Research Article

Preparation, characterization and physicochemical studies of diclofenac ionic liquids

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Abstract

Objective: In the present study, an effort was made to prepare active pharmaceutical ingredient (API) based ionic liquids (ILs) by combination of anionic diclofenac and cationic tetrabutylammonium bromide. The solid form of the low water soluble drug was converted into its liquid salt form to improve physicochemical properties and evaluate biological activity. **Materials and methods:** ILs were prepared applying solvent evaporation method using acetone as solvent in 1:1 molar ratio. The formation of ILs was confirmed analytically by differential scanning calorimetry (DSC), Fourier transformation-infrared spectroscopy (FTIR) and X-ray powder diffractometry (XRPD). ILs were subsequently assessed for their physicochemical properties and anti-inflammatory activity. **Results:** The physicochemical parameters like solubility, dissolution and log *P* of IL were not significantly different as compared to diclofenac. The sodium salt of diclofenac and liquid salt of diclofenac showed similar anti-inflammatory activity and also found to be less than pure diclofenac upon evaluation by carrageenan induced rat paw edema method. **Conclusion:** It could be concluded that ILs of diclofenac could be prepared, unfortunately possessing non significant improvement in their physicochemical and biological performance.

Keywords: Diclofenac, ionic liquids, tetrabutylammonium bromide, physicochemical studies; anti-inflammatory activity.

Introduction

Diclofenac is a non steroidal anti-inflammatory drug, chemically known as 2-[(2, 6-dichlorophenyl) amino] benzene acetic acid (Figure 1) (Mali et al., 2015). It produces various effects such as analgesic, antipyretic and anti-inflammatory and is used for the treatment of moderate pain and inflammation, the common symptoms of various diseases. It inhibits cyclooxygenase (COX), an enzyme converting arachidonic acid into prostaglandins (PGs), thromboxanes, and prostacyclins (Sakat et al., 2014; Naveed and Qamar, 2014). Diclofenac is low water soluble drug and hence various solubility enhancement techniques were used in case of diclofenac such as solid dispersions (Pavankumar et al., 2012), use of β-cyclodextrin (Manca et al., 2005) and mixed solvency (Khan, 2015). The conversion of solid form of the API into its liquid salt form is also one of the techniques used for the enhancement of physicochemical parameters.

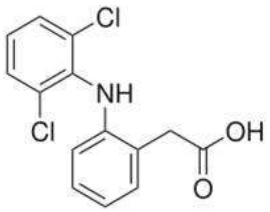

Figure 1. Chemical structure of diclofenac

Ionic Liquids (ILs) are defined as salts synthesized by combination of judicious choice of cations-anions and are in liquid form at room temperature or below 100°C, depending on their chemical composition (Romeli and Wilfred, 2014; Singh and Kumar, 2008; Wilkes, 2002; Khupse and Kumar, 2010). They are used as solvents in chemistry, reaction media for many organic transformations, and catalyst media in synthesis of drug delivery systems. Their use has been extended in pharmaceutical field in order to improve physicochemical properties and biological activity by synthesizing API-based ILs and these are referred as third

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generation ILs (Ferraz et al., 2011; Miwa et al., 2016). The low water soluble anti fungal API, Ketoconazole was converted into IL in order to improve its solubility by using API as cation and organic acids as anion (Keramatnia et al., 2016). ILs were also synthesized by using cholinium as benign cation with APIs like nalidaxic acid, 4 amino salicylic acid, pyrazinoic acid and picolonic acid as anions which improved physical, chemical, and biopharmaceutical properties of those APIs (Araujo et al., 2014).

The literature survey revealed that, API based ILs are categorized into three types; ILs via ionic bonding where API is either as cation or anion, ILs via covalent bonding and API-IL with dual activities in which similar or different APIs are combined in one IL (Egorova et al., 2017). Hence based on the first type of IL, the solid form of the pure diclofenac was converted into its IL.

Therefore, the objective of present work was designed to synthesize diclofenac IL using anionic diclofenac and cationic tetrabutylammonium bromide in order to improve physicochemical properties. The diclofenac IL was synthesized by using solvent evaporation method. The ionic bond formation between the nitrogen atom of tetrabutyl ammonium bromide and carboxylic acid group of diclofenac tend to form API-based IL. The synthesized diclofenac IL was characterized by differential scanning calorimetry (DSC), Fourier transformation infrared spectroscopy (FTIR) and X-ray powder diffractometry (XRPD). The saturation solubility of pure diclofenac and corresponding IL were determined in distilled water, complementary evidenced by determination of octanol/water coefficient (Log *P*). The release rate studies were conducted in phosphate buffer 6.8 pH. All samples were further examined for anti-inflammatory activity using carrageenan induced rat paw edema method.

Materials and methods

Diclofenac sodium was obtained from Abbott Laboratories Pvt. Ltd, India as a gift sample. Tetra butyl ammonium bromide was purchased from Loba chemie Pvt, Ltd. Mumbai, India. Analytical grade reagents and glass distilled water were used for all the experimental procedures. The substances were used without any further purification.

Preparation of pure diclofenac

Diclofenac sodium was dissolved in water and then acidified with conc. HCl until a pH value of 1-3 was reached to achieve the complete precipitation of pure diclofenac. The precipitate was filtered, thoroughly washed with distilled water, air dried and stored in desiccators. The formation of diclofenac was confirmed by melting point, λmax and FTIR spectroscopy. The prepared pure diclofenac was further used for synthesis of ILs (Pasquali et al., 2007).

Synthesis of diclofenac IL

Diclofenac-IL was synthesized by adopting solvent evaporation method. 1:1 molar ratio of diclofenac and tetra butyl ammonium bromide was added to 40 ml of acetone separately and was dissolved by sonication for 20 min. The clear solution was obtained. This solution was left for 5 days for solvent evaporation (Keramatnia et al., 2016). The product was collected and stored in desiccators until further analysis.

Differential scanning calorimetry (DSC)

DSC analyzer (TA Instruments SDT Q600 USA) was used to perform the thermal analysis of diclofenac sodium, pure diclofenac, tetrabutylammonium bromide and its IL. A sample (5mg) was heated under a nitrogen atmosphere at a heating rate of 10°C/min over the temperature range of 0-300°C.

Fourier transformation-infrared spectroscopy (FTIR)

Attenuated Total Reflectance (ATR) is a sampling technique used in conjunction with infrared spectroscopy which enables samples to be examined directly in the solid or liquid state without further preparation. ATR (BRUKER-ECO- ATR – ALPHA, Germany) was used for the IR analysis of all samples. The samples were directly placed on the sample pan and analyzed from 600 to 4000 cm-1 spectral range with 24 scans.

X-ray powder diffractometry (XPRD)

X-ray diffractometer (Bruker – D2 PHA-SER, Germany) with tube anode Cu was used to record XPRD patterns of all samples over the interval 10-90°/2θ. The operational data were as follows: Generator tension (voltage) 30 kV, Generator current 10 mA.

Saturation solubility studies

An excess amount of diclofenac sodium, pure diclofenac and / or its IL was added to 10 ml distilled water in the solubility tubes. These were shaken on an orbital shaker (BTI-05) at room temperature (25 ± 2°C) until reaching equilibrium (24 h). A portion of the solution was withdrawn, filtered through Whatman filter paper no. 41. It was adequately diluted with distilled water. The amount of pure drug, sodium and liquid salt of diclofenac solubilized was determined at 276 nm by UV-Vis spectrophotometer (Shimadzu 1800 Japan).

Determination of partition coefficient (log *P*)

The partition coefficient was determined by adding 10 ml each of n-octanol and water in glass tubes. It was allowed to stand overnight for 24 h at room temperature. Accurately weighed 25 mg of pure drug, sodium and / or liquid salt of

diclofenac was added to the tubes and shaken on an incubator shaker (REMI-CIS 24 plus Incubator shaker, Mumbai, India) for 24 h at 25± 2°C. These mixtures were then transferred to the separating funnel and allowed to stand about 4 h for equilibration. Separation of aqueous and organic phases occurred. The concentrations of pure drug and its salts were analyzed spectrophotometrically (Shimadzu 1800, Japan) at 276 nm. The formula used to calculate partition coefficient was,

$$\text{Partition coefficient } (\log P) = \log (\text{C octanol/C water})$$

Where, C is the concentration of drug in octanol and/or water phase (Jadhav and Pore, 2016).

Release rate evaluation

The dissolution studies of diclofenac and ILs were performed in triplicate in a dissolution test apparatus (ELECTROLAB–TST-06L/ LX, New Mumbai, India) according to USP type II. Samples were placed in dissolution vessel containing 900 ml Phosphate buffer 6.8 PH maintained at 37 ± 0.5°C at 50 rpm according to US FDA guidelines (US FDA website). 150 mg of diclofenac and / or its ILs was added to phosphate buffer 6.8 pH. 5 ml of samples were withdrawn at appropriate time intervals. The volume of dissolution media was adjusted to 900 ml by replacing each 5 ml aliquot withdrawn with 5 ml of fresh phosphate buffer 6.8 pH. The solution was immediately filtered through Whatman filter paper No.41 and adequately diluted if necessary and analyzed at 276 nm spectrophotometrically (Shimadzu 1800, Japan) (Mourao et al., 2010).

Anti-inflammatory activity of diclofenac and its ILs

All experiments were approved by the Institutional Animal Ethics Committee (the Approval No. RCP/IAEC/16-17/P09 dated 12.06.2017) and were carried out according to the guideline of the International Association for the Study of anti-inflammatory activity and were accordance with CPCSEA (committee for the purpose of control and supervision of experiments on animals). In the study, the anti-inflammatory activity of diclofenac and its IL was investigated using carrageenan-induced paw edema test. Male Wistar rats were selected for the study, randomized based on their body weight and divided into six different groups consisting of 6 animals each. Rats were injected subcutaneously (S.C.) by injection of carrageenan (0.1 ml of 1 7o solution in normal saline) into the plantar side of the left hind paw. The paw was marked with ink at the level of lateral malleolus. The paw volume was measured up to the mark using digital plethysmometer before (-1 h) and at 1, 2, 3, 4, and 6 h after injection of carrageenan for all the animals. Paw edema volume was calculated by subtracting -1 h paw volume from the respective paw volumes at l, 2, 3, 4, and 6 h (Soni et al., 2014; Amdekar et al., 2012).

Results and discussion

The crystalline solid compound of pure diclofenac with tetrabutylammonium bromide, after dissolving in acetone and complete solvent evaporation for 5 days appeared to be white with melting point below 100°C. Photograph of diclofenac IL is shown in figure 2. As not all the ionic liquids are liquid at room temperature, diclofenac ionic liquid appeared to be in solid form at room temperature. The formation of diclofenac ionic liquid was confirmed initially by its melting point (Sakat et al., 2014). The analytical evidences for the formation of diclofenac-IL were confirmed by DSC, FTIR and XRPD techniques.

Figure 2. Photograph of prepared diclofenac-IL in 1:1 molar ratio.

Differential scanning calorimetry (DSC)

DSC is an important tool for the investigation of interaction between API and excipients.. When the solid form of the drug is converted into its liquid salt form, their melting points usually shift to different temperatures or disappear. DSC pattern of all systems are shown in Figure 3.

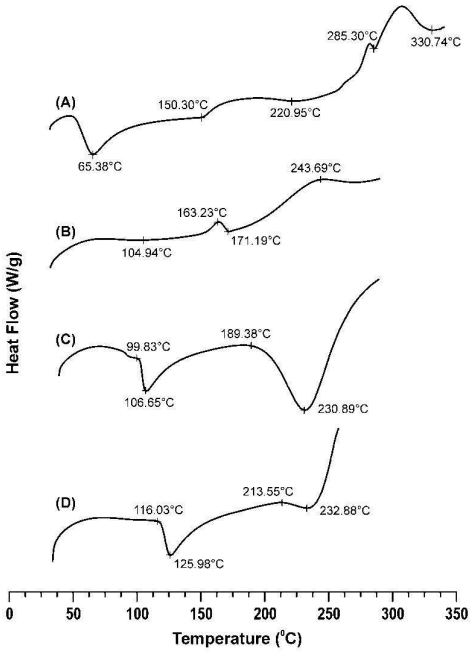

Figure 3. DSC thermograms of diclofenac sodium (A), diclofenac (B), tetrabutylammonium bromide (C), diclofenac-IL (D)

The DSC thermogram of diclofenac sodium showed

initially no peaks indicating amorphous nature but as the temperature was increased it showed exothermic peak at 285.30°C indicating the crystalline nature. In case of pure diclofenac prepared from its sodium salt, exothermic peak was observed indicating the crystalline nature of the drug while tetrabutylammonium bromide showed peak sharp melting endothermic peak at 106.65°C. The thermogram of diclofenac IL showed melting point peak at 125.98°C. This melting point suggests that many new ILs might be readily created by matching a desired cation from such a salt with different anion or vice versa. These type of compounds constitutes "incognito" ILs (Davis and Fox, 2013).

Fourier transformation-infrared spectroscopy (FTIR)

The comparative FTIR spectrum of all systems is represented in Figure 4. The principle absorption peaks of diclofenac sodium exhibited at 3257.19 (N-H stretch), 1568.73, 1502.11(C=C aromatic stretch), 1450.30 (C-N), 1091.81 (C-Cl), 743.38 (metasubstituted benzene). IR spectra of diclofenac showed principle absorption peak at 3321.45 (N-H stretch), 2885.59 (CH_2, aliphatic), 2565.68 (O-H stretch), 1690.97 (C=0, stretch), 1577.87, 1503.08 (C=C, aromatic stretch), 1449.57 (C-N), 1092.20 (C-Cl), 741.96 (metasubstituted benzene). In the IR spectra of tetrabutylammonium bromide, principle peaks were seen at 2954.03 (CH_3, stretch), 1464.31(C-N stretch), 1374.02 (C-H asymmetric bend). IR spectra of diclofenac-IL showed principle absorption peaks at 3415.07 (broad O-H, stretch), 2872.14 (CH_2, aliphatic), 1094.36 (C-Cl), 737.25 (metasubstituted benzene). The broad OH group indicated that nitrogen atom of tetrabutylammonium bromide might be involved in the interaction with OH group of diclofenac with the transfer of proton.The observations of IR spectra indicated that there was shift of the peaks.

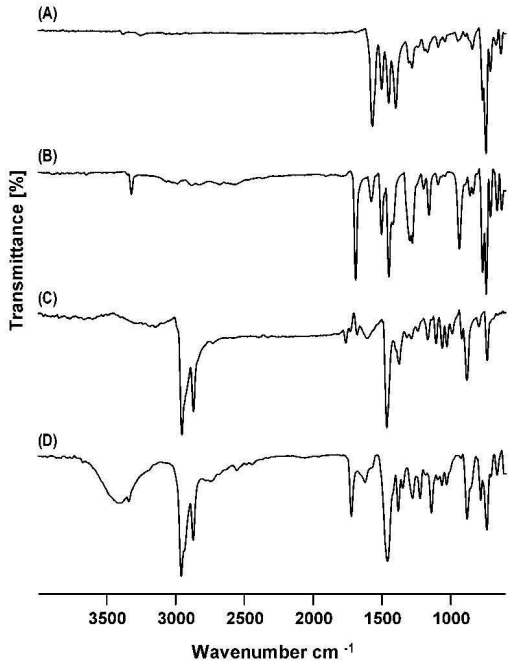

Figure 4. IR Spectra of Diclofenac sodium (A), Diclofenac (B), Tetrabutylammonium bromide (C), Diclofenac IL (D)

X-ray powder diffractometry (XPRD)

The XRPD patterns of all samples are presented in Figure 5. The diffractogram of diclofenac sodium showed less intense peaks as compared to the pure diclofenac indicating that the crystallinity of pure diclofenac increased as it was extracted from diclofenac sodium. The diffractogram of tetrabutylammonium bromide showed intense peaks specifying its crystalline nature. The diclofenac-IL showed less intense peaks as compared to the diclofenac sodium and pure diclofenac suggesting the phase conversion. The reduction of intensity of peaks of diclofenac-IL indicated the conversion of pure diclofenac into the ionic liquid.

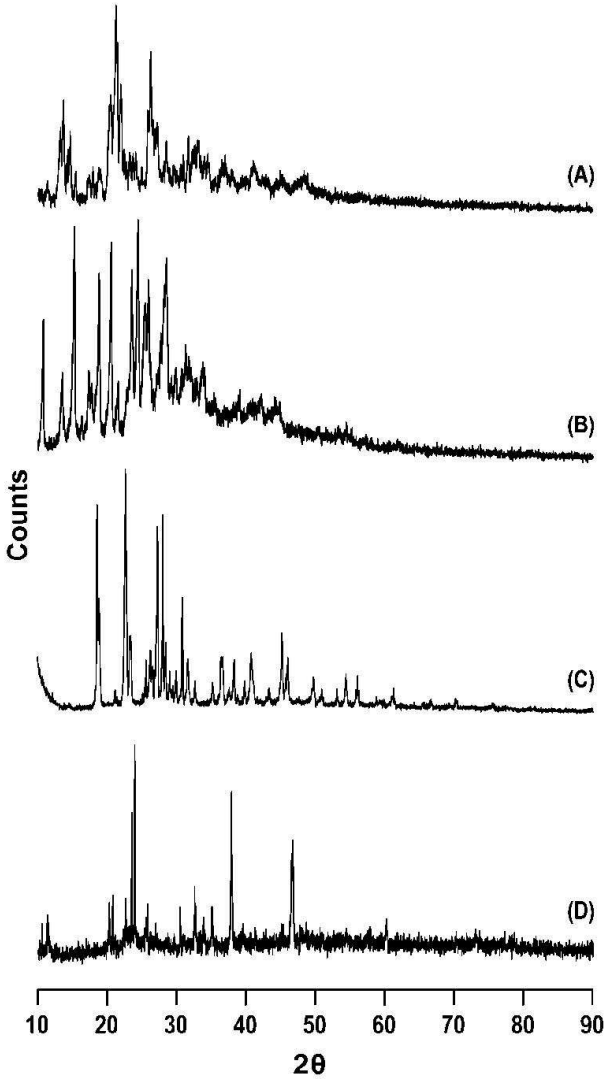

Figure 5. XRPD Patterns of Diclofenac sodium (A), Diclofenac (B), Tetrabutylammonium bromide (C), Diclofenac IL (D).

Saturation solubility studies

The saturation solubilities of diclofenac sodium, pure diclofenac, diclofenac IL was found to be 16.56 ± 0.03512, 0.0863 ± 0.00076, 0.1119 ± 0.00040 mg/ L respectively. The solubility of pure diclofenac and its IL was not increased as compared to diclofenac sodium. There was no

significant difference between solubility of pure diclofenac and its IL.

Determination of partition coefficient (log *P*)

The log*P* values of diclofenac sodium, pure diclofenac and its IL were observed to be 0.965 ± 0.00435, 2.96 ± 0.00577, 3.066 ± 0.02517 respectively. The increased log *P* values indicated the low aqueous solubility of pure diclofenac and diclofenac IL as compared to diclofenac sodium. The increased log *P* values of pure diclofenac and its IL compared to diclofenac sodium clearly indicated enhancement in lipophilicity of the pure drug and its IL.

Release rate evaluation

The diclofenac release profile by synthesizing its IL is reported in figure 6. The release rate profiles were given as the percentage of drug dissolved (vs.) time. The % dissolution efficiency (DE) at 10 min and 40 min was evaluated. The % drug release and % dissolution efficiency has been expressed in table. 1. During dissolution studies it was observed that release rate of pure diclofenac and its IL was not found to be significantly different ($p>0.05$) and did not increased as compared to diclofenac sodium. The conversion of solid form of the drug into liquid form at low melting point by combination of cation and anion did not enhanced dissolution profile of IL suggesting that the liquid salt of diclofenac is not reliable as compared to sodium salt of diclofenac.

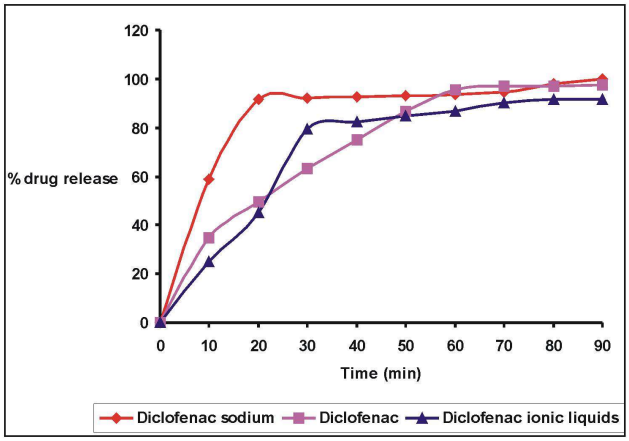

Figure 6. Dissolution profile of diclofenac sodium, pure diclofenac, diclofenac IL

Anti-inflammatory activity of diclofenac and its ILs

The anti-inflammatory activity of diclofenac sodium, pure diclofenac and diclofenac-IL was performed by using carrageenan induced rat paw edema method and expressed as % inhibition vs. time in hours shown in figure 7. The anti-inflammatory activity data of pure diclofenac and sodium and liquid salt of diclofenac has been expressed in table. 2. The % inhibition at 6h of pure diclofenac was high as compared to diclofenac sodium and diclofenac IL. There was no significant difference in the percent inhibition of diclofenac sodium and diclofenac IL indicating that the sodium salt of diclofenac and liquid salt of diclofenac showed similar activity.

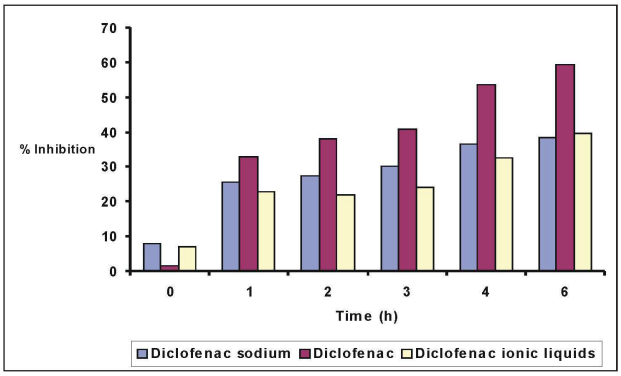

Figure 7. Anti-inflammatory activity (% inhibition vs. time in hours) of diclofenac sodium, pure diclofenac and diclofenac IL.

Hence the overall results concluded that even though the formation of diclofenac- IL was confirmed analytically, the physicochemical parameters were not improved as compared to sodium salt of diclofenac but the evaluation of biological activity proved to be significant as compared to pre diclofenac.

Conclusion

In the present investigation, IL of anionic diclofenac and cationic tetrabutylammonium bromide were successfully synthesized. The results revealed that there was no

Table 1. The % drug release and % dissolution efficiency of diclofenac sodium, pure diclofenac and its IL in phosphate buffer pH 6.8 at 37 ± 0.5°C

System	% DR*				% DE*	
	10 min	30 min	50 min	90 min	10 min	40 min
Diclofenac Sodium	58.86 ± 0.10	92.04 ± 0.45	93.1 ± 0.173	99.96 ± 0.12	29.43 ± 1.05	72.11 ± 0.13
Diclofenac	34.8 ± 0.12	63.16 ± 0.07	86.5 ± 0.183	97.53 ± 0.36	17.4 ± 0.53	46.19 ± 0.07[a]
Diclofenac IL	25.18 ± 0.03	79.59 ± .023	84.61 ±0.023	91.73 ± 0.02	18.59 ± 0.24	47.8 ± 0.02[b,c]

*Values expressed in mean ± S.D. (n=3); S.D.: standard deviation; IL: ionic liquid; %DR: %drug release; %DE: dissolution efficiency; [a]: diclofenac sodium vs. pure diclofenac significant difference ($p < 0.001$); [b]: diclofenac sodium vs. diclofenac IL significant difference ($p < 0.001$); [c]: pure diclofenac vs. diclofenac IL no significant difference ($p > 0.05$).

Table 2. Anti-inflammatory activity data of diclofenac sodium, pure diclofenac, and diclofenac-IL

Time/ System		Control	Diclofenac sodium	Diclofenac[a]	Diclofenac IL [b,c]
0	Increase in paw volume	1.87 ± 0.007	1.79 ± 0.01	1.84 ± 0.004	1.74 ± 0.10
	%inhibition	---	8	1.60	6.9
1	Increase in paw volume	2.5 ± 0.3	1.86 ± 0.06	1.88 ± 0.03	1.93 ± 0.05
	%inhibition	---	25.6	33	22.8
2	Increase in paw volume	2.66 ± 0.03	1.93 ± 0.05	1.95 ± 0.05	2.08 ± 0.07
	%inhibition	---	27.44	37.96	21.80
3	Increase in paw volume	2.8 ± 0.14	1.96 ± 0.04	2.04 ± 0.03	2.13 ± 0.1
	%inhibition	---	30	40.64	23.92
4	Increase in paw volume	2.98 ± 0.04	1.89 ± 0.028	1.98 ± 0.01	2.005 ± 0.28
	%inhibition	---	36.57	53.47	32.71
6	Increase in paw volume	3.01 ± 0.03	1.86 ± 0.03	1.90 ± 0.02	1.82 ± 0.09
	%inhibition		38.20	59.35	39.53

*Values expressed in mean ± S.D. (n=3); S.D.: standard deviation; IL: ionic liquid; % inhibition ; [a]:diclofenac sodium vs. pure diclofenac significant difference ($p < 0.001$); [b]: diclofenac sodium vs. diclofenac IL no significant difference ($p < 0.001$); [c]: pure diclofenac vs. diclofenac IL significant difference ($p > 0.05$).

significant difference in physicochemical properties and biological activity. The synthesized diclofenac ionic liquid was "incognito IL". The ionic hydrogen bond formation between the nitrogen atom of tetrabutylammonium bromide and free carboxylic group of diclofenac resulted in formation of diclofenac-IL. The analytical techniques confirmed the formation of ILs in solid state. The sodium salt and liquid salt form of diclofenac showed similar anti-inflammatory activity but less activity as compared to the pure diclofenac.

Conflict of interests

Authors report no conflict of interests.

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References

Amdekar S, Roy P, Singh V, Kumar A, Singh R and Sharma P. 2012. Anti-inflammatory activity of *Lactobacillus* on carrageenan induced paw edema in male wistar rats. International Journal of Inflammation, Article ID 752015, 6.

Araujo J, Florindo C, Pereiro AB, Vierira NS, Matias AA, Catarina DM, Rebelo LP, Marrucho IM. 2014. Cholinium based ionic liquids with pharmaceutically active anions. The Royal Society of Chemistry, 4: 28126-28132.

Davis JH, Fox PA. 2013. From curiosities to commodities: ionic liquids begin the transitions. Chemical Communications, 1209-1212.

Egorova KS, Gordeev EG, Ananikov VP. 2017. Biological activity of ionic liquids and their application in pharmaceutics and medicine. Chemical Reviews, 117(10): 7132-7189.

Ferraz R, Branco LC, Prudencio C, Noronha JP, Petrovski Z. 2011. Ionic liquids as active pharmaceutical ingredients. ChemMedChem 6(6): 975-985.

Jadhav P, Pore Y. 2016. Physicochemical, thermodynamic and analytical studies on binary and ternary inclusion complexes of bosentan with hydroxypropyl-β-cyclodextrin. Bulletin Faculty of Pharmacy, Cairo University, 55: 147-154.

Keramatnia F, Jouyban A, Valizadeh H, Delazar A. 2016. Ketoconazole ionic liquids with citric acid and tartaric acid: synthesis, characterization and solubility study. Fluid Phase Equilibria, 425: 108-113.

Khan MA. 2015. Enhancement of solubility of poorly water soluble drugs diclofenac sodium by mixed solvency approach. International Journal of Research and Development in Pharmacy and Life Sciences, 4(6): 1835-1837.

Khupse ND, Kumar A. 2010. Ionic liquids: New materials with wide applications. Indian Journal of Chemistry, 49A: 635-648.

Mali A, Jadhav S, Mane P, Tamboli A. 2015. Development

and validation of UV spectrophotometric estimation of diclofenac sodium bulk and tablet dosage form. PharmaTutor, 3(4): 21-25.

Manca ML, Zaru M, Ennas G, Valenti D, Sinico C, Loy G, Fadda AM. 2005. Diclofenac-beta cyclodextrin binary systems: physicochemical characterization and in vitro dissolution and diffusion studies. AAPS Pharma SciTech, 6(3): 464-472.

Miwa Y, Hamamoto H, Ishida T. 2016. Lidocaine self sacrificially improves the skin permeation of the acidic and poorly water soluble drug etodolac via its transformation into an ionic liquid. European Journal of Pharmaceutics and Biopharmaceutics, 102: 92-100.

Mourao SC, Silva C, Bresolin TM, Serra CH, Porta V. 2010. Dissolution parameters for sodium diclofenac containing hypromellose matrix tablet. International Journal of Pharmaceutics, 368(1-2): 201-207.

Naveed S, Qamar F. 2014. UV Spectrophotometric assay of diclofenac sodium available brands. Journal of Innovations in Pharmaceutical and Biological Sciences, 1(3): 92-96.

Pasquali I, Bettini R, Giordano F. 2012. Thermal behaviour of diclofenac, diclofenac sodium and sodium bicarbonate compositions. Journal of Thermal Analysis and Calorimetry., 90(3): 903-907.

Pavan Kumar KH, Chandramouli Y, Prakash Reddy CS, Sreekanth K, Murali D, Chakravarthi RN. 2012. Enhancement of solubility and dissolution rate of diclofenac sodium by solid dispersion method. International Journal of Advanced Pharmaceutics, 2(2): 110-118.

Romeli FJ, Wilfred CD. 2014. Synthesis and characterization of flufenamic ionic liquids. Journal of Applied Sciences, 14(23): 3373-3376.

Sakat SS, Mani K, Demidchenko YO, Gorbunav EA, Tarasov SA, Mathur A, Epstein OI. 2014. Release-active dilutions of diclofenac enhance anti-inflammatory effect of diclofenac in carrageenan-induced rat paw edema model. Inflammation, 37(1): 1-9.

Singh G, Kumar A. 2008. Ionic liquids: Physicochemical, solvent properties and their applications in chemical processes. Indian Journal of Chemistry, 47A: 495-503.

Soni RK, Irchhaiya R, Dixit V, Bhat ZA, Wani HA, Najar AH. 2014. Anti-inflammatory activity activity of *Kirgnelia Reticulata* (poir). Baill. root by carrageeenan induced rat paw edema model. International Journal of Pharmacy and Pharmaceutical Science, 6(1): 520-523.

Wilkes JS. 2002. A short history of ionic liquids- from molten salts to neoteric solvents. Green Chemistry, 4:73-80.