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Research Article

**FORMULATION DEVELOPMENT AND EVALUATION OF
DORZOLAMIDE HYDROCHLORIDE NANOPARTICLES****G. Soujanya*¹, Dr. G. Anil Kumar¹**¹Department of Pharmaceutics, Jayamukhi Institute of Pharmaceutical Sciences, Narsampet,
Warangal, Telangana-506132**Abstract:**

The objective of this present work was to develop Nanoparticle of Dorzolamide hydrochloride. The proposed Dorzolamide hydrochloride polymer loaded with nanoparticles was prepared by emulsification sonication method. Nanoparticles represent a promising drug delivery system of sustained and targeted drug release. They are specially designed to release the drug in the vicinity of target tissue. The aim of this study was to prepare and evaluate polymer loaded nanoparticles containing Dorzolamide hydrochloride in different drug to polymer ratio. SEM indicated that nanoparticles have a discrete spherical structure. FT-IR studies indicated that there was no chemical interaction between drug and polymer and stability of drug. The in vitro release behavior from all the drug loaded batches was found to be Peppas release and provided sustained release over a period of 48 h. The developed formulation overcome and alleviates the drawbacks and limitations of Dorzolamide hydrochloride sustained release formulations and could possibility be advantageous in terms of increased bioavailability of Dorzolamide hydrochloride.

Keywords: Dorzolamide hydrochloride, Nanoparticles.**Corresponding author:****G. Soujanya,**Department of Pharmaceutics, Jayamukhi Institute of
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INTRODUCTION:

Recent years it has become more evident that the development of new drugs alone is not sufficient to ensure progress in drug therapy. *In vitro* obtained are more exciting but very often followed by disappointing results *in vivo*. Main reasons for this therapy failure include:

- Insufficient drug concentration due to poor absorption, rapid metabolism and elimination (e.g., peptides & proteins),
- Drug distribution to other tissues combined with high drug toxicity (e.g., anticancer drugs),
- Poor drug solubility which excludes i.v. injection of aqueous drug solution,
- High fluctuation of variable plasma levels due to unpredictable bioavailability after peroral administration, including the influence of food on plasma levels (e.g., cyclosporine).

To overcome these biopharmaceutical challenges, versatile formulation approaches are required which will accommodate the physicochemical properties of the individual drug while simultaneously exploiting the physiological environment. Solid lipid nanoparticles have been reported as an alternative drug delivery device to traditional polymeric nanoparticles. SLNs are in submicron size range (50-1000nm) and are composed of physiologically tolerated lipid components. At room temperature the particles are in solid state. These are made of biocompatible and biodegradable materials capable of incorporating lipophilic and hydrophilic drugs.

The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site in the body to achieve promptly and then to maintain the desired drug concentration. That is, the drug delivery system should deliver drug at a rate dictated by the needs of the body over a specified period of treatment. This idealized objective points to the two aspects most important to drug delivery namely spatial placement and temporal delivery of a drug. Spatial placement relates to targeting of drug to a specific organ or tissue, while temporal delivery refers to controlling the rate of drug delivery to the target tissue. An appropriately designed controlled release drug-delivery system can be a major advance towards solving these two problems. It is for this reason that the science and technology responsible for development of controlled-release pharmaceuticals has been, and continues to be the focus of a great deal of attention in both industrial and academic laboratories.

1.1. CONVENTIONAL DRUG THERAPY¹:

To gain appreciation for the value of controlled drug therapy, it is useful to review some fundamental aspects of conventional drug delivery. Consider single dosing of a hypothetical drug that follows a simple one-compartment pharmacokinetic model for disposition. Depending on the route of administration, a conventional dosage form of the drug e.g.: A solution, suspension, capsule tablet etc. can produce a drug blood level versus time profile. The term drug blood levels refer to the concentration of drug in blood or plasma, but the concentration in any tissue could be plotted on the ordinate. Administration of a drug by either intravenous injection or an extra vascular route, e.g., orally, intramuscularly or rectally does not maintain drug blood levels within the therapeutic range for extended periods of time. The short-duration of action is due to the inability of conventional dosage forms to control temporal delivery. If an attempt is made to maintain drug blood levels in the therapeutic range for longer periods by for e.g., increasing the initial dose of an intravenous injection, toxic levels can be produced at early times. This approach obviously is undesirable and unsuitable. An alternative approach is to administer the drug repetitively using a constant dosing interval, as in multiple-dose therapy. In this case the drug blood level reached and the time required to reach that level depend on the dose and the dosing interval. There are several potential problems inherent in multiple dose therapy.

1. If the dosing interval is appropriate for the biological half-life of the drug, large peaks and valleys in the drug blood level may result. For e.g., drugs with short half-lives require frequent designs to maintain constant therapeutic levels.
2. The drug blood level may not be within the therapeutic range at sufficiently early times, an important consideration for certain disease states.
3. Patient non-compliance with the multiple-dosing regimens can result in failure of this approach.

In many instances, potential problems associated with conventional drug therapy can be overcome. When this is the case, drugs given in conventional dosage forms by multiple dosing can produce the desired drug blood level for extended period of time. Frequently, however these problems are significant enough to make drug therapy with conventional dosage forms less desirable than controlled-release drug therapy. This fact, coupled with the intrinsic inability of conventional dosage forms to achieve spatial placement, is a compelling motive for investigation of controlled-release drug delivery systems.

1.2. TERMINOLOGY^{2,3}:

Modified-release delivery systems may be divided conveniently into four categories:

1. Delayed release
2. Sustained release
3. Site-specific targeting
4. Receptor targeting.

Delayed-release systems are those that use repetitive, intermittent dosing of a drug from one or more immediate-release units incorporated into a single dosage form. Examples of delayed release systems include repeat-action tablets and capsules and enteric-coated tablets where timed release is achieved by a barrier coating.

Sustained-release systems include any drug delivery system that achieves slow release of drug over an extended period of time. If the systems can provide some control, whether this is of a temporal or spatial nature, or both, of drug release in the body, or in other words, the systems is successful at maintaining constant drug levels in target tissue or cells, it is considered controlled-release systems.

Site-specific and receptor targeting refer to targeting of a drug directly to a certain biological location. In the case of site-specific release, the target is adjacent to or in the diseased organ or tissues, for receptor release, the target are the particular receptor for a drug within an organ or tissue. Both of these systems satisfy the spatial aspect of drug delivery and are also considered to be controlled drug-delivery systems.

1.3. ADVANTAGES OF CONTROLLED RELEASE PREPARATIONS:

1. Decreased incidence and/ or intensity of adverse effects and toxicity.
2. Better drug utilization.
3. Controlled rate and site of release.
4. More uniform blood concentrations.
5. Improved patient compliance.
6. Reduced dosing frequency.
7. More consistent and prolonged therapeutic effect.
8. A greater selectivity of pharmacological activity.

1.4. OBJECTIVES⁴:

Control release systems include any drug delivery system that achieves slow release of drug over an extended period of time.

The objectives of oral sustained release formulations are:

1. Frequency of drug administration is reduced.
2. Patient compliance can be improved.
3. Drug administration can be made more convenient.
4. Better control of drug absorption can be attained.

1.5. THE CONCEPT OF TARGETING^{5,6}:

The concept of designing specified delivery system to achieve selective drug targeting has been originated from the perception of Paul Elrich, who proposed drug delivery to be as a "Magic Bullet". It was the very first report published on targeting (Paul Elrich, 1902) describing targeted drug delivery as an event where a drug-carrier complex/ conjugate delivers drug(s) exclusively to the preselected target cells in a specific manner. Gregoriadis, 1981 described drug targeting using novel drug delivery system as 'old drugs in new cloths'.

New drug delivery system represents a means by which drug may be continuously delivered either locally or systemically or a larger site in an effective and repeatable manner. Controlled and targeted drug delivery systems have been receiving more and more attention as new methods of drug delivery.

One of the most exciting is the target-organ oriented drug delivery system. Presenting drugs into whole body is not only wasteful but also likely to lead to harmful effects that can be eliminated if the drug is delivered only to specific target organ. Targeted delivery is not restricted to any one route of administration. Oral formulations, parenterals, transdermal and pulmonary route and many other routes are available for effective drug targeting.

Table 1.1: Examples of Novel Drug Delivery Systems

System	Features
Floating drug delivery system (FDDS)	It is based on gastric retentive system (GRS), aimed to prolong release and restrict the region of delivery to stomach. Drugs like cyclosporine, ciprofloxacin are better absorbed in stomach and upper small intestine can be made as FDDS to improve their availability
Bio(Muco) adhesive system	It is used to localize a delivery system to a specific area for local action or increase contact time at the absorption site.
Chronotherapeutic delivery system	Programmable pulsatile release of a drug (capable of releasing drug after predetermined time delay) is achieved, consistent with the demands of circadian rhythm on GIT physiology and on disease states
Targeted delivery through colloidal carriers (liposomes, nano-particles, erythrocytes, resealed)	Drug is delivered to selective site of action of organ at the predetermined rate there by eliminating wasteful distribution of drugs and subsequent reduction of adverse effects.
Drugs delivery through external pump	It consists of reservoir of drug whose flow in the body is actuated to release the drug at a zero order by powered devices (i.e. pumps and implantable infusion system)

Targeting can also be done by changing the formulation in a way that alters its distribution profile in the body, thereby minimizing contact with healthy tissues e.g., encapsulation in a liposome formulation.

A number of essential aspects, which should be considered for the designing of drug delivery systems to achieve this goal, include target carrier, ligand (s) and physically modulated components. Targeted drug delivery implies for selective and effective localization of pharmacologically active moiety at predefined (preselected) targets in therapeutic concentration, while restricting its access to non-target normal cellular linings, thus minimizing toxic effects and maximizing therapeutic index.

Drug targeting may be achieved by passive targeting e.g., intra-articular injection. Greater specificity may be required, such as delivery to particulate organ, to a set of cells within an organ or even to an intracellular structure. This usually requires active targeting. In some cases, it is possible to target to specific cells or intracellular structures by exploiting a natural

physiological process such as macrophage uptake of foreign materials.

The goal of optimal therapy is to deliver the drug to produce maximum simultaneous safety, effectiveness and reliability. All these rely on establishing technology of innovative dives that meets the need for effective delivery of drug to the site action. The future is aimed at optimizing therapy while offering patients' mobility and convenience.

METHODOLOGY:

Analytical Method Development

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

Procedure: For the preparation of calibration curve stock solution was prepared by dissolving 100 mg of accurately weighed drug in 100ml of Methanol (1mg/ml). Further 1ml of the stock solution was pipette out into a 100 ml volumetric flask and volume

was made up with phosphate buffer (5.5pH). From this stock solution pipette out 1ml and dilute to 10 ml with phosphate buffer and subject for UV scanning in the range of 200-400 nm using double beam UV spectrophotometer. The absorption maxima were obtained at 252 nm with a characteristic peak.

Preparation of calibration curve: It is soluble in Methanol; hence Methanol was used for solubilizing the drug. Stock solution (1 mg/mL) of Dorzolamide hydrochloride was prepared in Methanol and subsequent working standards (5, 10, 15, 20 and 25 µg/mL) were prepared by dilution with phosphate buffer of pH-5.5. These solutions were used for the estimation Dorzolamide hydrochloride by UV method. The whole procedure was repeated three times and average peak area was calculated. Calibration plot was drawn between concentrations and peak area. Calibration equation and R² value are reported.

Preparation of nanoparticles

Preparation of Dorzolamide hydrochloride loaded nanoparticles

Dorzolamide hydrochloride loaded Nanoparticle was prepared by previously reported emulsification sonication method. Dorzolamide hydrochloride was dissolved in organic solvent (10 ml, methanol). Polymers in different concentrations were dissolved in water. The organic phase was added drop wise into the polymeric solution for emulsification. Then the dispersion was sonicated (20 min) with the application of ultra-probe sonication (60 W/cm³, Hielscher, Ultra-sonics, Germany). The formulation was stirred at 1500 rpm for 6 h using a magnetic stirrer to evaporate the organic solvent. The prepared NPs were centrifuged at 15,000 rpm for 20 min at 4 °C (Remi, Mumbai, India).

Table: Composition of nanoparticles formulations (F1 to F9)

Excipients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Dorzolamide hydrochloride (%)	2	2	2	2	2	2	2	2	2
Eudragit RS 100 (mg)	100	150	200	-	-	-	-	-	-
Chitosan (mg)	-	-	-	100	150	200	-	-	-
Ethyl cellulose	-	-	-	-	-	-	100	150	200
Tween 80 (mL)	0.5	1	1.5	2	-	-	-	-	1
Span 60 (mL)	-	-	-	-	0.5	1	1.5	2	1
Distilled water (ml)	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Dichloromethane (ml)	15	15	15	15	15	15	15	15	15
Methanol	10	10	10	10	10	10	10	10	10

RESULTS AND DISCUSSION:

CALIBRATION PLOT OF DORZOLAMIDE HYDROCHLORIDE IN PHOSPHATE BUFFER OF pH -5.5:

A standard graph of Dorzolamide Hydrochloride in phosphate buffer of pH-5.5 was plotted using

Absorbance and concentration as shown in Table and Fig. Equation for linearity curve and R² were calculated as $Y=0.06X+0.003$ and $R^2=0.999$. Dorzolamide Hydrochloride showed maximum absorbance in phosphate buffer (pH 5.5) at 252 nm. The solution obeyed Beer-Lambert's law for concentration range of 5 to 25 µg/mL with regression coefficient of 0.998. Standard curve of prepared

Dorzolamide Hydrochloride in phosphate buffer pH

5.5 is shown below.

Table: calibration curve of Dorzolamide Hydrochloride in phosphate buffer pH 5.5

Concentration($\mu\text{g/mL}$)	Absorbance
0	0
5	0.122
10	0.246
15	0.369
20	0.485
25	0.597

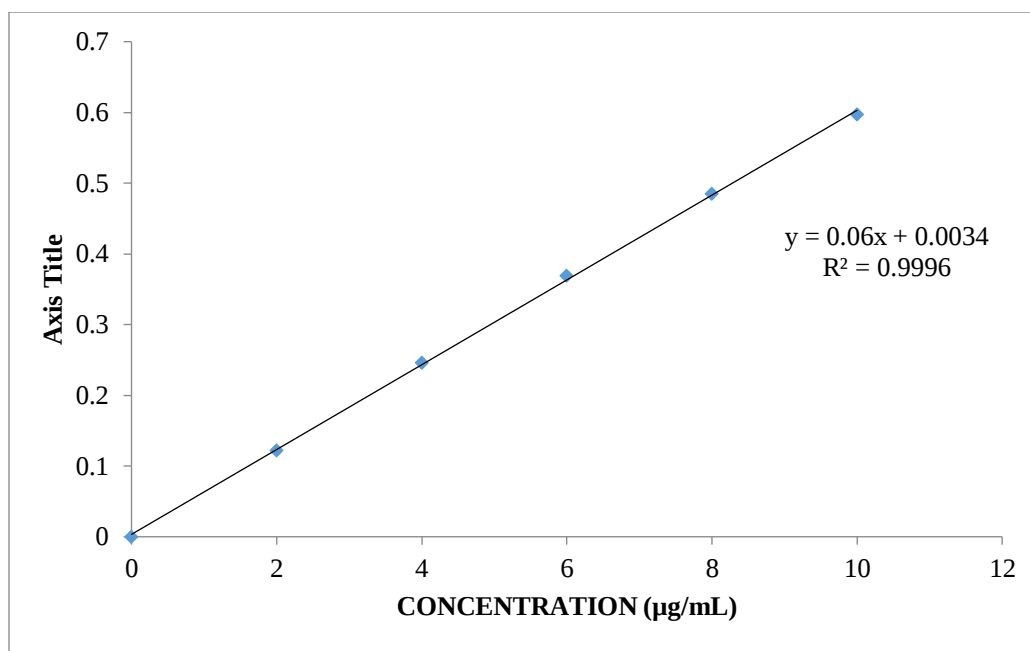


Fig: Calibration curve of Dorzolamide Hydrochloride in phosphate buffer pH 5.5

Characterization of nanoparticles:

Table: Percentage yield, Drug Content, Entrapment Efficiency of all nanoparticles formulations

FORMULATION	Percentage yield	Drug Content	Entrapment Efficiency
F1	86.15	90.87	75.61
F2	90.09	93.39	79.82
F3	92.28	95.51	81.30
F4	94.83	97.14	84.19
F5	80.18	89.69	72.43
F6	87.39	92.35	78.79
F7	90.27	94.12	81.54
F8	90.91	97.02	80.11
F9	92.81	96.18	83.28

Percentage yield of formulations F1 to F9 by varying drug to polymer was determined and is presented in Table. Highest drug content, Highest Entrapment efficiency observed for F4 formulation.

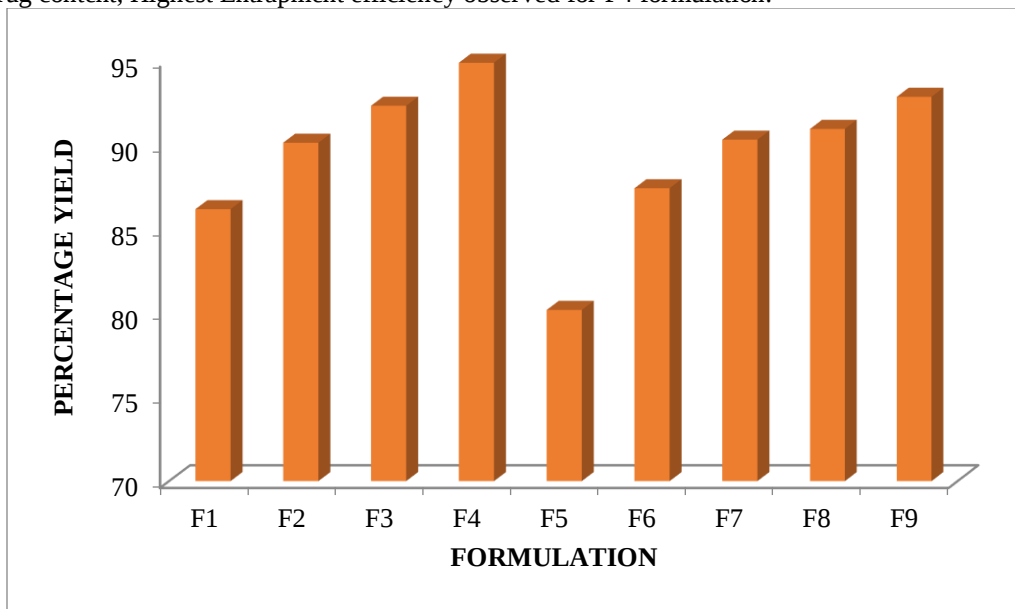


Fig: Percentage yield of all nanoparticles

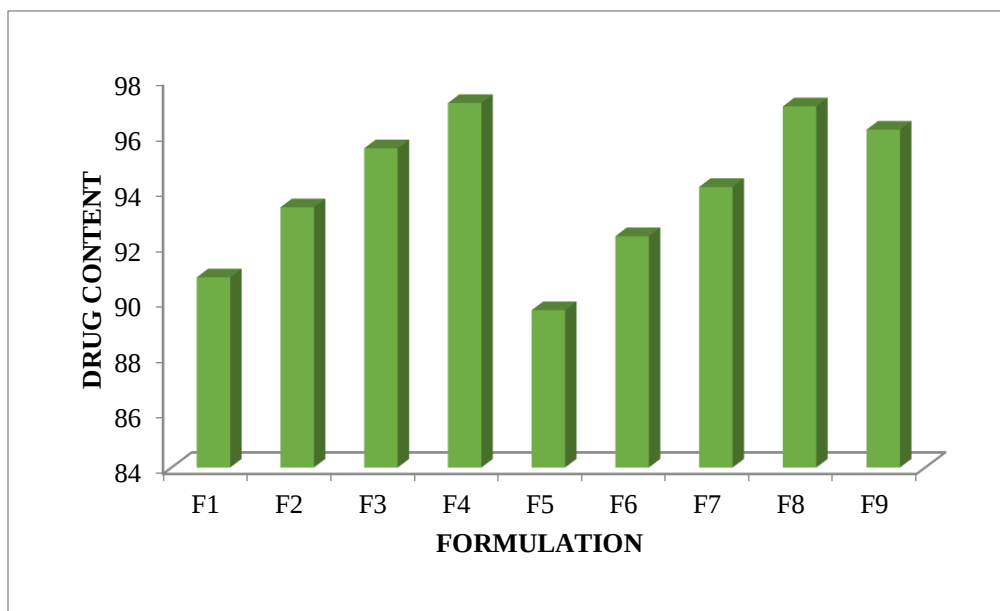


Fig: Drug Content yield of all nanoparticles

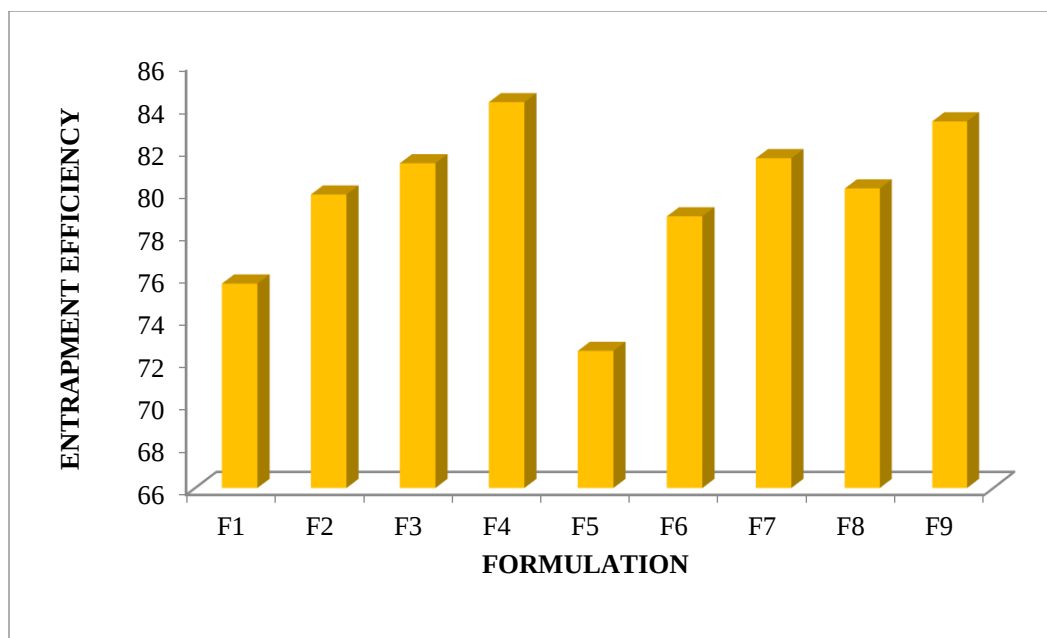


Fig: Entrapment Efficiency of all nanoparticles

Table: Particle Sizes, PDI, Zeta Potential of all nanoparticles formulations

FORMULATION	Particle Size (nm)	PDI	Zeta Potential (mV)
F1	1212.1	0.691	-23.12
F2	981.3	1.172	-28.81
F3	801.2	1.135	-27.52
F4	412.9	0.126	-36.25
F5	706.4	0.260	-20.55
F6	681.2	0.325	-24.83
F7	559.0	0.671	-29.59
F8	513.4	0.376	-32.11
F9	476.2	0.459	-30.80

The particle size of the all formulations was observed in the range of 412.9 to 1212.1. The less particle size, PDI observed in the F4 formulation i.e., 0.126 nm respectively. The Zeta potential range from -20.55 mV to -36.25 mV to all the formulations. The negative charge on the surface of the Nanoparticle is

believed to facilitate uptake from the intestine by the Payers patch, leading to the lymphatic circulation, also it is believed to prevent entangling of the nanoparticles in the negatively charged mucous owing to the repulsion of like charges.

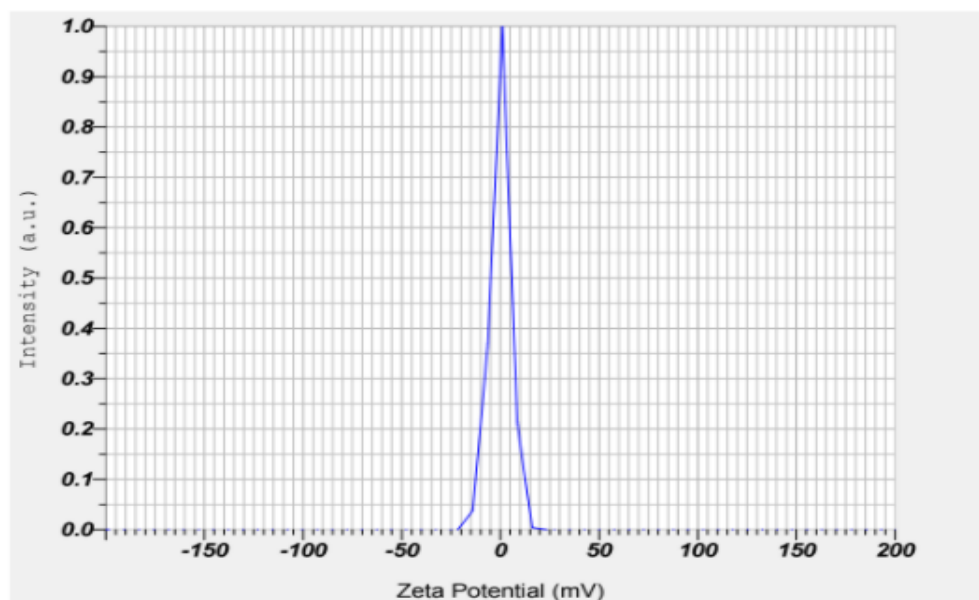


Fig: Zeta potential of F4 Formulation

DSC:

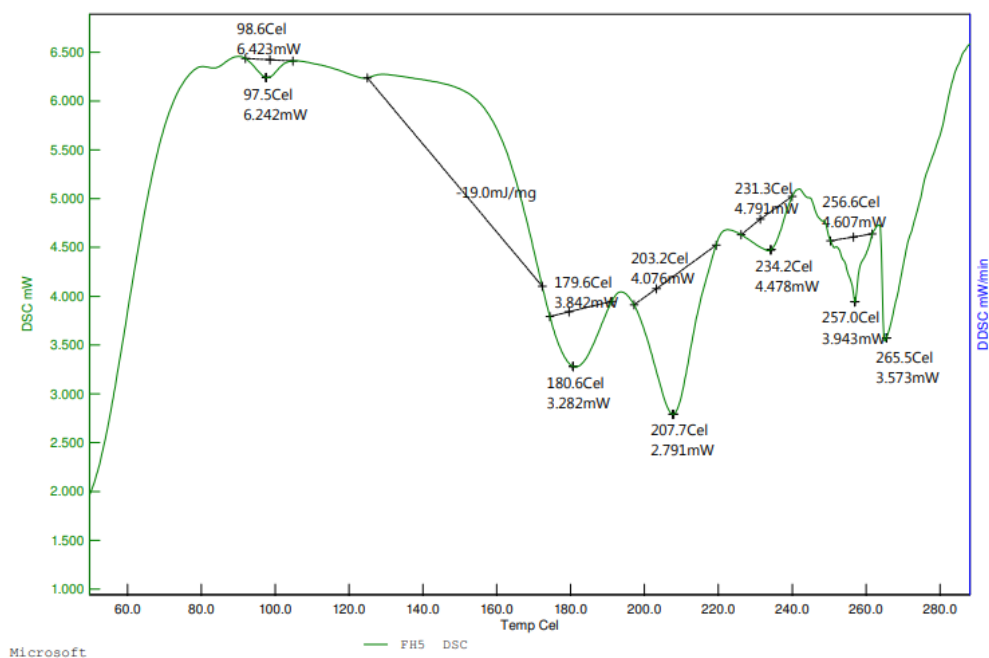


Figure: Dorzolamide Hydrochloride Pure

SEM

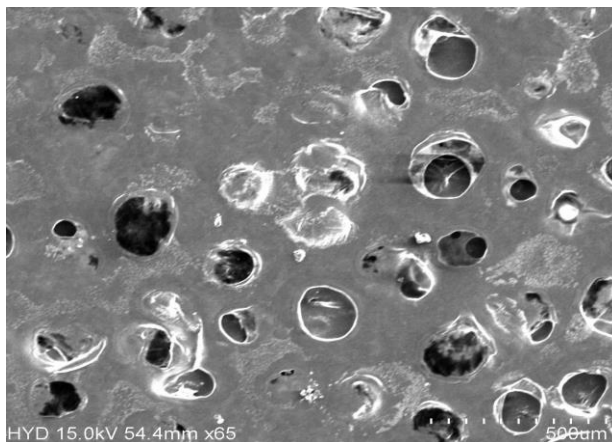


Figure: Dorzolamide Hydrochloride F4 optimised nanoparticles

SEM studies showed that the Dorzolamide Hydrochloride- loaded nanoparticles had a spherical shape with a smooth surface as shown in Figure.

XRD

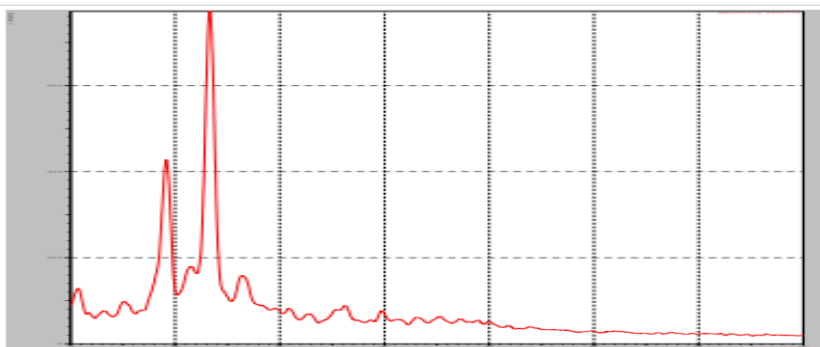


Figure: XRD Dorzolamide Hydrochloride F4 nanoparticles

Table: *In vitro* dissolution studies of F1-F9 nanoparticles formulations in percentage

Time (hour)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	16.50	26.93	32.53	38.41	16.05	20.31	27.92	23.96	20.45
2	35.82	42.14	48.29	49.78	22.62	32.80	38.78	28.34	27.98
4	42.73	50.31	56.09	56.57	30.21	40.92	47.63	34.50	30.82
6	50.61	56.25	62.93	62.5	34.18	50.88	56.49	46.99	43.87
8	56.01	68.19	74.03	69.03	45.29	59.35	63.27	56.87	52.34
10	62.12	73.50	78.11	74.78	51.44	64.58	75.65	63.33	60.91
12	68.98	77.99	82.93	79.09	56.91	76.75	79.18	68.97	64.04
18	77.30	83.92	89.88	84.39	65.09	83.26	84.05	76.56	70.85
24	83.13	90.41	93.87	94.23	74.43	89.52	90.72	81.14	78.90
48	90.02	95.11	97.45	99.19	83.92	93.07	96.30	88.97	85.59

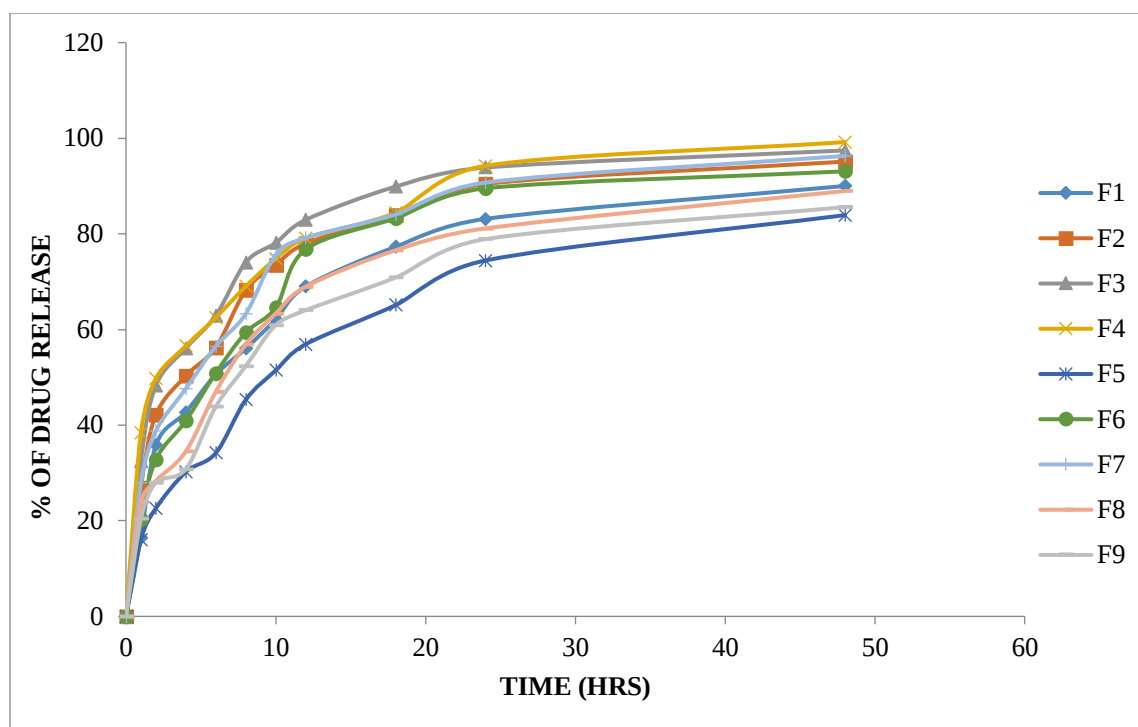


Fig: *In vitro* dissolution studies of F1-F9 nanoparticles formulations in percentage

In vitro drug release study of the selected nanoparticles (F1, F2, F3, F4, F5, F6, F7, F8 and F9) was carried out. The nanoparticles exhibited 48 hours sustained release pattern. Forty nine of the incorporated amounts of drugs were found to be released during the first 2 hours, followed by a slowed release of 99.19 % of the drug up to 48 hours. The Dorzolamide Hydrochloride -loaded nanoparticles F4 showed a better release profile of 99.19% by 48 hours. The prolonged release at 48 hours can be attributed to slow diffusion of drug from

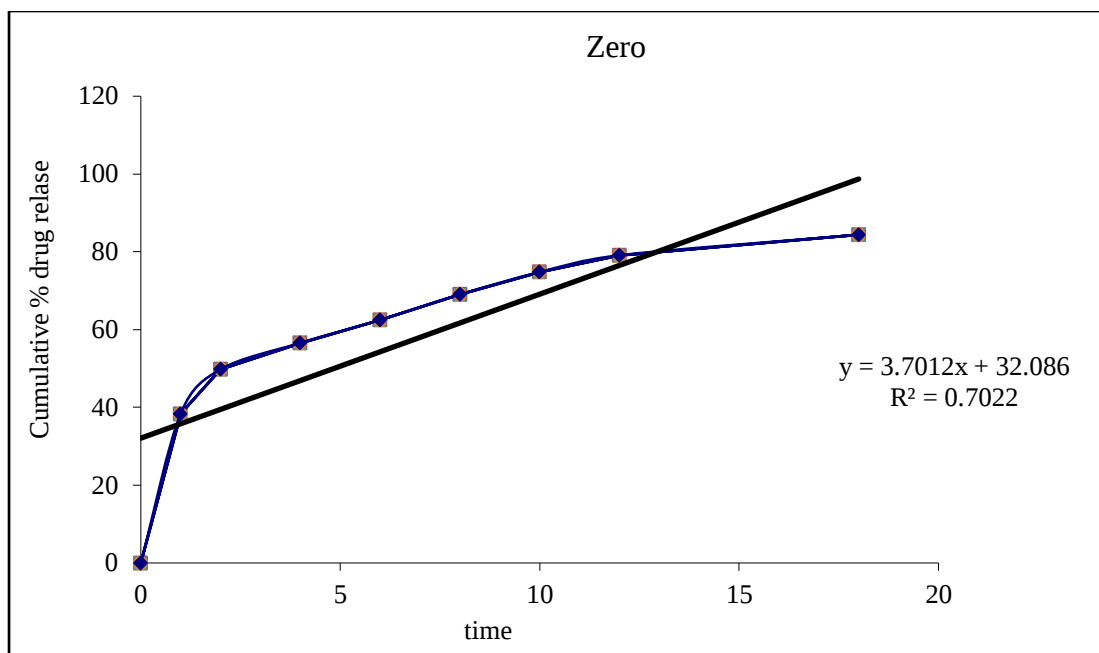
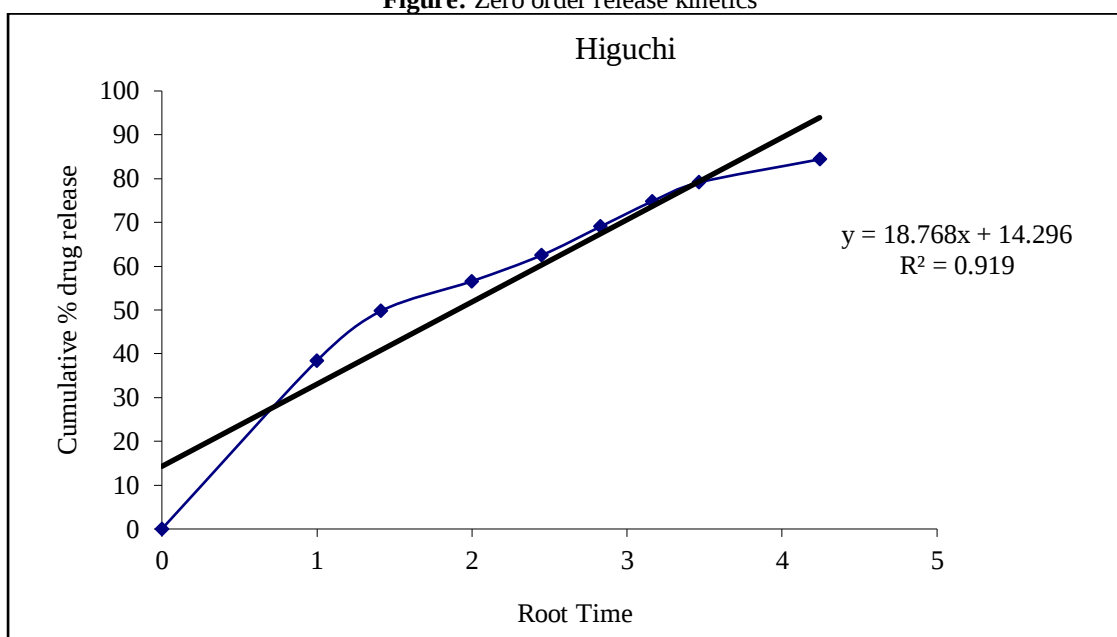
polymer matrix. The results of *in vitro* drug release are depicted in above Table.

Release Kinetics

To analyze the drug release mechanism the *in vitro* release was fitted into various release equations and kinetic models first order, zero order, Higuchi and Korsmeyer-peppas. The release kinetics of optimized formulation F4 (Chitosan) is shown in Table and in following Figures.

Table: Release kinetics of optimised formulation

CUMULATIVE (%) RELEASE Q	TIME (T)	ROOT (T)	LOG(%) RELEASE	LOG (T)	LOG (%) REMAIN	RELEASE RATE (CUMULATIVE % RELEASE / t)	1/CUM% RELEASE	PEPPAS log Q/100	% Drug Remaining	Q01/3	Qt1/3	Q01/3-Qt1/3
0	0	0			2.000				100	4.642	4.642	0.000
38.41	1	1.000	1.584	0.000	1.790	38.410	0.0260	-0.416	61.59	4.642	3.949	0.692
49.78	2	1.414	1.697	0.301	1.701	24.890	0.0201	-0.303	50.22	4.642	3.689	0.952
56.57	4	2.000	1.753	0.602	1.638	14.143	0.0177	-0.247	43.43	4.642	3.515	1.127
62.5	6	2.449	1.796	0.778	1.574	10.417	0.0160	-0.204	37.5	4.642	3.347	1.294
69.03	8	2.828	1.839	0.903	1.491	8.629	0.0145	-0.161	30.97	4.642	3.140	1.501
74.78	10	3.162	1.874	1.000	1.402	7.478	0.0134	-0.126	25.22	4.642	2.933	1.709
79.09	12	3.464	1.898	1.079	1.320	6.591	0.0126	-0.102	20.91	4.642	2.755	1.887
84.39	18	4.243	1.926	1.255	1.193	4.688	0.0118	-0.074	15.61	4.642	2.499	2.142
94.23	24	4.899	1.974	1.380	0.761	3.926	0.0106	-0.026	5.77	4.642	1.794	2.848
99.19	48	6.928	1.996	1.681	-0.092	2.066	0.0101	-0.004	0.81	4.642	0.932	3.709

**Figure:** Zero order release kinetics**Figure:** Higuchi release kinetics

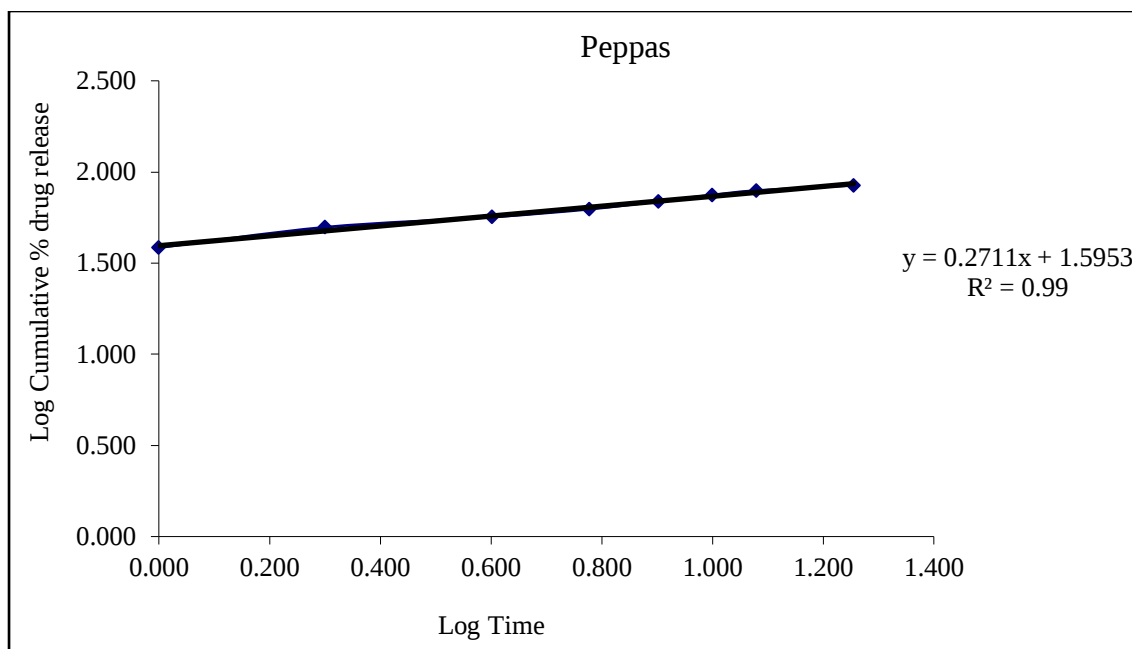


Figure: Peppas release kinetics

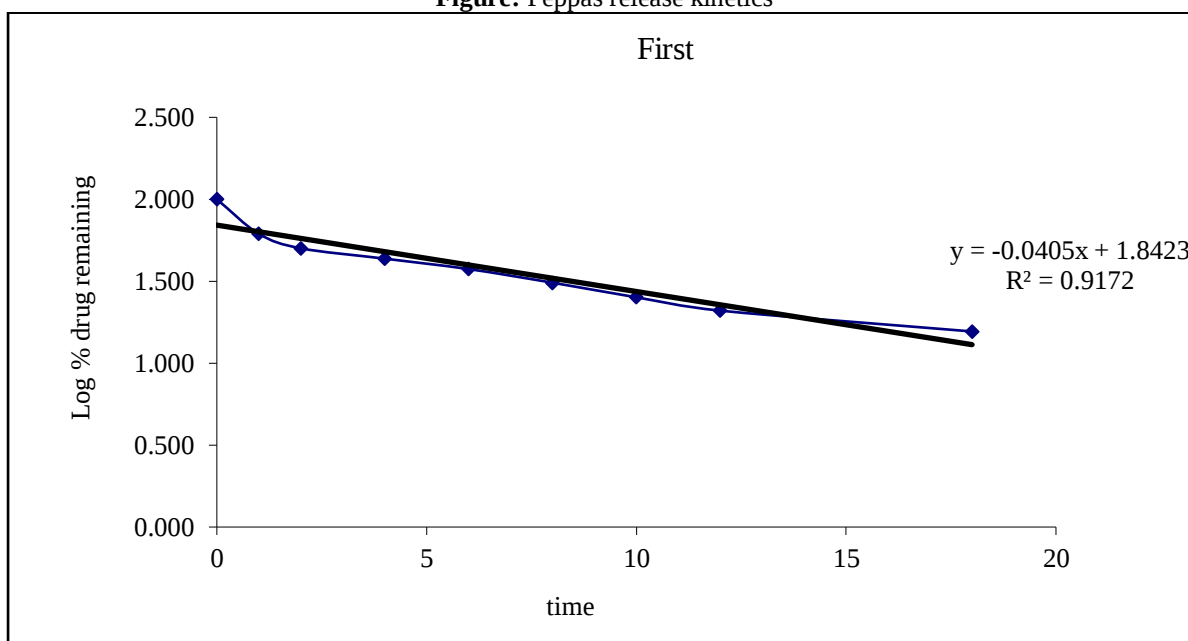
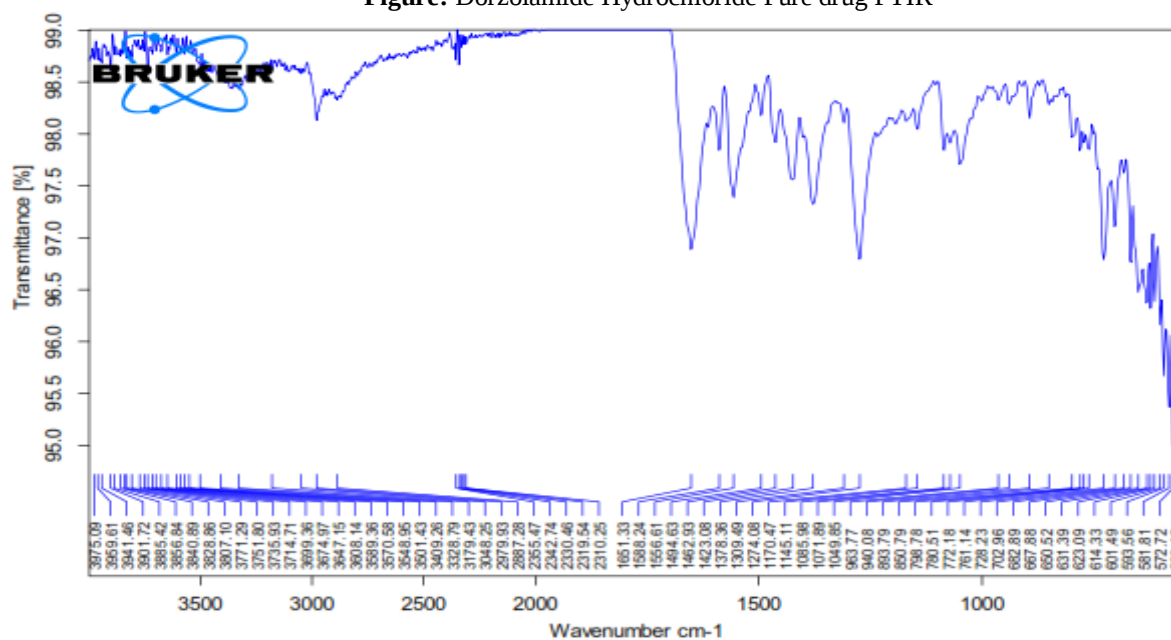
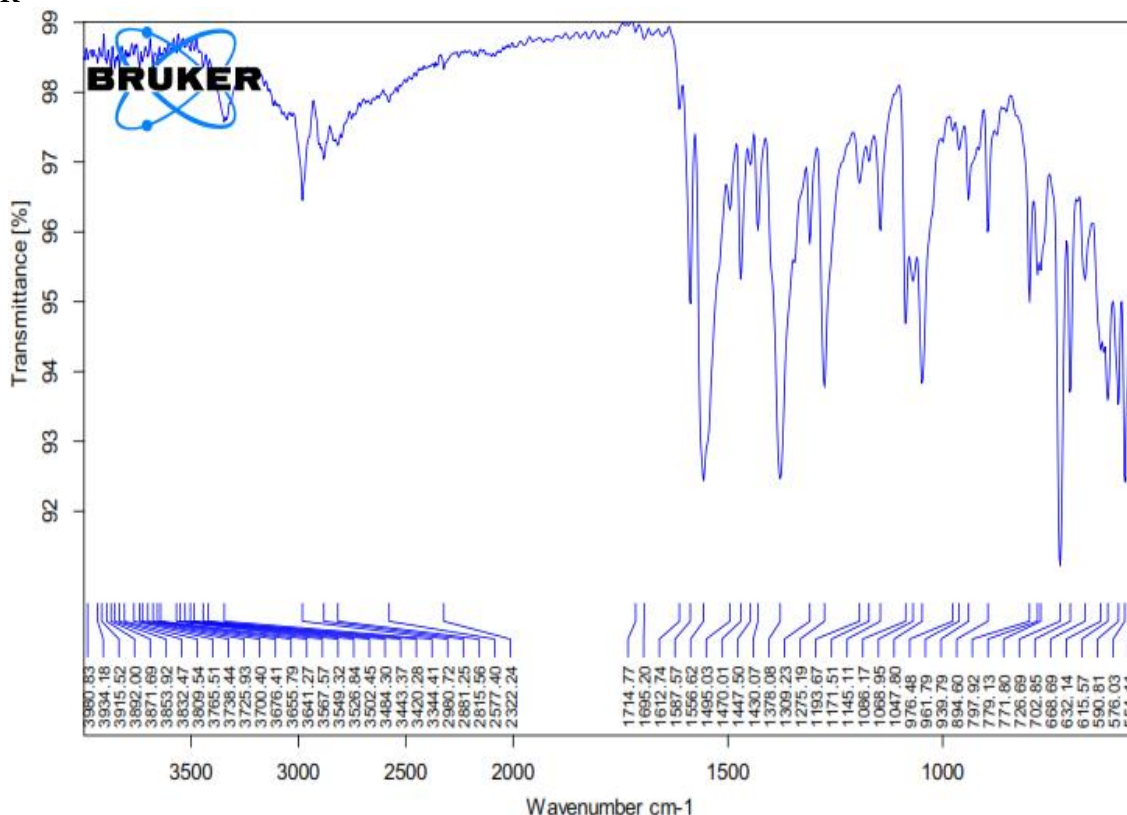


Figure: First order release kinetics

The prepared F4 optimised Chitosan nanoparticles were subjected to the drug release kinetics and release mechanism. The formulations were studied by fitting the drug release time profile with the various equations such as Zero order, First order, Higuchi

and Korsmeyer pappas. The optimised formulation F4 optimised Chitosan nanoparticles was analyzed for the drug release mechanism. The best correlation coefficient value (0.99) indicates the best release mechanism (Peppas release).

FTIR



Infrared studies were carried out to confirm the compatibility between the polymer, drug, and selected excipients. From the spectra it was observed that there was no major shifting, as well as, no loss of functional peaks between the spectra of the drug and

drug-loaded nanoparticles. This indicated no interaction between the drug and other excipients.

CONCLUSION:

Site-specific and receptor targeting refer to targeting of a drug directly to a certain biological location. In

the case of site-specific release, the target is adjacent to or in the diseased organ or tissues, for receptor release, the target are the particular receptor for a drug within an organ or tissue. Both of these systems satisfy the spatial aspect of drug delivery and are so considered to be controlled drug-delivery systems.

Dorzolamide hydrochloride loaded nanoparticles were successfully formulated and loaded. Drug and excipient compatibility were studied by FTIR, and no incompatibility was observed.

Evaluation parameters revealed that the percentage of polymer have significant effects on the particle size, drug content, entrapment efficiency and *in vitro* release from the nanoparticles formulation. Nanoparticles formulation F4 was the most effective formulation with optimum particle size, high entrapment efficiency and improved release profile.

The optimized Dorzolamide hydrochloride polymer loaded nanoparticles formulations (F4) were in nano size range (412.9 nm) with high drug release (99.19%) adequate encapsulating efficiency exhibiting a homogenous and effective..

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