No. 40 sieve to achieve a uniform particle size. Accurate weights were measured for each ingredient according to the batch formula, ensuring precise control over the composition of the tablets. The ingredients were thoroughly mixed in a blender to obtain a homogenous powder blend. Subsequently, the powder blends were compressed using a 10mm punch on a tablet punching machine, applying a pressure of 0.5 ton and a turret speed of 2 rpm. This process ensured the formation of mucoadhesive buccal tablets capable of adhering to the buccal cavity. The direct compression method allowed to produce tablets with consistent weight and composition, providing an effective drug delivery system [16,17].

Pre formulation studies:

Tapped Density:

It is the proportion of the powder's total mass to its tapped volume. After tapping the powder 750 times, the volume was calculated. tapped volume was noted if the difference between these two volumes is less than 2% [18, 19].

$Dt = M / Vt$

Carr's Index:

A material having values less than 20 to 30% is defined as the free-flowing material, based on the apparent bulk density, and tapped density, the percentage compressibility of the bulk drug was determined by using the following formula.

CI =TD-BD / TD×100

Hausner's ratio:
It indicates the flow properties of the powder and the ratio of Tapped density to bulk density of the powder or granules is called Hausner's ratio. It is measurement of frictional resistance of the drug. The Ideal range should be 1.2 – 1.5.
HR =TD / BD

Angle of repose
It is defined as maximum angle possible between the surface of the pile of powder and the horizontal plane. The angle of repose was determined by the funnel method suggested by Newman. Angle of repose is determined by the following formula.
Tan θ = h / r

Evaluation test of prepared tablets
All the batches were evaluated for average thickness, average weight and weight variation, hardness, friability, swelling index, surface pH, in vitro drug release, mucoadhesive strength, residence time and in vivo bioavailability studies.

Weight variation
20 tablets were collected from each formulation. The tablets were individually weighed from all the selected formulations; the average weight and standard deviation of 20 tablets was calculated.

Thickness
Thickness of the prepared tablets were measured using Vernier calipers. 20 tablets were collected from each formulation. Then the average thickness and standard deviation of 20 tablets was calculated [20].

Friability
Friability of the tablets was determined by using Roche friabilator. From each batch, 20 tablets were initially weighed and transferred into the friabilator. The friabilator was operatedat 25 rpm for 4 min. After 4 min the tablets were weighed again. The friability wasthen calculated using the formula [20].

$$\text{Friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \text{ X } 100$$

Hardness
Monsanto hardness tester was used for this purpose. The hardness of 10 tablets from each batch was measured. Then the average hardness and standard deviation was calculated [21].

Drug content:
The tablets were tested for their drug content uniformity. At randomly selected 6 tablets from each formulation were finely powder and dissolved in 100ml of phosphate buffer solution at pH 6.8. The solution was shaken thorough, and concentration of drug was determined spectrophotometrically.

Surface pH:
The surface pH of the buccal tablets was determined Battenberg method to investigatethe possibility of any in-vivo side effects likean acidic or alkaline pH may cause irritation to the buccal mucosa. A combined glass electrode was used for this purpose. The tablets were allowed to swell by keeping it in contact with distilled water (pH 6.5 ± 0.05) for 2 hrs at roomtemperature. The pH was measured by bringing the electrode in contact with the surface of the tablet and allowing it to equilibrate for 1 min [22].

In-vitro swelling studies
The swelling rate of mucoadhesive tablets were evaluated using 2% w/v agar gel plate. For each formulation, 10 tablets were weighed and average weight of each 10 tablets were calculated (W1). Then the tablets were placed with the core facing the gel surface in petridisheswhich are placed in an incubator at 37±0.1°C. The tablets were removed at time intervals of 1, 2, 3, 4, 5 and 6 hours, excess water on surface was absorbed using filter paper and swollen tablets were weighed. The average weight (W2) was determined and thenswelling index was calculated using this formula [23].
% Swelling index = [(W2-W1)/ W2] x 100

Determination of surface pH of tablets
Each batch's mucoadhesive tablets were allowed to swell on the surface of an agar plate for two hours.The surface PH was measured using pH paper placed on core surface of the swollen tablet.

In-vitro release studies
The USP type II dissolve test apparatus was used to examine the drug release rate from buccal tablets. The dissolution medium was 900 ml of phosphate buffer with a pH range of 6.8–0.5. At a rotational speed of 50 rpm and a temperature of 37 0.5°C, the release was conducted. The backing layer of the tablet was attached to the glass disc with cyanoacrylate adhesive because the tablet was only intended to release the medicine from one side. The disc was put in the dissolution vessel's bottom. At predetermined intervals, samples (5 mL) were removed and replaced with new media. After being filtered through filter paper, the samples were examined with a UV spectrophotometer at 480 nm.

Release kinetics.
In order to examine the release mechanism of drug from the tablets, the in-vitro drug release data of best buccoadhesive tablet formulation of Ketorolac was subjected to following release models.

Zero order equation
The zero order release kinetics can be obtained by plotting cumulative % drug released (vs) time (hours). It is ideal for the formulation to have release profile of zero order to achieve pharmacological prolonged action.

$$C = K_0 t \text{.....Equation 1}$$

Where, K_O = Zero order constant in conc. time t = Time in hours

First order equation
The graph was plotted as log % cumulative drug remaining (vs) time in hours.

$$\text{Log } C = \log Co + Kt/2.303 \text{..... Equation 2}$$

Where,
Co = Initial drug concentration K = First order constant t = Time in hours.

Higuchi Kinetics
The graph was plotted as % cumulative drug remaining (vs) square root of time.

$$Q = Kt^{1/2} \text{.....Equation 3}$$

Where,
K= Constant reflecting design variable system (Differential rateconstant) t = Time in hours.
The drug release rate is inversely proportional to the square root of time.

Korsmeyer – Peppas equation
To evaluate the mechanism of drug release, it was further plotted in Peppas equation as log cumulative % of drug released (vs) log time.

$$Mt/M\alpha = Kt^{n} \text{..... Equation 4}$$

Where,
Mt/Mα= Fraction of drug released at time tt = Release time
L = Kinetics constant (Incorporating structural and geometric characteristics of the formulation) n = Diffusional exponent indicative of the mechanism of drug release.

Table 2: Release mechanisms based on n-value.

Release mechanisms	n-value
Fickian diffusion	n<0.5
Non-Fickian transport	0.45<n<0.89

Case II transport	n=0.89
Super case II transport	n>0.89

The n value obtained is used to characterize different release mechanisms for cylindrical shaped matrices.
Hixson and Crowell erosion equation

$$Qo^{1/3} - Qt^{1/3} = KHCt \quad \text{..... Equation 5}$$

Where,
Qt = Amount of drug released at time t Qo = Initial amount of drug
K_{HC} = Rate constant for Hixson Crowell equation

Results
Identification of Drug: Organoleptic Properties: Color: White to off-white **State:** Crystalline powder **Odour**: odour less
Determination of Melting Point: Melting point of Naproxen was found to be 153 ºC. The official melting point range for Donepezil is between 152 - 154°C. Hence, results were compiled the limits specified in official Book.

Solubility Study:

Table 3: The solubility of naproxen various solvents

S.No.	Name of solvent	Solubility	Parts of solvent required for 1 part of solute
1	pH 6.8 phosphate buffer	Freely soluble	From 1 to 10
2	Methanol	Freely soluble	From 1 to 10
3	Ethanol	Sparingly soluble	From 30 to 100
4	Water	Freely soluble	From 1 to 10

8.1.1 Pre-compressional Evaluations

8.1.1.1 Calibration curve

The calibration curve of drug obeyed Beer Lambert's law in the concentration range of 0-10 µg/ml (R^2 = 0.9982) at 331nm and the result is shown in table 4 and plot is shown in fig. 1.

Table 4: Calibration curve of Naproxen in pH 6.8

Sl. No.	Concentration (µg/ml)	Absorbance at 322nm
1	2	0.099
2	4	0.227
3	6	0.400
4	8	0.612
5	10	0.722

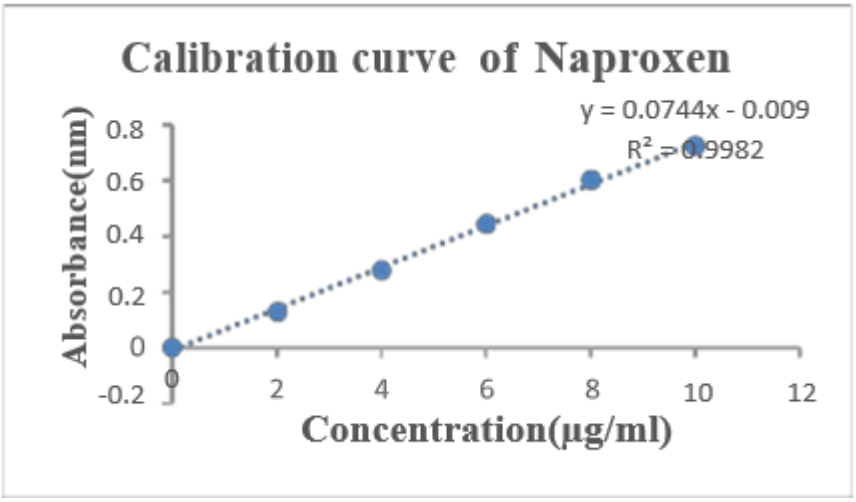

Figure 1:

FTIR spectrum of Naproxen confirmed the presence of different functional groups as in Table and Figure. The different peaks obtained from IR spectrum were also found to match with the IR spectrum of naproxen given in the official books of reference.

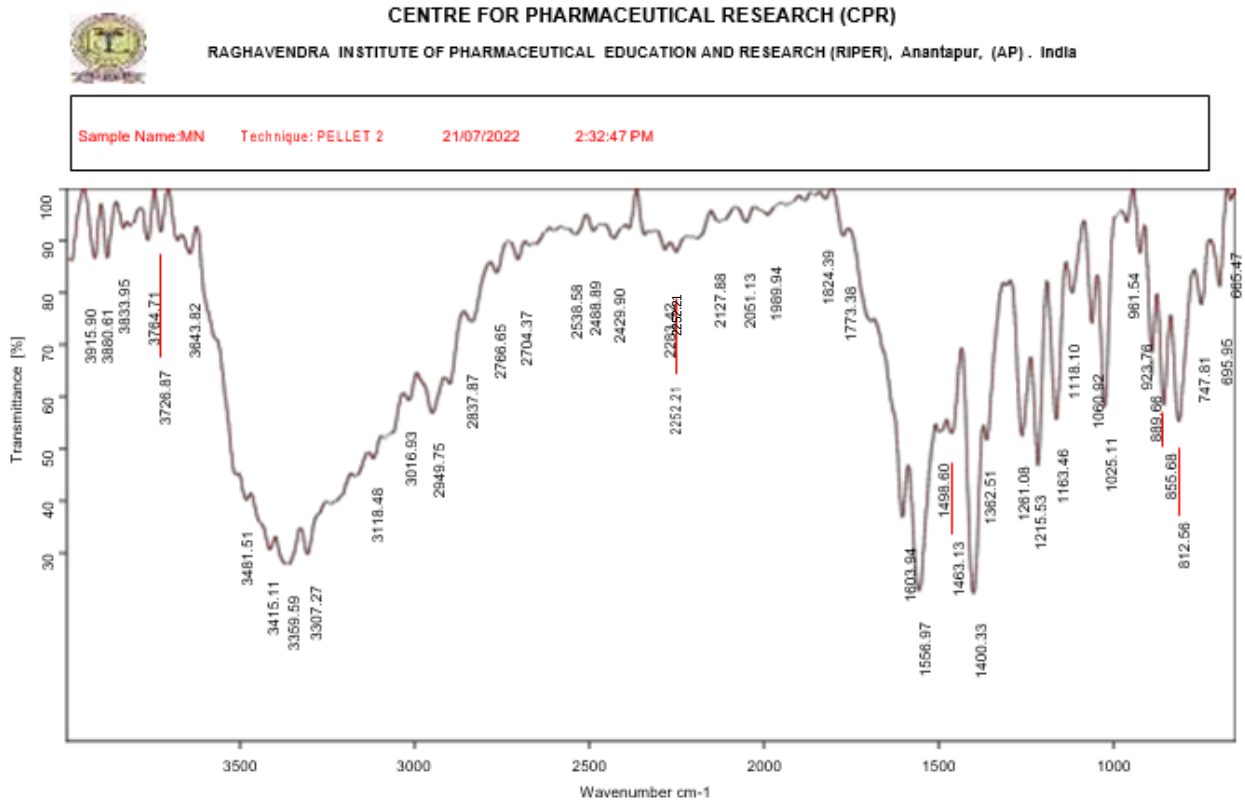

Figure 2: FTIR spectrum of naproxen Table 5: IR Spectral Analysisof naproxen

FTIR range	Absorption	Group	Compound
1261.08	1275-1200	C-O stretching	Alkyl aryl ether
1603.94	1650-1566	C=C stretching	Conjugate alkene
2949.75	3000-2840	C-H stretching	Thiol
3359.59	3533-3267	C-H stretching	Alkyne
1382.51	1440-1395	O-H bending	Carboxylic acid

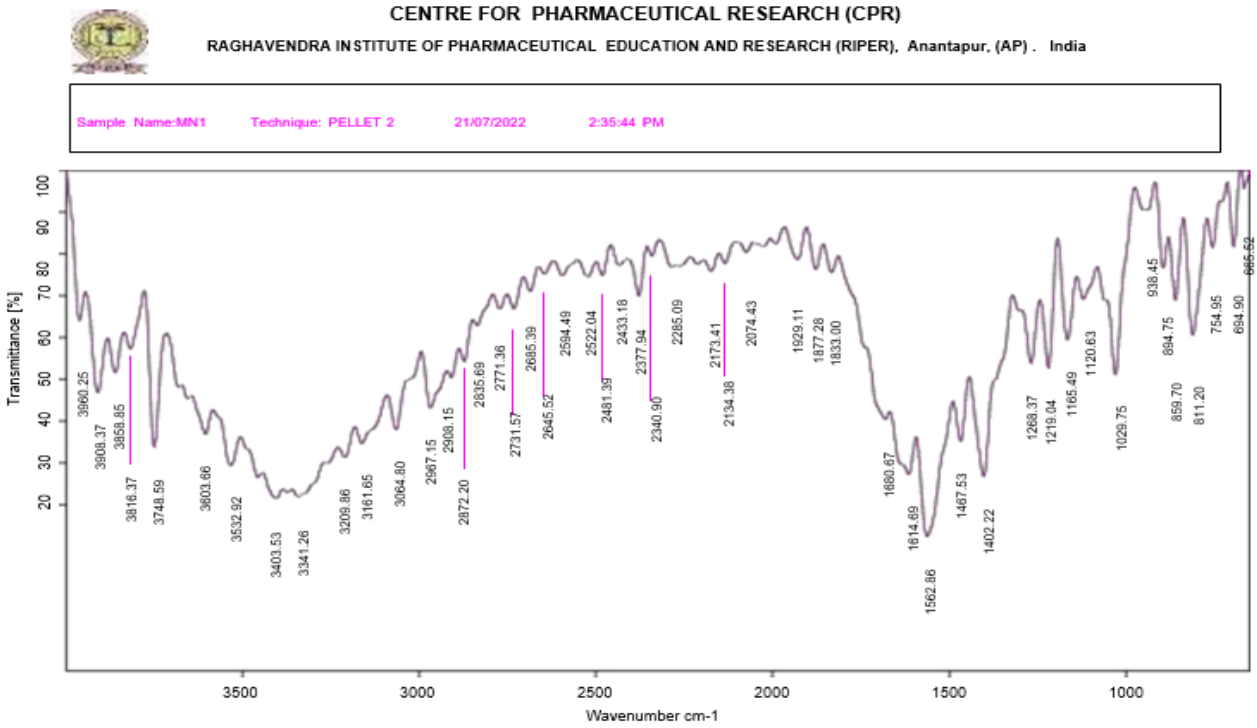

Figure 3: FTIR spectrum of Naproxen with sodium alginate

Table 6: IR Spectral Analysis of naproxen with sodium alginate

FTIR range	Absorption	Group	Compound
1268.37	1275-1200	C-O stretching	Alkyl aryl ether
1614.69	1650-1566	C=C stretching	Conjugate alkene
2967.15	3000-2840	C-H stretching	Thiol
3341.26	3533-3267	C-H stretching	Alkyne

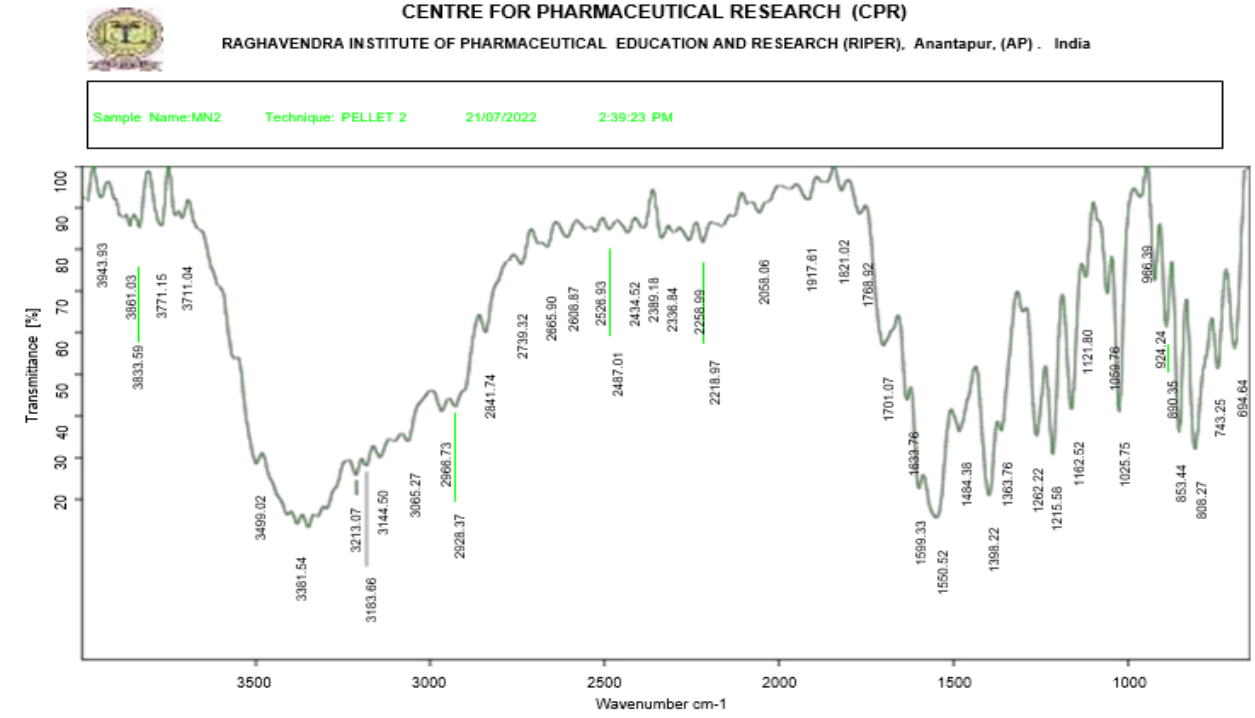

Figure 4: FTIR spectrum of Naproxen with Carbopol

Table 7: IR Spectral Analysis of naproxen with Carbopol

FTIR range	Absorption	Group	Compound
1262.22	1275-1200	C-O stretching	Alkyl aryl ether
1633.76	1650-1566	C=C stretching	Cyclic alkene
2928.37	3000-2840	C-H stretching	Thiol
3381.54	3533-3267	C-H stretching	Alkyne
1398.22	1440-1395	O-H bending	Carboxylic acid
1633.76	1650-1600	C=C stretching	Conjugate alkene

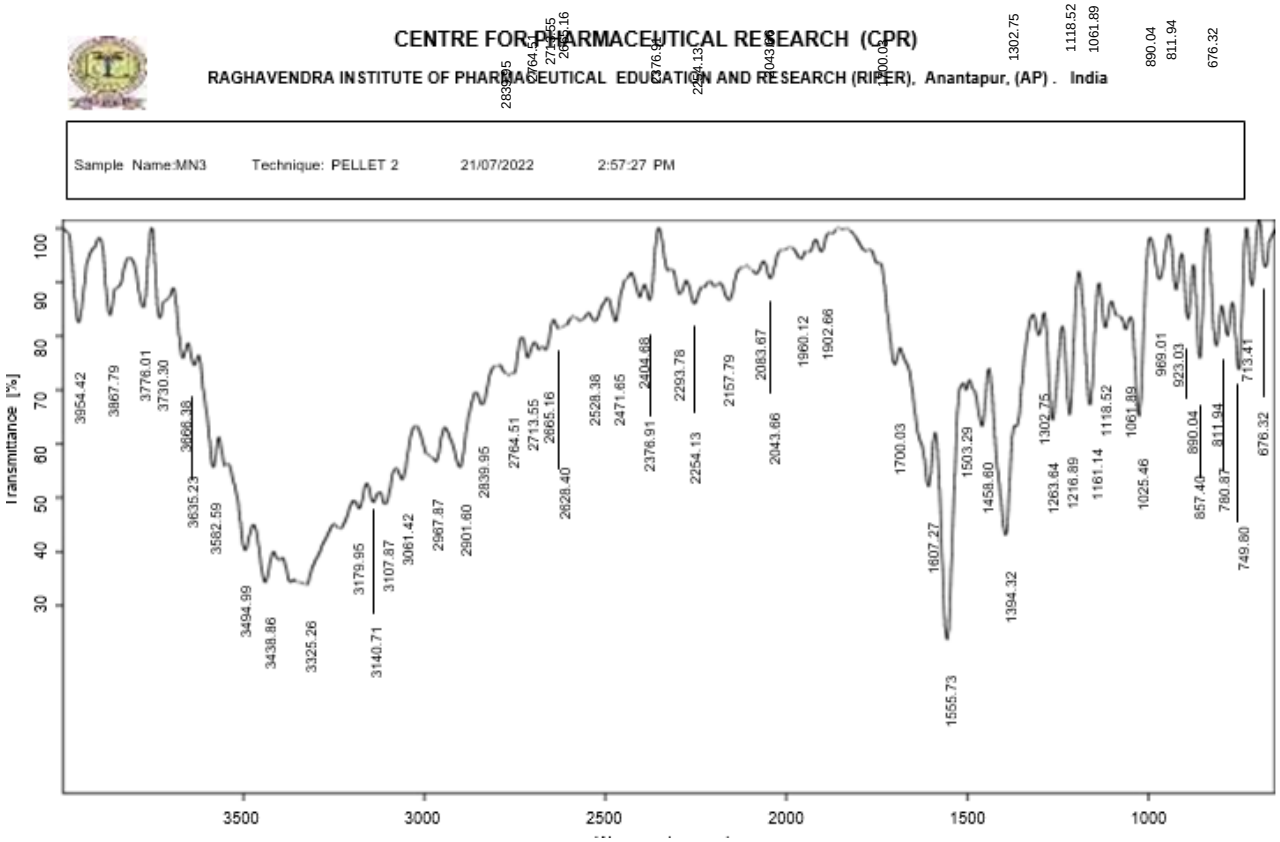

Figure 5: FTIR spectrum of naproxen with chitoson

Table 8: IR Spectral Analysis of naproxen with chitoson

FTIR	Absorptio	Group	Compound
1263.64	1275-	C-O	Alkyl aryl ether
1607.27	1650-	C=C	Conjugate
2967.87	3000-	C-H	Thiol
3325.26	3533-	C-H	Alkyne
1394.32	1440-	O-H bending	Carboxylic acid

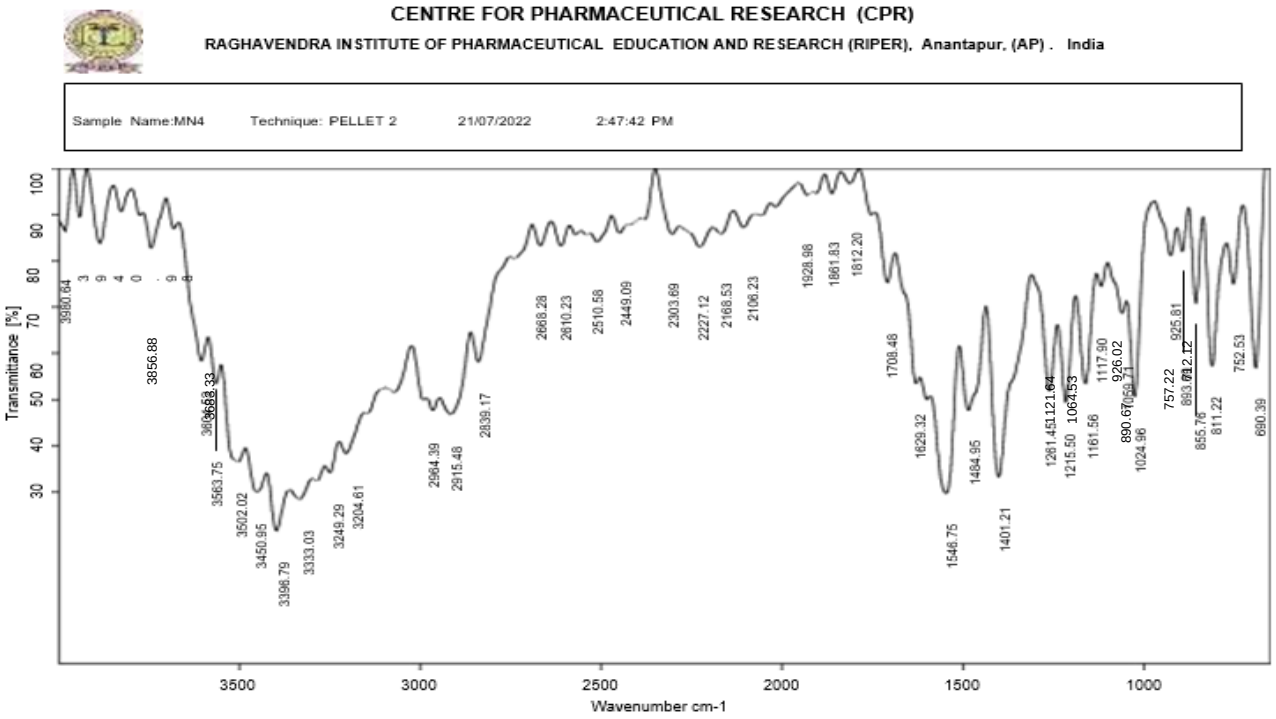

Figure 6: FTIR Spectrum of naproxen with HPMCK4M

Table 9: IR Spectral Analysis of naproxen with HPMCK4M

FTIR range	Absorption	Group	Compound
1261.45	1275-1200	C-O stretching	Alkyl aryl ether
1629.32	1650-1566	C=C stretching	Cyclic alkene
2915.48	3000-2840	C-H stretching	Thiol
3396.79	3533-3267	C-H stretching	Alkyne
1629.32	1650-1600	C=C stretching	Conjugate alkene

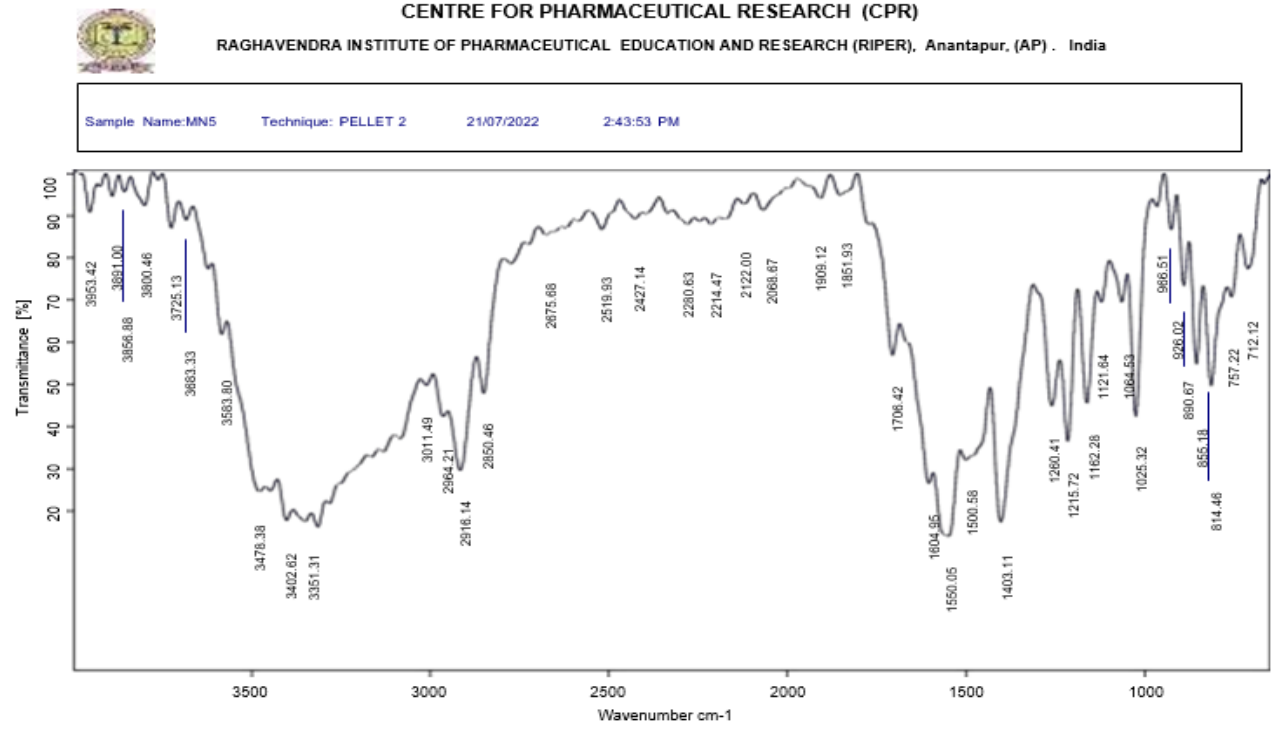

Figure 7: FTIR spectrum of naproxen with magnesium stearate

Table 10: IR Spectral Analysis of naproxen with magnesium stearate

FTIR	Absorption	Group	Compound
1260.41	1275-1200	C-O stretching	Alkyl aryl ether
1604.95	1650-1566	C=C stretching	Conjugate alkene
2916.14	3000-2840	C-H stretching	Thiol
3351.31	3533-3267	C-H stretching	Alkyne

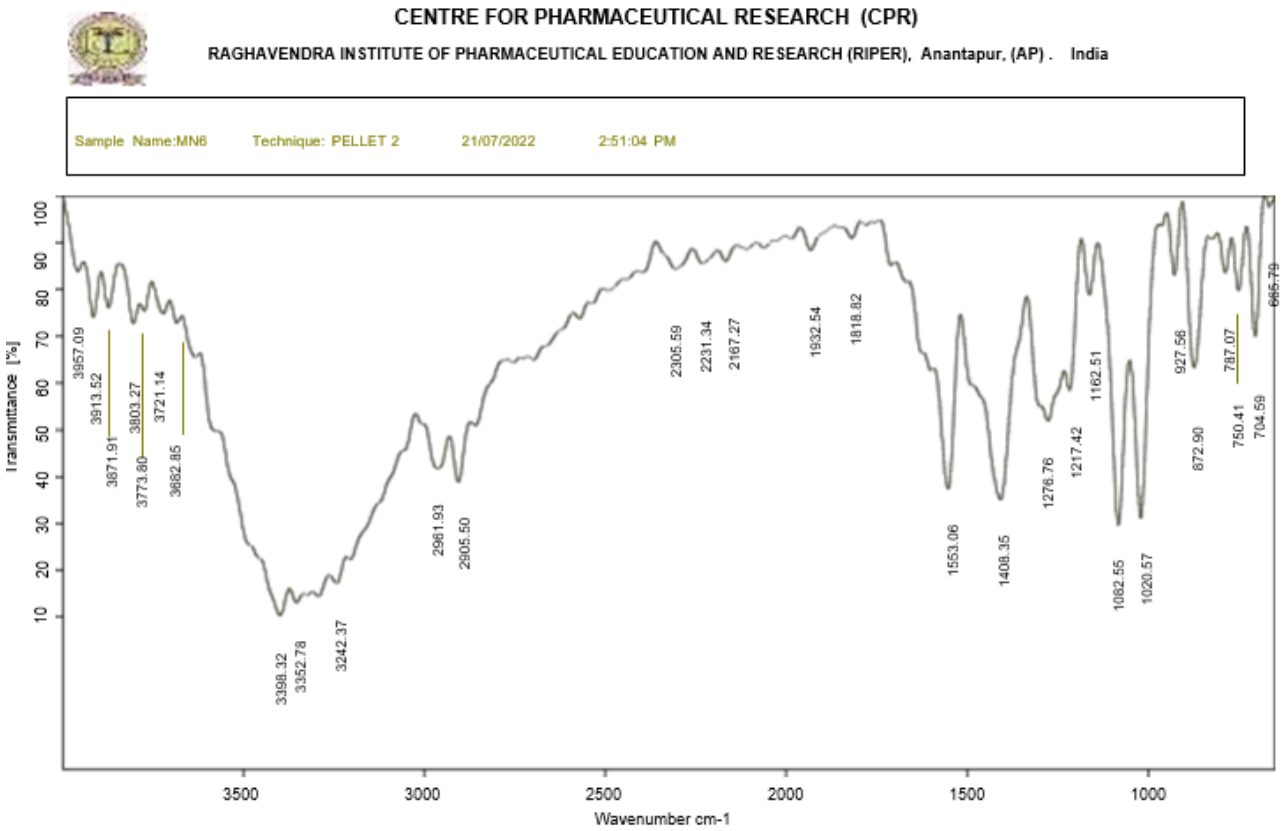

Figure 8: FTIR spectrum of naproxen with Micro crystalline cellulose

Table 11: IR Spectral Analysis of naproxen with Micro crystalline cellulose

FTIR	Absorptio	Group	Compound
1276.76	1275-1200	C-O stretching	Alkyl aryl ether
2961.93	3000-2840	C-H stretching	Thiol
3352.78	3533-3267	C-H stretching	Alkyne

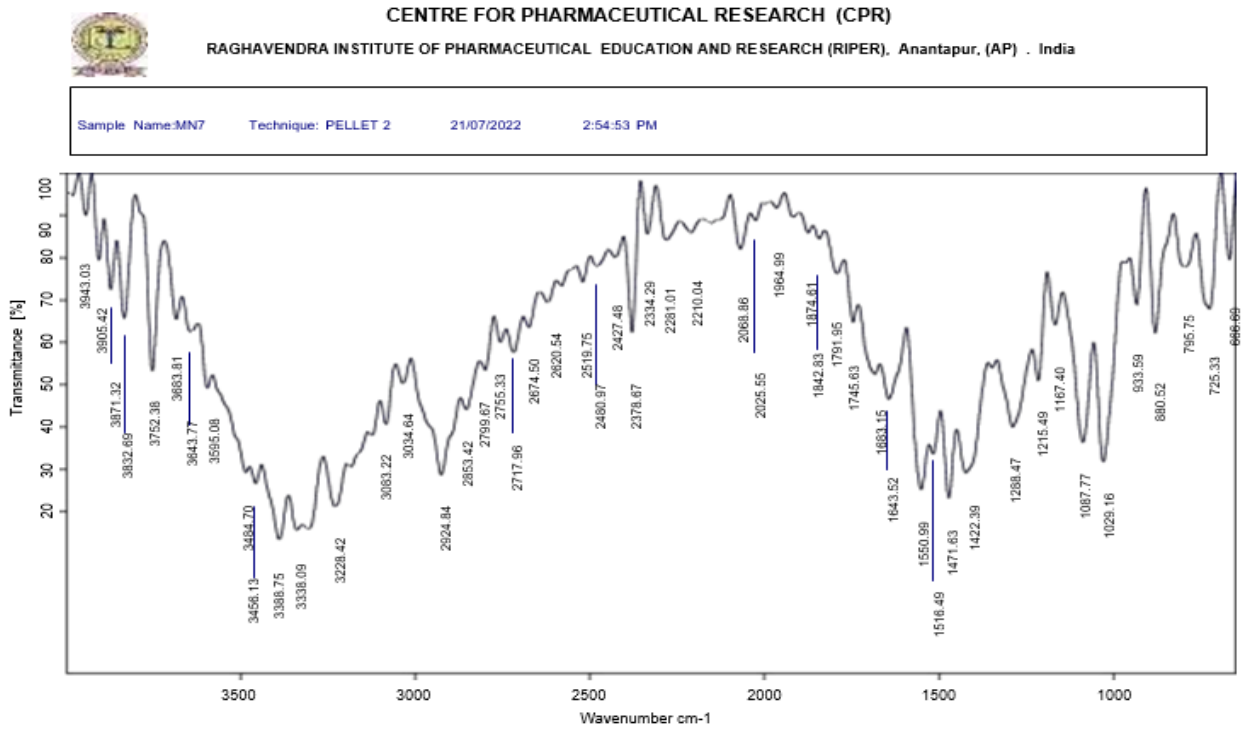

Figure 9: FTIR spectrum of naproxen with mannitol

Table12: IR Spectral Analysis of naproxen with mannitol

FTIR range	Absorption	Group	Compound
1288.47	1275-1200	C-O	Alkyl aryl ether
1643.52	1650-1566	C=C	Cyclic alkene
2924.84	3000-2840	C-H	Thiol
3338.09	3533-3267	C-H	Alkyne

Differential scanning calorimetry studies:

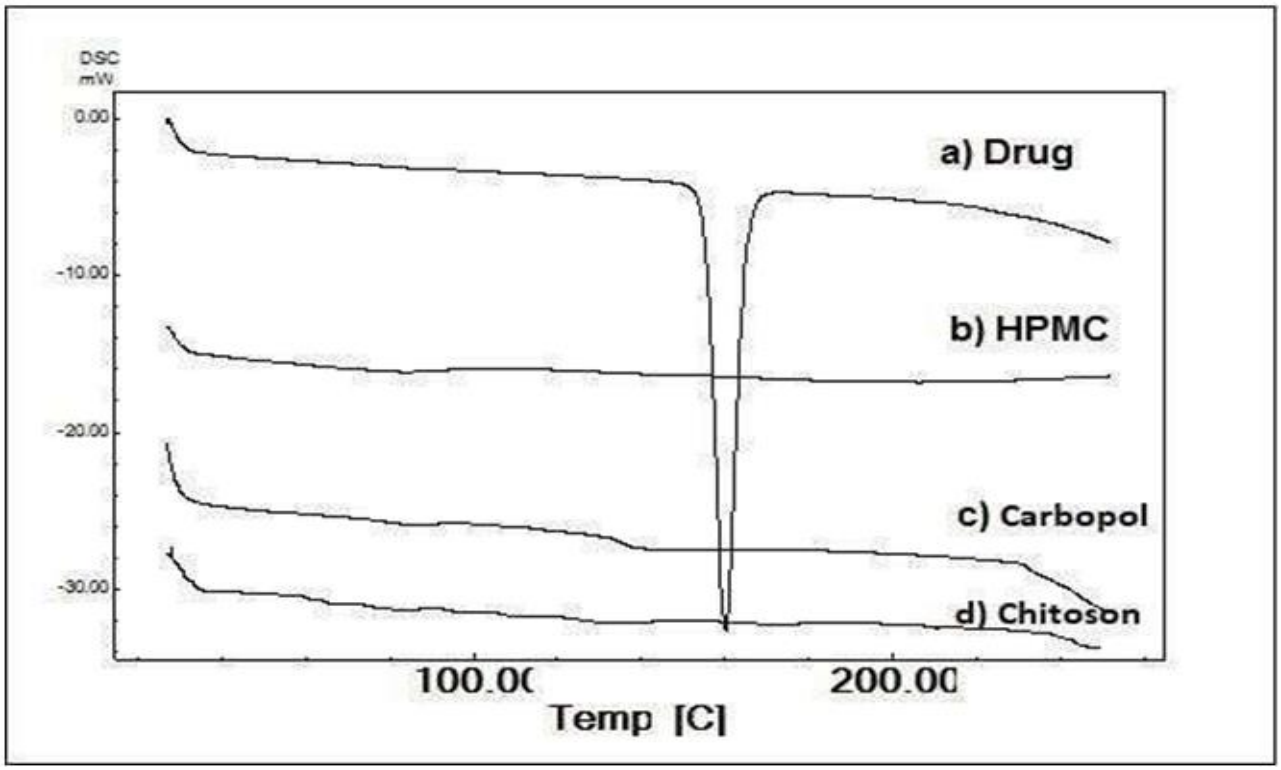

Figure 10: DSC thermograms of a) naproxen, b) HPMC and c) Carbopol d)

Chitoson
Thermal analysis of pure was carried out using DSC. Naproxen showed a sharp endothermic peak at 161.12ºC corresponding to the melting of the drug with a heat of fusion (ΔH) of -990.12 mJ.

Pre formulation studies results:
Powder ready for compression containing drug and various excipients were subjected for various pre compression evaluation parameters such as bulk density, tapped density, compressibility index, Hausner's ratio and angle of repose. Pre-compressional parameters (Micrometrics properties) were studied to determine the flow properties of granules, to achieve uniformity of tablet weight. The results of all the preformulation parameters are giventable17.

Angle of repose (θ):

The data obtained from angle of repose for the formulations were found to be in the range of $27^{O}.23'$±0.062 to $29^{O}.68'$±0.012. All the formulations showed the angle of repose less than 30°, which reveals good flow property.
density:
Tapped bulk density (TBD) for the blend was performed. The tapped bulk densities for the formulations from 0.610±0.16 gm/cc to 0.640±0.12gm/cc. The results were shown in table No.
Carr's consolidation index:
The results of Carr's consolidation index or compressibility index (%) for the formulation ranged from 12.92±0.019 % to 18.14±0.084 %
Hausner ratio:
Hausner ratio of formulations showed between 1.12 to 1.20 and indicates better flow properties.

Table 13: Precompression parameters

Formulation	tapped density (gm/cm^3)	Carr's Index (%)	Hausner's ratio	Angle of repose(^{O})
F1	0.621±0.11	16.34±0.025	1.15	27.56±0.054
F2	0.623±0.14	14.54±0.023	1.20	29.62±0.086
F3	0.634±0.12	13.23±0.014	1.14	29.54±0.054
F4	0.610±0.16	15.45±0.016	1.16	27.58±0.009
F5	0.616±0.15	14.56±0.054	1.12	29.68±0.012
F6	0.626±0.24	16.78±0.085	1.14	29.45±0.057
F7	0.635±0.21	12.92±0.019	1.19	27.23±0.062
F8	0.640±0.12	17.54±0.092	1.18	28.54±0.067
F9	0.639±0.18	18.14±0.084	1.20	27.58±0.089

Evaluation test results of prepared tablets:
All the tablet formulations were evaluated for parameters such as shape, colour, thickness, hardness, friability, weight variation, drug content, *in vitro* disintegration time, *in vitro* dissolution studies, model fitting of release profile and stability studies.

f) Generalappearance:
All the Buccal mucoadhesive tablets from each batch were found to be flat, white in colour, circular in shape and having good physical appearance. There was no change in the colour and odour of the tablets from all the batches.

g) Thickness:
Thickness of all prepared Buccal mucoadhesive ablets was measured by using calibrated vernier calipers. Tablet thickness should be controlled to facilitate packaging and consumer acceptance. The mean thickness was almost uniform in all the formulations and values of tablets prepared by all the polymers were ranged from 2.80 ±0.11 to 2.98±0.02.

h) Hardness:
Tablets require certain amount of strength, hardness to withstand mechanical shocks during manufacture, packaging, and shipping. The hardness of all the tablets was maintained within the range of 4.48±0.02 to 5.18 ±0.03 k g /cm^2. In all the formulations the hardness test indicates good mechanical strength. The obtained results revealed that the tablets were having good mechanical strength and compactness.

i) Friability:
Adequate tablet hardness and resistance to friability are necessary to prevent damage to the tablet during manufacture, packing and transport. The friability of the formulations wasless than 1.0%, showed the durability of the tablets; resistance to loss of weight indicates the tablet's ability to withstand abrasion in handling, packaging,

and shipment. The friability was found inall tablet formulations prepared by different polymers were well within the approvedrange (<1%) which indicates the tablets had good mechanical resistance. The friability of all the formulations were varied between 0.23 ±0.01 to 0.78 ±0.01 %. The results were shown in tableNo.

j) Weight variation:

The average weight of the prepared tablets was found between 390.12 ±0.32 to 407.85.
±0.82mg. The average weight of the tablets prepared by different polymers was found 399.
48. So, it was predicted that all the tablets exhibited uniform weight with low standard deviation values within the acceptable variation as per USP.

g) Surface pH:

pH of the solution of all the tablets prepared by all the three methods was found to be between 5.78 ± 0.07 to 7.03 ± 0.06, which suggest that the tablets can be administered oral cavity and will not cause any discomfort.

a) Drug content:

To evaluate a tablet's potential for efficacy the amount of drug in the tablet needs to be monitored from tablet to tablet and batch to batch. The percentage drug content was found to be in the range of 96.65±0.024 to 98.95±0.026% for all the tablets.

In-Vitro Swelling Studies

The swelling index of mucoadhesive tablets for a period of 8 hours was studied. The values obtained as shown in the Fig: 2. It is evident that an increase in the number of carbopol-934 causes decrease in swelling index, in case of Chitoson and sodium alginate. Among all the formulations, showed highest value of F6 3.10 ± 1.72 and F3 showed lowest swelling index value 1.78 ± 1.72 at end of 8hours.

- **Invitro disintegration time:**

Disintegration time was determined for all the formulations (F1 – F9). Formulation F1 shows the lowest disintegration time 142.30±3.25 min whereas formulation F6 showed the highest disintegration time 238.63±3.89min. the findings are displayed in table No.

- **Invitro dissolution studies:**

Dissolution rate was studied by using type -II apparatus (USP XXIII dissolution test apparatus at 50 rpm) using 900ml of phosphate buffer pH (6.8) as dissolution medium. Temperature of the dissolution medium was maintained at 37 ± 0.5^{O}C, aliquot of dissolution medium was withdrawn at every 1 hr interval and filtered. The absorbance of filtered solution was measured by UV spectrophotometric method at 331 nm and concentration of the drug was determined from standard calibration curve.

The dissolution of naproxen from the tablets is shown in Figure no. and table No. shows release profiles. The dissolution increases with increased concentration of polymers. The dissolution of the drug with HPMC at high concentration with carbopol releases the maximum drug within the 12hrs. The tablets are prepared with HPMC and sodium alginate with various concentrations (F1, F2 and F3) drug release at 5hrs was found to be 99.21±0.36, 98.92±0.89 and 98.72±0.78 respectively. F4, F5 and F6 formulations drug release at 12 hrs were found to be 98.56±0.44, 97.15±0.27 and 97.87±0.07respectively. F7, F8 and F9 formulations drug release at 07 hrs were found to be 98.82±0.62, 99.62±0.81and 98.17±0.78.

Table 14: Post compression parameters

Formulation code	Weight variation (mg)	Thickness (mm)	Friability (%)	Hardness (kg/cm^2)
F1	390.12±0.32	2.80 ±0.11	0.23±0.01	4.48±0.02
F2	398.32±0.54	2.85±0.04	0.41±0.03	4.89±0.04
F3	395.52±0.46	2.97±0.07	0.42±0.04	4.57±0.05
F4	396.45±0.85	2.87±0.05	0.57±0.03	5.01±0.07
F5	402.25±0.75	2.89±0.04	0.65±0.04	5.02±0.02
F6	403.65±0.69	2.91±0.03	0.78±0.05	5.12±0.01
F7	407.85±0.82	2.97±0.07	0.74±0.06	5.18±0.03
F8	402.96±0.83	2.84±0.03	0.54±0.07	4.90±0.04
F9	398.24±0.97	2.98±0.02	0.47±0.02	4.98±0.09

Table 15: Post compression parameters

Formulation code	Surface pH	Drug content (%)	In-Vitro Swelling Studies (%)	Invitro disintegration time in min
F1	5.89 ±0.01	98.95±0.026	1.93±1.54	142.30±3.25
F2	5.78±0.07	98.23±0.028	1.87±1.69	158.42±3.78

F3	5.92±0.09	96.45±0.026	1.78±1.72	169.86±3.43
F4	6.23±0.07	97.86±0.027	2.78±1.74	200.56±3.48
F5	6.70±0.02	96.78±0.025	2.98±1.73	227.20±3.67
F6	6.78±0.04	96.65±0.024	3.10±1.76	238.63±3.89
F7	6.23±0.06	97.23±0.028	2.45±1.78	175.70±3.63
F8	7.02±0.08	97.48±0.029	2.87±1.65	186.68±3.74
F9	7.03±0.06	96.98±0.024	2.70±1.59	195.78±3.24

Table 16: Cumulative percentage in-vitro drug release of naproxen buccal mucoadhesive tablet formulations F1, F2, F3

0	0	0	0
1	52.02±0.22	50.27±0.42	47.87±0.57
2	73.55±0.58	68.45±0.57	63.82±0.45
3	85.41±0.78	79.65±0.66	74.73±0.22
4	92.22±0.12	86.98±0.24	81.12±0.87
5	99.21±0.36	91.87±0.71	87.45±0.69
6	-	98.92±0.89	92.49±0.95
7	-	-	98.72±0.78
8	-	-	-

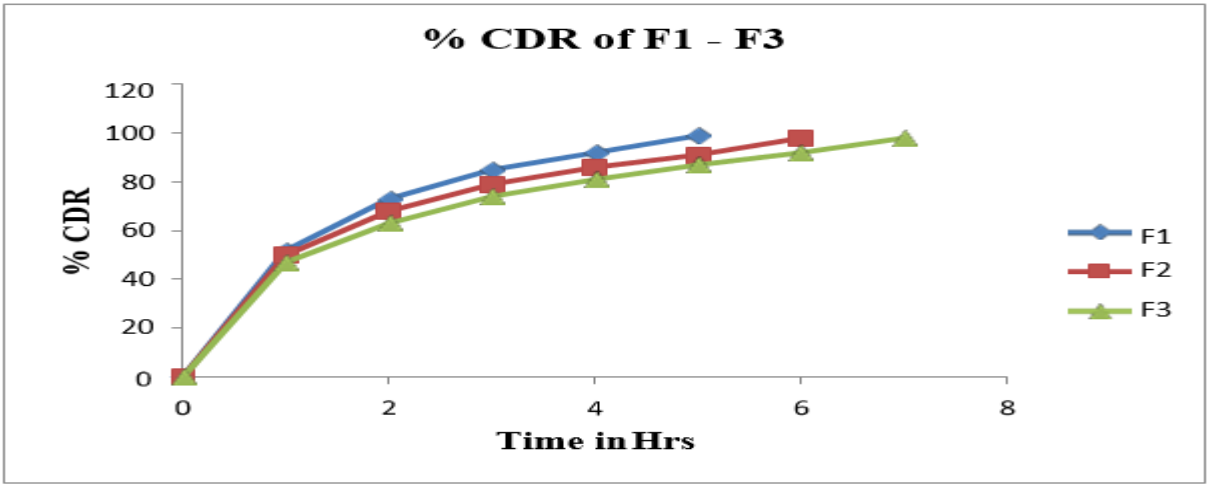

Figure 11: Cumulative percentage in-vitro drug release of naproxen buccalmucoadhesive tablet formulations F1, F2, F3

Table 17: Cumulative percentage in-vitro drug release of naproxen buccalmucoadhesive tablet formulations F4, F5, F6

Time in hrs	F4	F5	F6
0	0	0	0
1	23.45±0.48	21.41±0.14	18.11±0.25
2	29.52±0.32	27.56±0.89	23.02±0.57
3	34.45±0.11	31.24±0.77	29.75±0.98
4	40.56±0.02	38.15±0.54	34.69±0.74
5	48.48±0.07	46.47±0.96	42.84±0.61
6	59.87±0.14	57.52±0.98	51.26±0.24
7	67.98±0.27	64.61±0.78	59.32±0.45
8	76.52±0.45	72.89±0.40	67.12±0.70
9	90.41±0.74	84.36±0.76	73.24±0.28
10	98.56±0.44	88.49±0.10	79.85±0.14
11	-	97.15±0.27	85.54±0.04
12	-	-	97.87±0.07

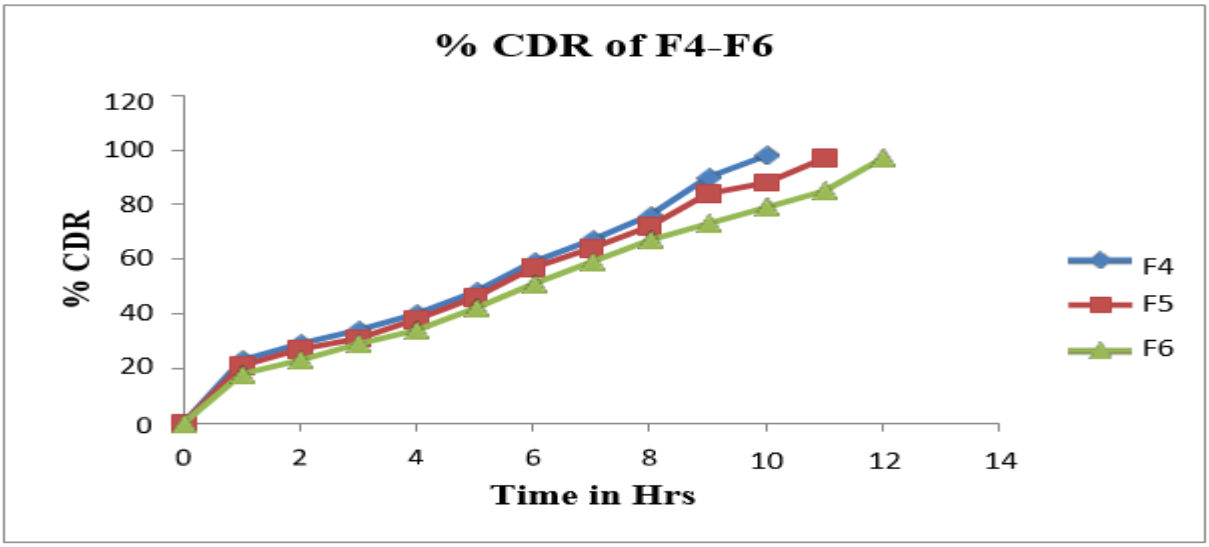

Figure 12: Cumulative percentage in-vitro drug release of naproxen buccalmucoadhesive tablet formulations F4, F5, F6

Table 18: Cumulative percentage in-vitro drug release of naproxen buccalmucoadhesive tablet formulations F7, F8, F9

Time in hrs	F7	F8	F9
0	0	0	0
1	35.47±0.31	33.14±0.32	29.47±0.11
2	49.64±0.51	45.25±0.41	38.65±0.89
3	61.22±0.24	58.41±0.58	49.24±0.66
4	72.54±0.99	69.22±0.36	62.12±0.87
5	83.69±0.85	76.37±0.88	71.14±0.54
6	92.74±0.71	88.59±0.66	82.58±0.63
7	98.82±0.62	92.55±0.62	89.36±0.44
8	-	99.62±0.81	93.14±0.68
9	-	-	98.17±0.78

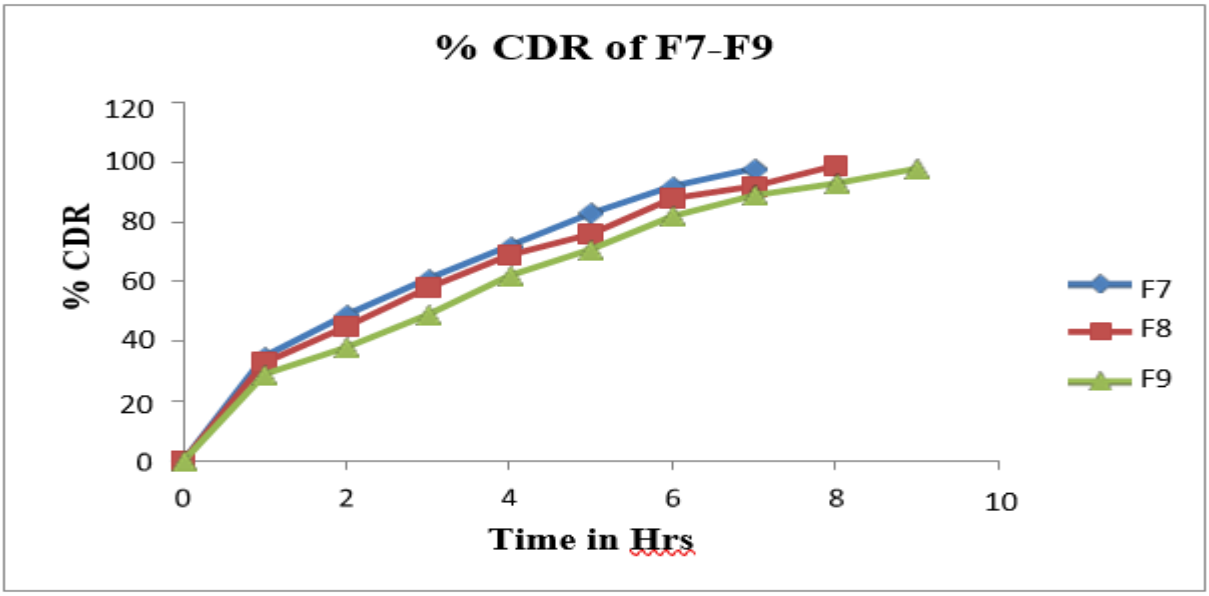

Figure 13: Cumulative percentage in-vitro drug release of naproxen buccal mucoadhesive tablet formulations F7, F8, F9

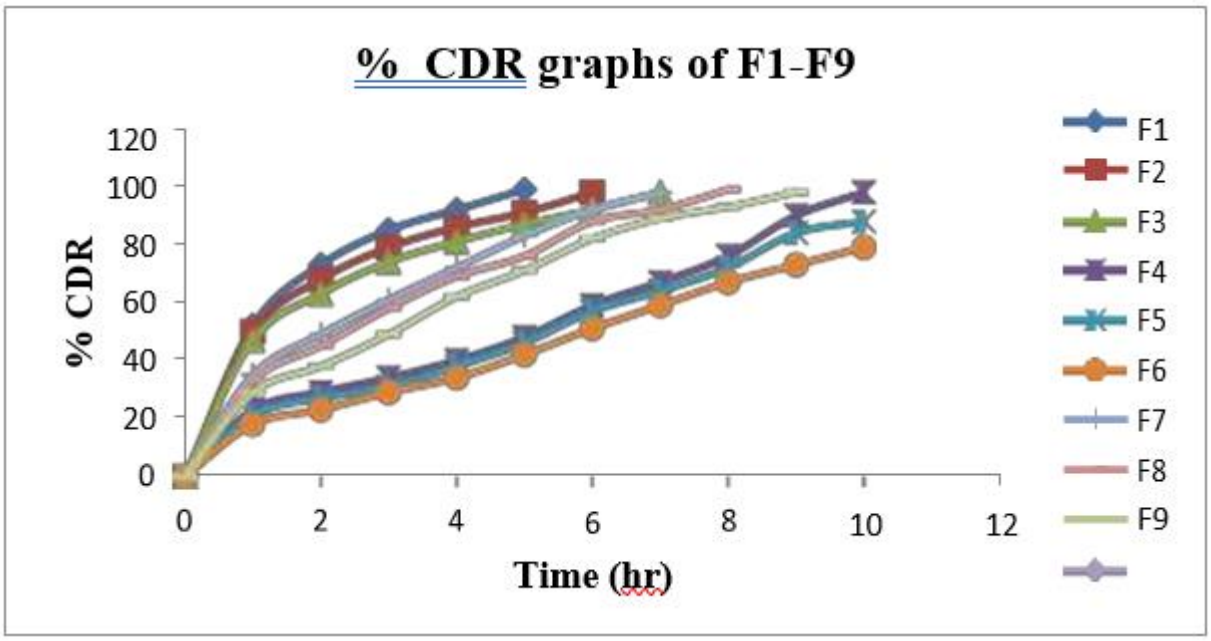

Figure 14: Cumulative percentage in-vitro drug release of naproxen buccalmucoadhesive tablet of all formulations F1- F9

Drug release kinetics for the buccal mucoadhesive tablet formulations:

The drug release kinetics for all formulations were calculated and the results are obtained are represented in table No. the zero-order profile, first order profile. Higuchi profile and korsmeyer-peppas plot is represented in figure no.

Table 19: Release kinetics and mechanisms of Ketorolac buccal tablet of optimized formulation

Formulation code	Zero order		first order		Higuchi		Korsmeyer - Peppas		Possible drug release mechanism
	Slope	R^2	Slope	R^2	Slope	R^2	R^2	N	
F1	23.927	0.9393	0.0476	0.0709	121.64	0.9178	0.4796	0.1968	Super case II transport
F2	19.89	0.9316	0.0576	0.0294	112.39	0.9339	0.1954	0.1145	Super case II transport
F3	17.086	0.932	0.0745	0.0001	106.01	0.9489	0.113	0.0403	Super case II transport
F4	9.8805	0.9922	0.1036	0.7499	73.53	0.9363	1.0022	0.6515	Super case II transport
F5	9.226	0.9924	0.757	0.918	68.869	0.9422	0.9677	0.662	Super case II transport
F6	8.3091	0.9935	0.0597	0.9636	62.099	0.9455	0.9117	0.6829	Super case II transport
F7	16.121	0.9706	0.0689	0.0068	80.834	0.8709	0.904	0.0293	Super case II transport
F8	14.299	0.9695	0.0939	0.0997	95.128	0.9687	0.4172	0.0003	Super case II transport
F9	12.618	0.9764	0.1078	0.3644	90.008	0.9693	0.7497	0.0901	Super case II transport

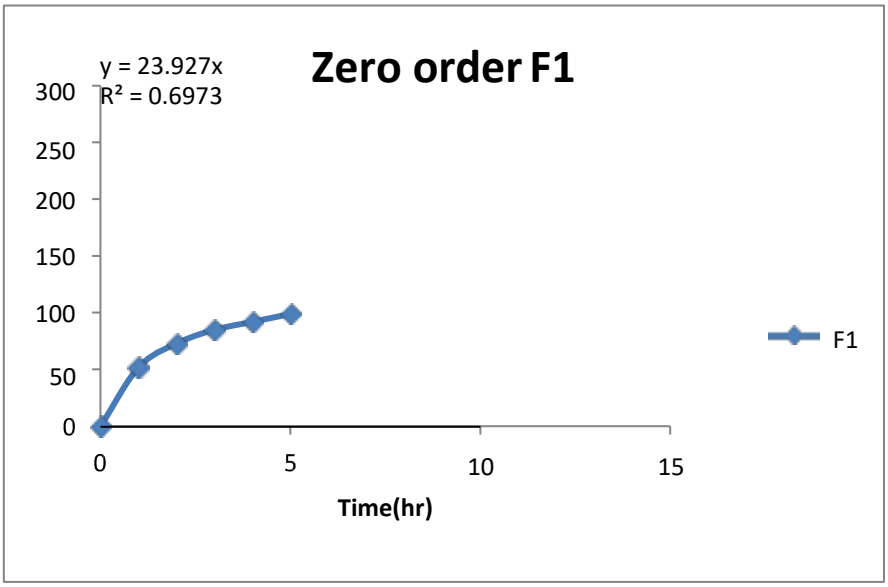

Figure No.21: Zero Order Graph of F1

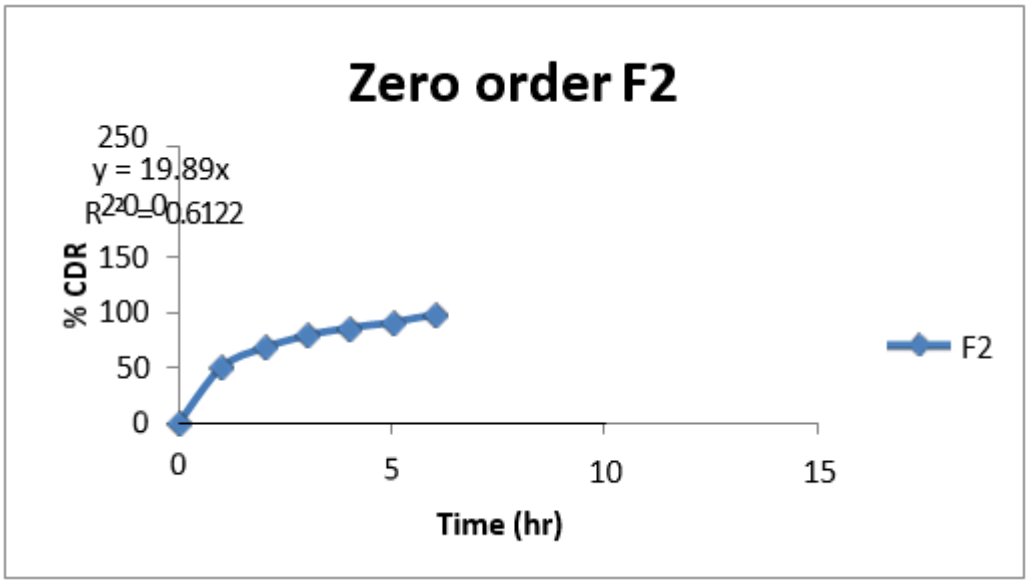

Figure No.22: Zero Order Graph of F2

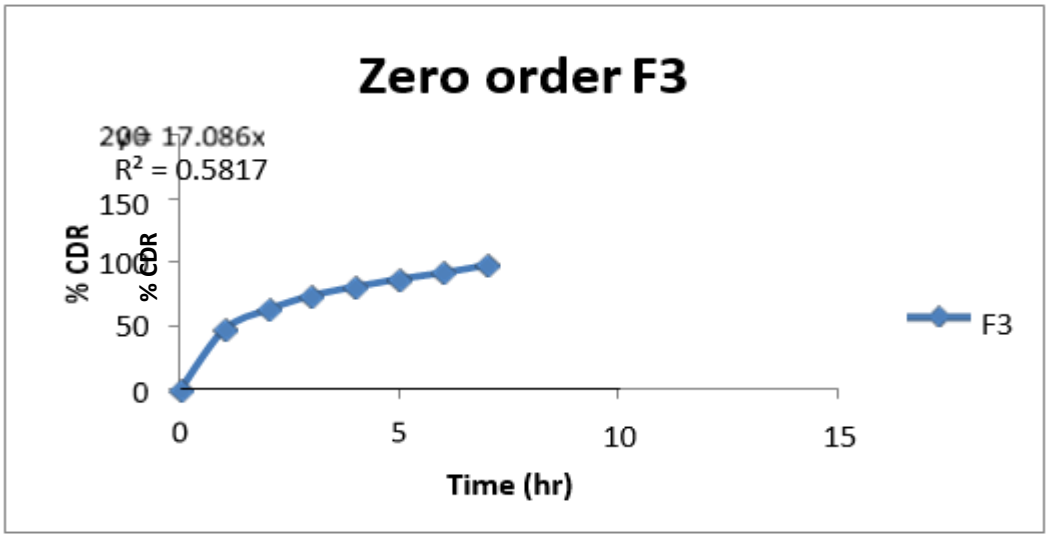

Figure No.23: Zero Order Graph of F3

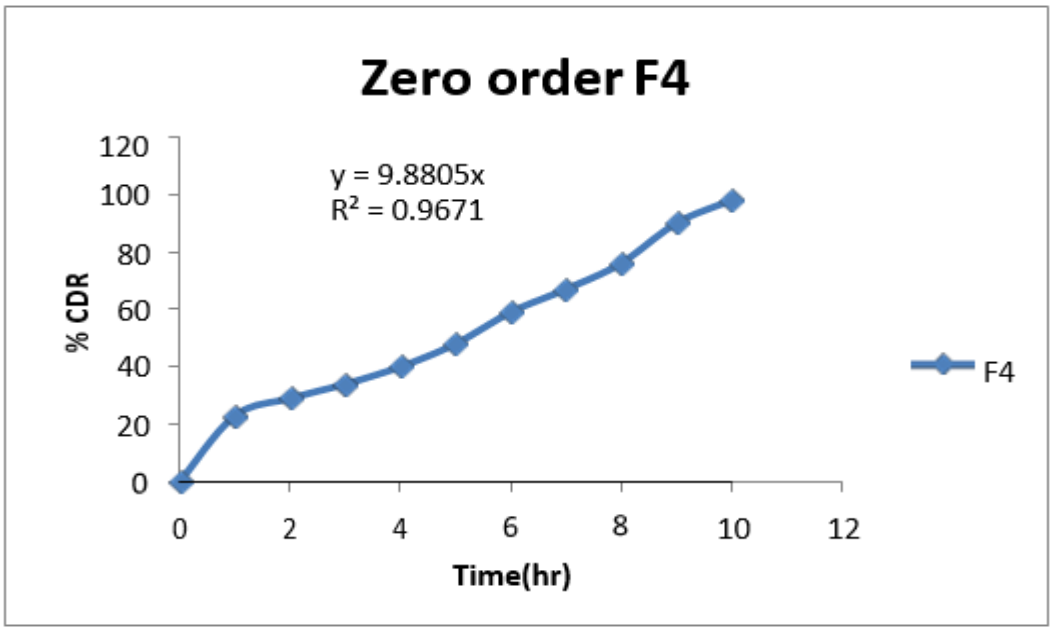

Figure No.24: Zero Order Graph of F4

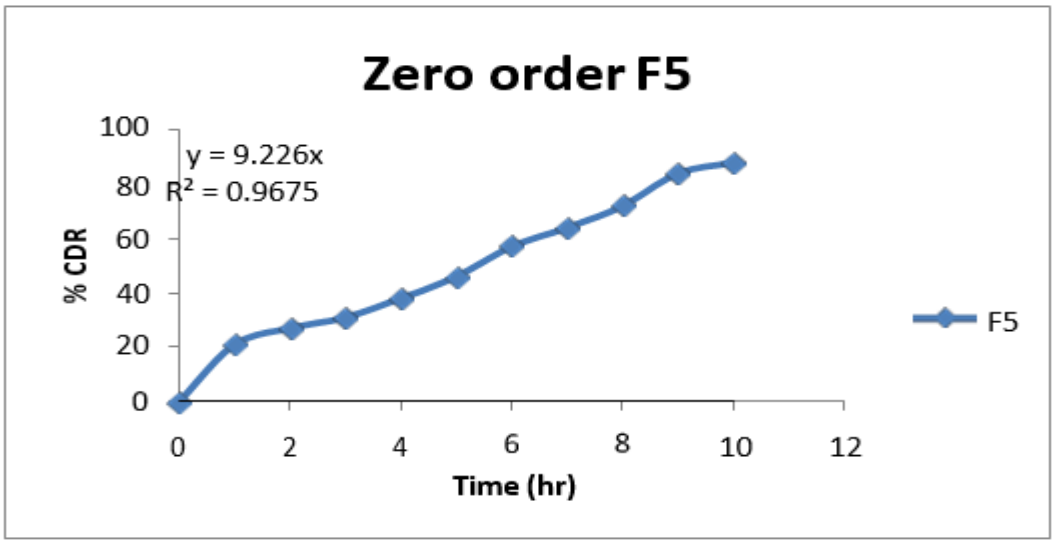

Figure No.25: Zero Order Graph of F5

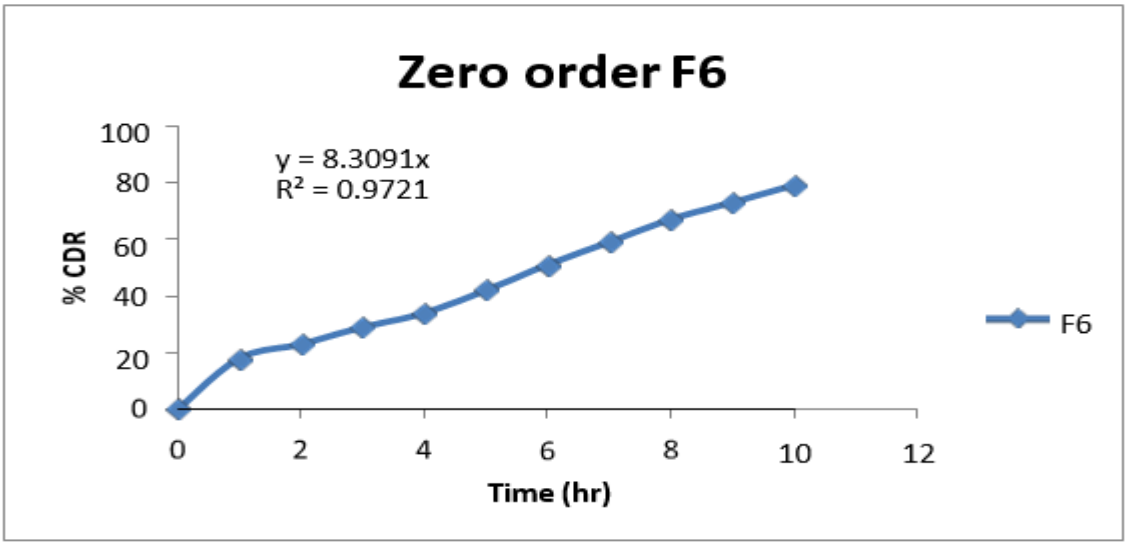

Figure No.8.15: Zero Order Graph of F6

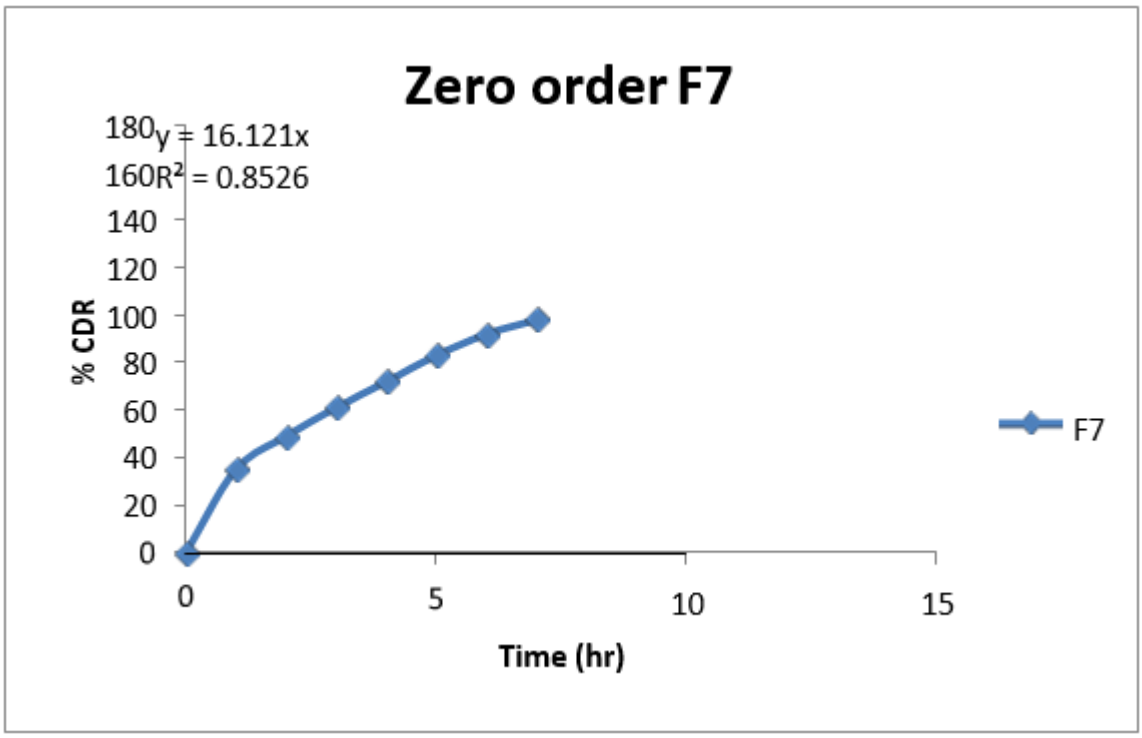

Figure No.27: Zero Order Graph of F7

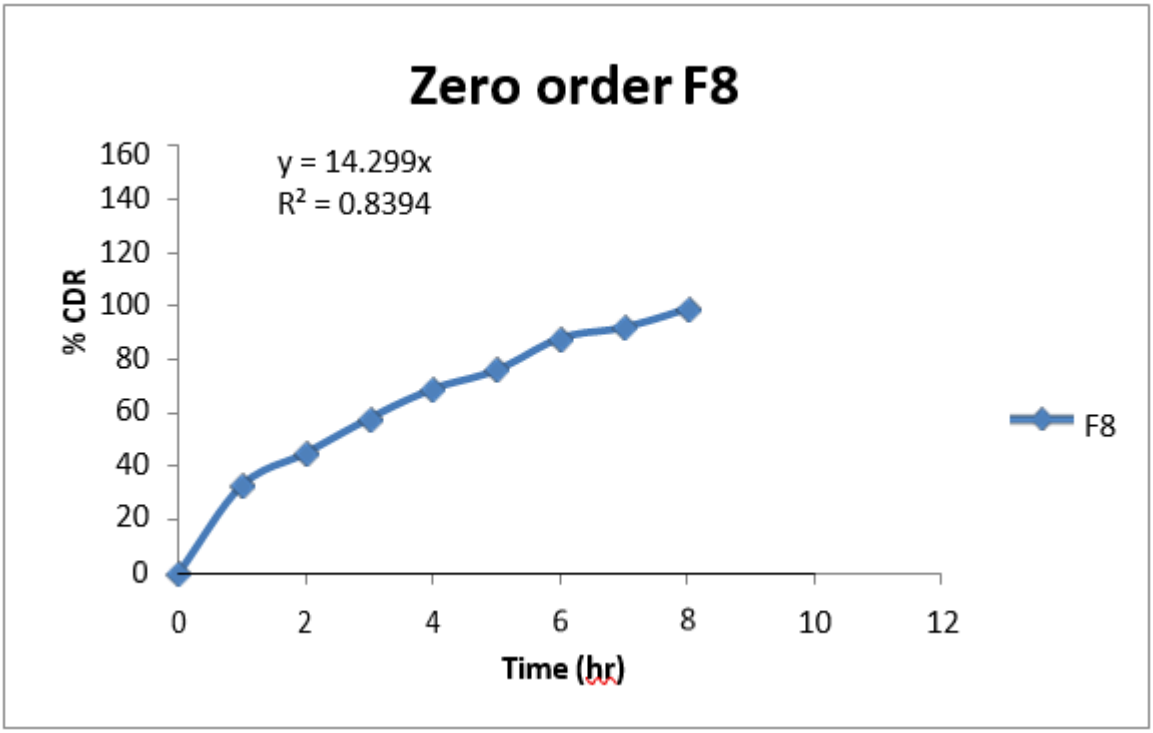

Figure No.28: Zero Order Graph of F8

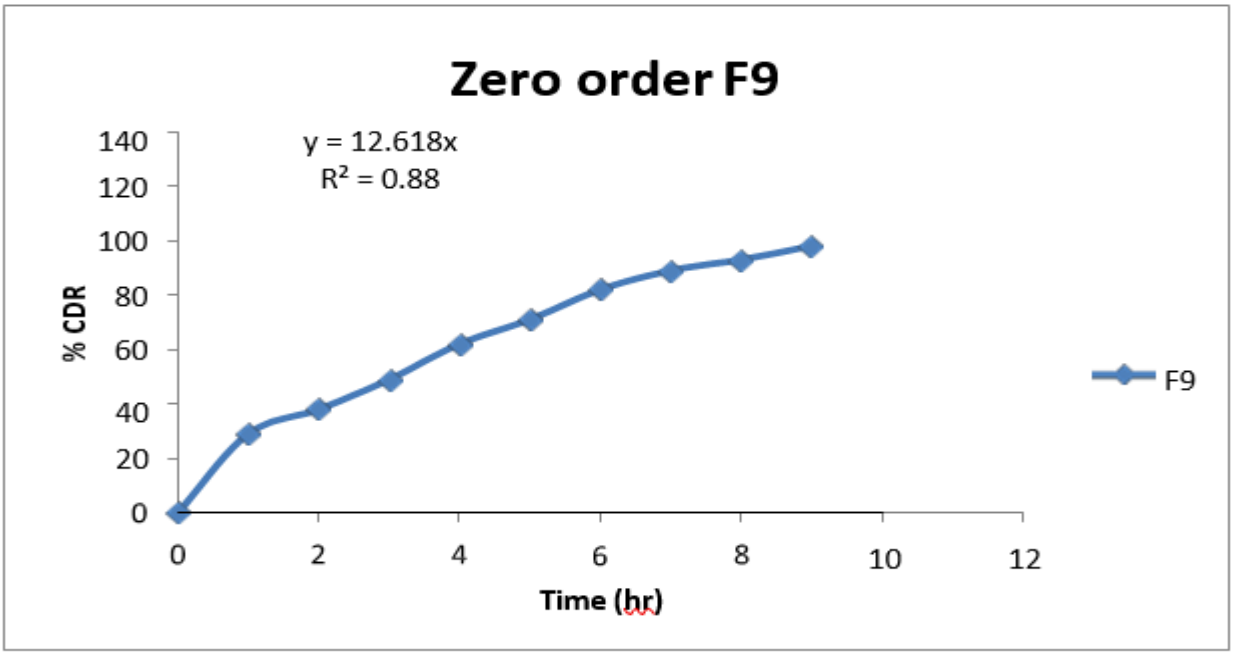

Figure No.29: Zero Order Graph of F9

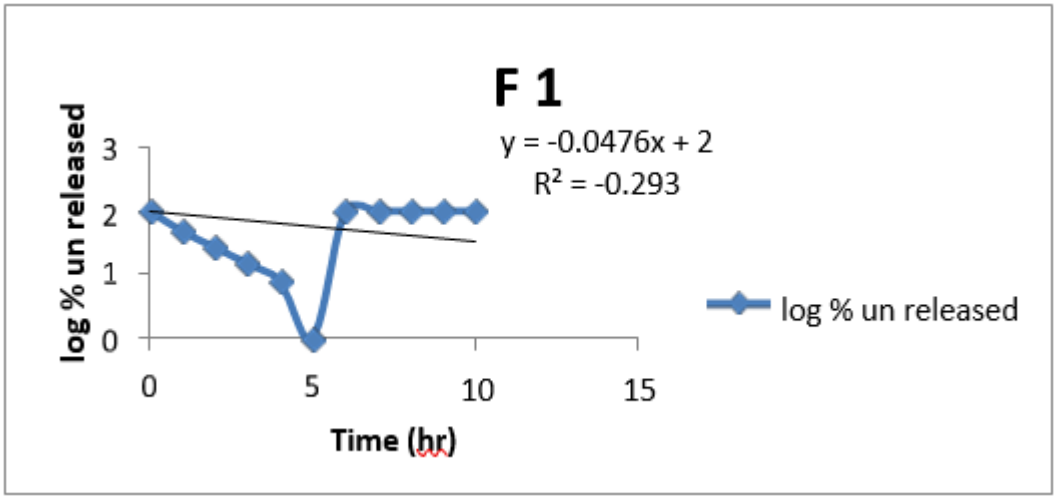

Figure No.30: First Order Graph of F1

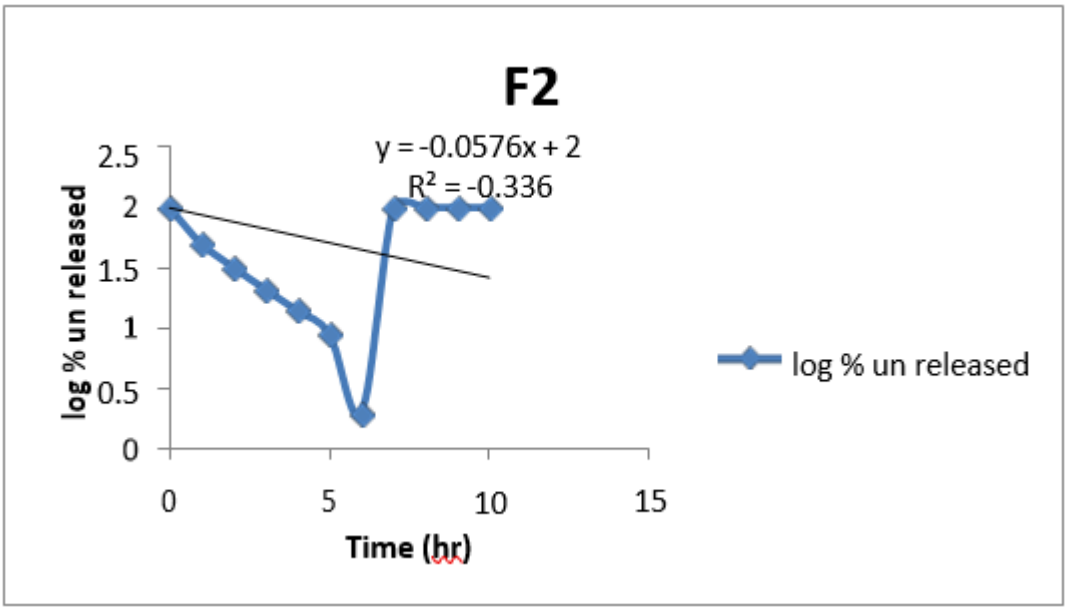

Figure No.31: First Order Graph of F2

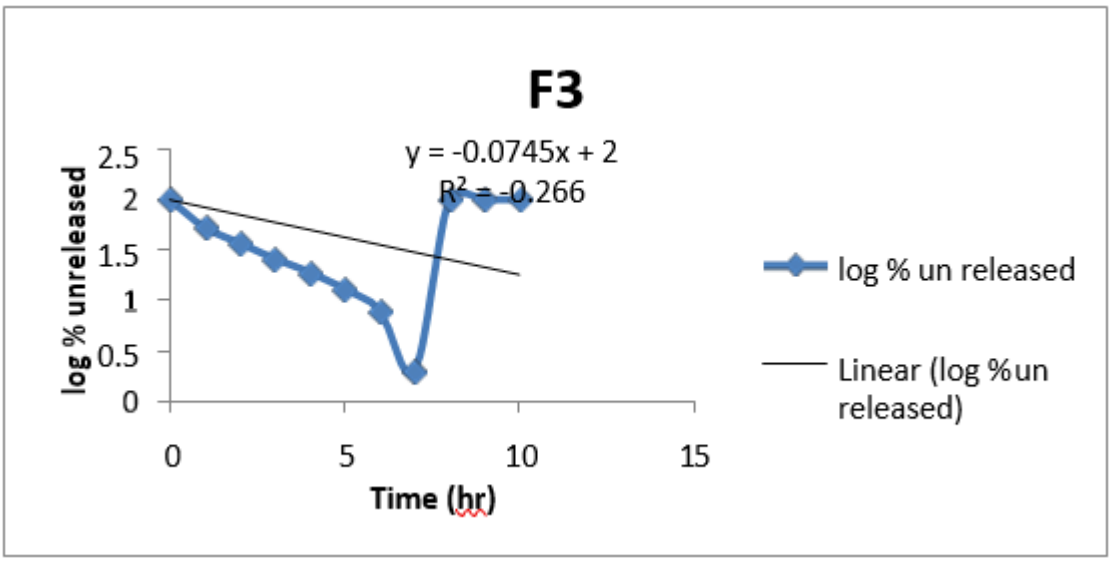

Figure No.32: First Order Graph of F3

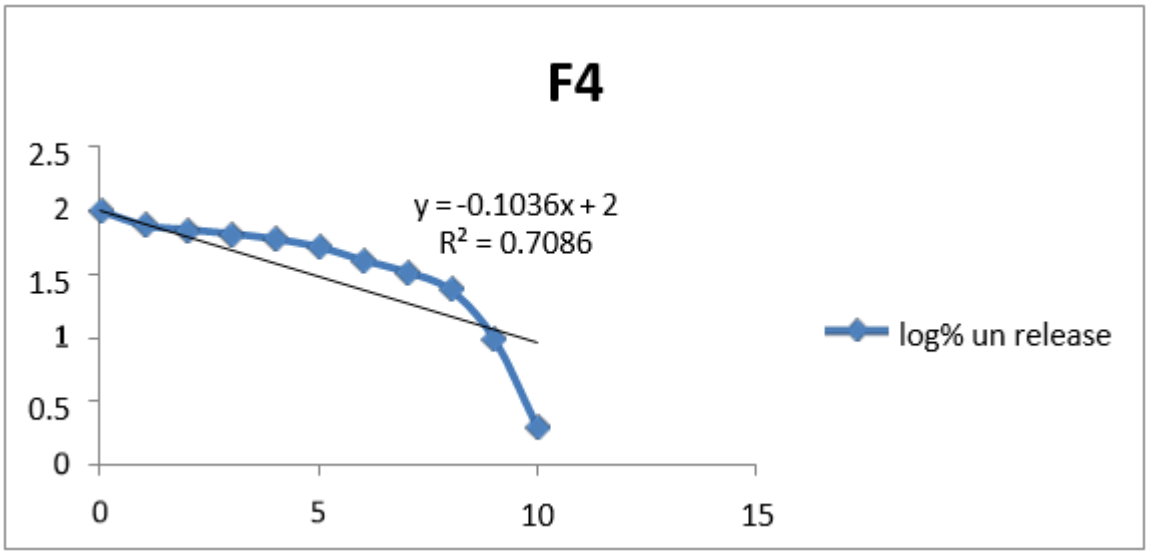

Figure No.33: First Order Graph of F4

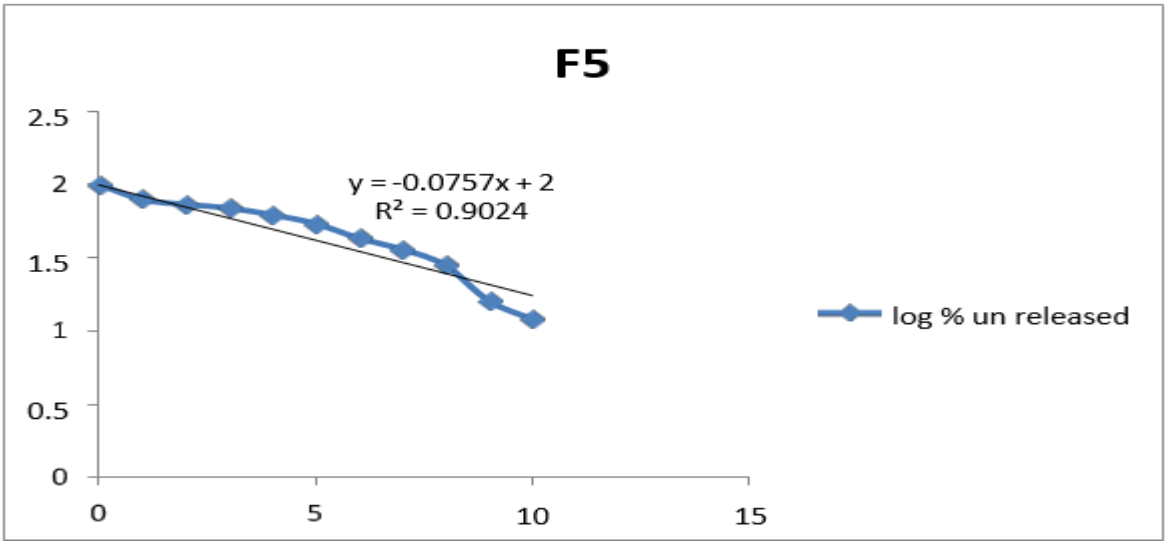

Figure No.34: First Order Graph of F5

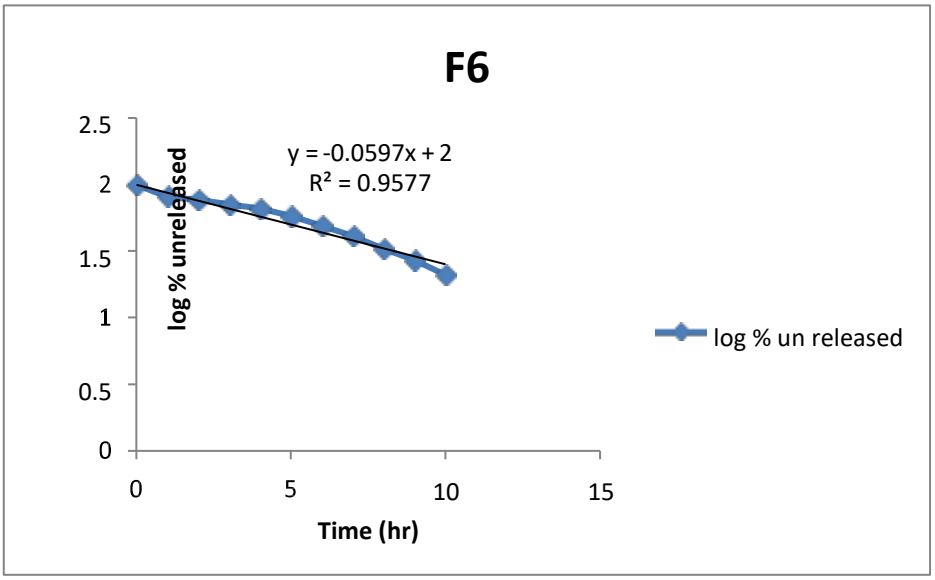

Figure No.8.16: First Order Graph of F6

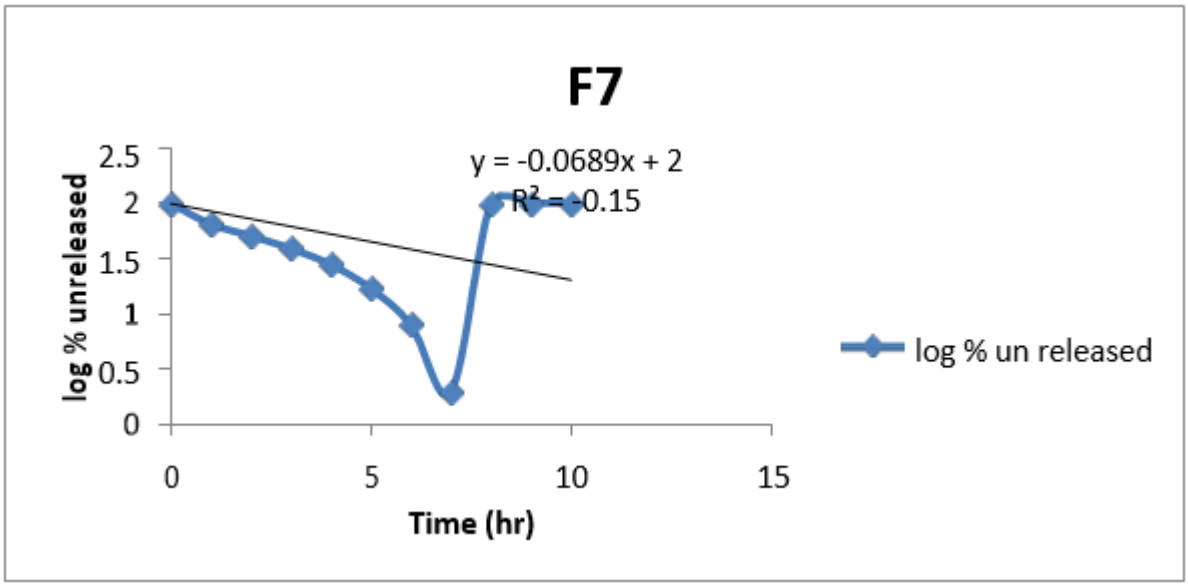

Figure No.36: First order graph of F7

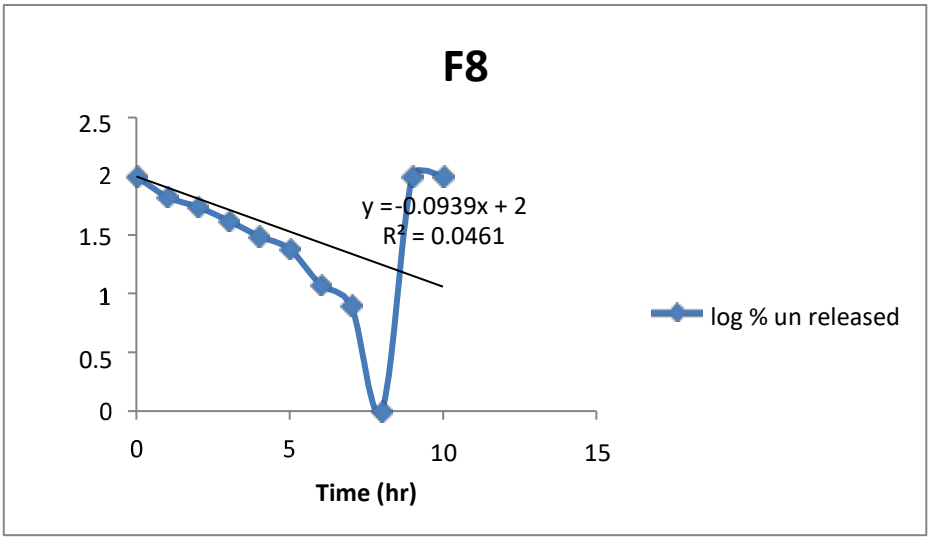

Figure No.37: First Order Graph of F8

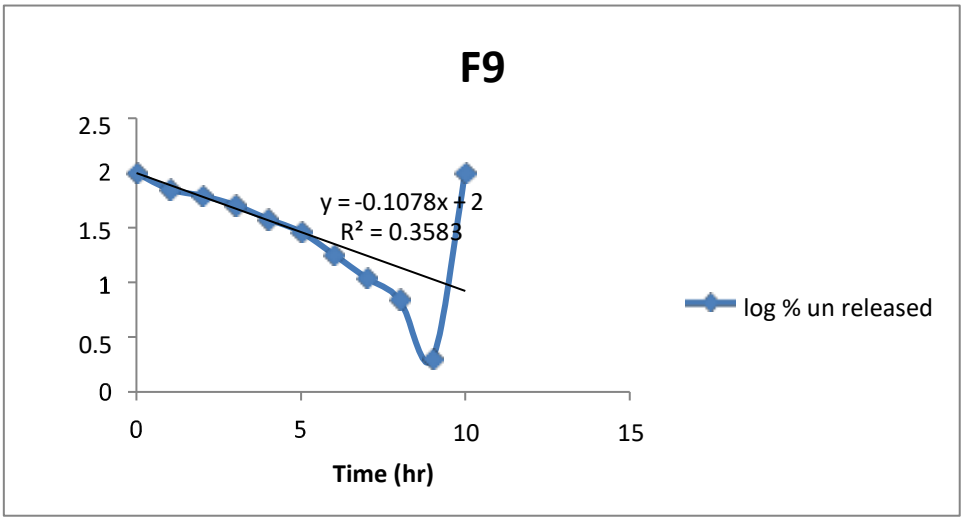

Figure No.38: First Order Graph of F9

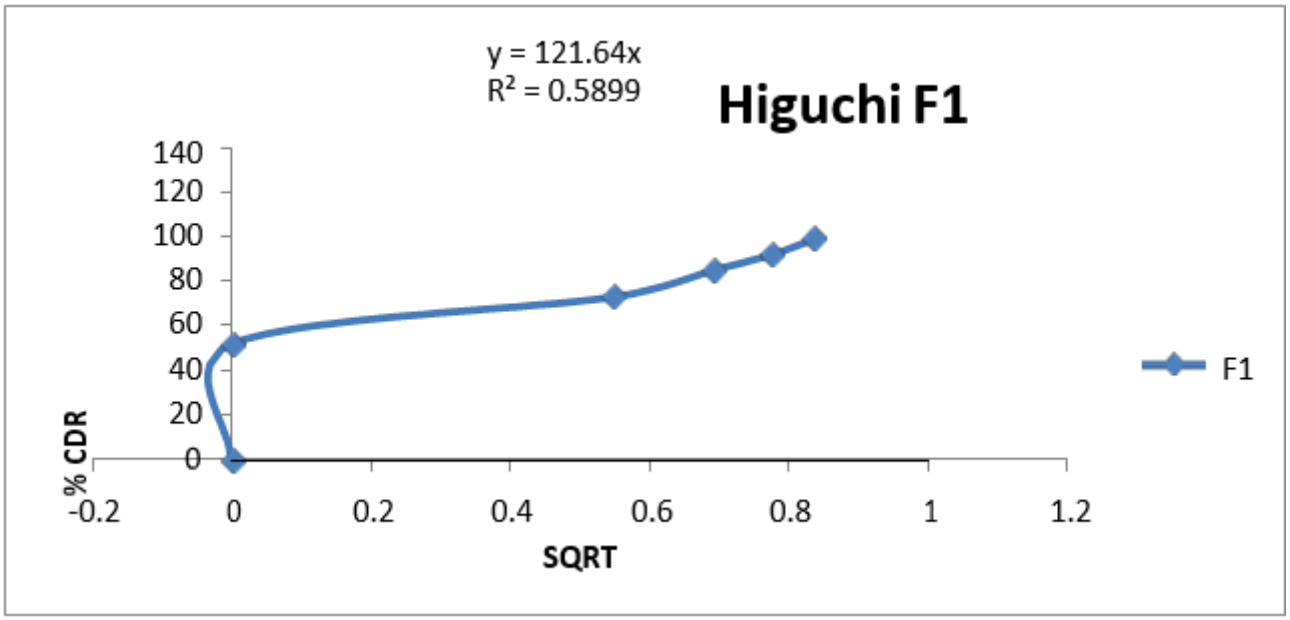

Figure No.39: Higuchi Graph of F1

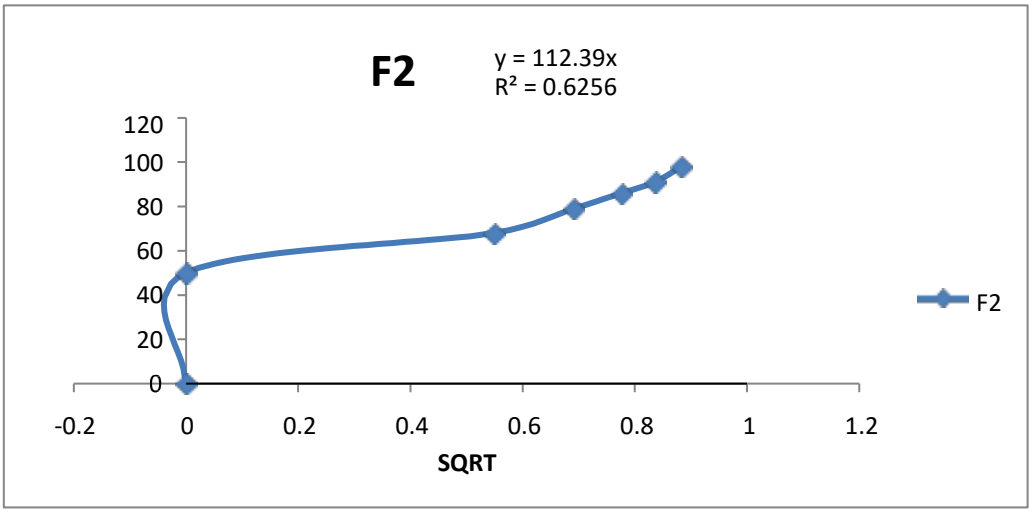

Figure No.40: Higuchi Graph of F2

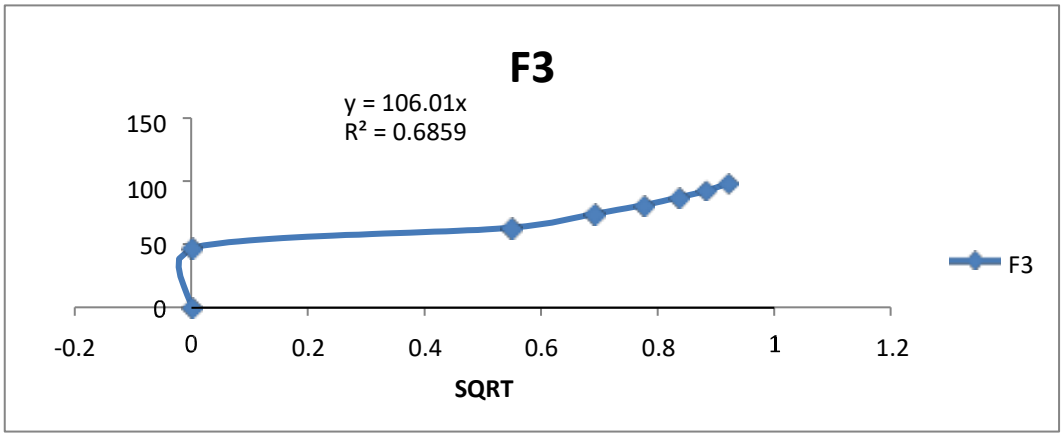

Figure No.41: Higuchi Graph of F3

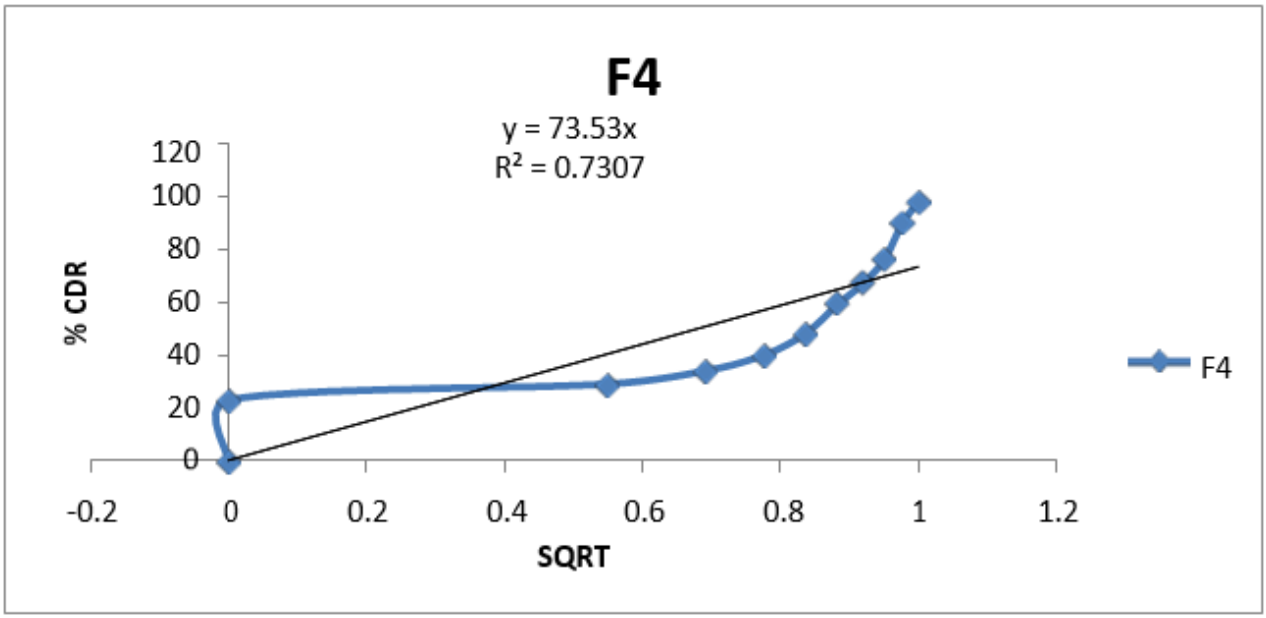

Figure No.42: Higuchi Graph of F4

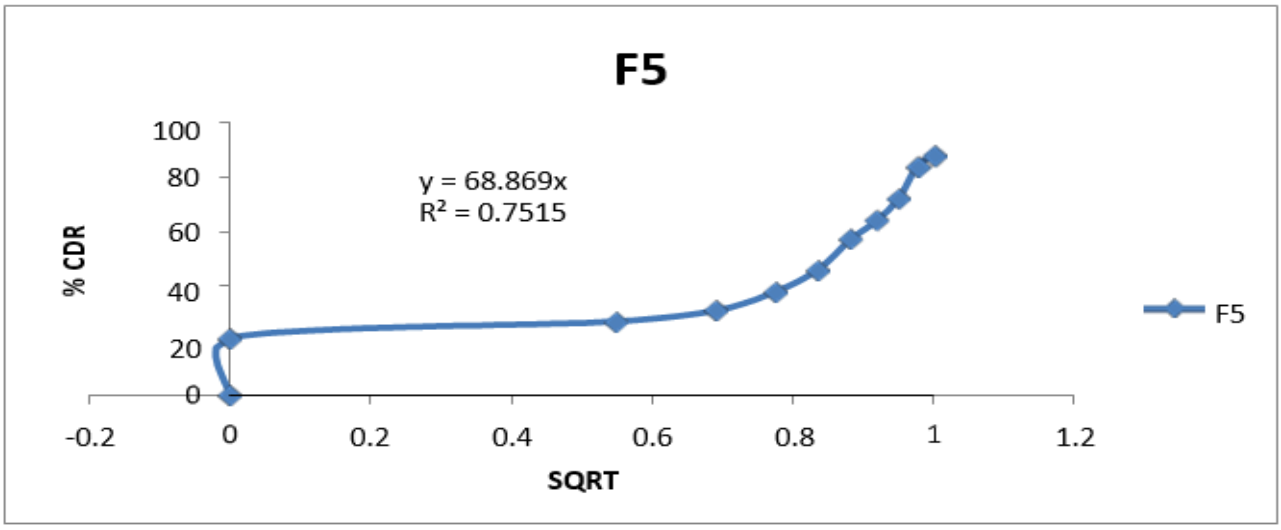

Figure No43: Higuchi Graph of F5

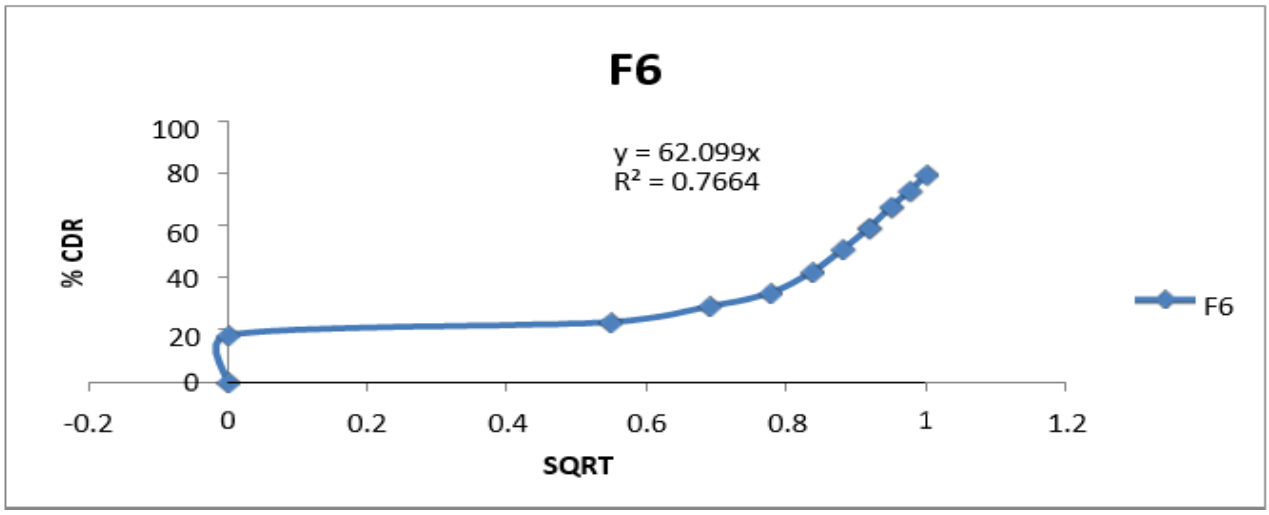

Figure No.8.17: Higuchi Graph of F6

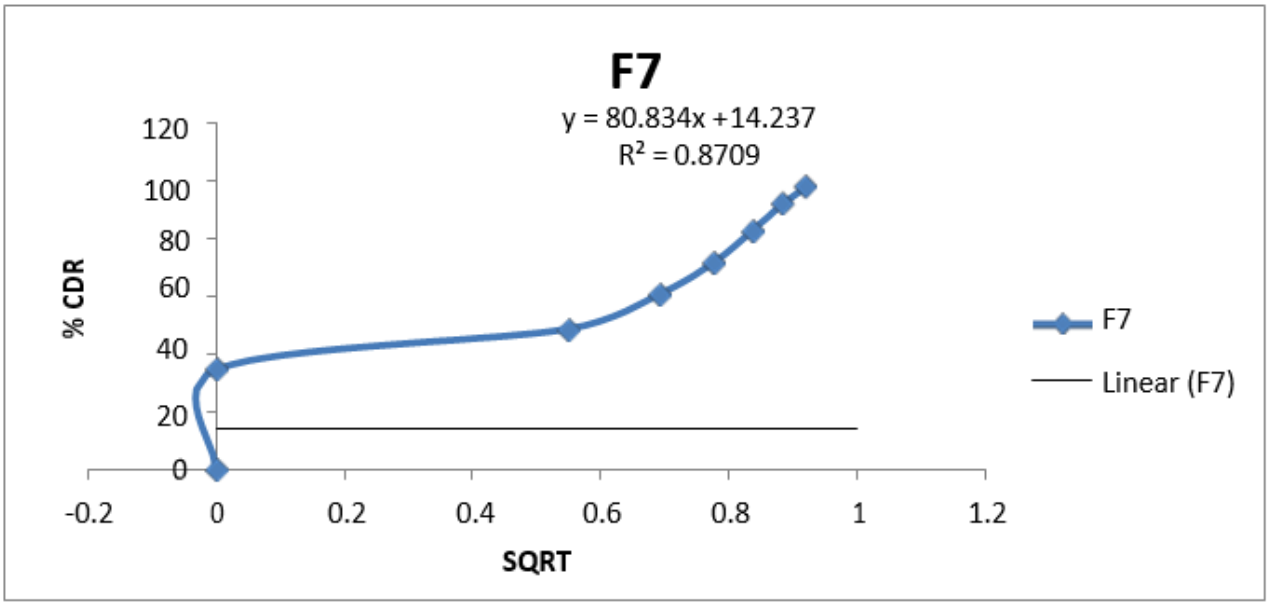

Figure No.45: Higuchi graph of F7

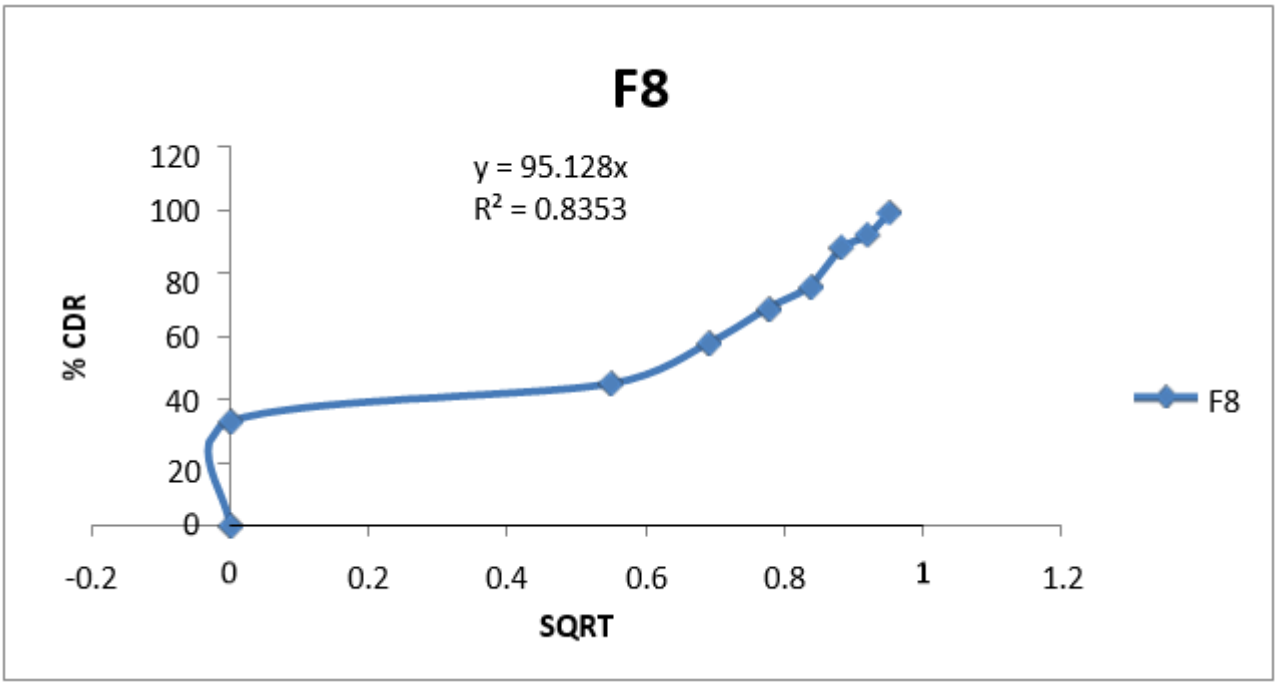

Figure No.46: Higuchi Graph of F8

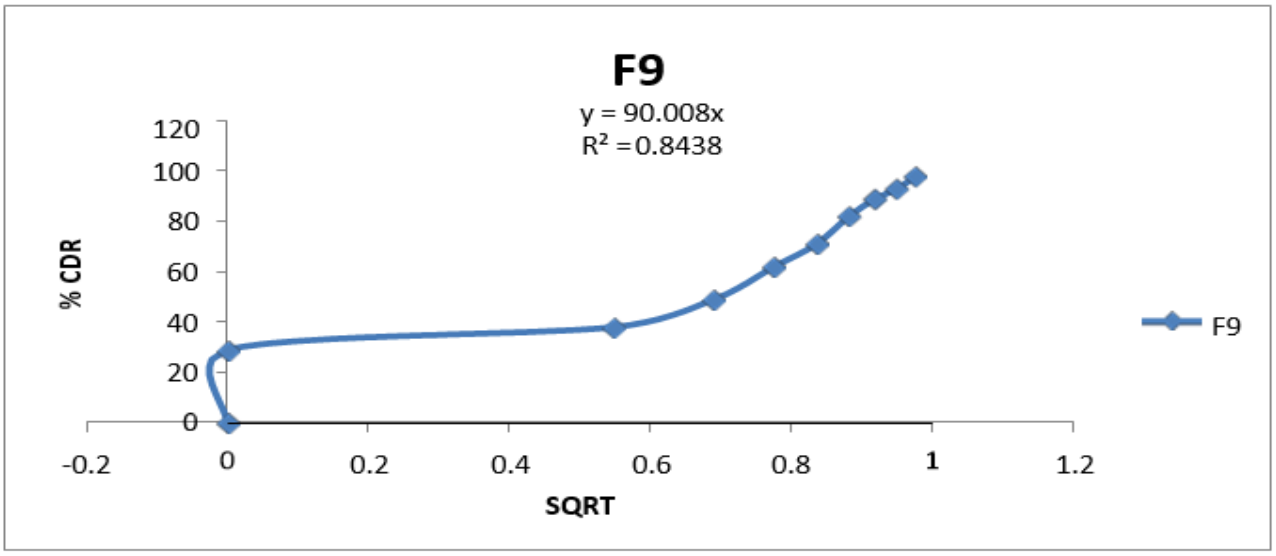

Figure No.47: Higuchi Graph of F9

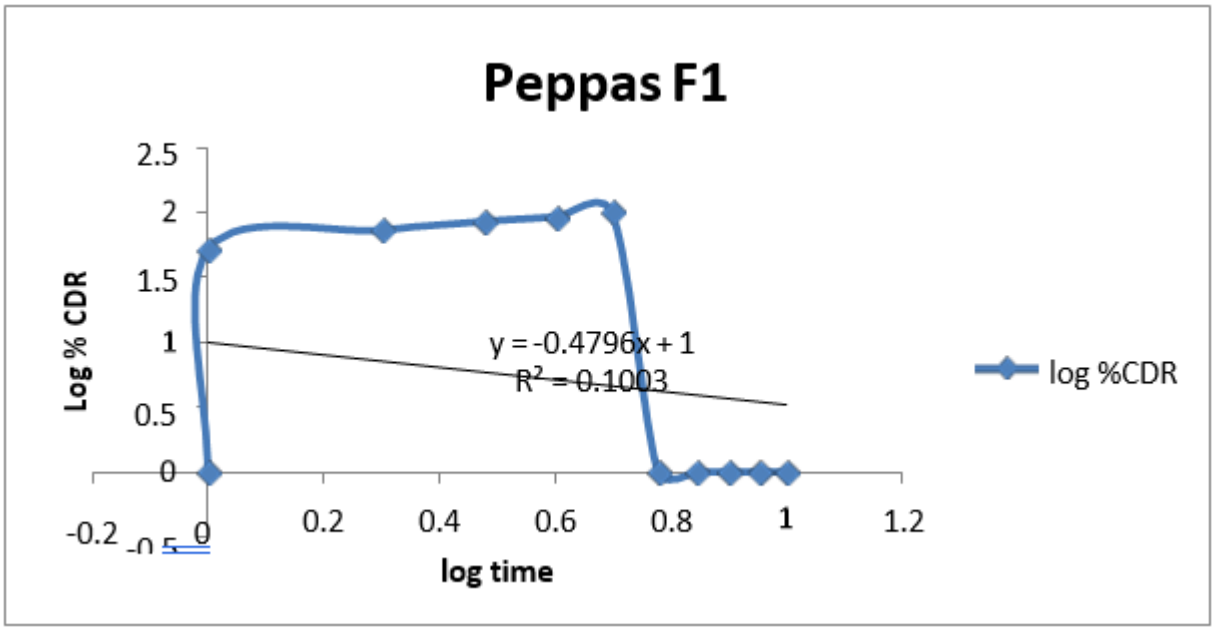

Figure No.48: Peppas Graph of F1

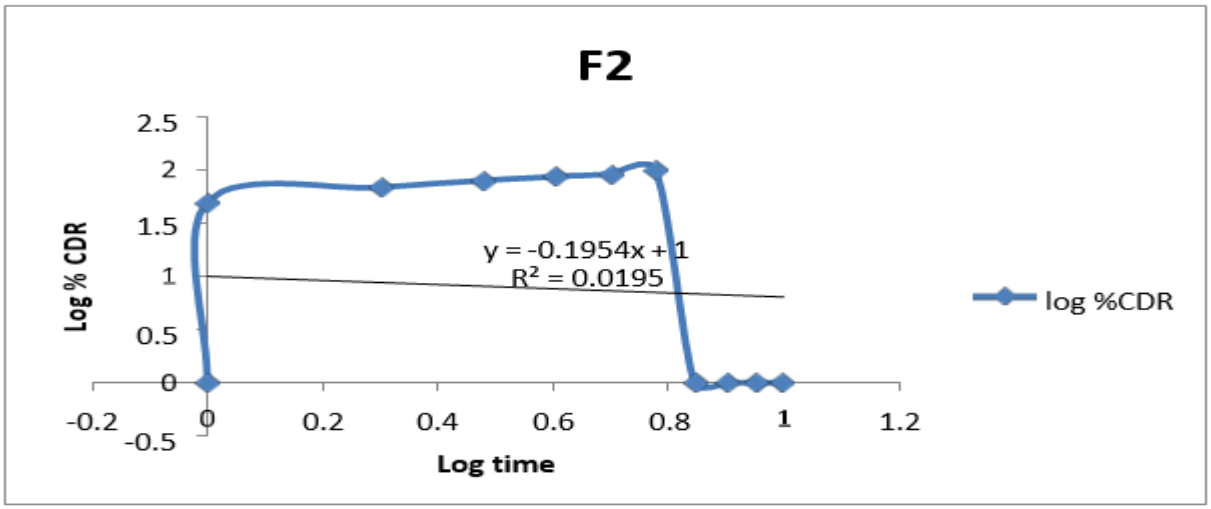

Figure No.49: Peppas Graph of F2

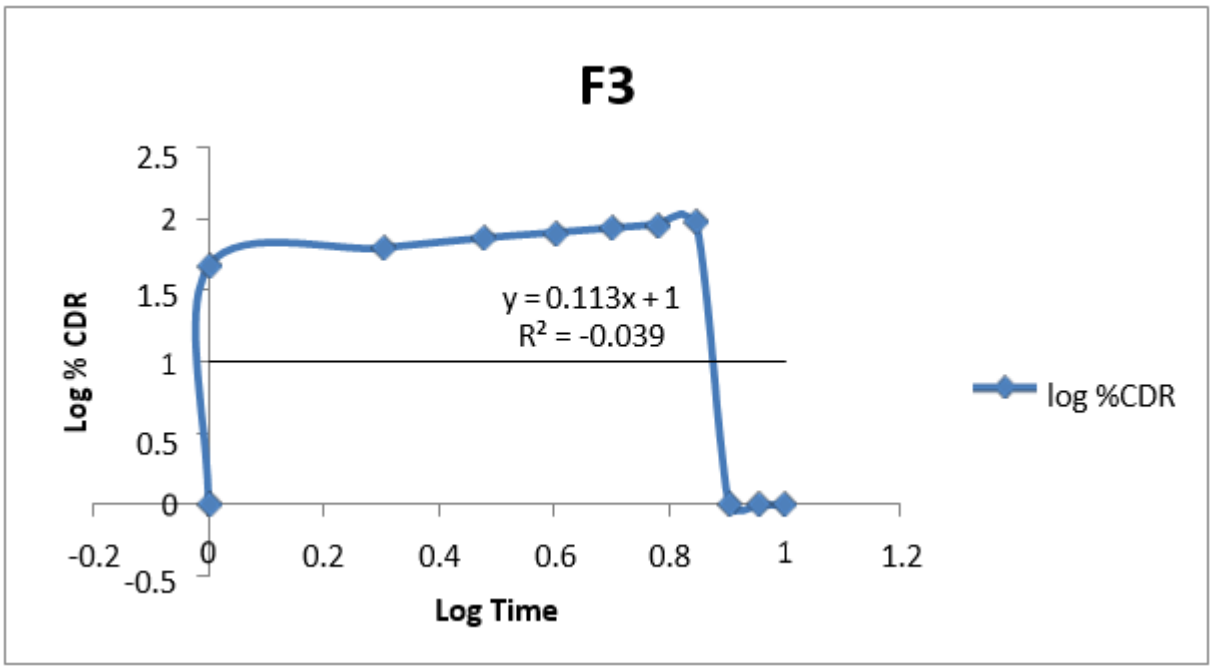

Figure No.50: Peppas Graph of F3

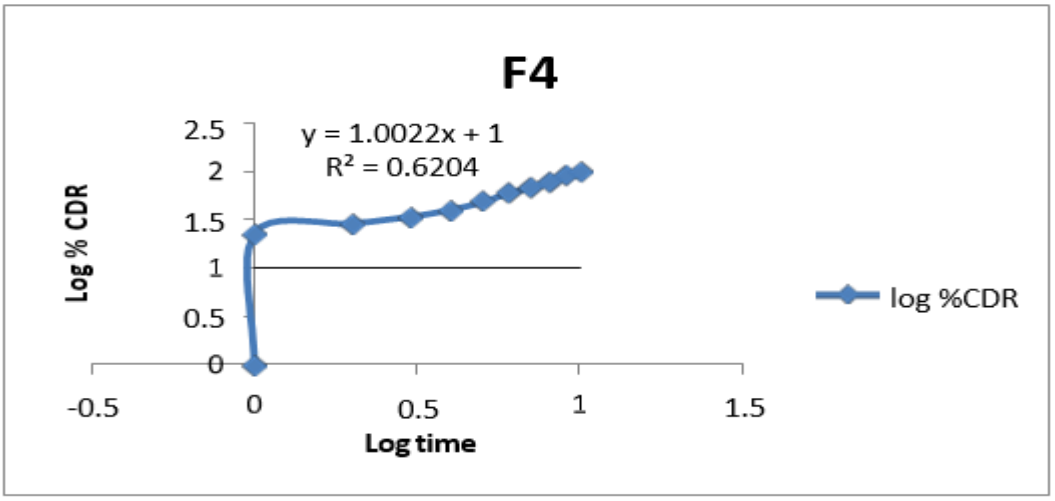

Figure No.51: Peppas Graph of F4

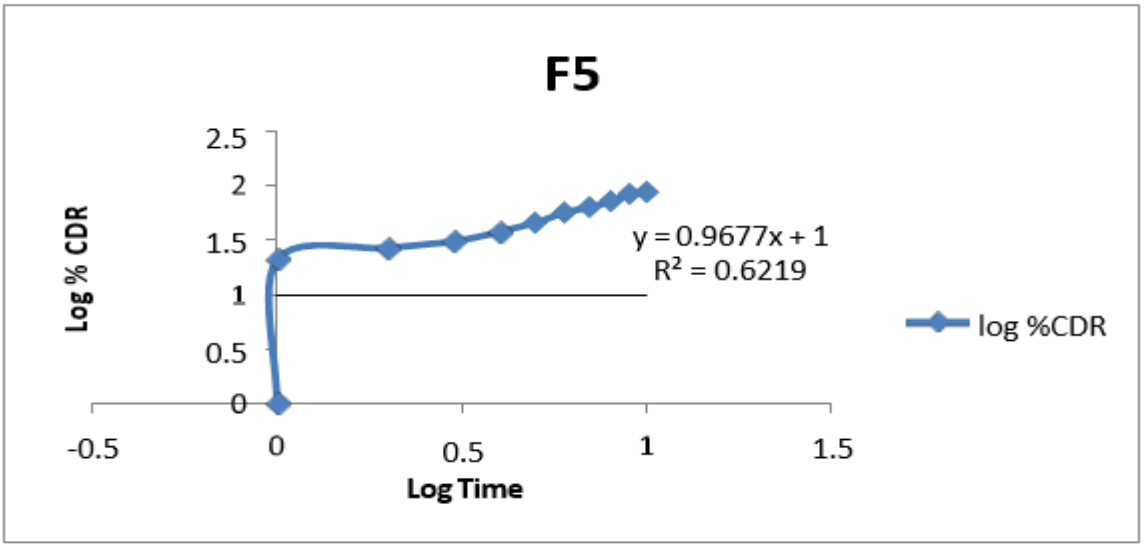

Figure No.52: Peppas Graph of F5

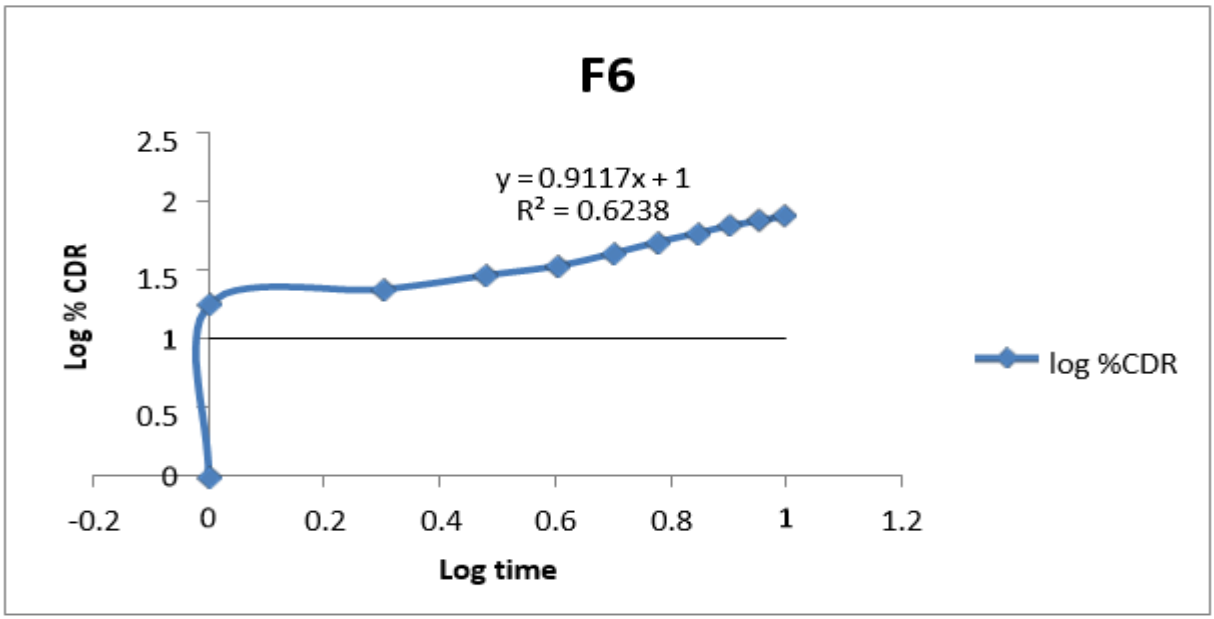

Figure No.8.18: Peppas Graph of F6

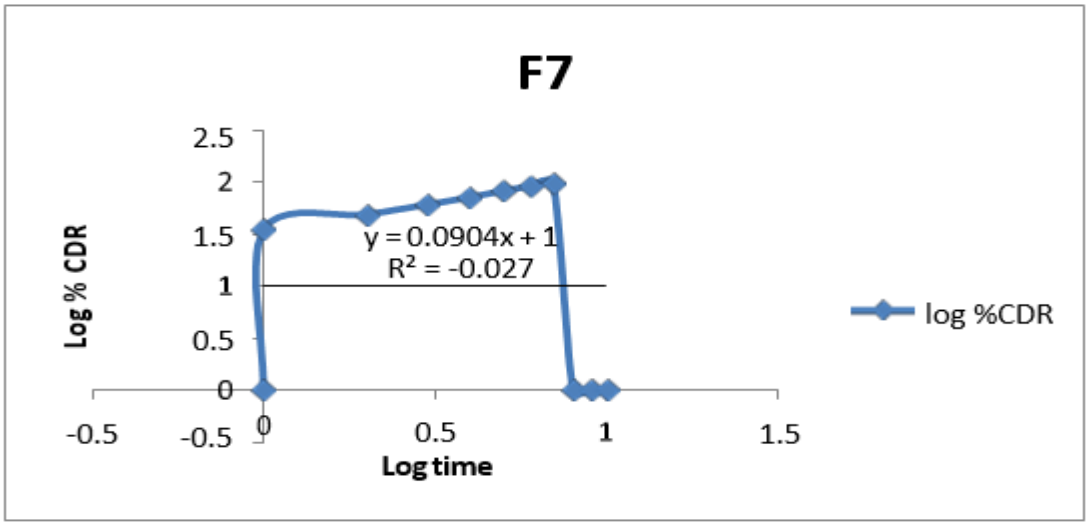

Figure No. 54: Peppas Graph of F7

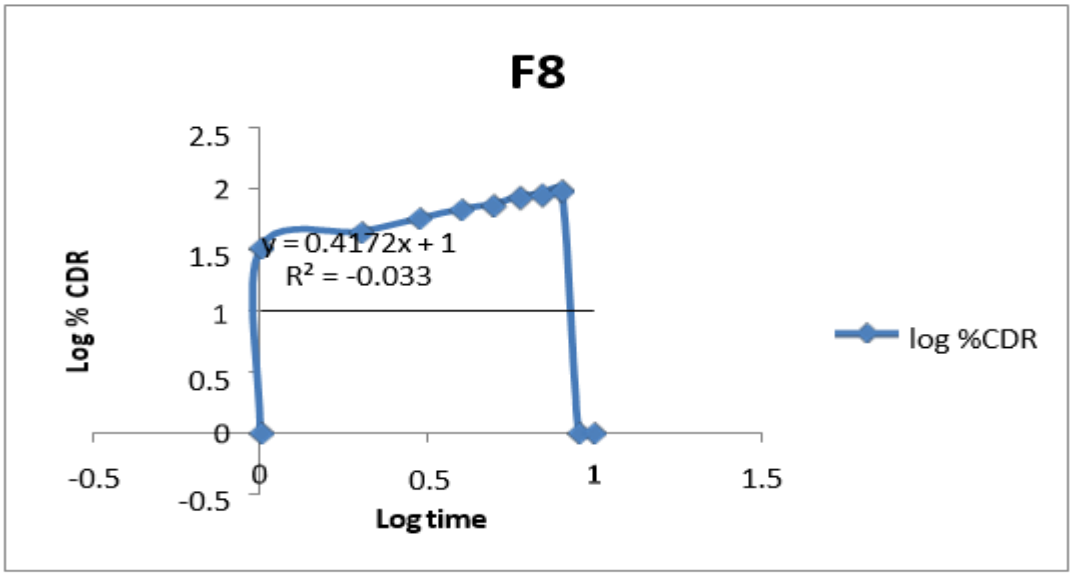

Figure No.55: Peppas Graph of F8

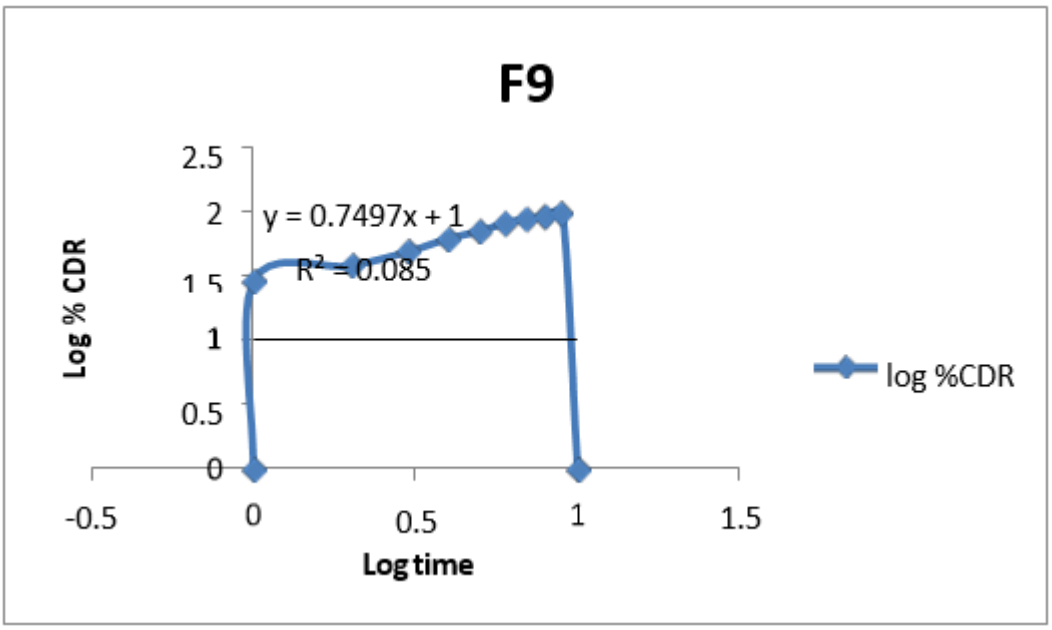

Figure No.56 Peppas Graph of F9

Discussion

The present study aimed to develop and evaluate mucoadhesive buccal tablets containing Naproxen using the direct compression method. Various excipients including Sodium Alginate, Carbopol, and Chitosan were used as polymers, and Magnesium Stearate was included as a stabilizer in the formulation.

To determine the linearity of Naproxen in 6.8 pH phosphate buffer, a calibration curve was constructed. The standard graph plotted between concentration vs. absorbance showed a linear relationship, indicating that Naproxen obeys Beer-Lambert's law. The value of R2 was 0.9996, indicating a high degree of linearity and accuracy in the measurement method. The FTIR spectra for pure Naproxen and the formulated tablet were analyzed. The peaks observed in the spectrum of Naproxen indicated the presence of specific functional groups, such as C=C stretching, C-O stretching, C-H stretching, and O-H stretching. The peaks observed in the spectra of Sodium Alginate, Carbopol, and Chitosan also indicated the presence of characteristic functional groups. The absence of interactions between the drug and excipients was confirmed. The slight shift in the thermogram suggested compatibility between the drug and excipients. The developed formulations were evaluated for various preformulation parameters including bulk density, tapped density, Carr's index, Hausner's ratio, and angle of repose. The results obtained for all these parameters were within the acceptable range as per the US Pharmacopeia (USP) standards. These findings indicate the suitable flow properties of the granules prepared for tablet manufacturing. The dissolution behavior of the formulated mucoadhesive buccal tablets was assessed through in-vitro drug release studies. Among all the formulations, F6 exhibited the highest drug release of approximately 97.87%. The dissolution profiles of different formulations indicated sustained release characteristics, with varying release rates. The release kinetics of formulation F6 were found to follow the Super Case II transport, indicating controlled drug release. These results suggest that the developed tablets have the potential to achieve the desired drug release profiles. The developed buccal tablets were evaluated for various parameters including hardness, thickness, weight variation, and disintegration time. The evaluation results showed that all the formulations met the specified limits as per the USP standards. The tablets exhibited desirable physical appearance, uniform thickness, sufficient hardness, and low friability. The drug content also fell within an acceptable range, ensuring accurate dosage delivery. These findings indicate the successful formulation of the buccal tablets with appropriate mechanical strength. In conclusion, the present study successfully developed Naproxen mucoadhesive buccal tablets using the direct compression method. The formulation exhibited desirable flow properties, adherence to Beer- Lambert's law, and compatibility between the drug and excipients. The tablets showed favorable physical characteristics, suitable mechanical strength, controlled drug release, and accurate dosage delivery. These findings have significant scientific implications for the development of Naproxen-based pharmaceutical products, improving drug delivery strategies, and optimizing therapeutic outcomes. The developed buccal tablets offer the advantage of bypassing the gastrointestinal tract and delivering the drug directly through the buccal mucosa. This route of administration can potentially avoid hepatic first-pass metabolism and minimize systemic side effects. Moreover, the sustained release characteristic of the tablets can provide a prolonged therapeutic effect, reducing the frequency of dosing and improving patient compliance. Further research may focus on optimizing the formulation to achieve more precise control over the drug release rate. Additionally, in-vivo studies, pharmacokinetic evaluations, and clinical trials can provide valuable insights into the performance and efficacy of Naproxen mucoadhesive buccal tablets in real-world scenarios. Overall, this study contributes to the existing scientific knowledge regarding Naproxen

and serves as a foundation for future research and development of Naproxen-based pharmaceutical products. The findings have the potential to advance drug delivery technologies and enhance the therapeutic outcomes of Naproxen treatment.

Conclusion

In conclusion, the development and evaluation of novel buccal drug delivery systems offer significant advantages in improving the bioavailability and reducing the frequency of administration of drugs. The buccal route provides a rapid onset of action, bypasses the first-pass metabolism, and allows for easy access and removal of drug delivery systems. Buccal adhesive systems adhere to the mucosal membranes, leading to increased drug concentration at the absorption site and improved bioavailability of systemically delivered drugs. The research work presented herein focuses on the development and evaluation of a novel buccal drug delivery system for naproxen, aiming to provide non-invasive administration and avoid the gastrointestinal side effects associated with oral administration. Given the current global scenario, scientists are actively researching and developing buccal adhesive systems using various formulation strategies. These strategies may include the incorporation of pH modifiers, enzyme inhibitors, and permeation enhancers to further improve the bioavailability of orally administered drugs. In conclusion, the development of buccal drug delivery systems holds great promise in enhancing drug delivery and improving patient compliance. Further studies and advancements in this field are necessary to explore the full potential and address the challenges associated with buccal drug delivery.

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Conflict of interest None

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