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Original Article

SYNTHESIS AND EVALUATION OF TASTE-MASKED IONIC LIQUID SALTS OF LORATADINE

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ABSTRACT

Objective: To synthesize and evaluate taste-masked ionic liquid (IL) salts of loratadine.

Methods: In the present work, pharmaceutically active IL salts of loratadine using selected counter-ions were synthesized. The synthesized IL salts were characterized using melting point, Ultraviolet (UV) spectroscopy, Fourier Transform Infra-Red (FTIR) spectroscopy, Differential Scanning Calorimetry (DSC), and X-ray Diffraction (XRD). These salts were also evaluated for solubility, dissolution, and palatability studies.

Results: All synthesized IL salts of loratadine exhibited melting points below 100 °C. UV spectral data and FTIR data confirmed the formation of new salt forms with selected counter-ions. The absence of sharp melting point peaks during DSC studies revealed the amorphous nature of new salt forms. During XRD studies, loratadine-indomethacin IL salt yields completely amorphous compound while the intensity of characteristic peaks of loratadine was found to be reduced with other counter-ions. Solubility studies revealed that the solubility of loratadine is reduced from 35.85 mg/ml to 3.63 mg/ml, 15.39 mg/ml, 5.31 mg/ml, and 3.71 mg/ml in case of IL-1, IL-2, IL-3, and IL-4, respectively. Dissolution studies further confirmed this finding. Except for oleate, all the IL salts were found to be palatable by subjects with the score ranging from 2.5 to 2.8, which is the standard range for palatability.

Conclusion: Results obtained in the present work indicated that IL salts of loratadine can be synthesized successfully using selected counter-ions. This approach can be used to mask the bitter taste of pure loratadine and thus can be used for the development of drug products intended for children.

Keywords: IL salts, Loratadine, Counter-ions, Taste masking

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INTRODUCTION

Ionic liquid (IL) salts are a new class of purely ionic, salts of compounds that have very low melting points. Many times they exist in the liquid state at room temperature. By the official definition, "Ionic liquids (IL) are ionic compounds that are liquid below 100 °C". At room temperature, such compounds appear either like liquids or fused or soft solids [1-3]. Although ionic in nature but the properties of IL salts differ from typical inorganic salts. In the IL salts, the charges are not confined/localized to one particular area in the molecule; rather, they are distributed over a large volume. Due to this, the intensity of charge in a localized area reduces and crystal packing becomes loose. This is the reason for the low melting points of IL salts. Typical inorganic salts, on the other hand, have symmetrical packing in their crystal structure and charges are well localized [4]. These IL salts have additional properties like non-flammable [1], thermally, mechanically, and electrochemically stable [5, 6], etc. Due to such unique properties of IL salts, these are used as solvents in synthesis and separation of organic compounds [1, 7-9], as thermal fluids [10], lubricants [10], electrolytes [10], electro-elastic materials [11], etc.

In pharmaceutical sciences also, ILs are used to facilitate synthesis and analysis of active pharmaceutical ingredients (APIs). Some researchers have used the concept of IL for synthesizing novel ionic salts of existing medicinal compounds to overcome the difficulties associated with them [12]. When combined with suitable counter-active/inactive ions, the IL salts of APIs may yield compounds with improved solubility, stability, bioavailability, palatability, and therapeutic activity [13]. When IL salts are prepared using two APIs, it has dual therapeutic activity and thus forms a very useful alternative for fixed-dose combination drugs [14].

Loratadine is Ethyl-4-(8-chloro-5, 6-dihydrobenzo [1, 2] cyclohepta [2,4-b] pyridine-11-ylidene) piperidine-1-carboxylate, second-generation antihistaminic drug. It is widely prescribed to patients of all age groups for the treatment of symptoms of rhinitis and other allergies. It is prescribed alone or in combination with nasal decongestants, analgesics or anti-inflammatory agents [15]. It is available in the form of tablets, chewable tablets, orally disintegrating tablets, oral solutions [16], and oral suspensions [17]. Being very bitter in nature, patient acceptability of its dispersible, orally disintegrating, and liquid dosage forms is very poor [18, 19].

In the present work, an attempt has been made to synthesize taste-masked IL salts of Loratadine to improve its palatability issues. Both inactive and active counter-ions were used to synthesize IL salts. The IL salts were characterized using melting points, Ultra Violet (UV) spectroscopy, Infra-Red (IR) spectroscopy, X-ray diffractometry (XRD) and differential scanning calorimetry (DSC). The IL salts were also evaluated for their dissolution profile and palatability and compared with the existing Loratadine hydrochloride salt.

MATERIALS AND METHODS

Material

Loratadine, oleic acid, salicylic acid, indomethacin, and diclofenac sodium were gifted generously by Zim Laboratories Ltd., Kalmeshwar, Nagpur. All other reagents and solvents used were of analytical grade.

Preparation of IL salts

Loratadine and selected counter-ion were mixed in the ratio mentioned in table 1 by continuous stirring in ethanol in a water bath for 10 min at 70-80 °C [20]. The resultant IL salt was collected by evaporating solvent at room temperature in airtight vials and stored at ambient condition till further characterization and evaluation. For convenience, all IL salts were given a code mentioned in table 1.

Table 1: IL salts of loratadine with selected counter-ions

Code of IL salts	Components (Ratio by weight)
IL-1	Loratadine: Oleic acid (1:0.5)
IL-2	Loratadine: Salicylic acid (1:1)
IL-3	Loratadine: Indomethacin (1:1)
IL-4	Loratadine: Diclofenac Na (1:1)

Characterization of IL salts

Melting point

Melting points of synthesized IL salts were determined using the melting point apparatus (Biotec India) and compared with the melting point of pure loratadine. One end of a capillary tube was sealed using heat and was filled with the sample and the capillary tube was then inserted into the melting point chamber and a thermometer was inserted into the thermometer chamber of the apparatus. The temperature at the onset and after the complete melting of the sample was recorded [21].

UV spectroscopy

UV spectra of pure loratadine and synthesized IL salts were recorded using Shimadzu 1800 (Kyoto, Japan) UV-spectro-photometer. About10 mg of pure loratadine was accurately weighed and dissolved in methanol. The solution was sonicated for 30 min, filtered and the spectrum was recorded in the range of 400 nm to 200 nm in a 1.0 cm cell using methanol as blank. The same procedure was repeated for the synthesized IL salts and counter-ions. The λmax of each compound was recorded.

FTIR spectroscopy

FTIR transmission spectra of pure loratadine and synthesized IL salts were recorded using FTIR-8300, Shimadzu, Japan. Samples were prepared in KBr disks by means of the hydraulic press at 6-8 tons pressure [22]. The scanning range was 500 to 4000 cm^{-1} and the resolution was 4 cm^{-1}.

DSC studies

Solid-state characterization allows direct insight into the spatial relationship between the cation and anion through the elucidation of crystal structures and this provides a strong basis from which structural features of the ionic liquid can be studied [23]. Both DSC and XRD techniques help to understand the changes in the crystal structures of the newly synthesized IL salts.

DSC analysis of pure loratadine and synthesized IL salts were performed using DSC-60 plus Shimadzu (Kyoto, Japan). Samples were heated in an open aluminum pan at a rate of 5 °C per min^{-1} in a-140 °C to 600 °C temperature range, under a nitrogen flow of 40 ml/min. Current.

XRD studies

XRD patterns of pure loratadine and synthesized IL salts were recorded on an X-ray diffractometer (PANalytic Spectric Pvt. Ltd., Singapore) using Ni-filtered, CuKα radiation, a voltage of 40 kV and a 25 mA current. The scanning rate employed was 1° per minover the 2° to 60° diffraction angle (2θ) range.

Evaluation of IL salts

Solubility studies

The solubility of loratadine and synthesized IL salts were determined in water. Wherever counter-ion was an active drug, the solubility of counter-ion was also determined. The excess of each compound was dissolved in distilled water (20 mg in 100 ml ~0.020 % w/v), sonicated for 30 min. The solution was then filtered (0.22 µm pore size) and the absorbance of each solution was recorded at the respective λmax using Shimadzu 1800 (Kyoto, Japan) UV spectrophotometer.

Dissolution studies

In vitro drug release or dissolution study was performed using USP apparatus II (Electrolab, Mumbai, India) in 900 ml of 0.1 M HCl as dissolution medium. The rotational speed of the paddle was set at 50 rpm at 37±0.5 °C. Aliquots (10 ml each) were withdrawn at predetermined time interval (15 min) for 75 min, sink conditions were maintained. The samples were analyzed for drug content using double beam UV spectrophotometer (UV 1800 PC, Shimadzu Corporation, Kyoto, Japan) at 246.8 nm.

Palatability evaluation

Healthy human volunteers of either sex, in the age group of 20-25 y were selected (n=6) on the basis of their taste sensitivities. The informed consent from these volunteers was obtained prior to the studies. The non-tasters and supertasters were rejected. The selected panel of volunteers were trained for taste evaluation by using solutions with bitterness ranging from tasteless to extremely bitter and were asked to score the bitterness on the scale of 0-5. The score 5 was assigned to an extremely bitter taste [21]. Each volunteer was asked to taste about a pinch of each compound and record the bitterness levels as per the scale given in table 4. After tasting of every compound, subjects were asked to spit out the contents and rinse the mouth thoroughly with purified water. The taste scale was validated by testing samples randomly. The washout period between testing of two samples was at least 15 min.

RESULTS AND DISCUSSION

Melting point

The melting point of loratadine and synthesized IL salts are presented in table 2. When compared with loratadine, the melting point of each synthesized IL salt showed a significant reduction in melting point. It was observed that upon combining loratadine with all other selected ions, the melting point of loratadine was lowered from 133 °C to less than 100 °C. All the synthesized IL salts of loratadine revealed melting points in the range from 85 °C to 100 °C. Further, it was noted that none of the synthesized IL salts showed a sharp melting point, which indicated that these synthesized compounds were not crystalline in nature.

Table 2: Melting point and ʎ max of pure drugs and their IL salts

Drugs	Melting points	ʎ max	Physical Appearance
Loratadine	133 °C–136 °C±0.2	246.8 nm	White Crystalline powder
Salicylic acid	157 °C–160 °C±1.3	304.2 nm	White Crystalline powder
Indomethacin	160 °C–164 °C±1.25	318.6 nm	Pale yellow crystalline powder
Diclofenac Na	286 °C–289 °C±3	275.6 nm	White powder
IL-1	85 °C–90 °C±1.2	247 nm	Pale white powder, soft to touch
IL2	94 °C–98 °C±2.2	244 nm, 304 nm	Pale white powder, soft to touch
IL3	96 °C–99 °C±2	254 nm, 318 nm	Pale yellow powder, soft to touch
IL4	95 °C–100 °C±1.2	246 nm, 275 nm	Pale white powder, soft to touch

*Data represented as mean±standard deviation [SD], n=3

UV spectroscopy

UV spectra and ʎ max of loratadine and synthesized IL salts are presented in table 2. From the UV absorption spectra, it is concluded that there is not a significant change in the ʎ max values of both (loratadine and IL salts) because of the presence of similar chromophores in both the structures. Therefore, the UV spectral data confirms that there is no change in the original structure during the reaction and only salt formation between the two species has occurred.

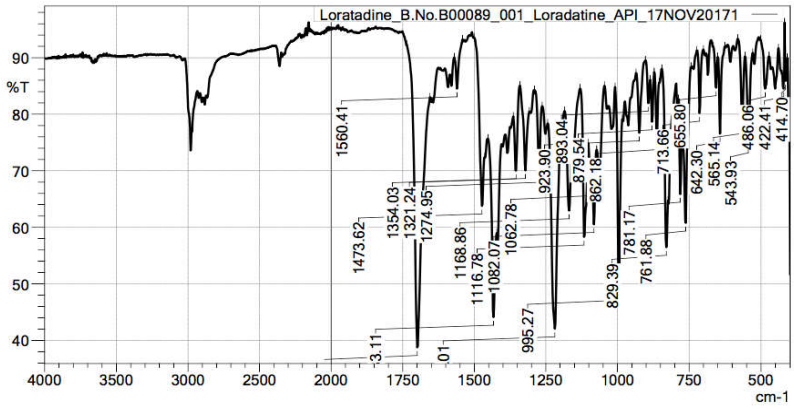
FTIR spectroscopy

FTIR studies were performed for the detection of possible molecular interaction between loratadine and counter-ions in IL salts. IR spectra of loratadine and synthesized IL salts are presented in fig. 1. Pure loratadine spectra shows aromatic C-H stretch at 2975 cm^{-1}, carboxyl O-H stretch at 2900 cm^{-1}, C=O stretch at 1699 cm^{-1}, aromatic C=C stretch at 1560 cm^{-1}, tertiary aromatic amine C-N=C stretch at 1321 cm^{-1}, ether C-O stretch at 1169 cm^{-1}, aryl chloride stretch at 1082 cm^{-1} and C-H bending at 714 cm^{-1}. Characteristic C-H stretch at 2975 cm^{-1} of loratadine is retained in all the IL salts. The C=O stretch of carbonyl group at 1699 $cm^{-1}$of loratadine was shifted to 1697 cm^{-1} in IL-1, 1694 cm^{-1} in IL-2, 1686 cm^{-1} in IL-3, and 1701 cm^{-1} in IL-4 respectively. This shows the involvement of carbonyl oxygen in the salt formation with positively charged nitrogen of diclofenac and indomethacin. The tertiary aromatic amine C-N=C stretch at 1321 $cm^{-1}$of loratadine shifted to 1325 cm^{-1} in IL-2, 1310 cm^{-1} in IL-3 and 1304 cm^{-1} in IL-4 respectively indicated salt formation between loratadine and counter-ions. Ether C-O stretch at 1169 cm^{-1} of loratadine shifted to 1167 cm^{-1} in IL-1, 1155 cm^{-1} in IL-2, 1220 cm^{-1} in IL-3, respectively indicated salt formation between loratadine and counter-ions. Aryl chloride stretch at 1082 cm^{-1} of loratadine shifted to 1080 cm^{-1} in IL-1, 1026 cm^{-1} in IL-2, 1067 cm^{-1} in IL-3 and unchanged in IL-4 respectively. This shows chloride in loratadine gets associated with the nitrogen of indomethacin and diclofenac in salt formation. This indicates that an interaction between loratadine and counter-ions takes place, confirming the formation of IL salts.

DSC studies

Thermal analysis by DSC is the primary analytical tool for understanding the presence of a new solid phase. DSC thermograms of pure loratadine and IL salts are presented in fig. 2. Loratadine exhibits a characteristic sharp peak at 134.61 °C and its melting range was 133.30 °C to 135.95 °C indicates the crystalline nature of the drug. DSC thermogram of IL-1 indicates the conversion of crystalline loratadine to amorphous oleate salt as revealed by the absence of any sharp peak in the thermogram. IL-2 shows peak at 121.33 °C and melt in the range of 118.95 °C to 134.31 °C indicating the lowering of the melting point of loratadine either due to the new salt formation or due to the presence of salicylic acid. The thermogram of IL-3 revealed the formation of new amorphous salt confirmed by the absence of any distinct melting endotherm. IL-4 shows two peaks, at 53.34 °C and 132.15 °C. These two peaks do not correspond to the melting points of individual components of the synthesized salt. The formation of a new compound in the IL-4 is further confirmed by the diffused nature of both of these peaks. The IR Spectra and DSC thermographs of the loratadine ionic liquid salts indicated that salt formation occurred in the ionic liquid and did not result in API degradation.

Thus, it can be concluded on the basis of DSC studies that attempt to synthesize new salt forms of loratadine using selected counter-ions was successful.



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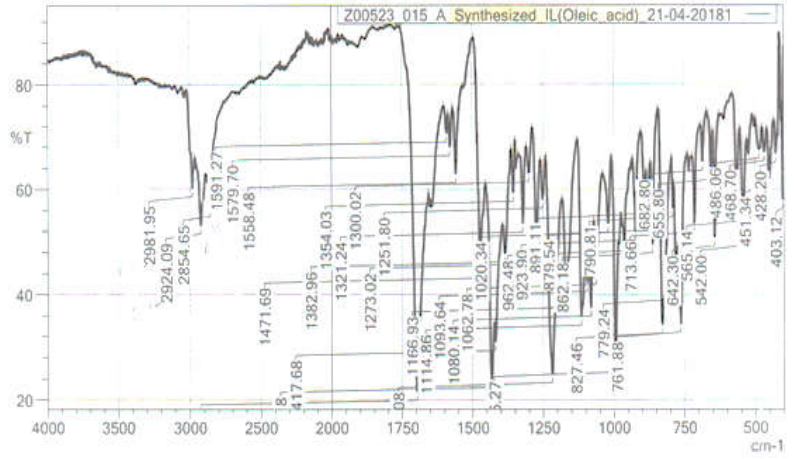

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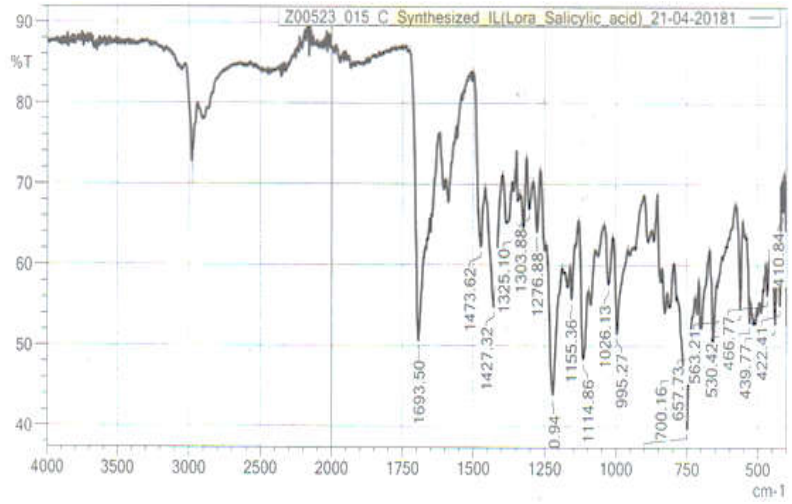

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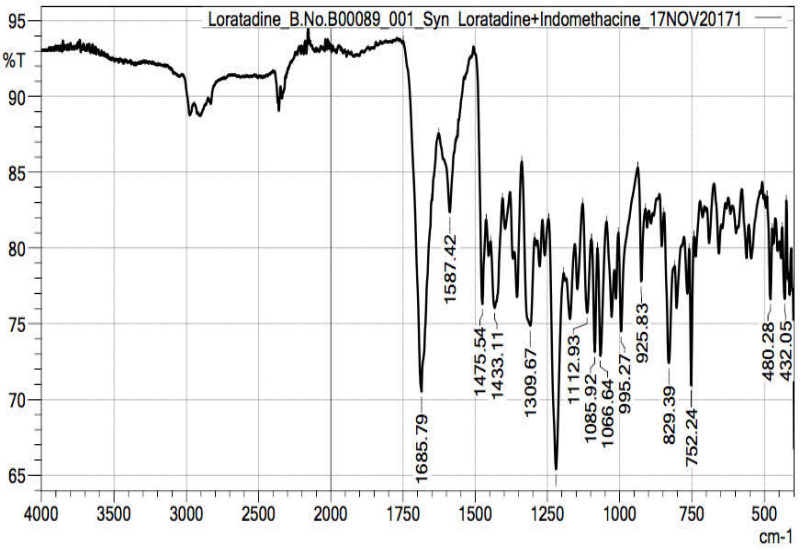

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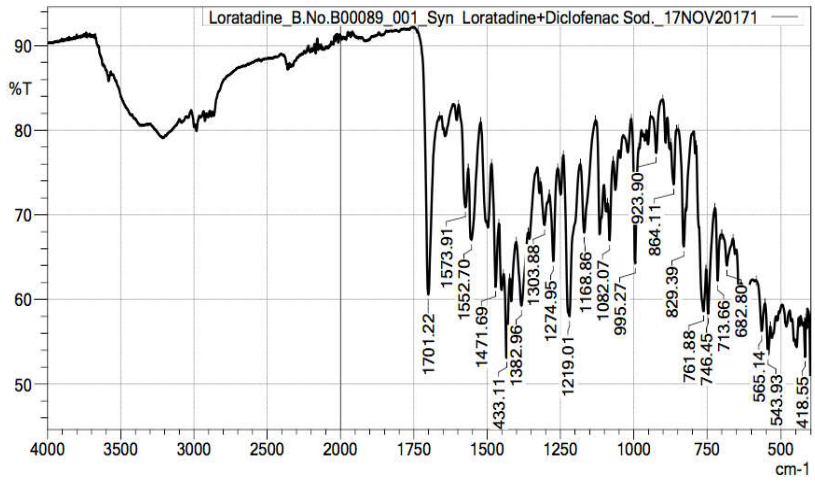


e

Fig. 1: FTIR Spectra of (a) Loratadine. (b) IL-1 (Loratadine+Oleic Acid) (c) IL-2 (Loratadine+Salicylic Acid) (d) IL-3 (Loratadine+Indomethacin) (e) IL-4 (Loratadine+Diclofenac Na)

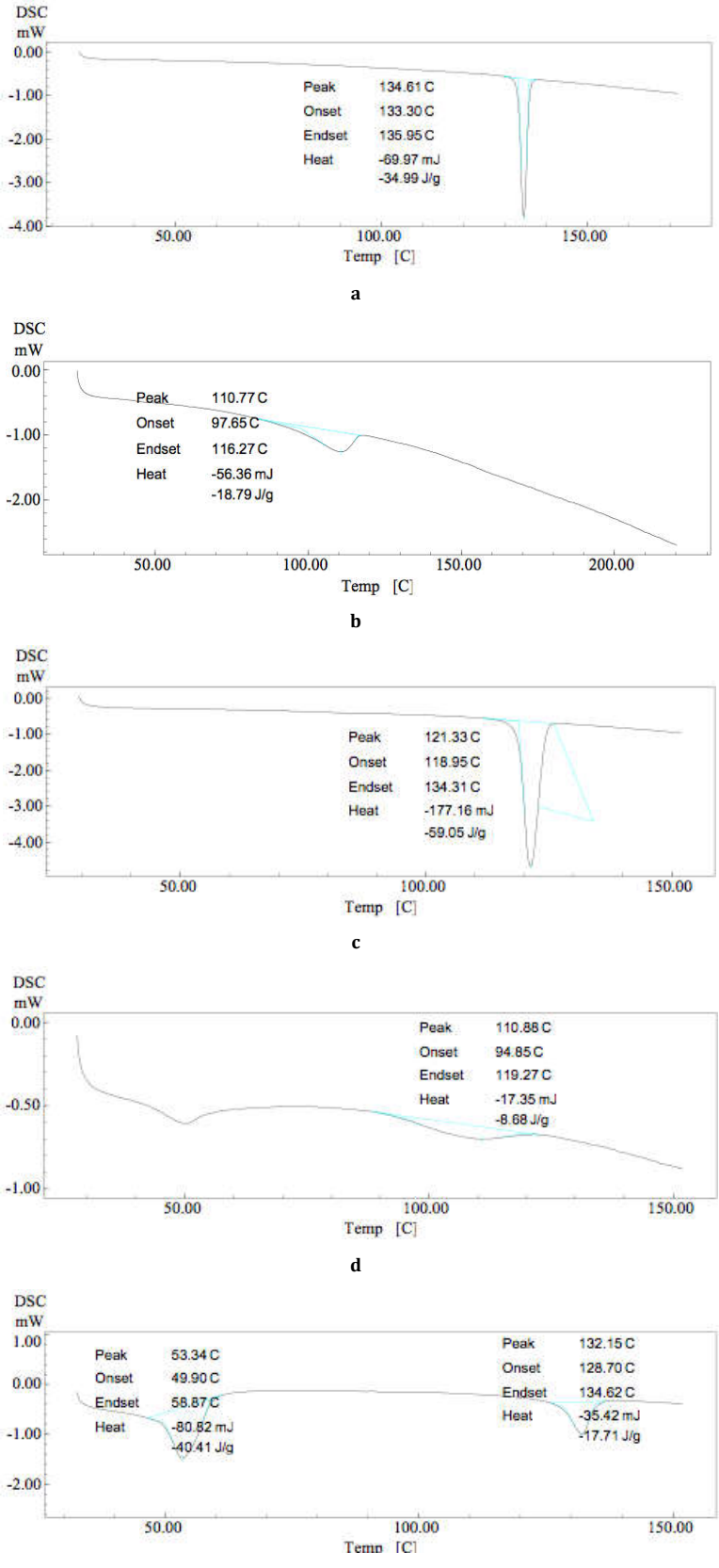
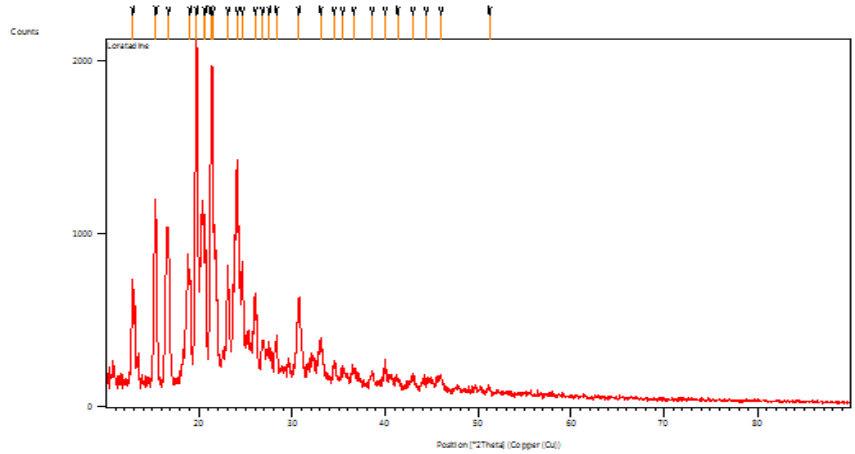


Fig. 2: DSC of (a) Loratadine. (b) IL-1 (Loratadine+Oleic Acid) (c) IL-2 (Loratadine+Salicylic Acid) (d) IL-3 (Loratadine+Indomethacin) (e) IL-4 (Loratadine+Diclofenac Na)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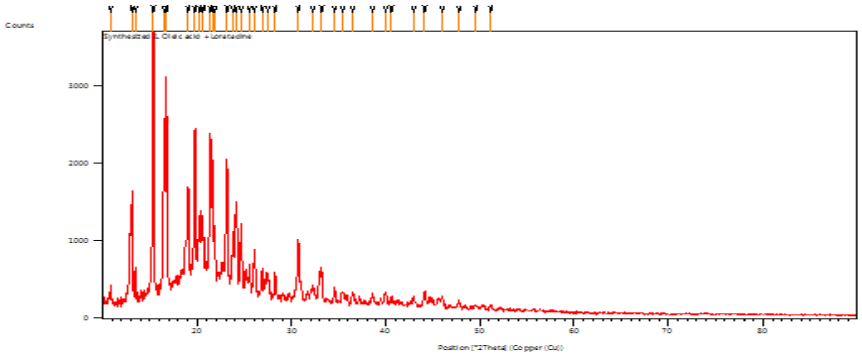
60
70
80
Position [°2Theta] (Copper (Cu))

a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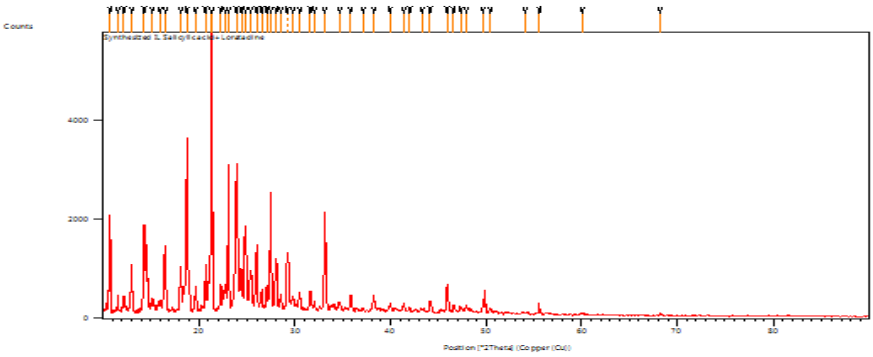
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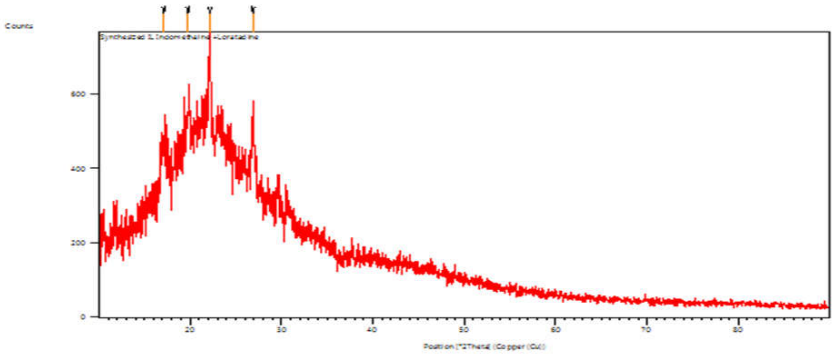
Position [°2Theta] (Copper (Cu))

c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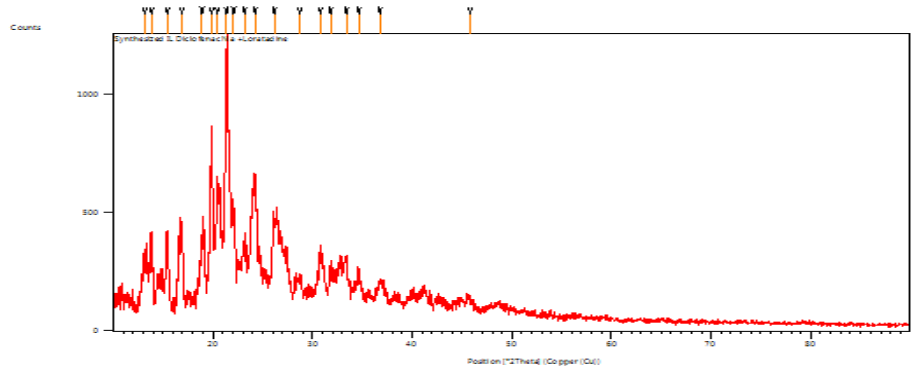

e

Fig. 3: XRD of (a) Loratadine. (b) IL-1 (Loratadine+Oleic Acid) (c) IL-2 (Loratadine+Salicylic Acid) (d) IL-3 (Loratadine+Indomethacin) (e) IL-4 (Loratadine+Diclofenac Na)

XRD studies

In diffractograms, the peak position (angle of diffraction) is indicative of a crystal structure and peak height is a measure of the sample crystallinity. The physical state of loratadine in IL salts were investigated by XRD, which could provide information on crystallinity and crystal orientation. X-ray diffraction pattern of pure loratadine and synthesized IL salts are presented in fig. 3. XRD analysis was performed to confirm the results of FTIR and DSC studies. The X-ray diffraction pattern of loratadine exhibit sharp, highly intense and less diffused peaks indicating the crystalline nature of the drug. The pure loratadine showed diffraction peaks at 2Θ degree of 19.76, 21.44, 21.20 and 24.10 shows that the drug was crystalline in nature. IL-1 shows only peaks like that of loratadine. IL-2 shows peaks at 21.29, 23.03, 23.87, 27.44 shows crystalline nature. In IL-3 and IL-4, peaks between 20 °-30 ° were broadened; indicating conversion of the crystalline structure to amorphous one and hypothesis was supported by FTIR and DSC studies. It has been reported that to achieve maximum therapeutic efficacy, it is important that ILs of API should be in amorphous form. Amorphous APIs have higher solubility, higher dissolution rate and reduced polymorphism than corresponding crystals [24].

The X-ray diffraction pattern of IL salts was simply a superimposition of each component with peaks of loratadine. In the case of IL salts, diffraction peaks (2Θ degree) showed sharp peaks with reduced intensity. This suggests that the crystallinity of loratadine was reduced in IL salts preparation.

Solubility studies

Synthesized IL salts were consisted of loratadine and counter-ions. These counter-ions affect the solubility of the resulting salt. The IL salts were tested for their solubility in distilled water. The solubility profile of loratadine and synthesized IL salts are given in table 3. From the solubility studies, it was evident that the solubility of synthesized IL salts was decreased in distilled water. Since all the selected counter-ions were lipophilic in nature; therefore, the effect on solubility in water was as expected. All the IL salts were found to have lower water solubility as compared to the pure loratadine. This indicates that the IL salts are more lipophilic than the pure loratadine. This increase in the lipophilicity of the resulting IL salt may increase the membrane permeability, hence, may have the potential of faster absorption in the gastrointestinal tract. This can be evaluated in future studies.

Table 3: Solubility of pure drugs and synthesized IL salts in water

Drug	*Solubility in water (mg/ml)	IL salts	*Solubility in water (mg/ml)	
			Loratadine	Counter-ion
Loratadine	35.85±1.5	IL-1	3.63±1.4	----------
Salicylic acid	8.94±1.2	IL-2	15.39±1.2	10.27±1.3
Indomethacin	7.55±0.2	IL-3	5.31±0.2	3.39±0.2
Diclofenac Na	15.90±1.23	IL-4	3.71±0.8	4.49±1.1

* Data represented as mean±standard deviation [SD], n=3

Dissolution studies

The dissolution profile of pure loratadine and synthesized IL salts are presented in fig. 4. It was evident from the data that the percentage drug released decreased in IL-1 due to the extremely lipophilic nature of oleic acid whereas in IL-2, IL-3 and IL-4, it was nearby or same as loratadine. The results are in agreement with that obtained from solubility studies, DSC and XRD. Thus, the *in vitro* dissolution study shows that drug release was less or the same as that of loratadine due to extremely low solubility of loratadine.

The dissolution of IL salts was slow due to physical nature of IL salts, which makes aggregate mass when comes in contact with aqueous media. Thus decreasing effective surface area available for dissolution, hence showed sustained release behaviour.

IL salts using counter-ions, oleic acid, salicylic acid, indomethacin and diclofenac sodium showed slower and lower dissolution as compared to loratadine due to high molecular weight or bulky nature or may have hindered drug release from IL salts. Hence they can be used for sustained release purposes.

Palatability evaluation

Palatability evaluations were carried out by the consents of human volunteers are presented in table 4 and fig. 5. IL-1 was rated as oily and tasteless. Because of the oily taste, the mean score was 3.66 ± 0.69 and hence was not very much acceptable. IL-2, IL-3 and IL-4 were rated as palatable by volunteers of the panel. The taste masking can be attributed to the reduction in water solubility of the synthesized ILs. Due to the lesser solubility, the loratadine IL salts do not solubilize when on the tongue and hence cannot interact with the taste buds for perceiving the taste. These studies suggested utility of IL approach for taste masking of bitter drugs.

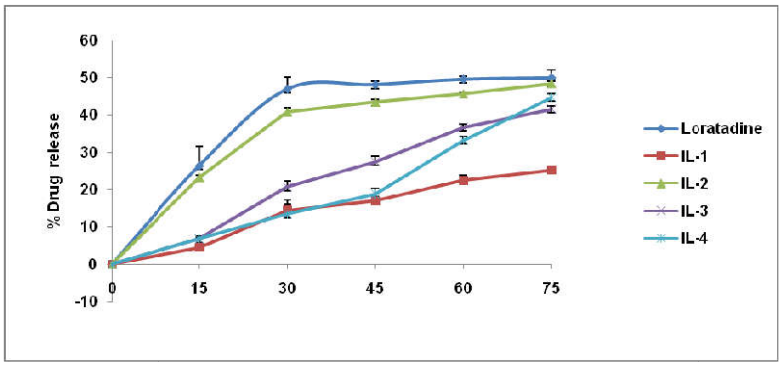

Fig. 4: *In vitro* dissolution profiles of loratadine and synthesized IL salts (n=6)

Table 4: Taste evaluation of loratadine, counter-ions and synthesized IL salts

Name of compounds	*Score	Remarks**
Loratadine	4 ± 0.53	Bitter
Oleic acid	4 ± 0.34	Oily
Salicylic acid	3 ± 0.34	Palatable
Indomethacin	3.2 ± 0.53	Palatable
Diclofenac	3.3 ± 0.46	Slighter bitter but, palatable
IL-1	3.6 ± 0.69	Oily and tasteless
IL-2	2.8 ± 0.63	Palatable
IL-3	2.8 ± 0.63	Palatable
IL-4	2.5 ± 0.46	Palatable

*Data represented as mean±standard deviation [SD], n=6, **Scale: 0: tasteless, 1:extremely palatable; 2:palatable; 3:slightly bitter; 4:bitter; 4:extremely bitter

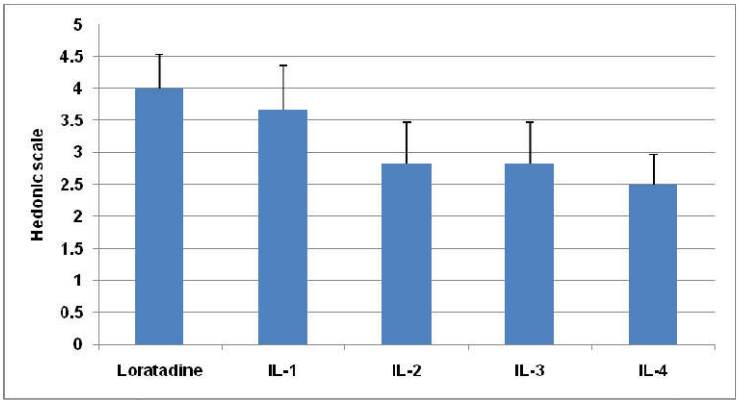

Fig. 5: Taste masking evaluation of loratadine and synthesized IL salts, *Data represented as mean±standard deviation [SD], n=6

CONCLUSION

It can be concluded from the above studies that the selected counter-ions can form ionic liquids with loratadine as confirmed from the change in melting point, as well as from FTIR, DSC, and XRD studies. The prepared ILs can effectively mask the bitter taste of loratadine as evident from the studies carried out on human volunteers for taste evaluation. Thus, the prepared ILs can be used for the formulation of the patient-friendly dosage forms like syrups, solutions, orally disintegrating tablets, etc. IL salts of loratadine indomethacin and diclofenac can be used in the fixed-dose combinations where both anti-histaminic and anti-inflammatory properties are desired.

ACKNOWLEDGEMENT

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Nil

AUTHORS CONTRIBUTIONS

Of the above three authors, Nidhi P. Sapkal designed and guided the whole project and writing of the manuscript. Nidhi Jaiswal executed the studies. Pradnya Gondane helped in writing the manuscript and also acted as a corresponding author.

CONFLICT OF INTERESTS

Declared none

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