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(REVIEW ARTICLE)

Reported estimation techniques for quantification of zaltoprofen: A review

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Abstract

Zaltoprofen is a nonsteroidal anti-inflammatory drug used as an analgesic, antipyretic, and antinflammatory agent. It is a selective COX-2 inhibitor and also inhibits bradykinin-induced pain responses without blocking bradykinin receptors. Zaltoprofen is prescribed for treating pain and inflammatory conditions caused by various disorders such as dental pain, musculoskeletal pain, postoperative pain, and lumbar pain, and frozen shoulder, osteoarthritis and cervico branchial syndrome. There are various analytical methods for estimation of drug. This paper list out the various analytical methods for the drug.

Keywords: Zaltoprofen; Nonsteroidal anti-inflammatory drug; Analytical methods; Review

1. Introduction

Zaltoprofen is chemically known as 2-(10,11-Dihydro-10-oxo-dibenzo[b,f]thiepin2yl)propionic acid. Zaltoprofen is known as a nonsteroidal anti-inflammatory drug, which prevents the development of inflammation by blocking the synthesis of prostaglandins. It is freely soluble in acetone, chloroform, soluble in methanol, slightly soluble in ethanol, benzene, partially insoluble in water, cyclohexene. The pka value for strongest acidic is 3.67 and for strongest base is 7.6. Molecular weight of 298.36g/mol. The structure is given in fig. 1.

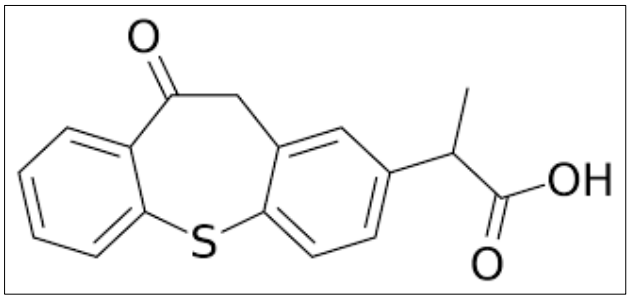

Figure 1 Structure of Zaltoprofen

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2. Various Analytical Methods

2.1. DSC methods

The Zaltoprofen, 4,4'-Bipyridine system gives rise to two co-crystals of different compositions both endowed - in water and in buffer solution at pH 4.5 - with considerably higher solubility and dissolution rate than the pure drug. The qualitative and quantitative analysis of the DSC measurements, carried out on samples made up of mixtures prepared according to different methodologies, allows us to elaborate and propose an accurate thermodynamic model that fully takes into account the qualitative aspects of the complex experimental framework and which provides quantitative predictions (reaction enthalpies and compositions of the co-crystals) in excellent agreement with the experimental results. Co-crystal formation and cocrystal compositions were confirmed by X-ray diffraction measurements as well as by FT-IR and NMR spectroscopy measurements. The quantitative processing of DSC measurements rationalizes and deepens the scientific aspects underlying the so-called Tammann's triangle and constitutes a model of general validity. The work shows that DSC has enormous potential, which however can be fully exploited only by paying adequate attention to the experimental aspects and the quantitative processing of the measurements [1].

Though ionic liquids (ILs) as novel enhancers had garnered wide attention, detailed studies elucidating molecular design of drug-ILs were missing and mechanisms of their formation and skin permeation were still lacking. Herein, we systematically investigated effects of counterions structures on formation and skin permeation of drug-ILs. Firstly, effects of counterions on formation of drug-ILs were dependent on polarizability, molecular weight and polar surface area of counterions. It was caused by strong charge assisted hydrogen bond and van der Waals interactions revealed through FT-IR, X-ray photoelectron spectroscopy and molecular docking, which undermined ionic interactions and reduced total interaction strength, thereby produced lower lattice energy. Then, skin permeability of drug-ILs had a good parabola relationship with molecular weight polarizability and log P of counterions. The underlying mechanism was the increased drug miscibility with stratum corneum, which caused conformational disorder and phase transition of lipid bilayers characterized by ATR-FTIR, DSC and confocal laser scanning microscopy. Finally, the drug-ILs proved to be non-irritating using *in vivo* skin erythema analysis. In conclusion, the quantitative structure-activity relationship models based on counterions structure to predict formation and skin permeation of drug-ILs were developed, which provided basic theory for design of drug-ILs with high permeation enhancing efficiency [2].

At present, transdermal permeation enhancing dynamics studies on permeation enhancers are still limited. In this study, these dynamics were established based on the content of enhancer Plurol Oleique CC in skin (CPOCC) and the increment of drug permeation amount (ΔQ). A new concept deemed “permeation enhancement window” (ΔCPOCC), comprised of a threshold dose (Cthr), maximal dose (Cmax) and permeation enhancement efficiency (Eff) was used to evaluate the enhancement effect of POCC for different drugs. According to results of FT-IR, ATR-FTIR and DSC analyses, the higher CPOCC of patches containing acidic drugs vs. basic drugs resulted from their stronger interaction with pressure-sensitive adhesives, leading to more free POCC and a greater disturbing effect on stratum corneum (SC) lipids. Below Cthr, a longer lag phase for acidic drugs resulted from more POCC required to compete with ceramide. When CPOCC exceeded Cmax by about 400 μg/g, plateau phases for all drugs were reached due to the upper limit of SC lipid fluidity, as confirmed by SAXS and Raman imaging. In summary, the differences in the permeation enhancement window for the test drugs resulted from the varied interaction strengths among POCC, drugs and adhesives, as well as changeable SC lipid fluidity [3].

The aim of this study was to develop a controlled release drug-in-adhesive patch containing escitalopram (ESP) using ion-pair technique. Special attention was paid on the mechanism of how counter ion controlled the release of ESP. Five organic acids were chosen as the counter ions. Formulation factors including adhesive matrix, drug loading and permeation enhancers were investigated through *in vitro* experiments using rat skin and the optimized patch was evaluated using *in vivo* pharmacokinetic study. Drug-counter ion-PSA interactions were characterized by FTIR, molecular modeling and DSC at molecular level. The optimized patch prepared with ESP-BA showed zero-order skin permeation profile and a satisfied permeation amount of three days (1059 ± 104.9 μg/cm^2) *in vitro*, which also showed a steady-state drug plasma concentration lasting 36 h *in vivo* and the Cmax was significantly controlled compared with the control group. The controlled release of ESP was attributed to the interactions among ESP-counter ion-PSA by hydrogen bonding, and counter ion enhanced the interaction between ESP and PSA molecule, which acted as a “bridge” between them. In conclusion, a controlled release ESP transdermal patch was developed and a novel insight of ion-pair controlled release was proposed at molecular level [4]

Pharmaceutical cocrystals are a promising tool to enhance the solubility and dissolution of poorly soluble drugs. Zaltoprofen (ZFN) is nonsteroidal anti-inflammatory drug with a prevalent solubility problem. The present study was undertaken to enhance the solubility and dissolution of ZFN through pharmaceutical co-crystals by screening various

coformers. Cocrystals of ZFN were prepared in 1:1 and 1:2 ratio of drug:coformer by the dry grinding method. The melting point and solubility of the crystalline phase were determined. The potential cocrystals were characterized by differential scanning calorimetry (DSC), infrared spectroscopy, and powder X-ray diffraction (PXRD). Cocrystals were subjected to dissolution rate and stability study. ZFN-nicotinamide (NIC) cocrystals demonstrated deviation in melting point and solubility. The cocrystals were obtained in both 1:1 and 1:2 ratios with NIC. The infrared analysis noticeably indicated the shifting of characteristic bands of ZFN. The crystallinity of the cocrystals was evident from the XRPD pattern and notable difference in the 2θ values of intense peaks. The DSC spectra of the cocrystals exhibited altered endotherms analogous to melting point. The cocrystals showed a faster dissolution rate and a 55% increase in the extent of dissolution compared to pure drug. The cocrystals were stable at room temperature and accelerated conditions [6].

The aim of the study was to develop a drug-in-adhesive patch system for transdermal delivery of zaltoprofen (ZAL). The formulation was designed in combination with the ion pair and chemical enhancer strategy. Seven organic amines were chosen as counter ions, and the prepared ion pairs were characterized by Fourier transform infrared spectroscopy (FTIR) and differential scanning calorimetry (DSC). The *in vivo* pharmacokinetic performance of ZAL was studied on rabbits following transdermal and intravenous administration. A deconvolution method was applied to determine the correlation between the *in vitro* permeation and the *in vivo* absorption. Acetic acid-induced writhing response was conducted on mice to evaluate the analgesic effect. *In vitro* permeation results showed that both ion pairs and chemical enhancers were effective in modulating ZAL skin permeation from patches. The enhancement ratio was negatively correlated to the polar surface area (PSA) of counter ions, and was positively correlated to the octanol-water partition coefficient (log Ko/w) of chemical enhancers, respectively. The optimized formulation contained 10% (w/w) ZAL-triethylamine and 10% (w/w) isopropyl myristate, with DURO-TAK 87-4098 as the pressure sensitive adhesive matrix. Furthermore, the *in vitro* permeation data were well correlated with the *in vivo* absorption data. The analgesic effect of the optimized patch was comparable to the commercial indometacin plasters. In conclusion, it was feasible for transdermal delivery of ZAL by the synergistic action of ion pair and chemical enhancer, and the *in vitro* permeation data were indicative of the *in vivo* performance for the developed patches [7].

Zaltoprofen spherical agglomerates were prepared by spherical crystallization technique using a three solvent system comprising a good solvent (acetone), a bad solvent (water) and a bridging liquid (dichloromethane) by using a hydrophilic polymer sodium CMC in different concentrations for enhancing micromeritic properties and dissolution rate. The preparedzaltoprofen spherical agglomerates were evaluated in terms of flow properties, particle size analysis, compression and dissolution behavior. Physical characters of the crystals were studied for the morphology of crystals using scanning electron microscope (SEM), identification of polymorphism done by X-ray powder diffraction (XPRD) and for thermo dynamic properties using differential scanning colorimetry (DSC). The prepared agglomerates were improved the micromeritic properties, packability, wettability, solubility and compaction behavior, as well as dissolution behavior in comparison to pure zaltoprofen drug [8].

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confirmed by SAXS and Raman imaging. Insummary, the differences in the permeation enhancement window for the test drugs resulted from the varied interaction strengths among POCC, drugs and adhesives, as well as changeable SC lipid fluidity [10].

This work aimed to investigate the co-grinding effects of β-cyclodextrin (β-CD) and cucurbit [7]uril (CB[7]) on crystalline zaltoprofen (ZPF) in tablet formulation. Crystalline ZPF was prepared through anti-solvent recrystallization and fully analyzed through single-crystal X-ray diffraction. Co-ground dispersions and mono-ground ZPF were prepared using a ball grinding process. Results revealed that mono-ground ZPF slightly affected the solid state, solubility, and dissolution of crystalline ZPF. Co-ground dispersions exhibited completely amorphous states and elicited a significant reinforcing effect on drug solubility. UV-vis spectroscopy, XRPD, FT-IR, DSC, ssNMR, and molecular docking demonstrated the interactions in the amorphous product. Hardness tests on blank tablets with different β-CD and CB [7] contents suggested the addition of β-CD or CB [7] could enhance the compressibility of the powder mixture. Disintegration tests showed that CB [7] could efficiently shorten the disintegrating time. Dissolution tests indicated that β-CD and CB [7] could accelerate the drug dissolution rate via different mechanisms. Specifically, CB [7] could accelerate the dissolution rate by improving disintegration and β-CD showed a distinct advantage in solubility enhancement. Based on the comparative study on β-CD and CB [7] for tablet formulation combined with co-grinding, we found that CB [7] could be considered a promising drug delivery, which acted as a disintegrant [11].

2.2. FT-IR Methods

The aim present work is Formulate and Evaluate the Immediate release tablets of Zaltoprofen. Zaltoprofen is a nonsteroidal anti-inflammatory drug (NSAID) used as an analgesic, antipyretic, and anti-inflammatory agent. Hence in this investigation an attempt was made to develop oral disintegrating tablets of Zaltoprofen with super disintegrating agents like Explotab, Primojel, Solutab were used to super diintegrants, The superdisintegrants were taken in different ratios. The formulations were prepared by direct compression technique, Taste masking was done by Sweetning agent. As a result of the studies, the blend of all formulations showed good flow properties such as angle of repose, bulk density, tapped density, Carr's index, Hausner's ratio. The prepared tablets were shown good post compression parameters a like Hardness, Thickness, weigh variation, friability, Content uniformity, disintegration time, *In vitro* dissolution studies. The FTIR studies all the excipients are tested for compatibility with drug, which revealed that there was no physical and chemical interaction occurred. The drug release rate from tablets was studied using the USP type?? Dissolution test apparatus. The dissolution medium was 900 ml of pH 6.8 phosphate buffer at 50 rpm at a temperature of 37±0.5 °C. The formulation F8 consisting of Solutab was found be best among all the formulations it has exhibited faster disintegrating time (2 min) when compared to other formulations and it showed 99.56 % drug release in 30min [12].

The main objective of this study is to formulate polymeric nanoparticles (NPs) loaded with zaltoprofen, an NSAID drug. The optimization, in terms of polymer concentration, stabilizer concentration and pH of the formulation was employed by 3-factor-3-level Box-Behnken experimental design. : The NPs of zaltoprofen were fabricated using chitosan and alginate as polymers by ionotropic gelation. The ionic interaction between the ionic polymers was studied using Fourier transform infrared and differential scanning calorimetry study: For different formulation the average particle size ranged between 156 ± 1.0 nm and 554 ± 2.8 nm. The drug entrapment ranged between 61.40% ± 3.20% and 90.20% ± 2.47%. The ANOVA results exhibited that all the three factors were significant. The resultant optimized batch was characterized by particle size 156.04 ± 1.4 nm, %entrapment efficacy 88.67% ± 2.0%, zetapotential + 25.3 mV and polydispersity index 0.320. The scanning electron microscopy showed spherical NPs of average size 99.5 nm. The optimized NPs were loaded in carbopol gel, which was subjected to study of drug content, viscosity, spreadability, *in vitro* drugdiffusion and *in vivo* antiinflammatory test on rats. This study showed that zaltoprofen NPs prepared using the ratio of polymer CS:AG:1:1.8, stabilizer concentration 0.98% and pH 4.73 was found to be of optimized particle size, maximum drug entrapment. The NPs loaded gel showed controlled release for 12 h following Korsmeryer-peppas model of the diffusion profile. The *in vivo* antiinflammatory study showed prolonged effect of NPs loaded gel for 10h [13].

At present, how the release kinetics of permeation enhancers affected their enhancement efficacy on drug skin absorption and its molecular mechanisms remained unclear. Herein, the release kinetics of permeation enhancer (Plurol Oleique CC (POCC)) which involved release percent (PR), release duration (RD) and release kinetic constant (k) and its enhancement efficacy on drug skin absorption were investigated with *in vitro* skin retention study and *in vitro* skin permeation study, respectively. POCC released from the acidic-drug loading patches followed with the Higuchi release model and had short RD (8–16 h), resulting in its unsustainable enhancement efficiency for acidic drugs. However, POCC released from the basic-drug loading patches followed with zero-order model with long RD (12–24 h), inducing a sustainable and efficient enhancement efficiency for basic drugs. The lower variance of an innovative parameter permeation enhancement coefficient (CPE) represented the relatively sustainable and effective enhancement effect and was listed as followed: 0.20(Zaltoprofen (ZPF)), 0.31 (Diclofenac (DCF)), 0.27 (Indomethacin (IMC)), 0.07 (Azasetron

(AST)), 0.11 (Oxybutynin (OBN)) and 0.06 (Donepezil (DNP)). According to the results of FT-IR, MTDSC, 13C NMR spectra, molecular dynamics simulation, SAXS and Raman imaging, the Higuchi release model was caused by strong interaction between the acid drugs and pressure sensitive adhesive (PSA). This strong interaction induced faster diffusion speed of POCC from acidic drug loading patches and make the swell degree of long periodicity phase (LPP) of stratum corneum (SC) lipids reached plateau early. The zero-order release model was because the weak interaction between basic drugs and PSA making most of POCC was still bound to PSA, which in turn lead to LPP swelled at a slow but sustainable process. In conclusion, zeroorder release kinetic of POCC lead to sustainable and efficient penetration enhancement efficiency on basic drug, while the Higuchi release kinetic showed opposite effect for acidic drugs. A deep understanding of release kinetics of enhancer and its enhancement efficiency may drive the ideal selection of permeation enhancers and rational optimization of transdermal patches [14].

The study was carried out to investigate the mechanism of the ion-pair strategy in modulating zaltoprofen (ZAL) skin permeability. Seven organic amines were chosen as counter ions and the formation of ion pairs was confirmed by Fourier transform infrared and proton nuclear magnetic resonance spectroscopy. *In vitro* permeation studies showed that the permeation of ZAL was significantly promoted with alkylamines and cycloalkanolamines, while significantly retarded with alkanolamines. The results were further visualized by confocal laser scanning microscopy studies. Investigations from the standpoint of solubility, partition, and diffusion indicated that the modulation mechanism of ion pairs was mainly attributed to an alteration of ZAL diffusion in the skin, which was accomplished by masking the carboxyl of ZAL and adding the hydrogen-bonding groups of counter ions. A negative correlation was observed between the enhancement ratio of ion pairs and the polar surface area of counter ions. Molecular modeling revealed that ion pairs acted with the nature of different affinity to ceramide, which would be responsible for the diffusion retardation. The study indicated that the maximum effect of ion pairs tended to be achieved with counter ions of lower hydrogen bonding potential [15].

The aim of this study was to investigate the influence of drug physicochemical properties on drug release behaviors and their relationship with skin permeation behaviors, which provided transdermal enhancement strategies for the design of transdermal drug delivery system. Six model drugs with different physicochemical properties were selected and hydroxyl pressure sensitive adhesive (PSA) was synthesized. Horizontal diffusion cell was used to evaluate drug release and skin permeation behaviors. The relationship between physicochemical properties and release behaviors was conducted with regression analysis. Release behavior of 0.25% drug loading was linear related with polar surface area, which represented the hydrogen bond. Release behavior of 2.0% drug loading was dependent on the polarizability and log P, which represented dipole-dipole interaction and lipophilicity, respectively. According to the results of Fourier transform infrared spectroscopy, it was inferred that hydrogen bond was limited in controlling release of drug due to the limited quantity of bonding site, thus dipole-dipole interaction and log P became dominate control factors. Combining the drug release study and drug skin permeation study, it was concluded that drugs with different physicochemical properties should be applied with different transdermal enhancement strategies, which was useful for the design of transdermal drug delivery system [16].

2.3. HPLC methods

We investigated the pharmacokinetic profile of (R)- and (S)-zaltoprofen (ZPF) in rats using rapid and selective liquid chromatography with solid-phase extraction (SPE). The ZPF enantiomers were extracted from a small volume of plasma (0.2 mL) by means of SPE using cartridges and were analyzed on a Chiralcel OJ-H (4.6 mm × 150 mm, 5 μm) column with ultraviolet detection at 244 nm. The lower limit of quantification of the ZPF enantiomers in plasma was 0.1 μg/mL. The validated method was successfully applied to chiral pharmacokinetic studies of oral administration of racemic ZPF to rats. (S)-ZPF showed significantly higher AUC, Tmax, and Cmax and a longer half-life than (R)-ZPF, indicating higher bioavailability of the (S)-isomer. A total of 8 samples (about 12% of the total number of samples) were selected for incurred sample reanalysis (ISR). The % difference between the re-assay concentrations and the original concentrations were all less than 15% of their mean values and met the acceptance criteria for ISR [17].

Simple, rapid, precise, and economical spectrophotometric method has been developed for quantitative analysis of zaltoprofen (ZLT) in pharmaceutical formulations. Materials and Methods: A mixture of methanol and water was used as a solvent. Initial stock solution of ZLT was prepared in methanol and subsequent dilution was done in water. The standard solution of ZLT in water showed two absorption maxima, one at 243.5 nm and another at 338.0 nm. Results: The drug obeyed Beer Lambert's law in the concentration range of 1-40 μg/mL with régression 0.9999 at 243.5 nm and 5-100 μg/ mL with regression 0.9999 at 338.0 nm. The overall % recovery was found to be 99.53% and 99.77% at 243.5 nm and 338.0 nm, respectively, which reflect that the method is free from interference of the impurities and other additives used in tablet formulation. Relative standard deviations of absorbance from six measurements were always less than 2%. Conclusions: The results of analysis have been validated as per ICH guidelines. Both the wavelengths can

be adopted in routine analysis of ZLT in tablet dosage form rapid, precise, and economical spectrophotometric method has been developed for quantitative analysis of zaltoprofen (ZLT) in pharmaceutical formulations. Materials and Methods: A mixture of methanol and water was used as a solvent. Initial stock solution of ZLT was prepared in methanol and subsequent dilution was done in water. The standard solution of ZLT in water showed two absorption maxima, one at 243.5 nm and another at 338.0 nm. The drug obeyed Beer-Lambert's law in the concentration range [18].

Zaltoprofen is a non-steroidal anti-inflammatory drug (NSAID) belonging to the propionic acid class. It has strong inhibitory effects on acute and chronic inflammation. Although zaltoprofen is well tolerated orally compared to other NSAIDs, it has to be administered in three to four doses per day and was associated with ulcerogenicity,bellyache and indigestion. This makes administration of zaltoprofen unsuitable for patients with gastric ulcer and is also associated with drug interactions. Therefore, it is important to develop an alternative dosage form which is easier to administer and avoids first-pass metabolism. The transdermal route meets all the above advantages. In this study, zaltoprofen gels were prepared using carbomer with mixture solution of polyethylene glycol (PEG) 400, Tween 80 and (2-hydroxypropyl)-βcyclodextrin (HPCD) (called as T2), subsequently oleic acid as a penetration enhancer was added. Zaltoprofen gel containing T2 and oleic acid could promote the percutaneous absorption of zaltoprofen and increase AUC by 183% compared to zaltoprofen gel without T2 and oleic acid. Also, there was a finding zaltoprofen gel containing T2 and oleic acid did not cause dermal irritations in an experimental animal. A Simple, rapid, selective and sensitive HPLC method was developed and validated for the determination of zaltoprofen from human plasma. The drug was extracted with ethyl acetate. Zaltoprofen was measured in plasma using a validated a HPLC method with UV detector at 254nm chromatographic peaks were separated on 5µm intensil,C18 column (4.6 x 250 mm x 5µm) using 40: 60 v/v Phosphate buffer pH3, Acetonitrile as mobile phase at a flow rate of 1 ml/min. The chromatograms showed good resolution and no interference from plasma. The retention time of zaltoprofen and internal standard (Nevirapine) were approximately 4.0±0.05 min and 10.7±0.03 min respectively. The mean recovery from human plasma was found to be above 50%. The method was linear over the concentration range of 0.15 to 20µg/ml with coefficient of correlation (r2) 0.9983. Both intraday and interday accuracy and precision data showed good reproducibility. This method was successfully applied to pharmacokinetics studies. Zaltoprofen is a non-steroidal anti-inflammatory drug (NSAID) belonging to the propionic acid class. It has strong inhibitory effects on acute and chronic inflammation. Although zaltoprofen is well tolerated orally compared to other NSAIDs, it has to be administered in three to four doses per day and was associated with ulcerogenicity, bellyache and indigestion. This makes administration of zaltoprofen unsuitable for patients with gastric ulcer and is also associated with drug interactions. Therefore, it is important to develop an alternative dosage form which is easier to administer and avoids first-pass metabolism. The transdermal route meets all the above advantages. In this study, zaltoprofen gels were prepared using carbomer with mixture solution of polyethylene glycol (PEG) 400, Tween 80 and (2- hydroxypropyl)-β-cyclodextrin (HPCD) (called as T2), subsequently oleic acid as a penetration enhancer was added. Zaltoprofen gel containing T2 and oleic acid could promote the percutaneous absorption of zaltoprofen and increase AUC by 183% compared to zaltoprofen gel without T2 and oleic acid. Also, there was a finding zaltoprofen gel containing T2 and oleic acid did not cause dermal irritations in an experimental animal [19].

A simple reversed-phase chiral HPLC method has been developed and validated for direct separation of the enantiomers of zaltoprofen. Separation of the enantiomers was tested on numerous commercial chiral HPLC columns. Separation was best (resolution, RS= 3) on a Chiralcel OJ-RH stationary phase. Typical retention times of the S and R enantiomers were approximately 14 and 16 min, respectively. Mobile phase composition was systematically studied to find the optimum chromatographic conditions. Validation of the method under [20]. The objective of this study was to compare the pharmacokinetic parameters of zaltoprofen and those of its sodium salt in rats. Zaltoprofen, a potent non-steroidal anti-inflammatory agent, was virtually insoluble in water, but its sodium salt had excellent water solubility. To investigate the effect of aqueous solubility differences upon their pharmacokinetic parameters, minicapsules containing the drug powders were administrated orally to rats, and blood samples were taken via the common carotid artery. A column-switching high-performance liquid chromatographic analytical procedure was developed and validated for the quantitation of zaltoprofen in rat plasma samples. Our study demonstrated that the time required to reach maximum plasma concentration (Tmax) of zaltoprofen sodium was significantly reduced and its maximum plasma concentration (Cmax) was increased 1.5-fold, relative to the values for zaltoprofen. It is anticipated that the sodium salt of zaltoprofen will allow the rapid onset of the drug's action in the treatment of inflammatory diseases [21].

A particular, easy, and precise reverse phase liquid chromatographic technique was developed for the determination of Zaltoprofen in human plasma. The ODS C18 (250mm x 4.6mm, 5µm) column was utilized for determination. The mobile phase contains buffer and acetonitrile (55:45 v/v). The rate of flow was 1.0 ml/min. The volume of infused sample was 10 µl. The column was kept at a temperature of ~30°C and equilibrated for no less than 30 min, prior to injection of the solutions. The detection wavelength was set at 331 nm. The linearity experiment was performed for Zaltoprofen in the

range of 0.15 to 20 µg/ml. The observed recovery of Zaltoprofen was 98.32 % the suggested technique has been validated and has proved to be very helpful for zaltoprofen determination in human laboratories [22].

A new RP-HPLC method was developed and validated for determination of Zaltoprofen in bulk and tablet dosage form. The estimation was carried out on Enable C18G (250 mm ×4.6 mm, 5 µm) column using Acetonitrile and Methanol in the ratio of 90:10 (v/v) as mobile phase. The flow rate was 1.0 ml/min and the effluent was monitored by UV detector at 331 nm. The retention time was 3.639 min and linearity was observed in the concentration range of 5-50 µg/ml. The percentage recovery was in good agreement with the labelled amount in the pharmaceutical formulations and the method was simple, precise and accurate for the determination of Zaltoprofen in bulk and pharmaceutical formulations [23]. A particular, easy, and precise reverse phase liquid chromatographic technique was developed for the determination of Zaltoprofen in human plasma. The ODS C18 (250mm x 4.6mm, 5µm) column was utilized for determination. The mobile phase contains buffer and acetonitrile (55:45 v/v). The rate of flow was 1.0 ml/min. The volume of infused sample was 10 µl. The column was kept at a temperature of ~30°C and equilibrated for no less than 30 min, prior to injection of the solutions. The detection wavelength was set at 331 nm. The linearity experiment was performed for Zaltoprofen in the range of 0.15 to 20 µg/ml. The observed recovery of Zaltoprofen was 98.32 %. The suggested technique has been validated and has proved to be very helpful for zaltoprofen determination in human plasma [24].

2.4. UV Methods

This work aimed to investigate the co-grinding effects of β-cyclodextrin (β-CD) and cucurbituril (CB [7]) on crystalline zaltoprofen (ZPF) in tablet formulation. Crystalline ZPF was prepared through anti-solvent recrystallization and fully analyzed through single-crystal X-ray diffraction. Co-ground dispersions and mono-ground ZPF were prepared using a ball grinding process. Results revealed that mono-ground ZPF slightly affected the solid state, solubility, and dissolution of crystalline ZPF. Coground dispersions exhibited completely amorphous states and elicited a significant reinforcing effect on drug solubility. UV-vis spectroscopy, XRPD, FT-IR, DSC, ssNMR, and molecular docking demonstrated the interactions in the amorphous product. Hardness tests on blank tablets with different β-CD and CB [7] contents suggested the addition of β-CD or CB [7] could enhance the compressibility of the powder mixture. Disintegration tests showed that CB [7] could efficiently shorten the disintegrating time. Dissolution tests indicated that β-CD and CB [7] could accelerate the drug dissolution rate via different mechanisms. Specifically, CB [7] could accelerate the dissolution rate by improving disintegration and β-CD showed a distinct advantage in solubility enhancement. Based on the comparative study on βCD and CB [7] for tablet formulation combined with co-grinding, we found that CB [7] could be considered a promising drug delivery, which acted as a disintegrant [25].

A simple, rapid, precise, and economical spectrophotometric method has been developed for quantitative analysis of zaltoprofen (ZLT) in pharmaceutical formulations. A mixture of methanol and water was used as a solvent. Initial stock solution of ZLT was prepared in methanol and subsequent dilution was done in water. The standard solution of ZLT in water showed two absorption maxima, one at 243.5 nm and another at 338.0 nm. The drug obeyed Beer–Lambert's law in the concentration range of 1–40 µg/mL with regression 0.9999 at 243.5 nm and 5–100 µg/mL with regression 0.9999 at 338.0 nm. The overall % recovery was found to be 99.53% and 99.77% at 243.5 nm and 338.0 nm, respectively, which reflect that the method is free from interference of the impurities and other additives used in tablet formulation. Relative standard deviations of absorbance from six measurements were always less than 2%. The results of analysis have been validated as per ICH guidelines. Both the wavelengths can be adopted in routine analysis of ZLT in tablet dosage form. ICH guidelines, UV Spectrophotometric, validation, zaltoprofen [26].

Two methods for simultaneous estimation of Pracetamol and Zaltoprofen in combined tablet dosage form have been developed. The first UV spectrophotometric method was a determination using the simultaneous equation method at 245 nm and 227 nm. The second UV spectrophotometric method is the Q – analysis (absorption ratio) method, which involves the formation of absorbance equation at 237.5 nm (isobestic point) and at 227 nm the maximum absorption of Zaltoprofen. The linearity ranges for Paracetamol and Zaltoprofen were 2 – 18 µg/ml and 2 – 18 µg/ml respectively. The accuracy of the methods was assessed by recovery studies was found to be 100.02 ± 0.467 and 99.87 ± 0.532 for simultaneous equation method and 99.82 ± 0.483 and 99.84 ± 0.512 for Q analysis (absorption ratio) method for Paracetamol and Zaltoprofen respectively. These methods are simple, accurate and rapid; those require no preliminary separation and can therefore be used for routine analysis of both drugs in quality control laboratories [27].

2.5. Hydrotropy Methods

In the present investigation, mixed-solvency approach has been applied for the enhancement of aqueous solubility of a poorly water- soluble drug, zaltoprofen (selected as a model drug), by making blends (keeping total concentrations 40% w/v, constant) of selected water-soluble substances from among the hydrotropes (urea, sodium benzoate, sodium

citrate, nicotinamide); water-soluble solids (PEG-4000, PEG-6000); and co-solvents (propylene glycol, glycerine, PEG-200, PEG-400, PEG-600). Aqueous solubility of drug in case of selected blends (12 blends) ranged from 9.091 ± 0.011 mg/ml43.055 ± 0.14 mg/ml (as compared to the solubility in distilled water 0.072 ± 0.012 mg/ml). The enhancement in the solubility of drug in a mixed solvent containing 10% sodium citrate, 5% sodium benzoate and 25 % S cosolvent (25% S cosolvent contains PEG200, PEG 400, PEG600, Glycerine and Propylene glycol) was more than 600 fold. This proved a synergistic enhancement in solubility of a poorly water-soluble drug due to mixed cosolvent effect. Each solubilized product was characterized by ultraviolet and infrared techniques. Various properties of solution such as pH, viscosity, specific gravity and surface tension were studied. The developed formulation was studied for physical and chemical stability. This mixed solvency shall prove definitely a boon for pharmaceutical industries for the development of dosage form of poorly water soluble drugs [28].

In present work mixed solvency concept was used for solubility enhancement of poorly water soluble drug. Aqueous blends of hydrotropes, cosolvents and water soluble solids were used as solvent for poorly water soluble model drug zaltoprofen. In mixing solvency above additives are mixed in different ratio and their aqueous solution served as solvent for water insoluble drug. These solvent systems have extreme potential of increasing solubility of poorly water soluble drugs. In this research work standard curve of drug in different individual aqueous solution of above mentioned type of substances as well as in their blend were plotted and from the curve, solubility of drug in that solvent system is estimated using excess solute addition method. The results obtained shows that solubility of drug in mixed blend is more as compared to their individual solvent systems [29] .

Solubilisation of poorly soluble drugs is encountered as a challenge in screening studies of new chemical entities as well as its formulation development is obstacle. A number of methodologies can be adapted to improve solubility of poor water soluble drug and its bioavailability. Hydrotropes possess the ability to increase the solubility of sparingly soluble and poorly soluble drugs in water. It is a molecular phenomenon, adding a second solute (i.e. hydrotrope) helps to increase the aqueous solubility of poorly soluble drug. The presence of a excess quantity of one solute enhances the solubility of another solute. Various organic solvents are used for the development of analytical methods for poorly water soluble drugs. The major drawback of such solvents is cost, toxicity and environmental hazards. To overcome these issues less costly hydrotropic agents have gain wide application for the development of analytical methods for routine analysis of marketed dosage form and developed dosage forms. The mixed hydrotropy approach suggests the minimum amount of the hydrotropic agents as a blend of two or more agents. Such blends results in lesser quantity as that of single hydrotropic agents. Similarly the hydrotropic agents are now days widely used to develop dosage forms as solid dispersion, mouth dissolving tablets, injections to improve therapeutic effectiveness and bioavailability for poorly water solubility [30]. Poor water solubility and slow dissolution rate are issues for the majority of upcoming and existing biologically active compounds. Zaltoprofen is a novel non–steroidal antiinflammatory class of drug, but problem associated with is the poor solubility in biological fluids. Zaltoprofen is BCS Class-II having low solubility and high permeability. The purpose of the present investigation was to increase the solubility and dissolution rate of Zaltoprofen by the preparation of Nano suspension by nanoprecipitation technique. Prepared Nano suspension was evaluated for its particle size and in-vitro dissolution study and characterized by differential scanning calorimetry and scanning electron microscopy. The optimized formulation showed an average particle size (237 nm) and zeta potential (-21.5 mV). The rate of dissolution of the optimized Nano suspension was enhanced (89 % in 50 min) relative to micronized suspension of Zaltoprofen (30 % in 50 min), mainly due to the formulation of Nano sized particles. Stability study revealed that Nano suspension was more stable at room and refrigerator condition with no significant change in particle size distribution. These results indicate that the Zaltoprofen loaded nanosuspension significantly improved in – vitro dissolution rate and thus possibly enhance fast onset of therapeutic drug effect [31].

2.6. UPLC methods

The aim of this study was to compare UPLC-MS/MS and HPLC-UV methods for the determination of zaltoprofen in human plasma. In HPLC-UV, zaltoprofen was separated using 1% (v/v) aqueous acetic acid (pH 2.2) and acetonitrile (ACN) mixed with methanol as a mobile phase (1% aqueous acetic acid/ACN/methanol, 36/60/4, v/v/v) by isocratic elution at a flow rate of 1.0 mL/min with a Zorbax ODS column (250 × 4.6 mm, 5 μm). Quantification of zaltoprofen was performed8 using a UV detector (330 nm). In UPLCMS/MS, zaltoprofen was separated using 0.1% (v/v) aqueous formic acid containing 0.5% (v/v) of 10 mM ammonium formate (pH 3.2) buffer (pH 2.3) and ACN as a mobile phase by gradient elution at a flow rate of 0.3 mL/min with a KINETEX core–shell C18 column (50 × 2.1 mm, 1.7 μm). Quantitation of UPLC-MS/MS was performed on a triple quadrupole mass spectrometer using electrospray ionization, operating in the multiple reaction monitoring positive ion mode. The calibration ranges for zaltoprofen in HPLC-UV and UPLC-MS/MS were 0.05–20 and 0.005–10 μg/mL, respectively. The developed methods satisfied the international guidance criteria and can be successfully applied to pharmacokinetic study of an 80 mg zaltoprofen tablet after oral administration to humans [32].

3. Conclusion

The collected methods are various analytical methods for the estimation of zaltoprofen. This is a NSAID drug. A few DSC, FTIR, HPLC, UV, Hydrotropic, UPLC methods have been for estimation zaltoprofen. UV and other analytical methods have been reported for the literature of estimation of zaltoprofen.

Compliance with ethical standards

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Disclosure of conflict of interest

No conflict of interest.

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