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Fabrication and Characterization of Ketoprofen Nanoparticles by Double Emulsification-Solvent Evaporation Technique Using PLGA

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ABSTRACT

Nanoparticles are a rapidly developing field of nanotechnology with numerous applications in drug delivery. The capacity to incorporate drugs into nanocarriers presents the latest model in drug delivery that could be used for drug targeting. Therefore, nanoparticles hold promise for the attainment of the goal of controlled, site-specific drug delivery and therefore have attracted the broad attention of researchers. The present study aimed to prepare nanoparticles containing ketoprofen. The purpose of nanoparticles in drug delivery is to attain higher intracellular uptake than free drugs. PLGA nanoparticles are biocompatible; they release the drug in a controlled manner and improve the stability of active substances able to reach target specific tissues. Because of its biodegradability and low systemic toxicity, the US Food and Drug Administration (FDA) approved PLGA to be used in the research of nanoparticle drug delivery systems. PLGA nanoparticles can be formulated using diverse methods, such as double emulsification solvent evaporation (DESE), solvent displacement or nanoprecipitation, solvent diffusion, and phase-inversion technique. In the present study, the nanoparticles were prepared using a double emulsification-solvent evaporation technique with ketoprofen, PLGA, and PVA. The double emulsification procedure is based on a combination of a volatile non-aqueous miscible solvent and an aqueous solution, which are emulsified together by applying high shear force. As the volatile solvent is evaporated nanoparticles are formed. DESE is a beneficial method for the preparation of nanoparticles, as it is nontoxic, rapid, and fabricates nanoparticles of a very small size. The *in-vitro* drug release profile of optimized was evaluated at the end and the release kinetics of the nanoparticles were determined. The entrapment efficiency and loading efficiency, particle size, polydispersity index, zeta potential, and cumulative percentage drug release of the best formulation were found to be 79.5±0.02%, 0.94mg/ml, 302±2.5 nm, 0.213±0.05, 5.38±0.53mV, and 98±0.04% respectively. Invitro drug release investigation showed sustained release of ketoprofen over 24 h. The drug release kinetics showed the finest fitted to the first-order rate model and Korsmeyer-Peppas model. The obtained results signify that ketoprofen can get entrapped in the nanoparticles with good physicochemical behavior.

1. INTRODUCTION:

Ketoprofen (2-(3-Benzoylphenyl) propanoic acid) is a good candidate for pain reduction. Ketoprofen is a nonsteroidal anti-inflammatory drug (NSAID) with anti-inflammatory, analgesic, and antipyretic effects. Ketoprofen restricts the activity of the *cyclooxygenase* I and II enzymes, ensuing in a decreased formation of precursors of prostaglandins and thromboxanes. The consequential decrease in prostaglandin synthesis, by prostaglandin synthase, is liable for its therapeutic effects. Ketoprofen decreases the formation of thromboxane A_2, by acting on thromboxane synthase, thus inhibiting platelet aggregation[1]. It is a drug that is used for symptomatic treatment of ankylosing spondylitis, primary dysmenorrhea, and pain associated with musculotendinous trauma, postoperative (including dental surgery).

Ketoprofen is available as a solid and is practically insoluble in water[2]. *COX*-2 inhibitors combine with cyclooxygenase enzymes and prevent the formation of prostaglandins, eicosanoids, and thromboxanes. Ketoprofen is absorbed orally, with peak plasma levels taking place within 0.5 to 2 hours. In 24 hours, roughly 80% of an administered amount of ketoprofen is excreted in the urine, chiefly as the glucuronide metabolite. It gets rapidly metabolized in the liver via conjugation to glucuronic acid. Ketoprofen has anti-bradykinin activity, with lysosomal membrane-stabilizing action. Anti-pyretic effects might be due to action on the hypothalamus, ensuing in an increased peripheral blood surge, vasodilation, and successive heat dissipation.

Colloidal particles ranges in between 10 and 1000 nm are known as nanoparticles. They are manufactured from polymers and ideally suited to optimize drug delivery and reduce toxicity to target tissues. The success of nanoparticles as drug delivery material is based on their capability to infiltrate through numerous anatomical barriers, controlled release of their contents, and their stability. On the other hand, the shortage of safe polymers with regulatory consent and their high price has restricted the widespread use of nanoparticles. To overcome these restrictions of polymeric nanoparticles, lipids have been put ahead as a substitute carrier, predominantly for lipophilic drugs. These nanoparticles are called as solid lipid nanoparticles[3]. These are a new generation of nano-sized lipid emulsions where the liquid lipid (oil) has been substituted by a solid lipid.

Nanoparticles present exclusive properties such as small size, huge surface area, and high drug entrapment and are attractive for their ability to improve the performance of pharmaceuticals. Nanoparticles can be employed as an innovative colloidal drug carrier for intravenous administration[4]. The Nanoparticles are nano-sized colloidal carriers that are made up of mixed with water or surfactant solution and then emulsified at high shear forces.

Nanoparticles are spherical particles with 10-1000 nm in diameter includes a lipophilic matrix-like core that is made stable by the use of surfactants and can incorporate both hydrophilic and lipophilic therapeutic compounds[5]. While numerous methods have been fruitfully developed for the integration of mixture into nanoparticles, the fabrication of lipid-insoluble drugs is more exigent. At some stage in the preparation of nanoparticles, active ingredients with little lipid solubility are expelled from the lipid matrix into the aqueous phase. The twofold emulsification-solvent evaporation method produces a W/O/W emulsion, the outer aqueous layer can encapsulate the materials which show high aqueous solubility and the lipid phase acts as a diffusion barrier for hindrance of drug transport from the outer aqueous layer to the inner aqueous layer. Nanoparticles can be used, for the sustained drug release and targeting of drugs by encapsulating and protecting enzymes, proteins, and drugs. Due to the very small size, nanoparticles possess several applications with high reproducibility[6]. The delivery of bioactive molecules during the targeted delivery employing nanoparticles provides several challenges for the research and development of novel drug delivery systems. In the present study, ketoprofen-loaded nanoparticles were prepared using double emulsification-solvent evaporation with optimized physicochemical properties. In the course of preparation of nanoparticles, by manipulation of size, surface characteristics, and material used, the nanoparticles can be developed into smart systems, encasing therapeutic agents. Further, these nanoparticles can deliver the drug to target particular tissues and provide controlled release of drugs at preferred sites.

2. MATERIALS AND METHODS:

Materials:

Ketoprofen (Keto), (2-(3-Benzoylphenyl) propionic acid), was a gift sample from Madras Pharmaceuticals, Chennai. PLGA (50: 50), ethyl acetate was obtained from CDH Pvt. Ltd. Polyvinyl alcohol (PVA) was purchased from Sisco Research Laboratories. Sodium chloride (NaCl), potassium chloride, disodium hydrogen phosphate (Na_2HPO_4), potassium di-

hydrogen phosphate (KH_2PO_4) were purchased from the local market. All the reagents used were of analytical grade. De-ionized (DI) water was used as an aqueous medium.

Preparation of ketoprofen nanoparticles:

Ketoprofen-loaded PLGA nanoparticles were prepared using a double emulsion solvent evaporation method[7]. 1 ml aqueous ketoprofen solution containing 50 mg/ml was prepared using de-ionized water which was previously filtered through a 0.22 µm syringe filter. The aqueous phase was emulsified with an organic phase containing 5 ml of ethyl acetate containing PLGA utilizing homogenizer on an ice bath which is set at a speed of 10000 rpm for 2 minutes. The prepared W /O emulsion(1^o emulsion) was added using a syringe pump at a rate of 2 ml/min into 35 ml of 2% (w/v) PVA solution containing 5% (w/v) of sodium chloride. Homogenization was carried out at 20000 rpm for 10 minutes on an ice bath. To remove the organic solvent, the resultant emulsion was stirred for 5 hours on a magnetic stirring plate at 500 rpm maintained at 27°C. The nanoparticles were then settled down by centrifugation at 15,000 rpm using ultracentrifuge for 30 min at 4 °C and then washed twice with de-ionized water. The nanoparticles produced were then kept in refrigeration overnight.

Table No. 1: Composition of ketoprofen loaded nanoparticles containing different polymers

Ingredients	F-1 (mg)	F-2 (mg)	F-3 (mg)	F-4 (mg)	F-5 (mg)
Ketoprofen	50	50	50	50	50
PLGA	50	100	150	200	250
PVA(% w/v)	2	2	2	2	2
Nacl(% w/v)	5	5	5	5	5

Calibration Curve of Ketoprofen:

The standard graph for ketoprofen in 0.1 N HCl (pH 1.2) and distilled water were plotted by making serial dilutions from a stock solution containing 1 mg/ml. The prepared samples were analyzed spectrophotometrically at 260 nm[8]. The absorbance was recorded and plotted against their concentrations.

Characterization of Nanoparticles[9]:

Encapsulation Efficiency:

The formulated nanoparticles were destroyed using acetonitrile in 1 ml Eppendorf tubes in a vortex mixer, instantly following the washing step of fabrication. The resultant colloidal solution was allowed to pass through a 0.22 µm membrane filter, centrifuged, and the clear supernatant liquid was collected. The collected liquid from freshly prepared colloidal nanosuspension was used to determine the percentage of EE % and LE %. The amount of drug-loaded in the nanoparticles was determined by measuring the amount of the drug encapsulated per ml of nanoparticle suspension. Analysis of the free drug content in the supernatant was performed by spectroscopically by using UV-VIS spectrophotometer at 260 nm. The procedure was done in triplicate. EE% and LE% were calculated by the reduction of un- entrapped drugs from total drug contents using the following equations:

Entrapment Efficiency (EE) =

[Mass of initial drug - Mass of free drug / Mass of initial drug] x 100

Loading Efficiency (LE) =

[Mass of initial drug - Mass of free drug/ Weight of Nanoparticles] x100

Particle Size, Polydispersity Index and Zeta Potential[10]:

The dynamic light scattering (DLS) technique was employed to determine the mean particle size and polydispersity index (PDI) of prepared nanoparticles using a Malvern® zeta sizer. In this method, 1 mg of sample was dissolved in 1 ml of de-ionized water and sonicated for 30 minutes. The samples were then placed in a zeta sizer and particle size, polydispersity index, and zeta potential were then measured[11]. All the measurements were done in triplicate (n=3).

***In vitro* drug release studies:**

The release profile of ketoprofen from the colloidal suspension was studied *in-vitro* by using a dialysis bag. 7.4 pH phosphate buffer was used as the drug release medium. Ketoprofen colloidal suspension equivalent to 2.5 mg of ketoprofen was filled in a dialysis bag and was then immersed in 200 ml of the preheated phosphate buffer which was maintained at 37±2°C. At fixed time intervals; 1ml of the medium was collected and replaced by the same amount of

freshly prepared buffer. The concentration of ketoprofen in the collected samples was quantified using a UV spectrophotometer that was set at 260 nm. Drug release kinetics was investigated. The data were fitted to a variety of release kinetic models such as zero order, first order, Higuchi, Korsmeyer -Peppas models, and their suitable correlation coefficients were investigated. Comparative releases studies between various formulations were carried out to evaluate the best formulation with better release mechanisms and release kinetics.

Kinetic modeling of drug release[12]:

To investigate the method of drug release from the nanoparticles the *in vitro* dissolution profile was fitted to zero order, first order, Higuchi and Korsmeyer-Peppas model[13].

Zero order equation:

This equation illustrates the systems where the release rate is independent of the concentration of the dissolved species. A graphical representation of the concentration of drug vs time would yield a straight line with a slope equal to K_0 and the intercept at the origin of the axes. The zero order plots are derived by plotting the cumulative percent drug dissolved Vs time. The dissolution information is fitted into zero order equation.

$$\mathbf{Q = Q_0 - K_0 t}$$

Where

Q = quantity of drug released at time t

Q_0 = quantity of drug release initially

K_0 = rate constant

First order Equation:

The first order equation illustrates the drug release from the system, where the dissolution rate is dependent upon the concentration of the dissolving species. A graph of log concentration of drug remaining to be released Vs time yields line. The first order release equation is as follows:

$$\text{In } Q = \text{In } Q_0 - K_1 t$$

Where

Q = quantity of drug dissolved at any time, t

Q_0 = quantity of drug dissolved at t=0

K_1 = first order rate constant.

Higuchi Square Root law of diffusion:

The Higuchi square root law equation explains the mechanism release of drugs from a system where the drug is dispersed in the insoluble matrix and the rate of drug release is related to the rate of drug diffusion. Higuchi square root law of diffusion is given by the equation below:

$$Q=K_H.t^{1/2}$$

Where

Q = Amount of drug dissolved at a time, t

K_H = Higuchi rate constant

Korsmeyer and Peppas Model:

In this model, a plot of log (Mt/M) vs. log time was plotted and the slope was noted to explain the release pattern. The release rate was calculated using the following equation:

$$M_t/M = K_m . t^n$$

Where

Mt/M = Fraction of drug released

M_t = Amount of drug released at a time, t

M = Total amount of drug

n = Diffusion exponent

If n is less than 0.49, the drug release follows non-Fickian diffusions[14]. If n = 0.89, the drug release follows Zero order. If n is greater than 0.89, the drug release follows super case II transport. If the n value is in between 0.49 to 0.89, drug release follows anomalous non Fickian diffusion.

3. RESULTS AND DISCUSSION

Table No. 2: Construction of Calibration Curve for ketoprofen in 0.1N HCl

Sr. No.	Concentration (µg/ml)	Absorbance (X ± S.D.)
1.	0	0
2.	2	0.156±0.012
3.	4	0.305±0.023
4.	6	0.450±0.076
5.	8	0.612±0.043
6.	10	0.769±0.072

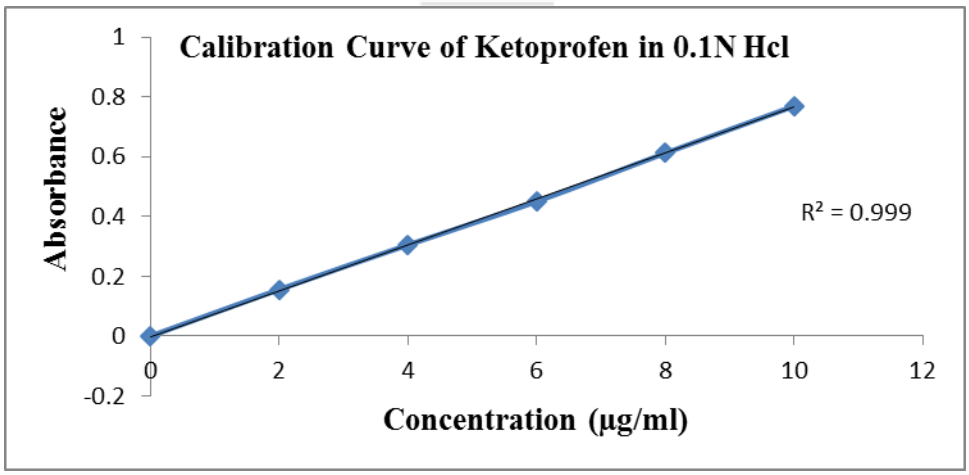

Fig. No. 1: Calibration Curve of Ketoprofen

The results for the EE, LE, particle size, polydispersity index, zeta potential, and cumulative drug release are shown in Table No. 3. Nanoparticles with a drug to polymer(PLGA) ratio of 1:4 i.e., formulation F-4 had the highest encapsulation efficiency of 74.5% as shown in Table No. 3.

The least mean particle size observed was 302±2.5 nm for the particles with drug/polymer ratio 1: 4, followed by 314±3.3 nm for drug/polymer ratio 1:5. Loading efficiency of F-4 formulation containing drug: polymer (1:4) had shown better loading efficiency 0.94 (mg/mL).

The polydispersity index was found to be less than 0.5 for all the samples. The particles with drug/polymer ratios 1:4 and 1:5 had the least PDIs. The highest PDI value observed was 0.347 Đ for particles with a drug/polymer ratio of 1:1. The highest zeta potential (5.38 mV) was observed for the particles with drug/polymer ratio 1:4 and the lowest value (4.42 mV) was observed for the particles with formulation F-1 (drug/polymer ratio 1:1). The cumulative percentage drug release profile had shown a 98% drug release after 24 hrs for F-4 formulation (Figure No. 6).

Table No. 3: Entrapment Efficiency, Loading Efficiency, Particle Size, PDI, Zeta Potential and Percentage Drug Release of Various Formulations of Ketoprofen nanoparticles

Formulation	EE (%)	LE (mg/ml)	Particle size (nm)	PDI	Zeta potential (mV)	% Drug release
F-1	71.8±0.01	0.82	312±4.2	0.247±0.09	4.42±0.34	79
F-2	73.3±0.06	0.87	334±6.3	0.238±0.06	4.83±0.87	84
F-3	77.8±0.04	0.89	359±6.2	0.232±0.04	5.17±0.41	87
F-4	79.5±0.02	0.94	302±2.5	0.213±0.05	5.38±0.53	98
F-5	72.1±0.02	0.83	314±3.3	0.211±0.01	5.40±0.44	91

DISCUSSION

Ketoprofen encapsulations into the nanoparticles modify the drug's pharmacokinetics by changing its physicochemical properties. The characteristics of the nanoparticle establish the pharmacokinetic parameters and stability of the drug. *In vitro* characterization of nanoparticles gives an idea about drug pharmacokinetics in physiological body fluids. High encapsulation efficiency was observed for particles with a drug/polymer ratio of 1:4 (Table No. 1). High encapsulation capability minimizes drug wastage throughout the fabrication process. It also ensures that high drug concentration at the intended site of action and

increased drug residence time. Various studies on nanoparticles have recorded that the encapsulation efficiency of water soluble drugs can be as high as 80% to 100% when the double emulsion solvent evaporation (DESE) method is used.

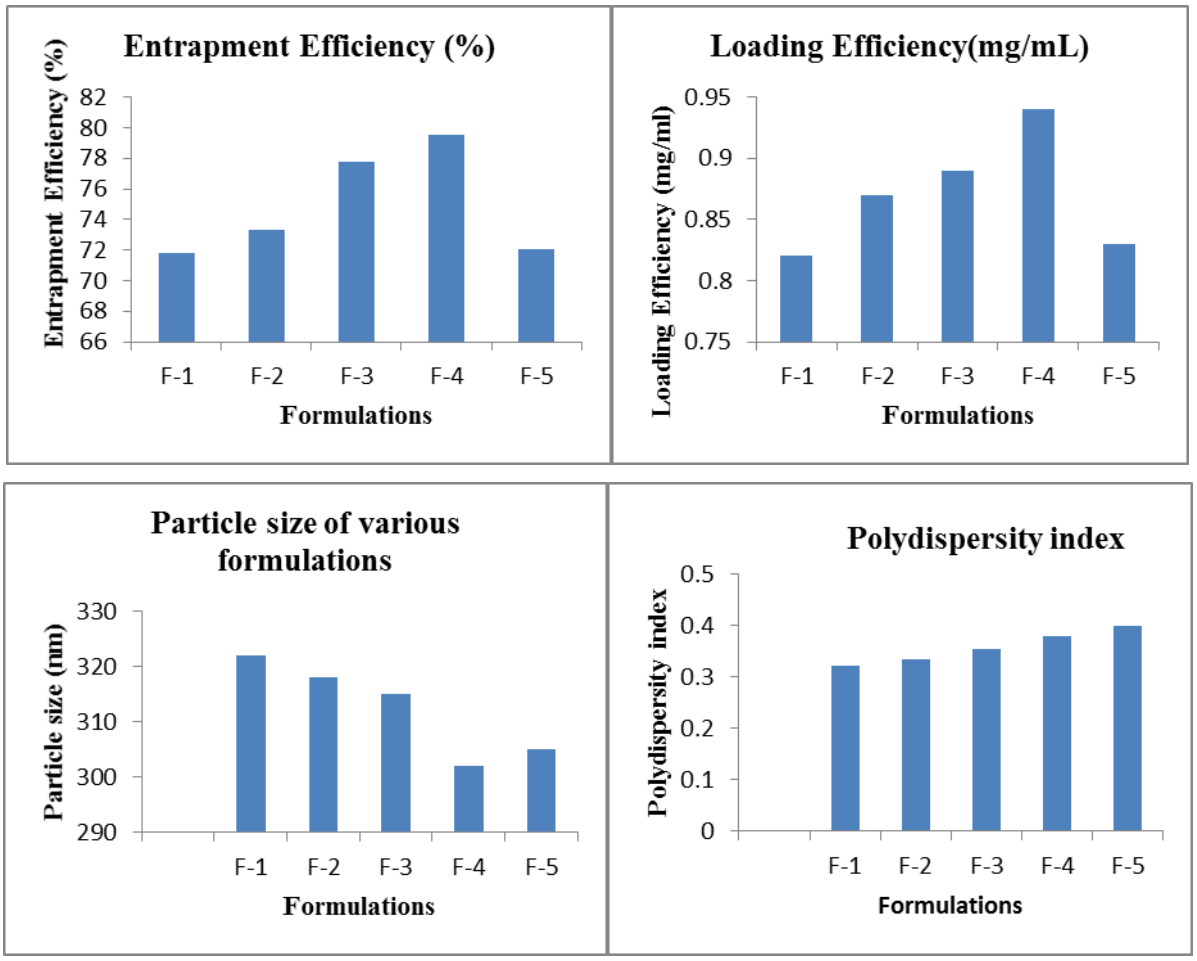

Fig No. 2: Comparison of Entrapment efficiency, Loading efficiency, Particle size and PDI values of various formulations.

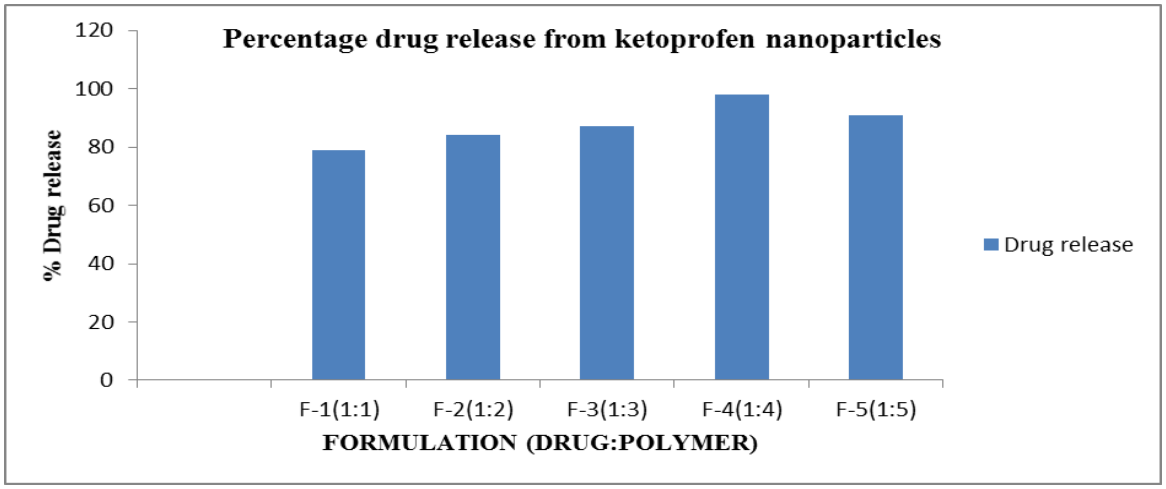

Fig No. 3: Comparison of drug release profile of ketoprofen-loaded PLGA nanoparticles

The less encapsulation efficiency observed in the present investigation (71.8%) can be due to low PLGA concentration in the dispersed phase. This leads to a less viscous solution which causes slow precipitation of the PLGA at the dispersed phase surface, ensuing in augmented drug diffusion across the phase boundary. Additional contributing factors include high PLGA solubility in ethyl acetate, the ratio of the dispersed phase to continuous phase, high stirring speed during fabrication in an attempt to lessen the final particle size and concentration of PVA which was employed as an emulsifier. Small particles are of immense concern as opposed to larger particles. The degree of nanoparticle aggregation in a liquid medium can be evaluated by the polydispersity index, values close to zero being good as opposed to those close to one, which specifies a high degree of aggregation.

The particles produced for all the five formulations with a different drug: polymer ratios were small (in the nanometer range) and formed mono dispersion in water; PDI < 0.5 indicating that there were a uniform size and shape distribution for the particles in each formulation. Monodispersion helps cellular uptake of the nanoparticles as contrasting to aggregated particles which interferes with it due to the big size. Although cell membranes permit easy passage of particles less than 1 nm in diameter, the PLGA nanoparticles can enhance ketoprofen delivery. They build a higher concentration gradient at the cell wall. The drug's pharmacokinetics can also be altered to favor drug delivery by increased circulation time of the drug in the bloodstream as systems such as the mononuclear phagocyte system remove particles with a minimum diameter of 1 micrometer from the circulation. Shearing speed during fabrication could result in decreased particle size.

For all five formulations with diverse drug/polymer ratios, zeta potential values were small (less than 10). The low zeta potential values can be a signal of how the ketoprofen is encapsulated in PLGA nanoparticles, protected in the polymer not adsorbed at the polymer surface. In contrast, low PDI values (close to zero) illustrate that all the samples formed nanodispersions in water, a scenario which is not possible in the presence of aggregating materials[14]. This indicates that the particles were stable regardless of the low zeta potential values. As PLGA is a large molecule (polymer), the stability could be more due to steric hindrance. The nature of the zeta potential values (small and positively charged) can enhance the pharmacokinetics of the drug by increasing the circulation time of the nanoparticles in the blood. The rapid release is due to the solubility of ketoprofen and penetration of water into the PLGA matrix. The results obtained after the evaluation of nanoparticles show a delayed

drug release profile. This can be attributed to the progressive ketoprofen release from the thicker ketoprofen depleted layer. Water present inside the matrix hydrolyses the PLGA into its oligomeric then monomeric soluble products. The drug freely passes and is released by erosion and diffusion until the solubilization of PLGA completes. The biphasic release profile may be encouraging since it can be used for controlled drug release. For the sample with a drug to polymer ratio of 1:4, the initial rapid release phase was not observed. This shows that ketoprofen is completely shielded by PLGA and no drug molecules are close to the polymer surface. This type of drug release (monophasic) may be suitable for the patient as it decreases dosing frequency and increases patient compliance. However, it takes little time before the onset of action is experienced.

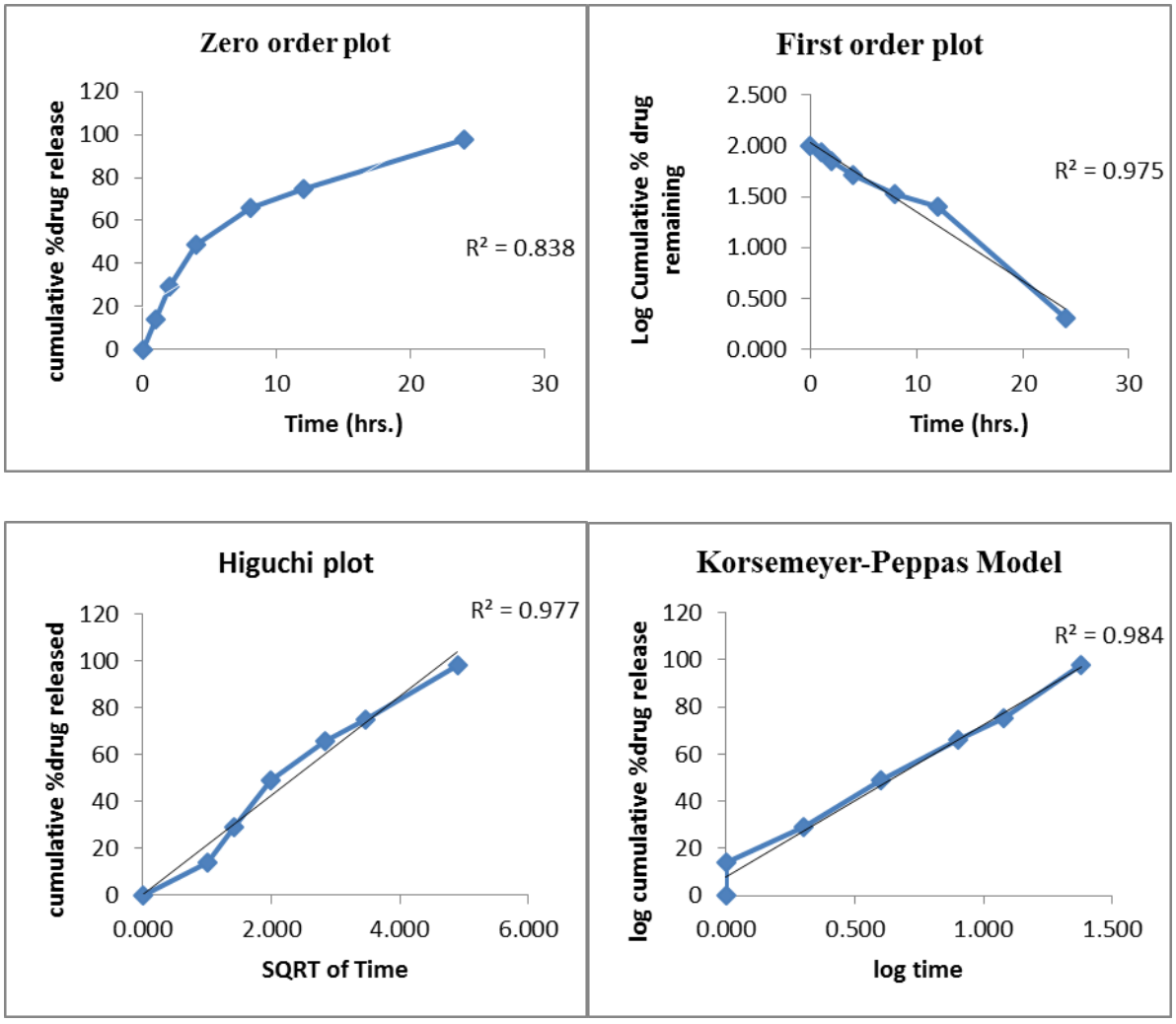

Fig No. 4: Mathematical Modeling Formulation (F-4) of Ketoprofen Nanoparticles

Table No. 4: Release kinetics of formulation (F-4) of ketoprofen nanoparticles

Formulation	Correlation Coefficient Value(R^2)				Exponential Coefficient (n)
	Zero Order	First Order	Higuchi	Korse-meyer	
F-4	0.838	0.975	0.977	0.986	0.752

From the above results (Table No. 4) it is apparent that the regression coefficient value closer to unity in the case of first order plot i.e. 0.975 indicates that the drug release follows a first order mechanism. This data indicates a lesser amount of linearity when plotted by the zero order equation. Hence it can be concluded that the major mechanism of drug release follows first order kinetics. Further, the mechanism of drug release is known by configuring the data into various mathematical modelings such as Higuchi and Korsmeyer plots. The mass transfer for the square root of the time has been plotted, revealed a linear graph with a regression value close to one i.e. 0.98, indicating that release was through diffusion. Further, the n value obtained from the Korsmeyer plots i.e. n=0.45 suggests that drug release was non-Fickian diffusion [15].

4. CONCLUSION:

The ketoprofen-loaded PLGA nanoparticles were produced by the double emulsion solvent evaporation method. The drug particles with the drug to polymer ratio 1:4 had shown the highest encapsulation efficiency of 79.5%, the lowest mean particle size of 302±2.5nm, and the highest zeta potential being 5.38±0.53 mV. The *in vitro* drug release changed from biphasic to monophasic from the drug/polymer ratios 1:1 to 1:5. The formulation F-4 containing drug/polymer ratio 1:4 produced better results compared to the remaining formulations. *In vitro* release studies were performed on optimized formulation containing ketoprofen to PLGA in a 1:4 ratio and the results show sustained release profile of the therapeutic compound from nanoparticles up to 24 hours. The kinetic of release was assumed to be first-order. Although, the obtained data suggest that nanoparticles can be considered as an alternative drug delivery systems for delivery of ketoprofen, and encapsulation of the drug in the interior aqueous phase can guard the therapeutic agent from environmental degradation. The regression coefficient (R^2=0.975) value is nearly equal to one, it indicates the system follows first order kinetics. Formulation F-4 has n value of 0.75 in Korsmeyer plot indicating that drug release was non-Fickian diffusion. Furthermore, from the therapeutic

point of view and for higher effectiveness in pain control, it is recommended that the final dosage form may include both delayed and immediate-release formulations with penetration enhancers for controlling acute pains as well as chronic pain.

5. REFERENCES:

1. Sarzi-Puttini P, Atzeni F, Lanata L, Bagnasco M, Colombo M, Fischer F, D'Imporzano M. Pain and ketoprofen: what is its role in clinical practice. Reumatismo. 2010 Jul-Sep;62(3):172-88.
2. Savjani KT, Gajjar AK, Savjani JK. Drug solubility: importance and enhancement techniques. ISRN Pharm. 2012;2012: 195727.
3. Mukherjee S, Ray S, Thakur RS. Solid lipid nanoparticles: a modern formulation approach in drug delivery system. Indian J Pharm Sci. 2009;71(4):349-358. doi:10.4103/0250-474X.57282
4. Das S, Chaudhury A. Recent advances in lipid nanoparticle formulations with solid matrix for oral drug delivery. AAPS Pharm Sci Tech. 2011;12(1):62-76.
5. Mishra V, Bansal KK, Verma A, et al. Solid Lipid Nanoparticles: Emerging Colloidal Nano Drug Delivery Systems. Pharmaceutics. 2018;10(4):191. Published 2018 Oct 18.
6. Date AA, Hanes J, Ensign LM. Nanoparticles for oral delivery: Design, evaluation and state-of-the-art. J Control Release. 2016;240:504-526. doi:10.1016/j.jconrel.2016.06.016
7. McCall RL, Sirianni RW. PLGA nanoparticles formed by single- or double-emulsion with vitamin E-TPGS. J Vis Exp. 2013;(82):51015.
8. El-Brashy A, Eid M, Talaat W. Kinetic spectrophotometric method for the determination of ketoprofen in pharmaceuticals and biological fluids. Int J Biomed Sci. 2006;2(4):406-413.
9. Lin PC, Lin S, Wang PC, Sridhar R. Techniques for physicochemical characterization of nanomaterials.BiotechnolAdv. 2014;32(4):711-726. doi:10.1016/j.biotechadv.2013.11.006
10. MohdIzham MN, Hussin Y, Aziz MNM, et al. Preparation and Characterization of Self Nano-Emulsifying Drug Delivery System Loaded with Citraland Its Antiproliferative Effect on Colorectal Cells In Vitro. Nanomaterials (Basel). 2019;9(7):1028. Published 2019 Jul 18.
11. Kaszuba M, Corbett J, Watson FM, Jones A. High-concentration zeta potential measurements using light-scattering techniques. Philos Trans A Math PhysEng Sci. 2010;368(1927):4439-4451.
12. Atty Deepthi*, Venugopal K, Sadak Vali C, Sunitha R, Suresh Kannan V, Sivakameswari S. Design and evaluation of mucoadhesive sustained release tablets of etodolac by using natural polymers. WJPR.2016; 5(2): 433-465.
13. Ngwuluka NC, Choonara YE, Modi G, et al. Design of an interpolyelectrolyte gastroretentive matrix for the site-specific zero-order delivery of levodopa in Parkinson's disease. AAPS Pharm Sci Tech. 2013;14(2):605-619.
14. Kashi TS, Eskandarion S, Esfandyari-Manesh M, et al. Improved drug loading and antibacterial activity of minocycline-loaded PLGA nanoparticles prepared by solid/oil/water ion pairing method. Int J Nanomedicine. 2012;7:221-234. doi:10.2147/IJN.S27709
15. Fu Y, Kao WJ. Drug release kinetics and transport mechanisms of non-degradable and degradable polymeric delivery systems. Expert Opin Drug Deliv. 2010;7(4):429-444.