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Assessing solubility of meloxicam in age-specific gastric and intestinal media relevant to adults and pediatric populations: implications for optimizing dosing in patients for postoperative pain

Sabreen Abu Omar[1], Rahma Nairat[1], Sara Khzimia[1], Iyad Maqboul[1,2], Mohammad Jaber[1,2] and Ramzi Shawahna[3,4*]

Abstract

Background Oral dose formulations must be soluble in gastrointestinal fluids for systemic absorption. The solubility of meloxicam was determined in 16 different age-specific simulated gastric and intestinal media that mirrored the microenvironments in pediatrics and adults.

Methods The solubility of meloxicam in the 16 different age-specific simulated gastric and intestinal biorelevant media was assessed using the standard US pharmacopeial method. The molecular descriptors of meloxicam were used to assess its intestinal permeability.

Results Meloxicam exhibited low solubility in the age-specific simulated gastric media for fasted and fed states and in pediatrics and adults. Similarly, meloxicam exhibited low solubility in the age-specific simulated media that mirrored neonates fed cow milk-based formula. On the other hand, meloxicam exhibited high solubility in the rest of the age-specific pediatric and adult intestinal media that simulated the fasted and fed states. The pediatric-to-adult solubility ratios were outside the 80–125% range in 7 (58.3%) and was borderline in 1 (8.3%) out of the 12 calculated ratios. These findings indicated that the solubility of meloxicam showed clinically significant differences in 8 (66.7%) of the compared media.

Conclusion Meloxicam exhibited low solubility in the age-specific simulated gastric media and high solubility in the simulated intestinal media for adults and pediatrics. Moreover, the pediatric-to-adult solubility ratios may have clinically significant implications. These differences can be translated into a higher likelihood of failing to demonstrate bioequivalence of different formulations containing meloxicam and variabilities in the performance of these formulations.

Keywords Meloxicam, Solubility, Permeability, Absorption, Bioavailability, Biopharmaceutical classification system, Drug development

*Correspondence:
Ramzi Shawahna
ramzi_shawahna@hotmail.com; ramzi.shawahna@najah.edu

Full list of author information is available at the end of the article

Background

Following surgical operations, postoperative pain is an expected ultimate consequence in the majority (>80%) of surgical patients [1]. Of the surgical patients, about 75% often report moderately to highly severe pain [1]. Postoperative pain deteriorates the quality of life of the affected patients, increases hospitalization, and costs of the overall treatment [2].

Although opioid analgesics can effectively control postoperative pain, these drugs can cause significant adverse effects including nausea/vomiting, ileus, respiratory depression, and dependence/addiction [3]. Currently, the American Society of Anesthesiologists guidelines recommend the use of a continuous regimen of non-steroidal anti-inflammatory drugs (NSAIDs) as a first-line treatment of postoperative pain [4, 5].

Meloxicam is an NSAID that can be used to control mild/moderate pains including postoperative pain [6]. In addition, meloxicam can be used to manage symptoms of juvenile rheumatoid arthritis and osteoarthritis in pediatric patients [7, 8]. Compared to COX-1, meloxicam has greater activity against COX-2 and therefore has reduced renal side effects compared to other NSAIDs [9, 10].

For orally administered drugs, solubility within the gastrointestinal tract is essential for systemic absorption. Previous studies have reported quantitative and qualitative differences in the gastrointestinal fluids of adults and different pediatric populations [11, 12]. Therefore, assessing the solubility of medications in gastrointestinal media may reveal potential differences in the performance of dosage forms and systemic bioavailability of medications.

The development of age-specific oral dosage forms for pediatric populations has been encouraged for several reasons including improving dosing accuracy, efficacy, compliance, and therapeutic outcomes of pediatric patients [11–13]. It is well-established that pediatric patients have unique physiologic characteristics when compared to adults [14]. These unique physiologic characteristics include differences in the pharmacokinetic parameters, including absorption, distribution, metabolism, and excretion (ADME) of drugs. It is noteworthy to mention that the children are a large group and include subpopulations such as neonates (birth to 27 days), infants (1 month to 12 months), toddlers (1 year to 3 years), preschool children (3 years to 5 years), school-aged children (6 years to 12 years), and adolescents (13 years to 18 years). Therefore, developing age-specific oral dosage forms allows tailoring the dosage forms to the pharmacokinetic variabilities in pediatric patients [11, 12]. This should improve the safety and efficacy of drugs in pediatric patients. Moreover, developing age-specific oral dosage forms also allows more precise dosing based on the weight and age of the pediatric patients. This should help avoid under- and over-dosing and improve outcomes of pediatric patients. In addition, children-friendly oral dosage forms can be developed as easy to administer with improved palatability. This should improve compliance to taking the drugs as prescribed. Moreover, regulatory agencies require that pharmaceutical manufacturers conduct studies in pediatric patients [11–13, 15]. Therefore, pharmaceutical manufacturers are encouraged to develop children-friendly dosage forms.

So far, the solubility values of meloxicam in the different age-specific biorelevant gastric and intestinal media that simulate the in vivo microenvironments in adults and pediatric populations were not assessed before. Additionally, variabilities in the solubility of meloxicam between adults and pediatrics were not examined. Therefore, the solubility of meloxicam was determined in 16 different age-specific biorelevant media that simulate the fasted and fed-states in vivo gastric and intestinal microenvironments in pediatrics and adults. The findings of this study might help predict the performance of orally administered dosage forms in adults and pediatrics.

Methods

Design and materials

This investigation was conducted in a laboratory setting. The following materials were used: meloxicam, egg lecithin, acetic acid, maleic acid, pepsin, acetonitrile, glyceryl monooleate, sodium hydroxide, sodium chloride, sodium taurocholate, sodium oleate, sodium hydroxide, hydrochloric acid, sodium acetate, methanol, dialysis tubes, ultra-pure (Milli-Q) water, infant formulas (1: Cow's milk-based formula: S-26® One Infant Formula, 0–6 months, Wyeth Nutrition, 2: Soy-based formula: Similac® Isomil 1, 0–6 months, Abbott, and 3) phenylalanine-free formula: Phenyl-Free® 1, Infant-Toddler, Mead Johnson Nutrition), and Eppendorf tubes.

Preparation of the age-specific gastric and intestinal biorelevant media

A total of 16 different age-specific biorelevant media were prepared as previously described and as shown in Supplementary Table S1 [11, 12]. The media were prepared to mimic the in vivo microenvironments observed in the stomach and upper gastrointestinal system during periods of fasting and feeding in both adults and pediatrics. The composition of the biorelevant media accounted for the intricate physiological and developmental differences between adults and pediatric subpopulations [11, 12, 16]. Differences in feed type, bile salt to lecithin ratios, pH range, pepsin concentrations, buffering capability, osmolality, and fat digestion products were considered [16, 17]. The pH of the biorelevant media was adjusted to the specified levels using sodium bicarbonate (1 M) or hydrochloric acid (1 M) as needed.

Pediatric fed-condition media were prepared using three distinct formulas: (A) a cow's milk-based formula, (B) a soy-based formula, and (C) a phenylalanine-free formula [11, 12]. Cow's milk-based formulas are the most frequently used nutritional options for infants and toddlers who are unable to be exclusively breastfed [18–20]. Cow's milk-based formulas closely resemble the nutritional profile of human breast milk and serve as a benchmark or reference for feeding in pediatric research [18]. Using a cow's milk-based formula for the preparation of pediatric fed-condition media should have facilitated the simulation of feeding conditions for the majority of infants and toddlers on standard formula diets. On the other hand, soy-based formulas are often used as feeding options for infants and toddlers who cannot tolerate cow's milk-based infant formulas because of lactose intolerance or other food allergies [21]. Additionally, phenylalanine-free formulas are used for infants and toddlers with phenylketonuria who cannot tolerate formulas containing phenylalanine [22]. Using soy-based formula and phenylalanine-free formula should have facilitated the simulation of feeding conditions in infants and toddlers with lactose intolerance, allergy, and phenylketonuria. The use of these three types of formulas should have ensured the representation of the different pediatric subpopulations with diverse nutritional needs.

Solubility assessment

Meloxicam was added in excessive amounts to each of the 16 age-specific simulated biorelevant media enough to completely saturate 10 mL of the borosilicate glass tubes. After that, the borosilicate glass tubes were wrapped with parafilm and put in a water bath that was shaking. To guarantee equilibrium solubility, tubes were then shaken for 48 h at a dwell temperature of 37 ± 0.5 °C in a water bath that was programmed to shake at 200 strokes per min. Each sample was centrifuged for 15 min at 8000 rpm before analysis. The centrifuge's temperature was set at 37 ± 0.5 °C. Through 0.45 m regenerated cellulose filters, the supernatants were aspirated. Before analysis, methanol was used to dilute each filtrate in a ratio of 1:1.

Solubility studies in media containing milk and formula

The presence of proteins in the fed-conditions media would make it difficult for these samples to pass through 0.45 m filters. To avoid the requirement for direct filtration, the solubility values of meloxicam in the media that simulated the fed states were assessed using equilibrium dialysis. Five mL aliquots of freshly made medium with a molecular weight limit of 12,000–14,000 Daltons were put in dialysis membranes. Twenty milliliters of the specific medium that contained either milk or formula were added to each centrifuge tube. The centrifuge tubes were then sealed and positioned in a water bath and were shaken at 200 times per min at a temperature of 37 ± 0.5 °C. The equilibrium solubility of meloxicam was tested in a pilot study after dwell times of 72 and 96 h.

Quantification of meloxicam in the samples

Concentrations of meloxicam in the filtrate were quantified using an HPLC-UV method as described in the US Pharmacopeia [23]. In this study, an Agilent Technologies 1200 series HPLC system (Santa Clara, CA) was used.

The test solution was prepared by dissolving 40 mg of meloxicam in a combination of 5 mL of methanol and 0.3 mL of 1 M sodium hydroxide. The solution was then diluted to 20 mL using methanol. The reference solution A was prepared by taking 2 mL of the test solution and diluting them with methanol to a final volume of 100 mL. After that, 5 mL of solution A were taken and diluted with methanol to a final volume of 100 mL. On the other hand, the reference solution B was prepared by dissolving 2 mg of meloxicam, 2 mg of meloxicam impurity A certified reference standard (CRS), 2 mg of meloxicam impurity B CRS, 2 mg of meloxicam impurity C CRS, and 2 mg of meloxicam impurity D CRS in a mixture of 5 mL of methanol and 0.3 mL of 1 M sodium hydroxide. The resulting solution was then diluted to a final volume of 25 mL with methanol. Before injection into the HPLC system, the solutions were passed through a 0.45 µm filter. A stainless-steel chromatography column (15 cm x 4.6 mm, filled with end-capped octadecylsilyl silica gel 5 µm particles) was used. The mobile phase A consisted of a solution containing 1 g/L of dihydrogen phosphate. The pH was adjusted (to pH 6) using a 1 M sodium hydroxide solution. The mobile phase B consisted of methanol. The final mobile phase was prepared by filtering and degassing a mixture of solution A and solution B at a ratio (63:37). The mobile phase was run at a flow rate of 1 mL/min. The temperature was set at 45 °C. Meloxicam was detected using the UV spectrophotometric method at 260 nm and 350 nm.

The physicochemical properties and pharmacokinetic parameters of meloxicam

The DrugBank database was used to obtain the physicochemical properties and the molecular descriptors of meloxicam, such as its empirically measured water solubility values and the n-octanol/water partition coefficient (LogP). The computational n-octanol/water partition coefficient (cLogP) was computed using ALOGPS v.2.1 (VCCLAB, Germany) and ChemAxon (ChemAxon, Hungary). Metoprolol, which served as a baseline for high or low paracellular intestinal permeability, was included in a correlation plot between LogP and cLogP for a group of 36 pharmacological compounds. Meloxicam's probable

bioavailability and polar surface area were also predicted by ChemAxon.

Data analysis

The data were entered into the GraphPad Prism for Windows v.6.0 software. The solubility ratios between pediatric and adult media were calculated and compared. In in vivo bioequivalence studies, products are considered bioequivalent when the 90% confidence interval of the ratio of the maximal drug blood or plasma concentration (C_{max}) and area under the blood or plasma concentration-time curve (AUC) of the compared products are within the range of 80% and 125% [24]. Similarly, a difference of more than 20% between the solubility of meloxicam in pediatric and adult media was considered to have clinically significant implications.

Results

Solubility of meloxicam

Solubility values of meloxicam in age-specific gastric and intestinal media are shown in Fig. 1.

Solubility values of meloxicam in the age-specific simulated fasted- and fed-state gastric media

Meloxicam exhibited low solubility (from 0.21 to 0.50 mg/100 mL) in the different age-specific simulated fasted-state gastric media as shown in Fig. 1A. On the other hand, meloxicam exhibited significantly higher solubility (7.4 to 13.0 mg/100 mL) in the different age-specific fasted-state intestinal media as shown in Fig. 1B.

Solubility values of meloxicam in age-specific simulated fasted- and fed-state intestinal media

Similar to the solubility in the different age-specific simulated fasted-state gastric media, meloxicam also exhibited low solubility (from 0.22 to 0.46 mg/100 mL) in the different age-specific simulated fed-state gastric media as shown in Fig. 1C. Contrarily, meloxicam exhibited significantly higher solubility (4.9 to 10.5 mg/100 mL) in the different age-specific fed-state intestinal media as shown in Fig. 1D.

In neonates and infants, meloxicam exhibited comparatively higher solubility compared to adults. Similarly, increasing the concentration of bile salts to 150% of the adult values further increased the solubility of meloxicam in the pediatric simulated fasted-state intestinal media.

There was an apparent variability in the solubility of meloxicam in the simulated fed-state gastric and intestinal media specific for adults and pediatrics.

Age-specific biopharmaceutical classification system solubility class of meloxicam

Using the principles of the BCS, active pharmaceutical ingredients are classified as high-solubility drugs when their D_0 values in the relevant media are ≤1. On the other hand, active pharmaceutical ingredients are classified as low-solubility drugs when their D_0 values in the relevant media are >1. The data and equations used in the calculation of D_0 values are shown in Supplementary Table S2.

The D_0 values of meloxicam in the different age-specific simulated gastric and intestinal media in the fasted and fed states are shown in Table 1. These D_0 values indicated that meloxicam exhibited low solubility in the different age-specific pediatric and adult simulated gastric media in the fasted and fed states. Similarly, meloxicam exhibited low solubility in the intestinal media representative of neonates fed milk-based formula. On the other hand, meloxicam exhibited high solubility in the rest of the age-specific pediatric and adult simulated media in the fasted and fed states.

Pediatric to adult solubility ratios of meloxicam

The pediatric-to-adult solubility ratios of meloxicam are shown in Fig. 2. When the solubility values of meloxicam in the age-specific simulated pediatric media were compared to those in the similar adult media, the solubility ratios were outside the 80-125% range in 7 (58.3%) and was borderline in 1 (8.3%) out of the 12 calculated ratios. These findings indicated that the solubility of meloxicam may have clinically significant implications in 8 (66.7%) of the compared media.

Permeability class

Meloxicam had an experimentally determined logP of 0.1. ALOGPS and ChemAxon programs predicted logP values for meloxicam of 2.28 and 1.6, respectively. Moreover, ChemAxon predicted a polar surface area for meloxicam of 99.6 $Å^2$. Compared to the benchmark of low/high intestinal permeability, meloxicam has lower experimentally determined (0.1 vs. 2.15) logP. While ChemAxon predicted a logP value for meloxicam lower than that of metoprolol (1.6 vs. 1.76), ALOGPS predicted a logP value for meloxicam higher than that of metoprolol (2.88 vs. 1.80). The polar surface area predicted for meloxicam was lower than that of metoprolol (99.6 $Å^2$ vs. 50.72 $Å^2$). The molecular descriptors of meloxicam are shown in Table 2.

Additionally, a correlation plot of experimentally determined n-octanol/water partition coefficient (LogP) and predicted (cLogP) values for 36 drugs is shown in Fig. 3.

The bioavailability of meloxicam was previously reported as about 90% [25–27]. The absorption of meloxicam was said to be nearly complete and was unaffected by food. Given these contradictory descriptors, meloxicam could not be conclusively classified as either low or high permeability BCS class.

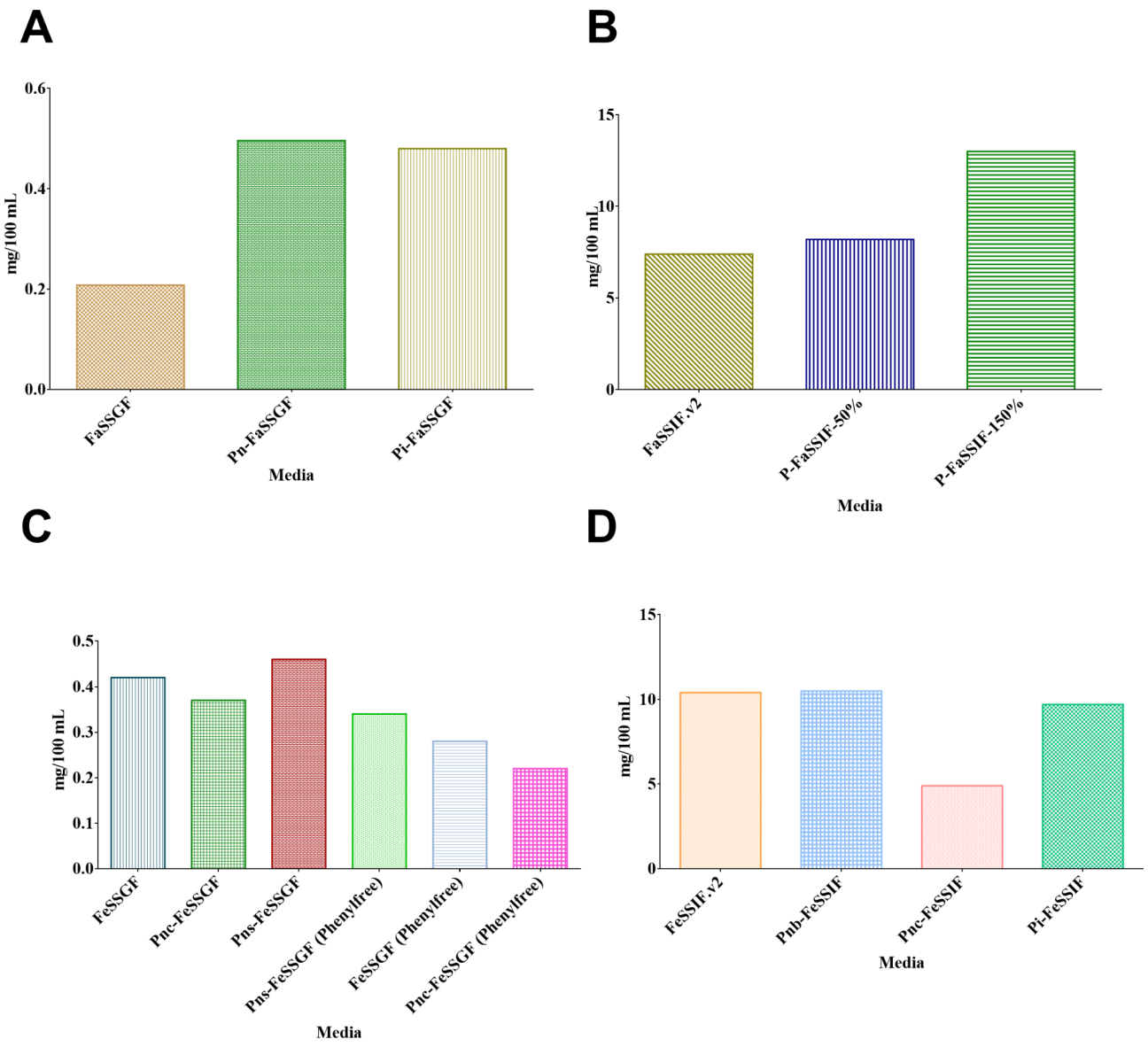

Fig. 1 Solubility values of meloxicam in the simulated **A** fasted-state gastric media, **B** fasted-state intestinal media, **C** fed-state gastric media, and **D** fed-state intestinal media. *FaSSGF* gastric fluid simulating the fasted-state in adults, *Pn-FaSSGF* gastric fluid simulating the fasted-state in neonates (birth to 27 days), *Pi-FaSSGF* gastric fluid simulating the fasted-state in infants (1–12 months), *FeSSGF* intestinal fluid simulating fed-state in adults, *Pnc-FeSSGF* gastric fluid simulating cow's milk-based formula fed-state in neonates (birth to 27 days), *Pns-FeSSGF* gastric fluid simulating soy-based formula fed-state in neonates (birth to 27 days), *FaSSIF.v2* intestinal fluid simulating fasted-state in adults, *P-FaSSIF-50%* intestinal fluid simulating fasted-state in pediatrics when the bile salt levels are 50% (i.e., 1.5 mM) of the adult bile salt levels, *P-FaSSIF-150%* intestinal fluid simulating fasted-state in pediatrics when he bile salt levels are 150% (i.e., 4.5 mM) of the adult bile salt levels, *FeSSIF.v2* intestinal fluid simulating fed-state in adults, *Pnb-FeSSIF* intestinal fluid simulating breastmilk fed-state in neonates (birth to 27 days), *Pnc-FeSSIF* intestinal fluid simulating cow's milk-based formula fed-state in neonates (birth to 27 days), *Pi-FeSSIF* intestinal fluid simulating cow's milk-based formula fed-state in infants (1–12 months), *PF* Phenyl free

Discussion

Many medications are commonly used outside their license or used off-label to treat neonates and children [28, 29]. These uses include when the drug is used for an indication that was not formally approved by the health authorities, used among a population of patients other than the population of patients for whom the drug was approved, used in dosage or regimen that was not formally approved by the health authorities, administered in a route that was not formally approved by the health authorities, combined with other drugs and the combination was not approved by the health authorities, or the drug was administered using a formulation other than the one that was approved by the health authorities. It is noteworthy to mention that the efficacy and safety of off-label and unlicensed drugs are limited. Given the

Table 1 D_0 values of meloxicam in the different age-specific simulated gastric and intestinal media in the fasted and fed states

Dose number (D0)																				
Media	**Age (years)**																			
	Neonate (birth-6 months)	**0.50**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**Adult (≥ 18)**
FaSSGF	31.86	31.86	31.82	31.87	31.83	31.84	31.86	31.87	31.85	31.86	31.98	31.79	31.82	31.82	31.80	31.93	31.90	31.88	31.89	33.65
FeSSGF	15.78	15.78	15.76	15.78	15.76	15.77	15.78	15.78	15.77	15.78	15.84	15.74	15.76	15.76	15.75	15.81	15.80	15.79	15.79	16.67
FaSSIF.v2	**0.90**	**0.90**	**0.89**	**0.90**	**0.89**	**0.89**	**0.90**	**0.90**	**0.90**	**0.90**	**0.90**	**0.89**	**0.89**	**0.89**	**0.89**	**0.90**	**0.90**	**0.90**	**0.90**	**0.95**
FeSSIF.v2	**0.64**	**0.64**	**0.64**	**0.64**	**0.64**	**0.64**	**0.64**	**0.64**	**0.64**	**0.64**	**0.64**	**0.64**	**0.64**	**0.64**	**0.64**	**0.64**	**0.64**	**0.64**	**0.64**	**0.67**
Pn-FaSSGF	13.36	13.36	13.35	13.36	13.35	13.35	13.36	13.36	13.36	13.36	13.41	13.33	13.34	13.34	13.33	13.39	13.38	13.37	13.37	14.11
Pi-FaSSGF	13.81	13.81	13.79	13.81	13.79	13.80	13.80	13.81	13.80	13.80	13.86	13.77	13.79	13.79	13.78	13.83	13.82	13.81	13.82	14.58
Pnc-FeSSGF	17.91	17.91	17.89	17.91	17.89	17.90	17.91	17.92	17.90	17.91	17.98	17.87	17.89	17.89	17.87	17.95	17.93	17.92	17.93	18.92
Pns-FeSSGF	14.41	14.41	14.39	14.41	14.39	14.40	14.40	14.41	14.40	14.40	14.46	14.37	14.39	14.39	14.38	14.44	14.42	14.41	14.42	15.22
P-FaSSIF-50%	**0.81**	**0.81**	**0.81**	**0.81**	**0.81**	**0.81**	**0.81**	**0.81**	**0.81**	**0.81**	**0.81**	**0.81**	**0.81**	**0.81**	**0.81**	**0.81**	**0.81**	**0.81**	**0.81**	**0.85**
P-FaSSIF-150%	**0.51**	**0.51**	**0.51**	**0.51**	**0.51**	**0.51**	**0.51**	**0.51**	**0.51**	**0.51**	**0.51**	**0.51**	**0.51**	**0.51**	**0.51**	**0.51**	**0.51**	**0.51**	**0.51**	**0.54**
Pnb-FeSSIF	**0.63**	**0.63**	**0.63**	**0.63**	**0.63**	**0.63**	**0.63**	**0.63**	**0.63**	**0.63**	**0.63**	**0.63**	**0.63**	**0.63**	**0.63**	**0.63**	**0.63**	**0.63**	**0.63**	**0.67**
Pnc-FeSSIF	1.35	1.35	1.35	1.35	1.35	1.35	1.35	1.35	1.35	1.35	1.36	1.35	1.35	1.35	1.35	1.36	1.35	1.35	1.35	1.43
Pi-FeSSIF	**0.68**	**0.68**	**0.68**	**0.68**	**0.68**	**0.68**	**0.68**	**0.68**	**0.68**	**0.68**	**0.69**	**0.68**	**0.68**	**0.68**	**0.68**	**0.68**	**0.68**	**0.68**	**0.68**	**0.72**
FeSSGF-PF	23.67	23.67	23.64	23.67	23.64	23.65	23.66	23.67	23.66	23.66	23.75	23.61	23.63	23.63	23.62	23.72	23.70	23.68	23.69	25.00
Pnc-FeSSGF-PF	30.13	30.13	30.09	30.13	30.09	30.10	30.12	30.13	30.11	30.12	30.23	30.05	30.08	30.08	30.06	30.18	30.16	30.14	30.15	31.82
Pns-FeSSGF-PF	19.49	19.49	19.47	19.50	19.47	19.48	19.49	19.50	19.48	19.49	19.56	19.45	19.46	19.46	19.45	19.53	19.51	19.50	19.51	20.59

High solubility values are in boldface

FaSSGF gastric fluid simulating the fasted-state in adults, *Pn-FaSSGF* gastric fluid simulating the fasted-state in neonates (birth to 27 days), *Pi-FaSSGF* gastric fluid simulating the fasted-state in infants (1–12 months), *FeSSGF* intestinal fluid simulating fed-state in adults, *Pnc-FeSSGF* gastric fluid simulating cow's milk-based formula fed-state in neonates (birth to 27 days), *Pns-FeSSGF* gastric fluid simulating soy-based formula fed-state in neonates (birth to 27 days), *FaSSIF.v2* intestinal fluid simulating fasted-state in adults, *P-FaSSIF-50%* intestinal fluid simulating fasted-state in pediatrics when the bile salt levels are 50% (i.e., 1.5 mM) of the adult bile salt levels, *P-FaSSIF-150%* intestinal fluid simulating fasted-state in pediatrics when the bile salt levels are 150% (i.e., 4.5 mM) of the adult bile salt levels, *FeSSIF.v2* intestinal fluid simulating fed-state in adults, *Pnb-FeSSIF* intestinal fluid simulating breastmilk fed-state in neonates (birth to 27 days), *Pnc-FeSSIF* intestinal fluid simulating cow's milk-based formula fed-state in neonates (birth to 27 days), *Pi-FeSSIF* intestinal fluid simulating cow's milk-based formula fed-state in infants (1–12 months), *PF* Phenyl free

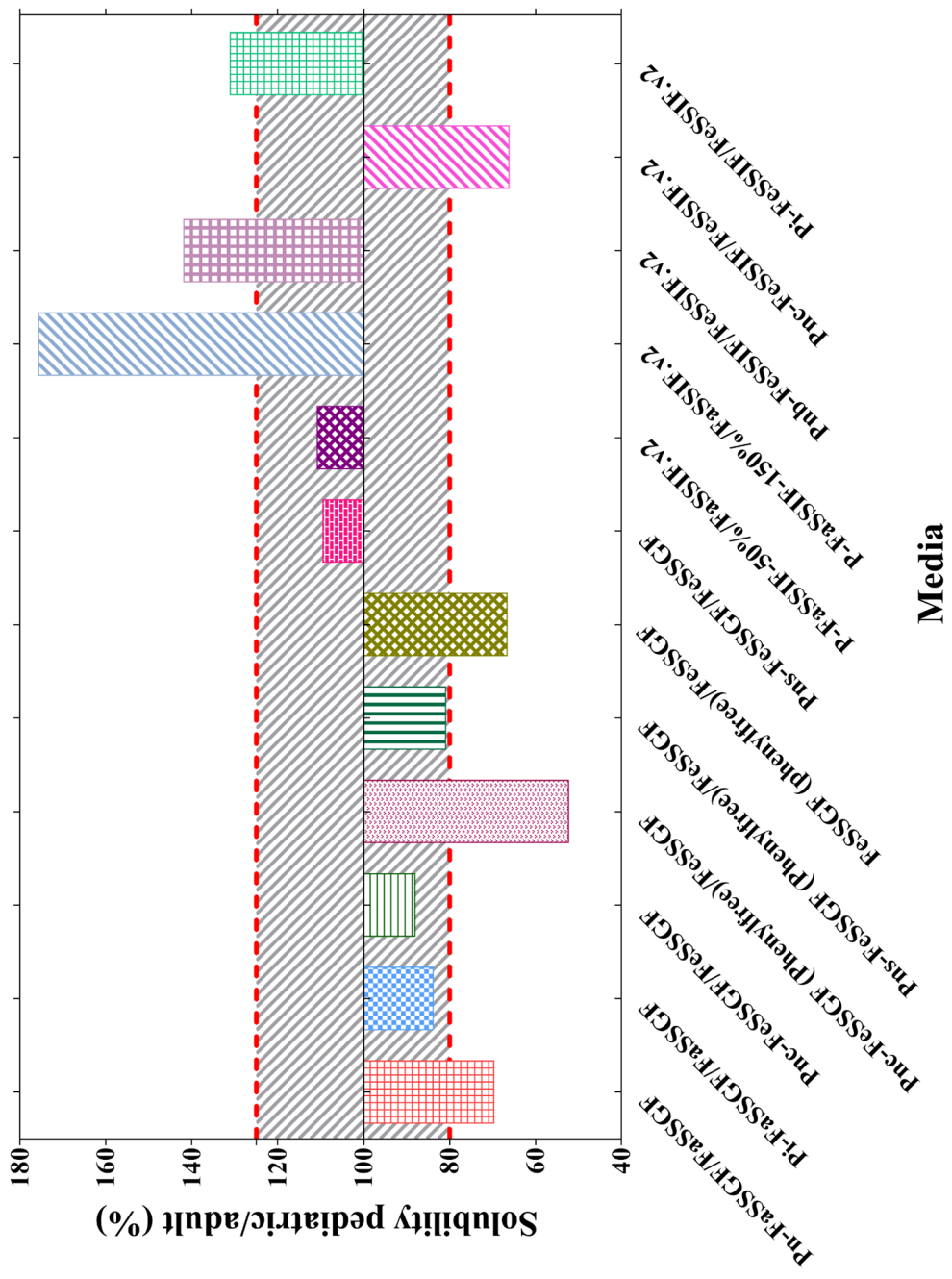

Fig. 2 Age-specific pediatric to adult solubility ratios of meloxicam. *FaSSGF* gastric fluid simulating the fasted-state in adults, *Pn-FaSSGF* gastric fluid simulating the fasted-state in neonates (birth to 27 days), *Pi-FaSSGF* gastric fluid simulating the fasted-state in infants (1–12 months), *FeSSGF* intestinal fluid simulating fed-state in adults, *Pnc-FeSSGF* gastric fluid simulating cow's milk-based formula fed-state in neonates (birth to 27 days), *Pns-FeSSGF* gastric fluid simulating soy-based formula fed-state in neonates (birth to 27 days), *FaSSIF.v2* intestinal fluid simulating fasted-state in adults, *P-FaSSIF-50%* intestinal fluid simulating fasted-state in pediatrics when the bile salt levels are 50% (i.e., 1.5 mM) of the adult bile salt levels, *P-FaSSIF- 150%* intestinal fluid simulating fasted-state in pediatrics when the bile salt levels are 150% (i.e., 4.5 mM) of the adult bile salt levels, *FeSSIF.v2* intestinal fluid simulating fed-state in adults, *Pnb-FeSSIF* intestinal fluid simulating breastmilk fed-state in neonates (birth to 27 days), *Pnc-FeSSIF* intestinal fluid simulating cow's milk-based formula fed-state in neonates (birth to 27 days), *Pi-FeSSIF* intestinal fluid simulating cow's milk-based formula fed-state in infants (1–12 months), *PF* Phenyl free

Table 2 Molecular descriptors of meloxicam

Descriptor	Value
Experimentally determined LogP	0.1
Experimentally determined pKa	4.08
cLogP predicted by ALOGPS	2.28
cLogP predicted by ChemAxon	1.6
pKa (Strongest Acidic) predicted by ChemAxon	4.47
pKa (Strongest Basic) predicted by ChemAxon	0.47
Polar Surface Area predicted by ChemAxon	99.6 $Å^2$
Bioavailability predicted by ChemAxon	100%

vulnerability of neonates and young children, the use of off-label and unlicensed drugs can jeopardize the health of these fragile patients. Not surprisingly, evaluation of the performance of these formulations in pediatric populations is essential before these formulations can be considered for use in these populations. The solubility of meloxicam in age-specific gastric and intestinal media was not assessed before. In this study, the solubility of meloxicam in 16 age-specific gastric and intestinal media was assessed. In this assessment, the potential effects of the changes in the volume and composition of the gastric and intestinal fluids on the subsequent behaviors of the formulations containing meloxicam were also evaluated. The findings reported in this study are valuable to researchers who are interested in developing formulations containing meloxicam for pediatric patients. Additionally, the findings are also important for pediatricians, surgeons, orthopedic specialists, pharmacologists, pharmacists, and other healthcare providers who care for pediatric patients.

Pediatric patients have long been considered miniature adults. However, this concept was refuted as there are significant quantitative and qualitative differences between the different pediatric and adult populations. Therefore, there have been many calls to adapt the biopharmaceutical classification system and other principles of biopharmaceutics for the different pediatric sub-populations [12, 13, 30]. In this study, the solubility of meloxicam was assessed in different gastric and intestinal media that were adapted to the different pediatric subpopulations. Ideally, human luminal gastric and intestinal fluids

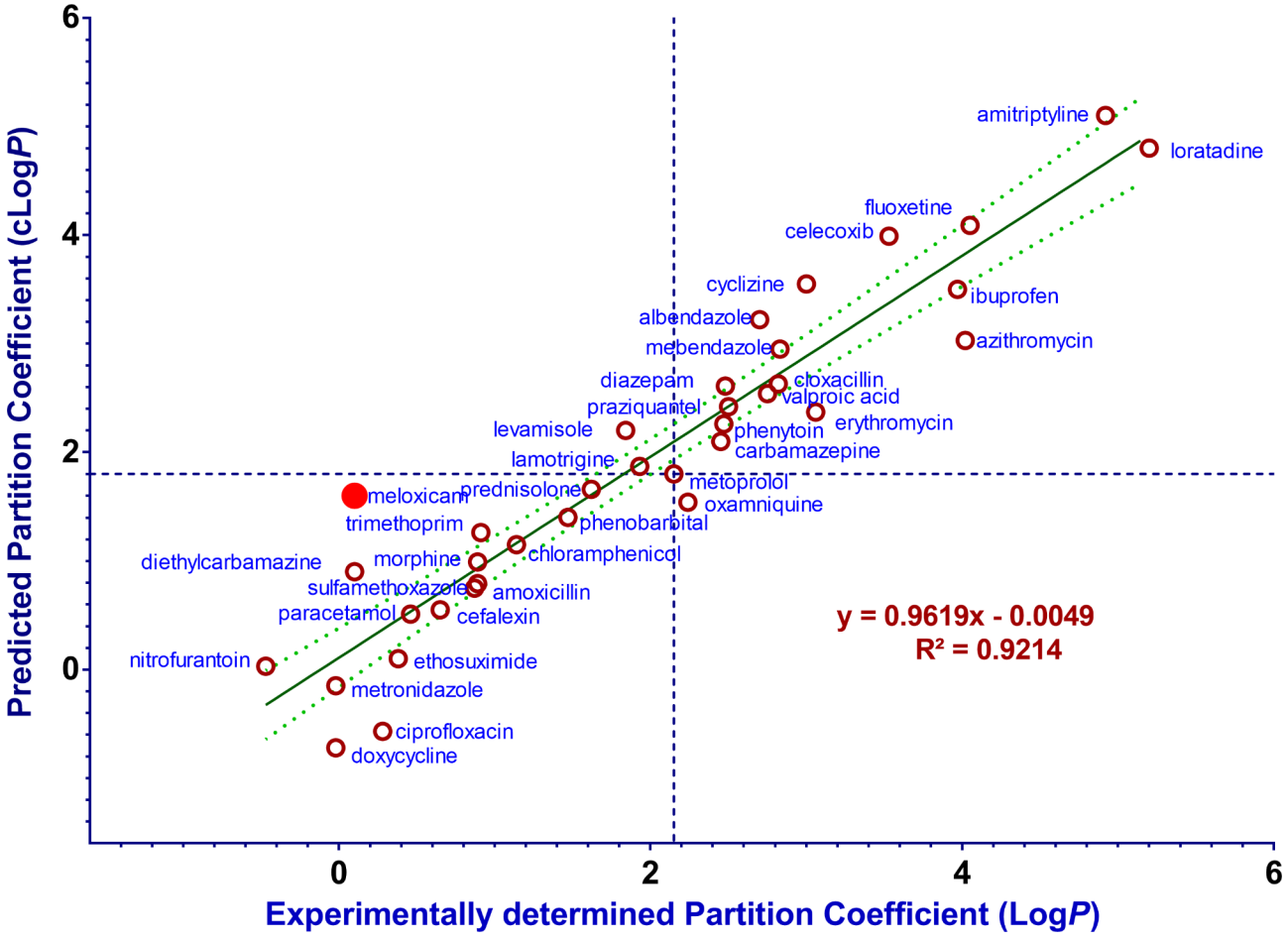

Fig. 3 Correlation plot of experimentally determined n-octanol/water partition coefficient (LogP) and predicted (cLogP) values for 36 drugs. The dotted lines represent the boundaries of the 95% CI and R^2 represents the goodness of fit

could be used to assess the solubility of meloxicam. However, obtaining such luminal fluids can be difficult due to logistic, safety, and ethical concerns [12, 13]. Therefore, the simulated age-specific gastric and intestinal media that were used in this study were suitable alternatives. In these simulated media, the unique intricacies of the gastric and intestinal environments of pediatrics and adults were mirrored [12, 16, 17]. The quantities of constituents including pepsin, byproducts of fat digestion, phospholipids, and bile salts were accounted for [16, 17]. The degree to which these media mirrored the real gastric and intestinal environments was previously assessed [12, 16, 31, 32].

Moreover, the simulated media used in this study also accounted for the feed type including breastmilk in addition to cow milk-based, soy-based, and phenylalanine-free formulas [16, 18, 33]. Therefore, this study accounted for the food effects on the solubility of meloxicam. Although human breastmilk samples could be obtained and used, previous studies have shown that there were significant quantitative and qualitative variabilities in the composition of human breastmilk samples obtained from different lactating women [16, 18, 33].

The findings of this study showed that meloxicam exhibited low solubility in the gastric media and high solubility in the intestinal media. Previous studies have reported that meloxicam exhibited poor aqueous solubility [34–36]. Although meloxicam exhibited low solubility at low pH values, the high solubility observed in the intestinal media at higher pH could explain the nearly complete absorption in the intestine as reported in the previous studies [25–27]. Similarly, the high solubility observed in fasted- and fed-stated simulated media was consistent with the previously reported data on the lack of effects of food on the absorption of meloxicam.

To be classified as high solubility drug based on the current BCS criteria, a drug molecule should exhibit high solubility over a pH range of 1.2–6.8. As meloxicam exhibited low solubility at lower (acidic) pH values, meloxicam can be classified as a low-solubility drug. On the other hand, using the molecular descriptors as compared to metoprolol and the reported bioavailability data, meloxicam cannot be conclusively classified as either a high or low-permeability drug. Therefore, more studies are still needed to assess the absorption kinetics of meloxicam before conclusive permeability classification can be made. Given the currently available data, meloxicam could be BCS class 2 or class 4.

When the solubility values of meloxicam were compared between pediatric and adult sub-populations, the pediatric/adult solubility ratios were outside 80–125% in more than half of the compared media. These findings indicate potentially significant variability in the performance of formulations containing meloxicam in pediatric and adult populations [12, 13, 16, 37]. The findings presented in this study could predict failures in demonstrating the bioequivalence of different formulations containing meloxicam.

Limitations of the study

The findings of this study should be interpreted after considering the following limitations. First, the data were based on in vitro solubility assessments. Therefore, the findings cannot be readily used without the support of in vivo data generated from clinical studies. Future studies should consider using in vivo methods. Second, the approach used in this study does not allow for capturing the complexities of dosage form performances in pediatric subpopulations. Therefore, there is a need for physiologically based pharmacokinetic models that would account for the age-specific differences in the pharmacokinetic parameters in adults and pediatric subpopulations. Third, this study focused mainly on the solubility of meloxicam in age-specific biorelevant media. It is important to note that many other factors including gastric emptying, stability in the gastrointestinal tract, permeability, intestinal transit time, and metabolism can also influence the performance of dosage forms.

Conclusion

Meloxicam exhibited low solubility in the simulated gastric and high solubility in the simulated intestinal media for adult and pediatric subpopulations. In addition, there were significant differences in the pediatric/adult solubility ratios for meloxicam. These differences may have clinically significant implications and can be translated into a higher likelihood of failing to demonstrate bioequivalence of different formulations containing meloxicam and variabilities in the performance of these formulations.

Supplementary Information

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Supplementary Material 1

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Author contributions

I.M., M.J., and R.S. were involved in the conception and design of the work, analysis and interpretation of data, and drafting and final approval of the manuscript. S.A.O., R.N., and S.K. were involved in the data acquisition, analysis, drafting of the work and final approval of the version to be published. All authors approved the final manuscript.

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Data availability
All data analyzed in this study were included in the manuscript and supplementary materials. The datasets used in the analysis or entered into statistical software can be obtained from the corresponding author upon making a reasonable request.

Declarations

Ethics approval and consent to participate
This was a laboratory-based study. No human subjects were involved in this study.

Consent to publish
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Department of Medicine, Faculty of Medicine and Health Sciences, An-Najah National University, Nablus, Palestine
[2]An-Najah National University Hospital, Nablus, Palestine
[3]Department of Physiology, Pharmacology, and Toxicology, Faculty of Medicine and Health Sciences, An-Najah National University, Nablus, Palestine
[4]Clinical Research Center, An-Najah National University Hospital, Nablus, Palestine

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