WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 5.990
Volume 4, Issue 12, 428-443. Research Article ISSN 2277– 7105

PHARMACOKINETICS AND *IN VIVO* EVALUATION OF BIODEGRADABLE *IBUPROFEN-LOADED* MICROPARTICLES: ANTI-INFLAMMATORY AND ITS ULCEROGENIC PROTECTION

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Article Received on
09 Oct 2015,

Revised on 31 Oct 2015,
Accepted on 22 Nov 2015,

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ABSTRACT

The purpose of this study is improve the bioavailability, anti-inflammatory and gastro-protective effect of ibuprofen using PLA as carrier. Ibuprofen loaded PLA-microparticles were formulated using solvent evaporation technique. The preparations were characterized for the flow, particle size, encapsulation efficiency and drug loading, as well as anti-inflammatory and gastro-protective activity in an animal model. Based on the *in vivo* study the efficacy and potency of the ibuprofen-loaded PLGA microparticles were determined and compared to that of the marketed sample as well as pure drug, The microparticles have relatively uniform particle size (231 ±0.2 µm) with relative poor flow properties. The encapsulation efficiency and loading efficiency ranges from 83.4- 89.3 and 23.4 - 30.1 %, respectively. Significant ($p< 0.05$) anti-inflammatory and gastroprotective effect compared to the reference samples. The ibuprofen-microparticles effectively enhanced the bioavailability, anti-inflammatory and gastro-protective effect of the incorporated drug. PLA showed a promising system for oral delivery of ibuprofen.

KEYWORDS: anti-inflammatory, gastroprotective, microparticles, ibuprofen.

INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) are the first choice of drugs in the treatment of pain, degenerative inflammatory joint diseases and rheumatic disorders. All the NSAIDs, despite differences in their chemical structure, inhibit the enzyme COX and production of prostaglandins. Ulcerogenicity of most of the NSAIDs are major setback in the clinical use of the drug as most patient were not favorably disposed to the drugs, thus non compliance is very common among the patients on the drug. Ibuprofen is a highly potent anti-inflammatory agent used in the treatment of various types of inflammatory conditions. It is also used in the relief of pain in a large number of conditions like rheumatic fever, rheumatoid arthritis and osteoarthritis.[1] However, the currently available formulations of ibuprofen have been shown to exhibit serious dose limiting toxicities and hypersensitivity reactions, which are a direct consequence of the formulation technique and the absence of selectivity for target tissues.[2] Additionally, short biological half-life requires administration thrice a day in order to attain effective plasma concentration for better pharmacological action.

Considerable research efforts have been spent on oral sustained-release drug delivery systems, with the majority of the systems being solid dosage forms. Microencapsulation in the form of microparticles has been employed to sustain the drug release, and to reduce or eliminate gastrointestinal irritation. Additionally, microparticles delivery systems based on polymeric carrier can be distributed widely throughout the gastrointestinal tract providing a possibility of achieving a longer lasting and more reliable release of drugs, with little or no gastrointestinal side effect. Thus, the prolong action of the carrier will also reduce the intake of large quantity of the drug while still achieving high therapeutic effects.

Polymeric microparticles (MPs) have shown some advantages such as higher stability, good biocompatibility, non-toxicity, biodegradability, and controlled delivery.[3,4] Biodegradable and biocompatible poly(D,L-lactic-co-glycolic acid) (PLGA) and poly-lactic acid (PLA) have been extensively used in controlled drug delivery and have been approved by the US Food and Drug Administration (FDA).[5,6] In addition, unwanted side effect due to retention of the carrier material is completely eliminated, as they are biodegradable.

It is generally understood that PLA is digested in the human gastrointestinal tract, and no toxic effect is associated with degradation of the polymer in the biological system. This suggests that if such important drug like ibuprofen is dissolved or dispersed in a PLA solution and further formulated into microparticles using solvent evaporation method, the challenges

of the ibuprofen will be resolved. The gastrointestinal (GI) tract acts as a physiological and chemical barrier setting several challenges for oral drug delivery systems (DDS). The development of composite formulation methods helps to improve bioavailability, and the potential of this emerging field is promising. In this context, increased knowledge on polymeric materials makes them more and more interesting for the formulation of poorly water soluble drugs and the formation of solubilized phases from which absorption may occur. Also the protection of the GIT from the ulcerogenicity of some drug became more important than ever before. It was these considerations and advantages that led to the objective of this study, which is to prepare and investigate oral microparticles sustained-release delivery system of the ibuprofen using PLA in rat models of acute inflammation. In an earlier work, we have ascertained the sustained release action of PLA loaded ibuprofen in an in vitro study.

EXPERIMENTAL

MATERIALS

The following material were used in this study: Ibuprofen (Spectrum, USA), ethanol (Fisher, UK), Poly lactic-acid (PLA) and polyvinyl alcohol (PVA) with molecular weight of 22000 (Acros Organics, USA). Dichloromethane (DCM) was obtained from Sigma Aldrich, St. Louis, MO. All other reagents used in the study were of analytical grade.

Preparation of the ibuprofen microparticles

Ibuprofen microparticles were prepared by emulsification/solvent evaporation method. Approximately 300 mg of PLA was dissolved in 5 ml of methylene chloride and 200 mg of Ibuprofen was weighed and dispersed in the polymer solution. This dispersion was emulsified into the aqueous continuous phase (100 ml) containing 400 mg of polyvinyl alcohol and 100 mg of sodium oleate. The coarse emulsion formed was further homogenized with an Ultra-Turrax® (T18 IKA, Germany) homogenizer at 7000 rpm for 5 min. The resulting microparticles were collected by centrifugation, washed with water and dried at room temperature. The above procedures were repeated using 300 and 400 mg of Ibuprofen and were labeled as (A, B and C). In addition, the blank microparticles (unloaded) was prepared following the same method.

Percentage yield of microparticles

The MPs formed were filtered from the solvent, dried in the desiccator and weighed to get the yield of the MPs formulated per batch. Eq. (1) was used to calculate the % yield:

$$\% \text{ yield} = \frac{W1}{W2 + W3} \text{ X } 100 \text{ ------ Eqn. 1}$$

where W1 is the weight of MPs formulated (g), W2 the weight of drug added (g) and W3 is the weight of carrier (g) used as the starting material.

Morphological study

A 5 mg quantity each of the samples was weighed using a Mettler M3 Microbalance into a microscopic slide and mixed well with two drops of distilled water, using a glass rod. The mixture was covered with a cover slip and viewed under X 10 objective and X 4 eye piece of binocular light microscope (Model 746862, Wetzler, Germany) to which a digital photographic camera had been fixed and connected to a computer. Three distinct regions of the slide were photographed and printed directly from the computer.

Encapsulation Efficiency (EE%)

A 50 mg quantity of microparticles was dispersed in 50 ml of phosphate buffer (pH 7.4). The dispersion was allowed to stand for 2 h after which it was mixed in a vortex mixer for 10 min and then centrifuged at 5000 rpm for 10 min. The amount of ibuprofen contained in the various microparticulate formulation samples was determined using HPLC. The ibuprofen encapsulation efficiency was then determined using Eq. (2)

$$EE = \frac{\text{Actual drug content}}{\text{Theoretical drug content}} \text{ X } 100 \text{ ----- Eqn. 2}$$

where EE is ibuprofen encapsulation efficiency, Actual Drug content is actual amount of ibuprofen in microparticles and Theoretical Drug content is the theoretical amount of ibuprofen in microparticles.

Loading capacity (LC)

LC is expresses as the ratio between the entrapped drug by the PLGA (carrier) and the total quantity of the carriers used in the formulation.[7] It is calculated as follows:

$$LC = \frac{\text{Total quantity of drug entrapped by the carrier}}{\text{Total quantity of the carrier in the formulation}} \text{ X } 100 \text{---- Eqn. 3}$$

Micrometric properties of the microparticles

The micrometric properties of the final powder such as bulk, tapped densities and angle of repose were determined. The compressibility indices of the particles were also evaluated from the bulk and tapped density using the following equations.

$$\text{Bulk density} = \frac{\text{Mass of Powder (M)}}{\text{Bulk volume of powder } (V_B)} \quad \text{----- Eqn. 4}$$

$$\text{Tapped density} = \frac{\text{Mass of sample (M)}}{\text{Tapped volume } (V_T)} \quad \text{----- Eqn. 5}$$

$$\text{Angle of repose } (\Theta) = \tan^{-1} h/r \text{ --- Eqn. 6}$$

$$\text{Carr's Index (\%)} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100 \text{ ----- Eqn. 7}$$

Particle size determination

Particle sizes were determined by photon correlation spectroscopy (PCS) at 25 ^{o}C using a multi angle particle size analyser (Zetasizer 3 Model AZ6004, Malvern England) modified with a 35mWHe–Ne laser (Model 127-35, Spectra Physics USA). The detection was performed at a scattering angle of 90^{o} in a cell AZ10 equilibrated at 293K and at an accumulation time of 240 s. Samples were diluted with filtrated double-distilled water (0.2 µm Sterifix® filter) and data were analysed by the cumulants method assuming spherical particles.

Measurement of zeta potential

The zeta potentials of the formulated microparticles were determined after 1 week of preparation in a Zetasizer Nano Series (Nano-ZS, Malvern Instruments England). Each sample was diluted with bi-distilled water and the electrophoretic mobility determined at 25 ^{o}C and dispersant dielectric constant of 78.5 and pH of 7. The obtained electrophoretic mobility values were used to calculate the zeta potentials using the software DTS Version 4.1 (Malvern, England) and applying Henry equation.[8]

$$UE = 2\varepsilon Zf\,(Ka)/3\eta \text{-------Eqn. 8}$$

where *Z* is the zeta potential, *U*E the electrophoretic mobility, ε the dielectric constant, η the viscosity of the medium and *f*(*K*a) is the Henry's function.

Animal Protocols

All the animal experiments in this work adhered to the principles of care and use of laboratory animals and approved by the Institutional Animal Care and Use Committee of Faculty of Pharmaceutical Sciences, University of Nigeria Nsukka and were in compliance with the Federation of European Laboratory Animal Science Association and the European Community Council Directive of November 24, 1986 (86/609/EEC).[10]

Anti-inflammatory activity

The anti-inflammatory activity of various ibuprofen microspheres formulations were studied by carrageenan-induced rat paw edema model.[11] Male Wister rats of average weight of 200 g were fed with a standard diet ad libitum and housed in a temperature-controlled room (25±2 ^{0}C). The animals were divided into six different groups of three rats each. The first and the second groups received pure ibuprofen dispersed in distilled water (positive control) and normal saline (negative control), respectively. The third group received the microparticles containing the 200 mg/kg body weight (b.w) of the drug. The fourth, fifth and sixth groups received the formulation containing 300 mg of ibuprofen, 400 mg of ibuprofen and conventional ibuprofen tablet according to their body weight (per oral), respectively. One hour before the administration of tests agent, a 0.2 % of γ-carrageenan solution was subcutaneously injected into the right hind paws. The paw volume was measured before drug administration and then at 1, 2, 3, 4, 5 and 6 hours after carrageenan injection, using a digital plethysmometer. The percentage inhibition of the edema formation of the test samples were calculated as follows:

$$\text{The percentage inhibition} = \frac{\text{Control group - Test group}}{\text{Control group}} \text{ X } 100 \text{ ------- Eqn. 9}$$

Safety of the formulation as a function of ulcerogenicity

The ulcerogenic potentials of the ibuprofen microparticles were determined using a method described by.[12] The studies were carried out on healthy Wistar rats (150 to 200 g). The animals were divided into three groups of five animals each. The ibuprofen MPs were crushed using mortar and pestle, the required dose was weighed out and dispersed in 2.5 ml of water. The control group received normal saline, the test group received ibuprofen MPs equivalent to 10 mg/kg of ibuprofen, while the reference group received pure sample of ibuprofen 10 mg/kg orally. The animals were fasted 8 h prior to a single dose of either the control or test compounds, given free access to food and water and sacrificed 20 h later. The

gastric mucosa of the rats was examined under a microscope using a 4× binocular magnifier. The lesions were counted and divided into large (greater than 2 mm in diameter), small (1 to 2 mm) and punctiform (less than 1 mm). For each stomach, the severity of mucosal damage was assessed according to the following scoring system: 0 – no lesions or one punctiform lesions; 1 – two to five punctiform lesions; 2 – one to five small ulcers; 3 – more than five small ulcers or one large ulcer; 4 – more than one large ulcers.

Pharmacokinetic study

An optimized batch was selected based on the result of the anti-inflammatory and GI protective effect. In this case batch C was finally selected for the pharmacokinetics evaluation. Fasted male Albino rats were intragastrically administered 2.0 ml of the crushed test sample in solution that contain 5 mg/kg body weight of the animal. Five hours after the administration the rats was anesthetized under ether 0, 0.5, 1, 2, 4, 6, and 8 h, later, at which time 0.5 ml of blood was collected from the inferior venae cavae and immediately extracted in acetonitrile (1 part blood:3 parts acetonitrile) and vortexed. The rats were euthanized immediately thereafter by an overdose with an anesthetic agent. The extracted samples were then subjected to low-speed centrifugation, and the supernatant collected were subsequent analysis high performance liquid chromatography (HPLC).

HPLC Analysis

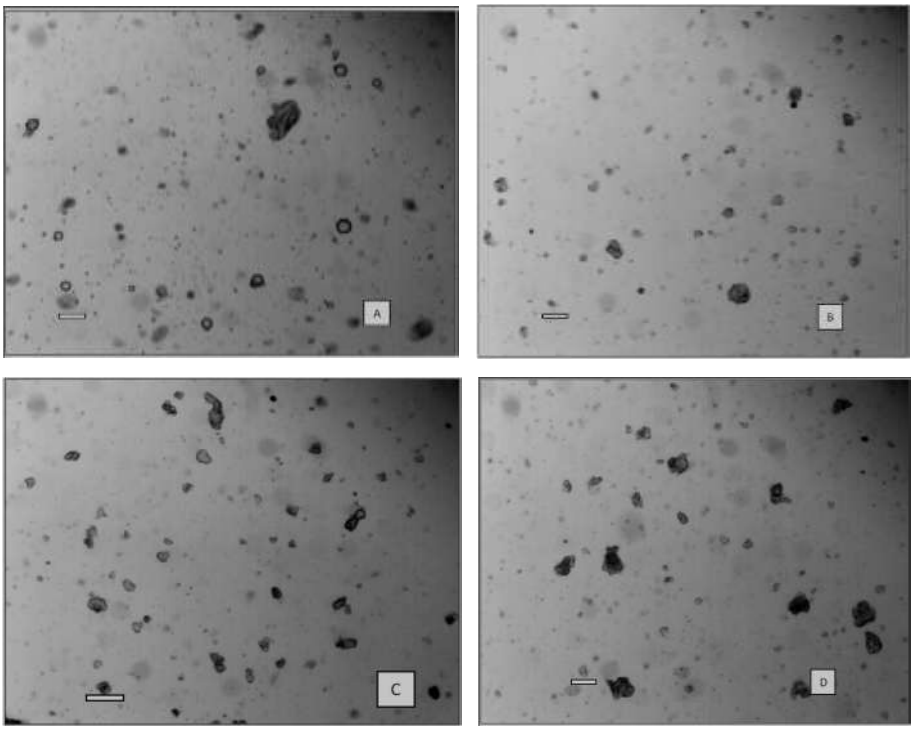
The ibuprofen content of the acetonitrile-extracted blood sample was determined using a high performance liquid chromatography (HPLC). The machine consisted of an Agilent 1100 series programmable separating module, quaternary pump G 1311 A (Agilent technology, Geneva, Switzerland), an auto degasser G1322A, and a variable wavelength detector G1314A (Marinfield, Germany). The column was a reverse phase ODS (C-18, 5 µm 4.6×250 mm, Supelcosol, Mumbai, India) equipped with a guard. The mobile phase consisted of acetonitrile and water (10:90), perchloric acid was used to adjust the pH to 3. The analysis was carried as previously discussed.

Statistical analysis

The data were expressed as mean ± SEM; statistical analysis was performed by one way ANOVA followed by student t- test. p values <0.05 were considered as significant.

RESULTS

The microscopic images of the MPs are shown in Figs. 2. The results indicate that when the ratio of drug to PLA used in formulating the MPs was low, the MPs produced were irregular in shape but when this ratio was increased, more spherical and smooth particles were produced.



Figures 1 (A-D). Photomicrographs of representative batches of microparticles: A, B, C, and D contain 200, 300, 400 and 0 mg of ibuprofen, respectively. Bar represents various sizes in µm.

The particle size distribution of the microparticles presented in Table 2 show low-sized uniform microparticles were obtained, except for microparticles prepared without drug (batch D). The table shows that increase in concentration of the drug reduced the particle size. Particles sizes of 99.6, 91.2 and 78.8 µm were obtained for batch A, B and C respectively, while that of the control (batch D) shows 124.1 µm in size. However, the sizes of the formulation were close, but the polydispersity indices (PI) were significantly different ($p < 0.05$), the microparticles show PI of 0.745, 0.785, 0.800 and 0.91 for A, B, C and D, respectively.

Results in **Table 1** show the flow indices of ibuprofen-loaded PLA formulations. Generally these values indicate poor flow properties with exception of batch A. The values show that

the addition of sodium oleate did not have any effect in the flow property. Usually, powders with good flow properties should have angle of repose<25^{o}, Hausner's ratio<1.25, and Carr's index <20%. However, the results here revealed angle of repose, Hausner's ratio, and compressibility indices for all the formulations range between 20–26 ^{o}C, 1.37–1.43, and 27.3–30.3%, respectively.

Table 1. Some micromeritics properties of various batches of Ibuprofen microparticles formulations

Batch	FR (g/s)	BD (g/cm^3)	TD (g/cm^3)	AR (^{o})	HI (%)	CI
A	1.288±0.14	0.418±0.25	0.575±0.12	23.94±0.07	1.376±0.08	27.3±0.06
B	1.308±0.15	0.429±0.08	0.615±0.04	20.11±0.09	1.434±0.01	30.3±0.04
C	1.298±0.03	0.442±0.08	0.595±0.06	26.56±0.03	1.427±0.07	29.9±0.03
D	1.299±0.08	0.325±0.23	0.435±0.02	28.16±0.22	1.389±0.43	28.2±0.12

Key: FR, Flow rate; BD= Bulk density; TD= Tapped density; AR= Angle of repose; CI= compressibility index; HI= Hausner's index; A-C are the formulation while, D is the control batch

Drug loading and encapsulation efficiency (%)

The results of the EE% (Table 2) show that drug EE% increased with increase in the concentration of ibuprofen up till 400 mg for all batches, yielding maximum EE% of 89.00, 84.60 and 83.00% for microparticles formulated with PLA (A-C), respectively. So, the microparticles loaded with 400 mg of ibuprofen resulted in higher EE%, while those loaded with 200 mg ibuprofen gave the least. However, all the batches had good EE% (83–89%). Table 2 also shows that maximum LC of 29.5, 30.10 and 23.40 % of ibuprofen were obtained for A, B and C respectively. Thus, formulation containing 300 mg of ibuprofen gave higher LC than those containing 200 mg or 400 mg of ibuprofen.

Table2. Some characterization of microparticles prepared with PLGA 50:50 loaded and unloaded with Ibuprofen

Batch code	PDI	ZP	DL	% EE	Particle size (µm)	% Yield
A	0.745	-53.0	29.5±0.4	83.4±0.2	99.6±0.41	85.2
B	0.785	-68.7	30.1±0.1	84.3±0.1	91.2±1.4	87.1
C	0.800	- 43.1	23.4±0.2	89.3±0.4	78.8±0.21	91.1
D	0.910	- 37.4	---	-----	124.1±0.1	86.8

PDI= Polydispersibility index, ZP= zeta potential, DL= Drug Loading , EE= encapsulation efficiency, % Y= percentage yield

In vivo anti-inflammatory effect

The results of the anti-inflammatory activities of the administered ibuprofen loaded PLA microparticles are depicted in **Fig. 2** as a function of time. The formulations administered reduced the level of inflammation induced by the 0.2 % of carrageenan solution. There was a significant difference ($p < 0.05$) in percent inhibition of inflammation when compared to the positive controls

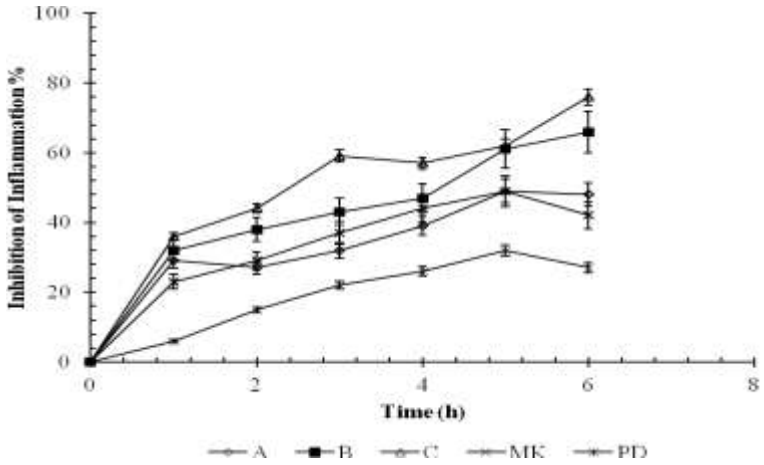


Fig. 2. Anti-inflammatory profiles of various doses of ibuprofen from the formulations loaded PLA. (A, B and C, contain 200, 300 and 400mg of ibuprofen respectively with an equal quantity of PLA while MK and PD are marketed sample of ibuprofen and pure powder of ibuprofen dispersed in water respectively).

Ulcerogenic properties of the formulation.

The results of ulcerogenic studies are presented in Table 3. Ibuprofen loaded microparticles did not show ulcer-inducing potentials (0.00). However, the reference pure drug powder (pure ibuprofen powder) showed a high ulcer index of 18.5± 0.54 which was significantly higher than that of the marketed sample (4.1 ± 0.22). However, the market sample showed little GIT abrasions tendency which was not significant enough to induce full blown ulcer. Thus, the test formulation was much better tolerated than the current marketed formulation of the drug used in this study.

Table 3: Gastro-protective effect of ibuprofen-microparticles and reference samples

Sample code	Ulcer index	gastro-protective (%)
Batch C	0.0 ± 0	100.00 ± 00
MKT-S	4.1 ± 0.22	93.10 ± 20
PD	18.5± 0.54	21.16 ± 10

Pharmacokinetics

Fig. 3 shows the Plasma concentration of ibuprofen vs. time plotting after oral administration of the ibuprofen-microparticles, reference sample and the pure drug. The formulated microparticles showed high peak and prolong release than the reference sample. The pharmacokinetic parameters (Table 4) of the formulated microparticles showed a characteristic of prolonged release formulation than the reference sample. Thus the formulation showed a longer time to reach a peak concentration than the reference sample Fig. 3. Its shows a consistence performance in all the parameters evaluated.

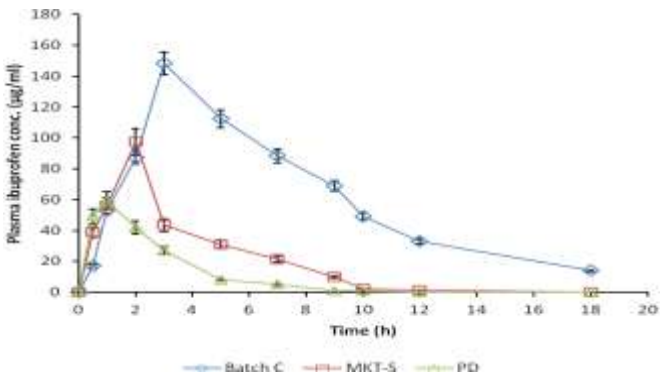


Fig. 3. Ibuprofen concentration in plasma over the study period in an animal model orally administered Batch C, reference drug (MKT-S) and pure ibuprofen powder (PD) at dose of 15 mg/kg. (n=5). Data is ± SD.

Table 4: Pharmacokinetics data on ibuprofen-microparticles, reference sample and pure ibuprofen powder

Sample code	C_{max} (mg mL^{-1})	T_{max} (h)	$T_{1/2}$ (h)	AUC (mg mL^{-1} h^{-1})
Batch C	148.21± 0.11	3.5	8.0	1241.78 ± 0.11
MKT-S	97.42± 0.61	1.5	3.0	741.12 ± 0.23
PD	58.01± 0.13	0.5	1.5	81.32 ± 0.71

DISCUSSION

Ibuprofen is an NSAID that is commonly used in clinical practice for the management of pain and inflammatory conditions. However, it usage was limited by its low potency, requiring large and multiple doses of up to 1.5 to 2.5 g/day to obtain effective therapeutics desire in

pain and inflammation management. Additionally the GI side effects of ibuprofen, although are considerably less than many other NSAIDs on the market, evidence is clear that subjects will be at a significant risk for developing peptic ulceration and bleeding if they take this drug for considerable length of time, especially in the management of certain chronic cases. Because of this need, we have undertaken this study to evaluate and compare the efficacy and potency of ibuprofen-microparticles loaded PLA to conventional ibuprofen in rat models. We also evaluate it gastrointestinal sparing effect of the formulation and make a similar comparism to the marketed sample. Polymeric particle prepared with PLA was selected in order to see the influence of the carrier system on the activities of ibuprofen. Solvent evaporation techniques have been exploited widely to encapsulate drugs in polymeric delivery systems.

The flow property of the formulation was poor with the exception of batch A, which show a relative good flow, an indication that addition of glidant is needed to enhance the flow property of the preparation. The various microparticles showed a near mono disperse particle configuration as the sizes of the microparticles were quite close and were within the sizes that are acceptable for microparticles.[13]

The anti-inflammatory activities of the formulations were significant ($p<0.005$) higher than the reference sample. However, the therapeutic activity of the loaded microparticles increased in a dose-dependent manner. The ibuprofen-loaded microparticles (A, B and C) lowered the oedema levels of the rats. The activity was slightly more at the initial stage in the pure drug and the commercial sample (senofen®) than the formulated microparticles and terminated within 5.30 h. However, the formulated microparticles maintained their activity over an extended period of 10 h. This effect could be associated to the polymer used in the formulation [13, 14]. Maximum oedema lowering effects were 80.0 ± 22, 83.7 ± 1.2 and 87.4± 0.3 % in batch A, B and C at 6 h respectively. Formulation containing 400 mg of ibuprofen demonstrated significantly ($P < 0.05$) higher anti-inflammatory activity compared to other formulations and the controls. This can be explained on the basis of the amount of drug release in the biological medium available for the anti-inflammatory activity. In another words, it may be due to increased absorption of drug *in vivo* in the presence of the polymer matrix carrier. Drugs encapsulated in biodegradable polymer matrix have been shown, in most cases, to be better absorbed than those incorporated in conventional solid dosage forms[15]. This could be due to the ease of wetting of hydrophobic drug particles in the

presence of polymer matrix.[16] The presence of other addictives such as surfactant in the formulation may further promote drug release and ultimately lead to an enhanced absorption.[15,17]

Ulcerogenic effect of the formulation

The ulcer inhibition properties of the ibuprofen microparticles showed (Table 3) that the polymer loaded drug inhibited the ulcerogenic potentials of ibuprofen. Also, the ratio of drug to polymer used in the formulations had significant effect on the result as shown in **Table 2.** The protective effect of the formulations were in the following order batch C > MKT-S > PD. The formulations therefore, showed good gastro-protective potentials as compared to the reference samples. Thus the formulation drastically reduced the ulcerogenic potentials of ibuprofen**.** This observation may be due to the presence of the polymer used in the formulations which might have helped to shield or protect the gastric mucosa from irritation induced by ibuprofen. Additionally, the slow release of ibuprofen from the microparticulate matrix is devoid of dose dumping may have also contributed to the GI protection. In an earlier research where lipid material was used as carrier [18], a similar result was observed. The author attributed their finding to the role of lipid in the mucosa wall of the GIT.

Pharmacokinetic analysis

A kinetic analysis of the appearance of ibuprofen in the blood was performed 0 to 18 h after fasted rats were intragastrically administered the optimized formulation at a dose of 50 mg/kg. The higher dose of the batch was used in these bioavailability studies to facilitate the detection and quantitation of circulating levels of the drug by HPLC. The pharmacokinetics profile of the test sample and the reference drug after the study period are depicted in **Fig. 3.** Pharmacokinetic parameters for ibuprofen, such as the maximum plasma concentration (C_{max}), peak time (T_{max}) and the area under the concentration-time curve (AUC), are listed in **Table 4**. The results shown in **Fig. 3** demonstrate that the concentration of ibuprofen in the blood increases rapidly and reaches peak values in rats dosed with either pure powder sample or reference market sample as compared to the test formulation that was slow but persistent over a long period of time. It was noted that the C_{max} for ibuprofen-microparticles were modestly lower at the initial time but, showed slightly higher rate than the reference sample afterward. Parameters such as C_{max}, T_{max} and AUC of the formulated microparticles are 1.5 times that of the reference sample (MKT-S) On the contrast to the exponential decay in ibuprofen blood levels over the 18-h study period seen in rats administered the reference

drug, circulating ibuprofen levels of rats that were administered the optimized sample showed a sharp decrease in the plasma concentration the first few hours (1-2 h), followed by a slower rate of decay for the remainder of the 12-h study period. The circulatory half-life ($T_{1/2}$) of optimized batch of the formulated microparticles was also prolonged 2.5 times as compared to that of reference samples. These differences in pharmacokinetics parameters were evident as shown in **Table 4**. It was observed the factor like AUC of the formulated microparticles (1241.78 ± 0.11) showed more efficient and sustained drug delivery which would maintain a better plasma concentration than the reference drug (741.12 ± 0.23). Thus the significant ($p<0.05$) pharmacological effects observed in the in the optimized formulated microparticles.

CONCLUSION

The sustained release and improved anti inflammatory and gastro-protective capacity of the prepared microparticles relative to the conventional marketed ibuprofen makes ibuprofen-loaded PLA microparticles an attractive target for development for use in acute and chronic pains and inflammatory conditions. However, higher evaluation using higher animal like human volunteers are needed to consolidate on this finding so as to establish its potential effects.

Declaration of interest

The authors of this manuscript do not have a direct financial relation with the commercial identity mentioned in this manuscript that might lead to a conflict of interest. The authors do not have any conflict of interest in the preparation of this manuscript and they received no funding for this research work.

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