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REVIEW ON BIOEQUIVALENCE STUDY AND BIO ANALYTICAL METHOD DEVELOPMENT OF ANTIARTHRITIC DRUGS USING HIGH PERFORMANCE LIQUID CHROMATOGRAPHY

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ABSTRACT

Rheumatoid arthritis (RA) is a chronic, systemic inflammatory disease predominantly affecting the joints and periarticular tissue. Several drugs such as parcetamol, opiates, Diproqualone, prednisone, prednisolone, methyl prednisolone, Methotrexate, Leflunomide, Hydroxychloroquine, chloroquine, cyclosporine, sulfasalazine, gold salts, Etanercept, infliximab, adalimumab, golimumab, anakinra, cetrolizumab, rituximab, abatecept. Bioavailability, bioequivalence and therapeutic drug monitoring studies have received major attention from the pharmaceutical industry, health authorities and clinic. These studies are performed to evaluate the safety and efficacy of a genetic structure. Which studies as well as drug product development studies require rapid, simple, sensitive and reliable bioanalytical methods to monitoring the target drug in human plasma sample. Several analytical methods have been developed to analyse drugs in plasma for pharmacokinetic and clinical trials. Current review is focused on bioanalytical method development for antiarthritic drugs using HPLC analysis.

KEYWORDS: Arthritis, pharmacokinetic, diclofenac, antiinflamatory, NSAID, HPLC-UV.

1. INTRODUCTION

1.1. Arthritis

Rheumatoid arthritis (RA) is a chronic, systemic inflammatory disease predominantly affecting the joints and periarticular tissue.[1] RA still remains a formidable disease, being capable of producing severe cripplingdeformities and functional disabilities and cartilage destruction and commonly leads to significant disability, caused by no. of proinfalmmatory molecules released by macrophages including reactive oxygen species and ecosanoids such as prostaglandins, leukotrines and cytokines. The regulation of these mediators secreted by macrophages and other immune cells1and modulation of arachidonic acid metabolism by inhibiting enzymes like Cox and LOX are the potential target for chronic inflammatory conditions. RA is a complex process, involving synovial cell proliferation and fibrosis, pannus formation and cartilage and bone erosion. This process is mediated by an interdependent network of cytokines, prostanoids and proteolytic enzymes.[2]

Proinfalmmatory cytokines, such as interleukin-1 (IL-1) and tumor necrosis factor (TNF-α), are central mediators in RA. This is illustrated in patients with RA, who experience an initial cell-mediated response that leads to the presence of elevated levels of IL-1 in the synovial fluid. Furthermore, IL-1 concentrations in the plasma have been reported to correlate with disease activity. It has also been demonstrated that patients with erosive RA have higher synovial and circulating levels of IL-1 than patients without erosions. Interleukin-6 (IL-6) is an inflammatory cytokine that is characterized by pleiotropy and redundancy of action, involved in inflammation, bone metabolism, immunity, endocrine functions and in particular it is a major regulator of the synthesis of acute phase reactants by the liver. IL-6 is produced by many different cells in the body including lymphocytes, monocyte, fibroblasts and endothelial cells. Adipose tissue is another major source of IL-6, accounting for about 30% of total circulating concentrations of IL-6 in healthy subjects. Excessive adipose tissue deposition leads to excessive production of IL-6, a high risk factor to the RA. Body mass index (BMI) is an established risk factor for knee osteoarthritis (OA).Weight loss can help to reduce the incidence of symptomatic knee OA.[3]

1.2. Antiarthritic drugs

Generally, a strategic treatment plan is employed for the treatment of the disease which includes four different classes of drugs: non-steroidal anti-inflammatory agents (NSAIDs), corticosteroids, disease modifying anti-rheumatic drugs (DMARDs) and biological agents. As the disease is more prevalent among the females, therefore the treatment strategies for females in the child bearing age need special caution as the treatment employed for curing their arthritic condition can have negative impact on their potential for conceiving and also during pregnancy.[4,5]

1.2.1. Non-Steroidal Anti-inflammatory Drugs (NSAIDs)

Ex: Parcetamol, opiates, Diproqualone
Analgesics reduce pain, and NSAIDS lessen pain and stiffness. Both drugs are used widely to control symptoms of rheumatoid arthritis, evidence for use of analgesics is modest but uncontroversial; support for use of NSAIDs is considerably stronger. The mode of action of these drugs was not known until JR Vane for the first time published the observations showing that these drugs work by blocking cyclooxygenase enzyme. NSAIDs have lost their historical role as first line treatment because of concern about their limited effectiveness, inability to modify the long term course of disease. One of the most common toxicity observed in case of regular use of these drugs is gastrointestinal disturbances or toxicity which generally includes the condition of burning, belching or irritation further leading to the development of gastric ulcers followed by bleeding During long term usage, NSAIDs also impair the renal as well as liver function of the body, predisposing the patients towards the cardiovascular diseases with their additional adverse effects on blood pressure.

1.2.2. Corticosteroids

Ex: Prednisone, Prednisolone, Methyl prednisolone
Corticosteroids like glucocorticoids have been used on large scale since last 60 years for the treatment of arthritis. Some of the commonly used glucocorticoids in disease remission are prednisone, methyl prednisolone etc. short term glucocorticoids reduce synovitis. Long term they decrease joint damage, but develops various infections, and osteoporosis, and their overall risk/ benefit ratio is deemed to be highly unfavorable.

1.2.3. Disease Modifying Anti-rheumatic Drugs (DMARDs)

Ex: Methotrexate, Leflunomide, Hydroxychloroquine, Chloroquine, Cyclosporine, Sulfasalazine, Gold salts.
Disease Modifying Anti-rheumatic Drugs commonly referred to as DMARDs do not, include any specific class of drugs but is a large and heterogeneous collection of various agents grouped together according to their use, convention and efficacy in treating arthritis. Methotrexate is dominant DMARD, sulfasalazine and Leflunomide are widely used. Hydroxyl chloroquine and chloroquine have DMARDS like properties, gold salts and cyclosporine are additional DMARDs, and their use is limited by toxic effects. DMARDs are sometimes combined, and several combinations of DMARDs have been proven efficacy. An example is methotrexate, sulfasalazine and hodroxy chloroquine termed triple therapy. Use of DMARDs combinations varies across different countries; in some regions they are used rarely.[6]

1.3.4. Biological therapies in rheumatoid arthritis

Ex: Etanercept, Infliximab, Adalimumab, Golimumab, Anakinra, Cetrolizumab, Rituximab, Abatecept
Biological agents for the treatment of disease includes the use of TNF-inhibitor, T- cell co-stimulatory blockers, B- cell depletion molecules, IL-1 receptor antagonist, etc. Interleukin -1 and TNF-α are proinfalmmatory cytokines involved in the pathogenesis of RA, when secreted by synovial macrophages, IL1 and TNFα stimulate synovial cells to proliferate and synthesize collagenase, thereby degrading cartilage, stimulating bone resorption, and inhibiting proteoglyco synthesis, TNFα inhibitors (Adalimumab, Etanercept, Golimumamab, Cetrolizumab and Infliximab). Have been shown to decrease signs and symptoms of RA, reduce progression of structural damage, and improves physical function clinical response can be seen within 2 weeks of therapy. If a patient has failed therapy with one TNF inhibitor, a trail with a different TNF inhibitor is appropriate. Many experts propose that a TNF plus methotrexate be considered as standard therapy for patients with rheumatoid and psoriatic arthritis. Indeed, TNF inhibitors can be administered with any of the other DMARDs, except for anakinra, IL-1receptor antagonist.[7]

1.3. Bio analytical studies in HPLC

Bioequivalence is defined as a comparative study between bioavailability of two drugs which have the same indications, administration route and dose. Thus, generic drugs should offer the same guarantee of safety and effectiveness as the original drugs, which is why they are submitted to the same quality rules. They are assessed through three pharmacokinetic parameters: plasmatic concentration area curve, maximum blood concentration and maximum time required to reach maximum concentration.[8,9]

Bioavailability, bioequivalence and therapeutic drug monitoring studies have received major attention from the pharmaceutical industry, health authorities and clinic. These studies are performed to evaluate the safety and efficacy of a genetic structure.[10] Which studies as well as drug product development studies require rapid, simple, sensitive and reliable bioanalytical methods to monitoring the target drug in human plasma sample. Also for clinical studies, it is essential to establish accurate, sensitive and selective analytical techniques that permit detection and quantitative measurement of drug entities in biological and pharmaceutical samples. Several methods have been reported for determination of drug sample including spectrophotometric, spectrofluorimetric, polarographic, conductometric, highperformance liquid chromatography (HPLC), gas chromatography mass spectrometry (GC-MS) and capillary electrophoresis in human plasma and other biological fluids. Some of these methods are not suitable for routine analysis because they need sophisticated instruments, not yet available in many routine control laboratories.[11-14]

Chromatography can be very simply defined as the process of separation of the individual components of a mixture based on their relative affinities towards mobile phases and stationary phases. HPLC is one of the modern chromatographic methods which is widely used in the fields of clinical research, biochemical research, industrial quality control etc. Applications of this method includes detection, analysis, determination, and quantification, derivation of molecules from mixtures of biological, plant and medical samples. This is a very highly improved form of column chromatography. In column chromatography the solvent is just allowed to drip through the column while in high performance thin layer chromatography, it is forced externally through the column at very high pressures of up to 400 atm. This will in turn make the process a lot faster. It also permits the use of very small particle size for the column packing material which offers a much greater surface area for interactions between the stationary phase and the molecules flowing through it. Thus, it permits a much better separation of the components of the mixture. High performance liquid chromatography is now one of the supreme powerful tools in analytical chemistry as it has the capacity to identify, separate and quantitate the compounds that are existing in any sample that can be dissolved in any liquid.[15-18]

1.4. Literature on bioequivalence study of antiarthritic drugs using HPLC

Gulsum GA et al., (2016) developed HPLC method, for quantitative analysis and therapeutic drug monitoring of diclofenac sodium in human plasma. The total run time was 7 min. Method showed linearity with very good determination coefficients (r^2=0.999), over the concentration range of 50 - 1600 ng/mL. Limits of detection (LOD) and quantification (LOQ) were 8.95 ng/mL and 27.12 ng/mL, respectively. Intra-day precision and accuracy were between 0.93-5.27; 1.74-9.81, respectively. Inter-day precision and accuracy were between 2.71-6.64; 2.03-9.16, respectively. This method was successfully applied for determination of DS plasma concentrations during a pharmacokinetic study in healthy volunteers (n=12) after an oral administration of Voltaren® 75 mg/tablet and remarkable variations in DS levels were observed.[19]

Samah AM et al., (2019) developed RP - HPLC method for the analysis of rhein (as the main metabolite of diacerein) in human plasma. The separation was performed using an ODS C18 column with a mobile phase consisted of acetonitrile: methanol: phosphate buffer pH 6.8 and the flow rate was1.0 mL/min. The flourimetric detection was performed at 2 excitation wavelengths ʎex =440 nm&338 nm and one emission wavelength at ʎem= 520 nm. The pharmacokinetic parameters of the test and the reference were determined and the analysis of variance (ANOVA) between parameters of the two brands was calculated. The relative bioavailability was found to be 89%. This method was successfully applied for the routine bioequivalence analysis of diacerein in plasma.[20]

Vivek U et al., (2017) developed HPLC-MS/MS method for estimation of methotrexate in human plasma. The sample extraction of methotrexate and methotrexate-d3 (Internal standard) was done from 200 µL of human plasma using solid phase extraction procedure. The chromatographic retention was done on Thermo Butyl Hypersil, 50 x 4.6 mm, 5µm column under isocratic conditions using acetonitrile, 10 mM ammonium formate and 0.5% Formic aid (70:15:15, v/v) as the mobile phase. The mass transition for methotrexate (m/z 455.3 → 308.2), and IS (m/z 458.3 → 311.2) were monitored in the positive ionization mode. The method was validated over a wide-ranging concentration of 0.500-1000 ng/mL. The extraction recovery for the analyte and internal standard was 85.6 %. Stability of methotrexate in plasma was examined under different storage conditions like bench top, wet extract, freeze-thaw and long-term stability.[21]

Emami J et al., (2007) developed reverse phase HPLC method for quantitate plasma levels of diclofenac sodium in human plasma. The drug, internal standard (naproxene) and orthophosphoric acid 1 M, were added to plasma samples and vortexed for 20 sec. A mixture of hexane /isopropyl alcohol (90:10) was then added and vortexed for 2 min. Samples were centrifuged and the supernatant layer was separated, evaporated to dryness under nitrogen gas stream, reconstituted in mobile phase and an aliquot of 50 µl was analyzed on a µ-bondapack C18 (150 × 4.6mm) column, with 45% acetonitrile in deionised water and 0.5% orthophosphoric acid, (pH = 3.5) at 276 nm. The standard curve covering 0.005 - 4 µg/ml concentration range, was linear, relative errors were within 0.13 to 16 % and the CV % ranged from 1.24 to 8.75. The limits of quantitation and detection of the method were 0.005 µg/mL and 0.002µg/mL, respectively. The method was suitable for bioavailability and pharmacokinetic studies of diclofenac in humans and applied in a randomized, two-way cross over bioequivalance study of two different diclofenac sodium preparations with twelve subjects and with a one-week washout period.[22]

Nguyen GTH et al., (2017) developed HPLC method to quantify rhein in human plasma. This method successfully applied to the bioequivalence study of two formulations of diacerein 50 mg in healthy Vietnamese populations. After dosing, serial blood samples were collected for a period of 24 hrs. The power of all primary pharmacokinetic parameters were greater than 80 % indicating that the number of subjects was enough to confirm the bioequivalence of two formulations. No subject withdrew from our study, and no adverse events were found on analysis of vital signs or laboratory test results during the study. No abnormalities were found in clinical or biochemical parameters when comparing baseline versus end-of-study assessments. The 90% confidence intervals for the ratios of Cmax (93.43 % - 102.80%), $AUC_{0\text{-}t}$ (90.17 % - 113.76%) and $AUC_{0\text{-}\infty}$ (90.48 % - 113.32%) suggested that a single dose of the test and reference formulations of diacerein met the FDA regulatory requirements of bioequivalence.[23]

Pervaiz AS et al., (2016) compare oral bioavailability and pharmacokinetic parameters of different lornoxicam formulations and to assess similarity in plasma level profiles by statistical techniques. An open-label, two-period crossover trial was followed in 24 healthy Pakistani volunteers (22 males, 2 females). Each participant received a single dose of lornoxicam controlled release (CR) microparticles and two doses (morning and evening) of conventional lornoxicam immediate release (IR) tablet formulation. The microparticles were prepared by spray drying method. The formulations were administered again in an alternate manner after a washout period of one week. Pharmacokinetic parameters were determined by Kinetica 4.0 software using plasma concentration-time data. Moreover, data were statistically analyzed at 90 % confidence interval (CI) and Schuirmann's two one-sided t-test procedure. Peak plasma concentration (C_{max}) was 20.2 % lower for CR formulation compared to IR formulation (270.90 ng/ml vs 339.44 ng/ml, respectively) while time taken to attain C_{max} (t_{max}) was 5.25 and 2.08 h, respectively. Area under the plasma drug level versus time (AUC) curve was comparable for both CR and IR formulations. The 90 % confidence interval (CI) values computed for Cmax, AUC0-24, and AUC0-, after log transformation, were 87.21, 108.51 and 102.74 %, respectively, and were within predefined bioequivalence range (80 - 125 %). The findings suggest that CR formulation of lornoxicam did not change the overall pharmacokinetic properties of lornoxicam in terms of extent and rate of lornoxicam absorption.[24]

Muhammad Akhtar et al., (2011) studied bioequivalence of two marketed formulations of celecoxib capsules in healthy human male volunteers. The study was conducted according to a single dose, randomized sequence, open label, two-period and crossover design. Both test and reference formulations comprised labeled dose of 200 mg celecoxib and were administered to each subject after an overnight fasting on two treatment days separated by one week of washout period. After drug administration, blood samples were collected at predetermined time points for a period of 48 h. Plasma separated from blood was analyzed for celecoxib concentrations using validated reverse phase-high performance liquid chromatographic (RP-HPLC) method. Various pharmacokinetic parameters including C_{max}, T_{max}, $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$, $T_{1/2}$ and Kel were determined from the plasma concentration for both formulations. C_{max}, $AUC_{0\text{-}t}$ and $AUC_{0\text{-}\infty}$, were evaluated for bioequivalence after log-transformation of data. The 90% confidence intervals for the ratio of C_{max} (93.26 to 100.70%), $AUC_{0\text{-}t}$ (87.00 to 117.50%) and $AUC_{0\text{-}\infty}$ (86.49 to 118.56%), values for the test and reference products were within the acceptance range of 80 to 125%, proposed by Food and Drug Administration (FDA) and European Medicines Evaluation Agency (EMEA). Based on these statistical inferences, it was concluded that two formulations of celecoxib are bioequivalent in their rate and extent of absorption.[25]

Setiawati E et al., (2009) studied bioavailability of a 550 mg naproxen sodium tablet (Sunprox, test) produced by Sunward Pharmaceutical Sdn Bhd was equivalent to that produced by the innovator. In each of the two study periods (separated by a washout of one week) single dose of test or reference drug was administered. Blood samples were taken up to 72 h post dose, the plasma was separated and the concentration of naproxen were determined by HPLC-UV method. In this study, the mean AUC_t, AUC_{inf}, C_{max}, and $t_{½}$ of naproxen from the test drug were 936.11 µg.h.mL-1, 977.03 µg.h.mL-1, 76.55 µg/mL, and 15.11 h, respectively. The geometric mean ratios (90% CI) of the test drug/ reference drug for naproxen were 96.46% (94.30 – 98.66%) for AUC_t, 96.33% (94.03 – 98.69%) for AUC_{inf}, and 100.37% (95.90 – 105.05%) for C_{max}. Based on this study, it can be concluded that the two naproxen sodium tablets (test and drug reference drug) were bioequivalent in term of the rate and extent of absorption.[26]

Bilal Y et al., (2014) developed high-performance liquid chromatography method for the determination of naproxen in human plasma. The method was validated on an Ace C18 column using ultraviolet detection. The mobile phase consisted of 20 mM phosphate buffer (pH 7) containing 0.1% trifluoroacetic acid–acetonitrile (65:35, v/v). The calibration curve was linear between the concentration ranges of 0.10 and 5.0 mg/mL. Intra-day and inter-day precision values for naproxen in plasma were less than 4.84, and accuracy (relative error) was better than 3.67%. The extraction recovery values of naproxen from human plasma were between 91.0 and 98.9%. The limits of detection and quantification of naproxen were 0.03 and 0.10 mg/mL, respectively.[27]

Zeyad AA et al., (2011) Twenty-four healthy volunteers were enrolled in this study. After overnight fasting, the two formulations (test and reference) of ibuprofen (100 mg ibuprofen/5 mL suspension) were administered as a single dose on two treatment days separated by a one-week washout period. After dosing, serial blood samples were drawn for a period of 14 hours. Serum harvested from the blood samples was analyzed for the presence of ibuprofen by high-pressure liquid chromatography with ultraviolet detection. Pharmacokinetic parameters were determined from serum concentrations for both formulations. The 90% confidence intervals of the lntransformed test/reference treatment ratios for peak plasma concentration and area under the concentration-time curve (AUC) parameters were found to be within the predetermined acceptable interval of 80%–125% set by the US Food and Drug Administration.[28]

Loya P et al., (2010) developed high-performance liquid chromatography method for the determination of actarit in human plasma. Coumarin was used as an internal standard. Chromatographic separation was achieved with a C8 column using a mobile phase of methanol: 1% acetic acid (50-50, v/v) with a flow rate of 1.0 ml/min. The calibration curve was linear over the range of 0.1–4.0 µg/ml (r > 0.99) and the lower limit of quantification was 0.1 µg/ml. The method was validated for sensitivity, accuracy, precision, recovery and stability. The method was used to determine the concentration-time profiles of actarit in the plasma following oral administration of 100 mg actarit tablets.[29]

Uttam Mandal et al., (2008) studied the bioequivalence of two oral formulations containing 400 mg of dexibuprofen. Both of the formulations were administered orally as a single dose separated by a one-week washout period. The concentration of dexibuprofen in plasma was determined by a validated HPLC method with UV detection using carbamazepine as internal standard. The results of this investigation indicated that there were no statistically significant differences between the logarithmically transformed $AUC_{0-\infty}$ and C_{max} values of the two preparations. The 90 % confidence interval for the ratio of the logarithmically transformed AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} were within the bioequivalence limit of 0.8-1.25 and the relative bioavailability of the test formulation was 99.04 % of that of reference formulation. These findings clearly indicate that the two formulations are bioequivalent in terms of rate and extent of drug absorption. Both preparations were well tolerated with no adverse reactions observed throughout the study.[30]

Laila HE et al., (2012) Developed HPLC method for determination of diclofenac sodium (DS) in human plasma. Butyl paraben was used as an internal standard (IS). Chromatographic separation was achieved using C18 reversed-phase column. The mobile phase was acetonitrile: water (pH 4) using isocratic elution at a flow rate of 1.0mL=min. The IS and DS were detected at 282 nm and eluted at 3.3 and 5.6 min, respectively. The lower limit of detection (LLOD), lower and upper limits of quantification (LLOQ and ULOQ) were 0.01, 0.02, and 2.00 lg=mL, respectively. The drug in plasma and stock solution in methanol were stable for 5 weeks and 3 months at 2^0C, respectively. This method was successfully applied for determination of DS plasma concentrations during a pharmacokinetic study in a healthy human male volunteer after an oral administration of Voltaren 100 mg tablet manufactured in two different sites (Novartis-Egypt and Switzerland) in a cross-over design.[31]

Huma Ali et al., (2016) developed and validated HPLC procedure for the estimation of diclofenac potassium in plasma. The process was validated in the range of 50 - 0.05 µg.mL-1 and used in bioequivalence trial of two products. The 90% confidence interval values using log transformed data for $AUC_{0-\infty}$ (0.997-1.024), AUC_{tot} (1.004-1.031), AUC_{last} (0.997 - 1.024), $C_{maxcalc}$ (0.994-1.007) and $T_{maxcalc}$ (0.996-1.013) for the trial and reference products were found within the FDA acceptable limits of 0.8-1.25. Results were further verified by the Schirmann’s one-sided t test. Results showed the bioequivalence of test and reference formulations. Both the products were well tolerated.[32]

Table 1: Details of HPLC parameters in bioanalytical method.

S. No	Drug	Mobile Phase	Column/ detector	Flow rate	Internal standard	Biological sample
1	Diclofenac sodium	Acetonitrile: Na_2HPO_4 buffer (42.5: 57.5, v/v)	C18 column (3.5 µm, 150x 4.6 mm i.d.) / UV detection at 381nm	1.5 ml/ min	Naproxen	Human blood samples
2	Diacerein	Acetonitrile: methanol: phosphate buffer pH 6.8 (20: 10: 70 v/v/v)	C18 column (4.6 mm i.d. x 150 mm)/ Fluorescence detection (λ_{ex} = 440 nm for Rhein, 338 nm for IS and λ_{em} = 520 nm for both rhein and IS)	1.0 ml/ min	Ranitidine	Human blood samples
3	Methotrexate	Acetonitrile: 10 mM ammonium formate: 0.5% formic acid (70: 15: 15 v/v)	Thermo Butyl Hypersil (50 × 4.6 mm, 5 µm) column/ mass spectrometer (transitions for methotrexate m/z 455.3 → 308.2 and m/z 458.3 → 311.2 for IS)	0.6 ml/ min	Methotrexate-d3	Human blood samples
4	Diclofenac sodium	Acetonitrile: Deionized water: Orthophosphoric acid (45:54.5:0.5)	C18 (150 × 4.6mm) / UV detection at 276 nm	1 ml/ min	Naproxene	Human blood samples
5	Rhein Diacerein	Acetonitrile: pH 2.7 acetic acid buffer (60:40 v/v)	C18 (250 mm x 4.6 mm, 5 µm particle size)/ UV detection at 256 nm	1.0 ml/ min	Diclofenac	Human blood samples
6	Lornoxicam	Phosphate buffer: acetonitrile (45:55 v/v)	ODS column (150 × 4.5 i.d, 5µm particle size, Agilent) / UV detector	1 ml/ min	Piroxicam	Human blood samples
7	Celecoxib	Acetonitrile: water: triethylamine (50: 50: 0.05)	Hypersil C8 column (150 × 4.6 mm I.D. × 5 µ particle size)/ UV detector (254 nm)	1.0 ml/ min	-	Human blood samples
8	Naproxene	Acetonitrile: KH_2PO_4 25 mM pH 3 (45:55 v/v)	C18 5µm, 3.9 x 20mm/ UV detection at 240 nm	1.0 ml/ min	Not specified	Human Blood samples
9	Naproxen	20 mM phosphate buffer: acetonitrile (65:35 v/v)	C18 column (5 mm, 4.6x 250 mm i.d.) / UV detection at 225 nm	1.0 ml/ min	Ibuprofen	Human blood samples
10	Ibuprofen	Acetonitrile: acetate buffer at pH 4.9	C18, Luna® 5 µm C18 column (150 × 4.0 mm)/ UV detection at 220 nm	0.8 ml/ min	Indomethacin	Human blood samples
11	Actarit	Methanol: 1% acetic acid (50-50 v/v)	C-18 column/ UV detection at 245 nm	1.0 ml/ min	Coumarin	Human blood samples
12	Dexibuprofen	Acetonitrile: 10 mmol phosphate buffer (45:55 v/v)	Luna C18 (250 x 4.6, 5 µm particle size) /UV detection at 223 nm	-	Carbamazepine	Human blood samples
13	Diclofenac sodium	Acetonitrile: Deionized water (pH 4), (55:45 v/v)	C18, 5 mm, (3.9 cmx 150mm i.d.)/ UV detection at 282 nm.	1 ml/ min	Butyl paraben	Human blood samples
14	Diclofenac potassium	0.01 N methanol in monobasic sodium phosphate: 0.01M ortho phosphoric acid (70:30)	C18 (250 x 4.6 mm x 5 µm)/ UV detection at 254 nm	1 ml/ min	-	Human blood samples

2. CONCLUSION

The bio analytical methods were used in the bioequivalence study of drugs, estimation of drugs in biological samples, pharmacokinetic studies and therapeutic drug monitoring. This review overviewed the HPLC analysis method in antiarthritic drug for bioanalytical studies. Thus the study will useful to researchers to find out the HPLC method for bioanalytical studies.

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