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DEVELOPMENT AND CHARACTERIZATION OF INNOVATIVE LIQUID SALT BASED FORMULATIONS OF SPARINGLY SOLUBLE DRUGS

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ABSTRACT: As a result of tremendous efforts in past few decades, various techniques have been developed in order to resolve solubility issues. However, majority of these techniques offer benefits associated with certain drawbacks; majorly including low drug loading, physical instability on storage and excessive use of environmentally challenging organic solvents. Hence, current effort was to develop an eco-friendly technique using liquid salt, which can offer improvement in dissolution while maintaining long term stability. The liquid salt formulations of poorly soluble model drugs ibuprofen, gemfibrozil and indomethacin were developed using 1-Ethyl-3-methylimidazolium ethyl sulfate (EMIM ES) as a non-toxic and environmentally friendly alternate to organic solvents. Liquid medications containing clear solutions of drug, EMIM ES and polysorbate 20, were adsorbed onto porous carrier Neusilin US2 to form free flowing powder. Liquid loading as high as 70% w/w was achieved while maintaining good flowability and compressibility. The liquid salt based formulations (LSF) demonstrated greater rate and extent of dissolution compared to crystalline drugs. The LSF samples exposed to 40°C/80% RH for 8 weeks, demonstrated excellent physical stability without any signs of precipitation or crystallization. The liquid salt formulation technique served as compelling alternate to the conventional techniques for the development of poorly soluble compounds.

INTRODUCTION: According to leading market research, the global oral drug delivery market share in 2010 was valued at $49 billion and expected to grow to $97 billion by 2017. Success of the oral drug formulations relies on the aqueous solubility and intestinal permeability of drug molecules which govern oral absorption.

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Despite of increased demand for oral formulations, now-a-days, majority of the new drug molecules discovered are poorly soluble and/or low permeable which are major obstacles in oral formulations development.[1] As there are very limited approaches that can enhance intestinal permeability, dissolution rate and extent are the only key factors to make an improvement in order to achieve optimum bioavailability through intestinal absorption.

Based on dissolution theories and Fick's diffusion laws, a concentration gradient across the membrane, which governs mass transfer through membrane barrier, can be altered by changing the solubility of the molecule. As a result of tremendous efforts in past few decades, various

techniques like amorphous solid dispersions, self-emulsifying drug delivery systems, nanoparticles or particle size reductions, and sophisticated technologies including spray drying and hot melt extrusion (HME) have been developed in order to resolve these problems.[2] Majority of these techniques offer benefits associated with certain drawbacks.

Conventional amorphous solid dispersion formulations aid to overcome solubility issue, but leads to the challenging physical instability associated with higher free-energy which reverts amorphous drug molecules in formulation to thermodynamically more stable and less soluble crystalline form.[3] Solid self-emulsifying systems practically restricted to lipophilic potent drugs due to low loading capacity and excessive use of surfactants associated with GI irritation.[4] Particle size reduction and sophisticated nanotechnology also show difficulties in development of stable formulations due to higher surface energy and corresponding aggregation.[5] Use of more advanced technique like HME is limited due to stress conditions applied on APIs.[6] Commercially feasible spray drying requires excessive use of organic solvents which are responsible for environmental harm.[7]

The authors report no declarations of interest. Hence, current effort was to develop an eco-friendly technique using liquid salts as green solvents which can offer improvement in dissolution while maintaining long term stability.

Any salts that exist in liquid state are referred as liquid salts. Liquid salts also known by various names including ionic liquids (IL), ionic fluids, fused salts, ionic melts and ionic glasses. Large size, delocalized charge and conformational flexibility of the ions involved in salt formation, lead to small lattice enthalpy and large entropy change that favor melting.

These poorly coordinated ions form salts, which remains in thermodynamically favored liquid state below 100°C or even at room temperature, are known as room temperature ionic liquids (RTIL).[8]Conventional salts that normally exist in solid state at room temperature, and exhibit liquid state without decomposition at elevated temperature are referred as molten salts.[9] As in present context of pharmaceutical application, RTIL are convenient and favorable compared to rest of liquid salts; for further discussions, liquid salt refers to RTIL with melting point well below room temperature.

Numerous possible combinations of bulky cations responsible for low melting and good solvation ability with relatively small anions responsible for stability, lead to large pool of custom tailored liquid salts providing desired properties to satisfy the specific application needs. Because of their fine-tuned properties they even called as “designer solvents”.[10] These liquid salts offer attracting properties like great solvation ability, low vapor pressure, low combustibility and good thermal stability. In addition to that, negligible vapor pressure even at elevated temperature makes them inevitable green solvents. As organic solvents produce volatile organic compounds responsible for increased worldwide air pollution, liquid salts can serve as environmentally friendly alternate.[10, 11]

These fascinating properties of liquid salts make them great solvents with superior solvation ability for wide range of compounds.

Pharmaceutical industry majorly rely on solid crystalline drugs which more often suffer from additional issues related to transformation into different polymorphs. Recently, Rogers and colleagues have published series of research and review articles suggesting possible applicability of ionic liquid concept to develop pharmaceutically active liquid salts, to overcome deficiencies associated with solid salts.[12-14] In recent works, it has been demonstrated that it is possible to combine two API (active pharmaceutical ingredients) ions to form dual functioning liquid salt to produce synergistic effect or alternatively combining ions of API with GRAS (Generally regarded as safe) excipients can assist delivery of API to the target. Lidocaine docusate, a liquid salt prepared from hydrophilic cation of lidocaine hydrochloride (a local anesthetic) and hydrophobic counter ion of sodium docusate (an emollient), demonstrated longer lasting antinociceptive effect than conventional lidocaine hydrochloride by increasing penetration through skin.[15]

Despite of numerous promises, in well regulated pharmaceutical industry, alteration of new drug molecule or drug molecule with proven efficacy is challenging due to associated risks of loss of activity or incorporation of new toxicity resulting from counter ions.

In recent studies, tetracycline, an antibiotic was combined with docusate in order to optimize solubility and hydrophilic-lipophilic balance. Resulting liquid salt, tetracycline docusate fails to meet desired properties, highlights importance and challenging nature of selection of ions to achieve goals.[16] Considering possible negative impacts, instead of altering every drug molecule as required, use of custom designed liquid salts as pharmaceutical green solvents or excipients can be superior and more beneficiary in terms of time and cost of development.

In recent publication, researchers evaluate various liquid salts as solvent for their ability to enhance HSA (Human Serum Albumin) binding of Nimesulide. Findings suggest possible use of liquid salts as drug solvents, for influence on biological processes such as drug distribution and absorption.[17] Microemulsion based formulation approach has been investigated and proven to be effective in delivering poorly soluble drugs.[18, 19] However, as majority of liquid salts used are lacking toxicity details, it is critical to choose appropriate liquid salt for pharmaceutical application. The current study explores toxicologically safe liquid salt, 1-Ethyl-3-methylimidazolium ethyl sulfate, for its applicability as eco-friendly solvent in formulation of poorly soluble drugs i.e. ibuprofen, gemfibrozil and indomethacin.

MATERIALS AND METHODS:

1-Ethyl-3-methylimidazolium ethylsulfate (EMIM $EtOSO_3$ or EMIM ES) is an ecologically friendly RTIL with a melting point less than -30°C. Out of large pool of liquid salts lacking toxicological details, data suggests that EMIM ES does not have harmful acute oral toxicity. EMIM ES was purchased from Sigma-Aldrich Chemical Co. (St. Louis, MO). Its physicochemical properties and toxicological data are summarized in **Table 1** and **Table 2** respectively.[20]

TABLE 1: PHYSICOCHEMICAL PROPERTIES OF 1-ETHYL-3-METHYLIMIDAZOLIUM ETHYL SULFATE (EMIM ES)

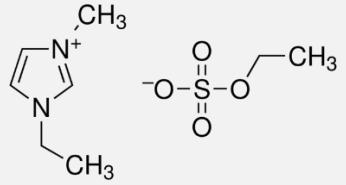
	EMIM ES
Chemical structure	
Molecular formula	$C_8H_{16}N_2O_4S$
Molecular weight	236.29 g/mol
Melting point	Less than -30°C
Density	1.239 g/cm3 at 20 °C
Viscosity	98.7mm^2/s at 25 °C
Solubility	Completely soluble in water and many organic solvents
Log P_{ow}	Less than 0.3

TABLE 2: TOXICOLOGICAL DATA OF 1-ETHYL-3-METHYLIMIDAZOLIUM ETHYL SULFATE (EMIM ES)

	EMIM ES
Acute oral toxicity	Not harmful
Skin irritation	Non-irritant
Eye irritation	Non-irritant
Sensitization	Non-sensitizing
Mutagenicity	Non-mutagenic
Toxicity to daphnia	Not acutely harmful
Oral LD_{50} – rat	> 2,000 mg/kg
Dermal LD_{50} – rat	> 2,000 mg/kg

Model compounds Ibuprofen (IBU) and Gemfibrozil (GEM) were purchased from Spectrum Chemicals Mfg. Corp. (New Brunswick, NJ). Indomethacin (INDO) was purchased from Sigma-Aldrich Chemical Co. (St. Louis, MO). Different grades of Neusilin (Magnesium aliminometasilicate) were generous gift from Fuji Health Science Inc. (Burlington Township, NJ).

Tween 20 was purchased from Spectrum Chemicals Mfg. Corp. (New Brunswick, NJ). Avicel PH 102 (Microcrystalline Cellulose) was received as free sample from FMC Biopolymers (Philadelphia, PA). Lactopress Spray Dried 250 (Lactose monohydrate) and Ludipress LCE (93% Lactose and 7% PVP) were gift from Mutchler Inc. (Harrington Park, NJ). All compounds were used as received without further purification or modification. All other reagents used in the experiments were analytical grade.

Preparation of Liquid Salt Formulations (LSF):

A liquid salt formulation technique was developed to prepare formulations of crystalline drugs

ibuprofen, gemfibrozil and indomethacin. Lead formulations were prepared by dissolving various proportions of drugs in EMIM ES by stirring, followed by sonication in water bath at room temperature for 15 min. As specified in **Table 3**, the ratios of drug to EMIM ES were determined based on solubility of drugs in EMIM ES. To the drug solutions, polysorbate 20 was added and further stirred until clear solutions were obtained. This prepared liquid drug solutions (liquid medications) were adsorbed onto neusilin US2 (NUS2) by blending together using spatula or overhead mixer to obtain free flowing powders. Weight ratios of liquid medication to the adsorbent were determined based on flow properties obtained from powder rheology.

TABLE 3: COMPOSITIONS OF THE LIQUID SALT FORMULATIONS

Formulations	API (mg)	EMIM ES (mg)	Tween 20 (mg)	NUS2 (mg)
IBU IL	200	300	7.75	217.5
GEM IL	150	375	18.75	233
INDO IL	100	500	25	268

Powder Rheology and Loading Capacity:

FT4 powder rheometer (Freeman technology, Gloucestershire, UK) was used for comparative study of power properties i.e. flow ability and compressibility, to determine optimum liquid loading capacity. The Basic Flow ability Energy (BFE) and %Compressibility were measured using 25mm x 25ml split vessel and 25 mm x 10 ml split vessels respectively. Samples were conditioned using 23.5 mm blade prior to each test, which removes packing history of powder and any operator influence, thus, generates homogenized uniform powder packing.

In BFE measurement, a blade is traversed through powder bed at helix angle of 5°. The energy required to move the blade through power in downward traverse direction is defined as BFE. In compressibility measurement, a blade was replaced with a vented piston to compress powder samples under normal stress range 1-15kPa. The percentage change in the volume of sample under a given normal stress was defined as % compressibility.

Differential Scanning Calorimetry(DSC):

The thermal properties of freshly prepared as well as stored samples were evaluated using TA Q200 modulated differential scanning calorimeter (TA instruments, New Castle, DE). Samples weighing between 6-12mg were loaded in hermetic aluminum pans with a pin-hole lids, and were crimp sealed. Samples containing ibuprofen and gemfibrozil were heated from 20 to 120°Cat rate of 3°C/min with modulation amplitude of ±1.59°C every 60 s. Due to higher melting temperature, indomethacin samples were scanned from 20to 200°C. In addition, to monitor any glass transition related changes and to erase thermal history, heat-cool-heat method was used. During heat cycles, ibuprofen and gemfibrozil samples were heated at the rate of 10°C/min from -75 to 125°Cfollowed by cooling at 5°C/min. In case of indomethacin, samples were analyzed from 0 to 200°C. The DSC thermo grams were analyzed using the Universal Analysis 2000 software (TA instruments, New Castle, DE).

Powder X-Ray Diffraction (pXRD):

The powder X-ray diffraction patterns were obtained by using Scintag X1 advanced theta-theta diffraction system (Scintag Inc. Cupertino, CA). The X-ray was generated at voltage of 45 kV and a current intensity of 40 mA. The test samples were scanned over a 2θ range of 5°-50° at scan rate of 0.04°/sec with a step size of 0.02. Diffraction patterns of sample were analyzed using DMS NT software. Diffraction patterns of liquid salt formulations were recorded and used to investigate the presence of crystal in stored samples.

Scanning Electron Microscopy (SEM):

The morphological analysis of LSF particle surface was performed using Hitachi S4000 FE SEM (Hitachi High Technologies America Inc. Dallas, TX). The samples were mounted on a sample stub followed by coating with a thin layer of Au/Pd to make surface conductive. The topographical features of sample surface were examined in Secondary Electron Imaging (SEI) mode. Images were digitally captured at 2048x1594 pixel resolution.

Dissolution Studies:
In-vitro dissolution of all liquid salt formulations, pure drugs and physical mixtures without ionic liquid were performed using USP dissolution apparatus II (Distek dissolution system 2100A, North Brunswick, NJ) at 50 RPM. Dissolution of liquid salt formulations equivalent to 200mg ibuprofen, 150mg gemfibrozil and 100mg indomethacin were assessed using 900ml of phosphate buffer at pH 6. Dissolution media was chosen based on solubility of model compounds. Temperature of dissolution media was maintained at 37 ± 0.5°C throughout study. Samples were collected at regular time intervals and amount dissolved were analyzed using appropriate analytical method.

Dissolution samples containing ibuprofen were analyzed using Shimadzu HPLC system (Simadzu Scientific Instrument Inc. Canby, OR) with detection by UV detector at wavelength of 214nm.Amount of indomethacin and gemfibrozil released were detected using Shimadzu UV-1800 UV-Vis spectrophotometer (Simadzu Scientific Instrument Inc. Canby, OR) at wavelength of 319 nm and 274 nm, respectively.

Stability Studies:
To determine physical stability on storage, open and closed vials containing LSF samples were stored in desiccators containing saturated sodium chloride solution which provides 80 ± 2% RH at 40 ± 1°C oven. At regular time intervals, samples were investigated for development of crystals using pXRD and DSC.

RESULTS AND DISCUSSION: Solvent impregnation techniques have been reported in the literature to load poorly soluble drugs onto porous material i.e. silica, in order to improve dissolution characteristics and bioavailability. The drug loading processes involve use of volatile organic solvents to dissolve drug, and resulting solution is adsorbed onto silica via impregnation, followed by solvent removal and drying at higher temperature and vacuum. Amorphous drug results in obtaining a better dissolution profile.[21] However, adsorbed drug upon storage due to higher energy in amorphous form, can induce crystallization to thermodynamically more stable and less soluble crystalline form. In addition to that, this technique involves excessive use of environmentally harmful organic solvents, and also requires 24 to 48 hours of solvent removal and drying stage that makes this technique unsuitable for large scale production. Therefore, in the present study, organic solvents were substituted with non-volatile and eco-friendly liquid salt i.e. EMIM ES, in order to make it industrially suitable and to stabilize the final product to maintain its performance on storage.

Depending on solubility of drugs in EMIM ES, concentrated solutions of ibuprofen, gemfibrozil and indomethacin were prepared in a drug to solvent weight ratio of 2:3, 2:5 and 1:5 (w/w) respectively. During preliminary investigations, it was observed that, due to concentrated drug solutions, portion of the solutions immediately precipitate on contact with dissolution media. This may be a result of supersaturated microenvironment and subsequent precipitation. In order to avoid immediate precipitation, relatively low amount i.e. 1, 2.4 and 2.8% of polysorbate 20 was added to IBU IL, GEM IL and INDO IL formulations respectively. Surfactant's capability to increase drug solubilization and to delay drug precipitation, is well established in various studies.[22, 23]Surfactant lowers interfacial tension between drug molecules and dissolution media, thus, facilitate solubilization and prevent precipitation.

Drug Loading and Powder Rheology:
Clear solutions containing drugs, EMIM ES and polysorbate 20, were adsorbed onto porous Neusilin US2 by blending together to form free flowing powder. The maximum adsorption capacity, while maintaining acceptable powder properties, was determined by comparing BFE and %compressibility obtained using FT4 powder rheometer. Furthermore, to justify the selection, flow properties and compressibility were compared with the properties of commercially available direct compressible materials i.e. Avicel PH 102, Ludipress LCE and Lactopress 250.

The BFE is measurement of work done by blade during downward traverse through previously conditioned powder bed. As shown in **Fig. 1(A)**, Neusilin US2 shows excellent flow behavior with

BFE as low as 28.5 mJ compared to Avicel PH 102 (334 mJ), Ludipress LCE (534 mJ) and Lactopress 250 (236 mJ) respectively. The BFE values of IBU IL sample with 70% w/w liquid load was measured as 117 mJ, which is significantly lower as compared to the controls. As liquid loading increased from 30% w/w to 70% w/w, BFE gradually increases in an exponential pattern. This kind of behavior is normally observed for powder samples that flow freely under gravity.

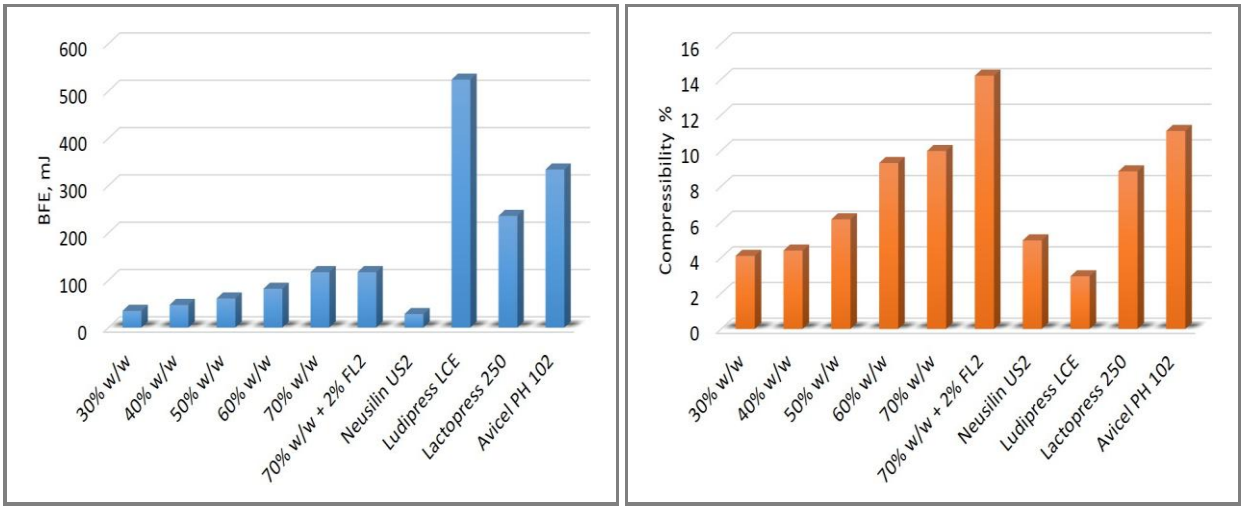


FIG.1: COMPARISON OF (A) BASIC FLOWABILITY ENERGY (B) PERCENTAGE COMPRESSIBILITY OF LIQUID SALT FORMULATION IBU IL WITH 30%, 40%, 50%, 60% AND 70% LIQUID MEDICATION LOADING, NEUSILIN US2 AND COMMERCIALLY AVAILABLE DIRECT COMPRESSIBLE MATERIALS AVICEL pH 102, LACTOPRESS SPRAY DRIED 250, LUDIPRESS LCE.

The degree of compressibility of the IBU IL samples and various controls are shown in **Fig. 1(B)**. The %compressibility represents decrease in the volume of the powder on application of a normal stress. It is evident from **Fig.1(B)**, that between applied loads of 1-15 kPa, the %compressibility of the IBU IL increases with increase in liquid loading in the range of 30-70% w/w. The %compressibility of 70% w/w IBU IL sample was 9.97%, which is two times higher than that of pure Neusilin US2 measured as 4.96%. Moreover, %compressibility of 70%w/w IBU IL sample was found to be similar or higher as compared to Lactopress 250, Avicel PH 102 and Ludipress LCE. Addition of 2% w/w fines i.e. Neusilin UFL2 to 70% w/w IBU IL, further increases %compressibility to 14.2% without affecting its flow.

Neusilin US2 possesses very large specific surface area (300 m^2/g), which facilitate high liquid adsorption while maintaining good flowability and compressibility.[24] 70% w/w liquid loading was achieved with acceptable powder properties for further processing in formulation. Loading higher than 70% w/w resulted into a damp mass and lost power behavior. Thus, for further studies, all formulations were prepared with 70% w/w liquid loading.

Thermal Analysis by Differential Scanning Calorimetry:

All liquid salt formulations were evaluated for glass transition (T_g) using DSC with an objective of determining phase homogeneity in freshly prepared samples followed by precipitation on storage. **Fig. 2(A, B&C)** represents T_g for amorphous IBU, GEM and INDO at -44, -29 and 45°C, respectively. The commonly observed gradual discontinuity in a DSC thermogram of conventional solid amorphous systems represents transition of a glassy state to a viscous liquid state.[25] The freshly prepared liquid salt formulations IBU IL, GEM IL and INDO IL did not exhibit discontinuity at glass transition temperatures as previously observed in pure drugs. The disappearance of the glass transitions is most likely due to dissolution of drugs in EMIM ES. This behavior indicates the fact that even after adsorption of liquid medication on NUS2, drug remains molecularly dispersed in a liquid state without any sign of precipitation or crystallization.

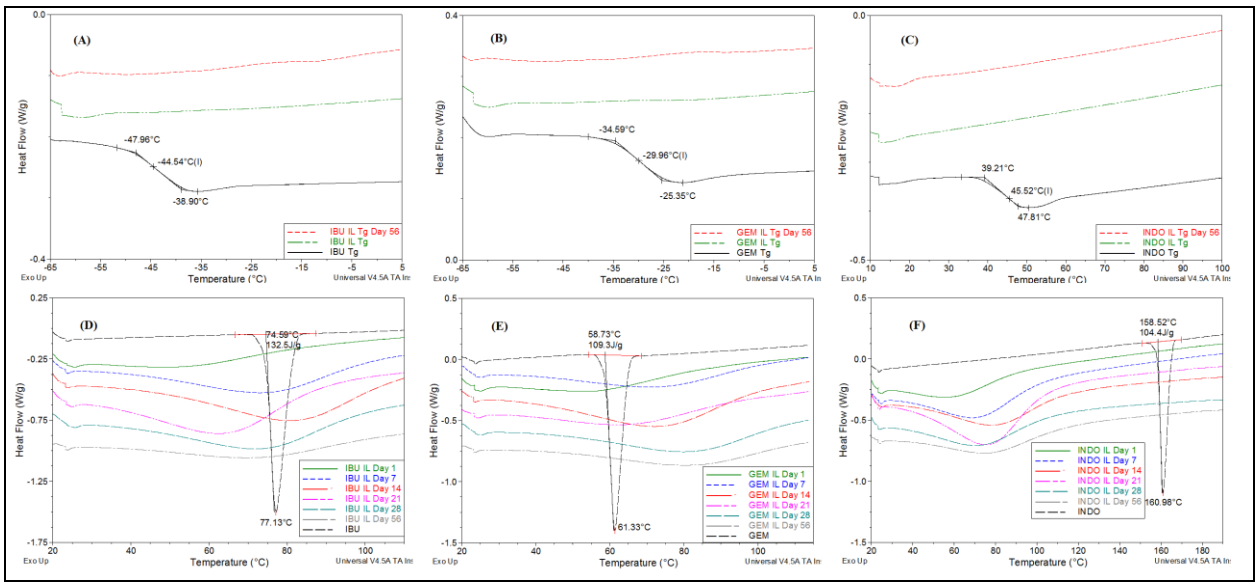


FIG.2: DSC THERMOGRAMS OF LIQUID SALT FORMULATIONS. (A) IBU IL, (B) GEM IL AND (C) INDO IL REPRESENTING GLASS TRANSITION OF PURE DRUG AGAINST ABSENCE IN LIQUID SALT FORMULATIONS. EACH FIGURE REPRESENTS THERMOGRAMS OF FRESHLY PREPARED LSF AND SUBSEQUENT CHANGES ON STORAGE AT 40°C/80% RH FOR 8 WEEKS. (E) IBU IL, (F) GEM IL AND (G) INDO IL REPRESENT ABSENCE OF MELTING ENDOTHERM AGAINST MELTING ENDOTHERM OF PURE DRUGS.

The glass transition temperature have been repeatedly utilized to determine phase homogeneity of a mixture containing two amorphous substances that have two separate T_g when measured separately.[26]Normally, thermodynamically unstable amorphous solid systems upon storage shows subsequent crystallization and phase separation which can be verified by transition from single T_g to two distinct T_g corresponding to two separate phase.[27] In contrast to conventional formulation techniques, liquid salt formulations IBU IL, INDO IL and GEM IL stored at 40°C/80% RH for 8 weeks, did not show evolution of T_g with respect to time. The EMIM ES keeps drug molecularly dispersed in liquid state without further precipitation or crystallization on storage. This behavior is indicative of good physical stability of formulation upon storage.

IBU and GEM demonstrate very low glass transition temperatures (-44 and -29°C, respectively) and recrystallize rapidly when exposed to relatively higher humidity. Therefore, due to higher molecular mobility, developing a physically stable amorphous system of these candidates could be challenging. Under accelerated conditions, any uptake of moisture would lower the T_g and consequently, an increase in the molecular mobility leading to rapid phase separation and crystallization. In contrast to amorphous systems, in liquid salt formulations IBU IL, GEM IL and INDO IL, drug remains in liquid state and purely behave as a molecularly dispersed drug solution even at lower temperature, which helps to overcome challenge of phase separation associated with solids. In liquid state, drug precipitation or crystallization depends on the solubility of drug in solvent i.e. EMIM ES. Hence, exposure of LSF to extreme conditions does not cause physical instability associated with higher mobility of molecules.

To confirm the absence of crystalline drugs in freshly prepared samples as well as stored samples, results were verified from absence of melting endotherms. **Fig.2 (D,E&F)** represents endotherms observed in IBU, GEM and INDO thermographsat 77, 61 and 160°C corresponds to the melting temperature of crystalline drug, respectively. Similar to results obtained from T_g study, the melting endotherms also were not observed in IBU IL, GEM IL and INDO IL formulations.

These results confirm that drugs in LSF remain dissolved in EMIM ES without any subsequent crystallization. However, the vaporization of the water absorbed on storage was clearly observable in form of broad endotherms ranging from 40 and 110°C. To verify this phenomenon, samples were heated at high heating rate of 10°C/min. It was

observed that with higher scanning rate, these broad endotherms shift toward 100°C. Moreover, these broad endotherms completely disappeared during second heating cycles. This confirms that water adsorbed on storage is responsible for broad endotherms.

Powder X-ray Diffraction Analysis:

To confirm results of DSC and to determine presence of any crystalline drug particles in the freshly prepared samples and subsequent crystallization on storage, all samples were evaluated for pXRD. **Figure 3** compares X-ray patterns of freshly prepared samples and succeeding changes at definite time intervals. High intensity sharp peaks in IBU, INDO and GEM in X-ray patterns indicated crystalline nature of these pure drugs. The liquid salt formulations did not show any signs of crystallinity.

Moreover, IBU IL, INDO IL and GEM IL samples stored at 40°C/80% RH did not develop any crystalline peak. In fact, X-ray patterns did not show any significant changes upon storage. However, in case of IBU IL, minor hump was observed starting at day 7, which did not show further development. Thus, these pXRD results in combination with DSC data, justifies good physical stability on storage.

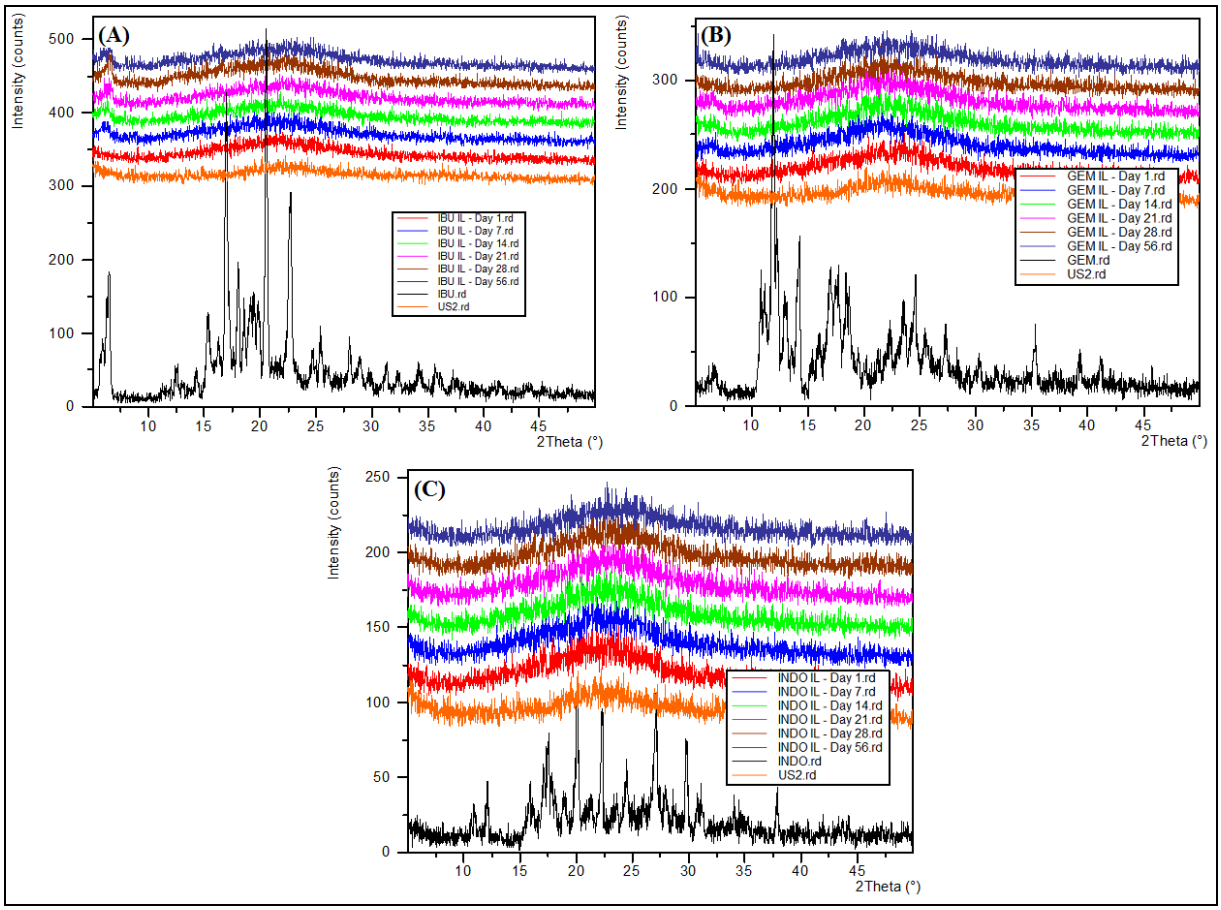


FIG.3: POWDER X-RAY DIFFRACTION PATTERNS OF LIQUID SALT FORMULATIONS (A) IBU IL, (B) GEM IL AND (C) INDO IL. EACH FIGURE REPRESENTS PXRD PATTERNS OF FRESHLY PREPARED LSF AND SUBSEQUENT CHANGES ON STORAGE AT 40°C/80% RH FOR 8 WEEKS.

Scanning Electron Microscopy:

The SEM images of NUS2, IBU IL, GEM IL and INDO IL are shown in **Fig. 4**. The NUS2 granules, at lower magnification, appear as non-adhering spheres. When observed with higher magnification at 1000x, the surface of NUS2 granules appears to be comparatively rough and porous. The porous sponge like mesh structure was found to be consistent deep inside the granules. The photomicrograph of LSF, at lower magnification of 100x, confirms non-sticking dry granules maintaining shape and appearance as of NUS2 granules without liquid medication loading. The surface of LSF seemed to be less porous and

comparatively smoother. The SEM result confirms that NUS2 adsorbs and lock the liquid medication deep inside the porous mesh, which contributes to the excellent powder properties of liquid salt formulations.

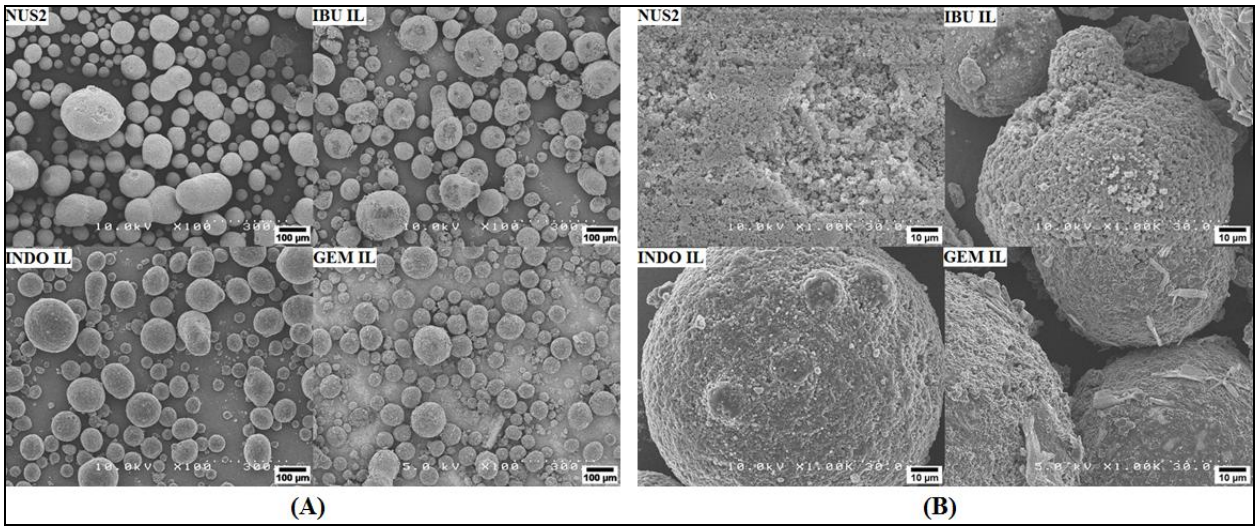


FIG.4: SCANNING ELECTRON MICROSCOPY PHOTOMICROGRAPHS OF NUS2, IBU IL, GEM IL AND INDO IL AT (A) 100X AND (B) 1000X MAGNIFICATION.

Physical Stability and Thermodynamics:

The conventional amorphous drug delivery techniques deal with solid state instability due to high free energy which leads to transformation to low energy crystalline state. The important assumption made in drug-polymer amorphous system is that the two components are mixed homogenously at molecular level. This assumption directly relates to solid state solubility of drug in polymer.[28] Till date, many theories have been proposed to predict solid-state solubility of drug in polymer to develop stable formulations. Irrespective of their application, majority of formulations face stability issues.

In contrast, concept of solubility of drug in liquid is well established and easy to predict the stability. The commonly observed crystallization and precipitation issues are solubility related processes, which majorly relies on solute concentration in solution. The thermodynamic driving force (DF) of crystallization is given by

$$DF = RT\ln(C/C_{eq}) = RT\ln S \quad (1)$$

Where C and C_{eq} represents the drug concentration in liquid medications and equilibrium saturated solutions, respectively. S represents degree of saturation. R is gas constant. T is temperature.[29]

The crystallization will be favored and will proceed in the forward direction if *DF* is positive. This is commonly observed phenomenon in supersaturated solutions where C is much higher than C_{eq}. Thus, in favor to form stable formulations, the amount of drugs incorporated in liquid salt formulations IBU IL, INDO IL and GEM IL, were slightly lower than their equilibrium solubility in EMIM ES. As previously described, liquid salt EMIM ES offers great solvation ability, which helped to develop formulations with higher drug loading without reaching to saturation solubility. Hence, the negative *DF* value of unsaturated liquid medication justifies good physical stability of liquid salt formulations on storage.

Dissolution Studies:

The primary goal behind formulating poorly soluble drug through liquid salt approach was to improve dissolution rate and extent. The dissolution profile of LSF, pure drugs and physical mixtures using USP apparatus 2 are shown in **Fig. 5**. At 20 min, more than 80% drugs were released from IBU IL and GEM IL, whereas remaining drugs gradually dissolves over the time. Rapid release of 80% of drug can be correlated with the ease of contact to the liquid medication available on outer openings of the pores. The remaining 20% liquid medication deep inside the pores contributed to slower release at later time points. The

dissolution of INDO IL was rapid in comparison, and concentration reached plateau in 10 min. The rapid release could be due to comparatively higher proportion of polysorbate 20 in the INDO IL formulation. The % drug release from IBU IL, GEM IL and INDO IL were significantly higher when compared to pure drugs IBU, GEM and INDO at 20 min, respectively.

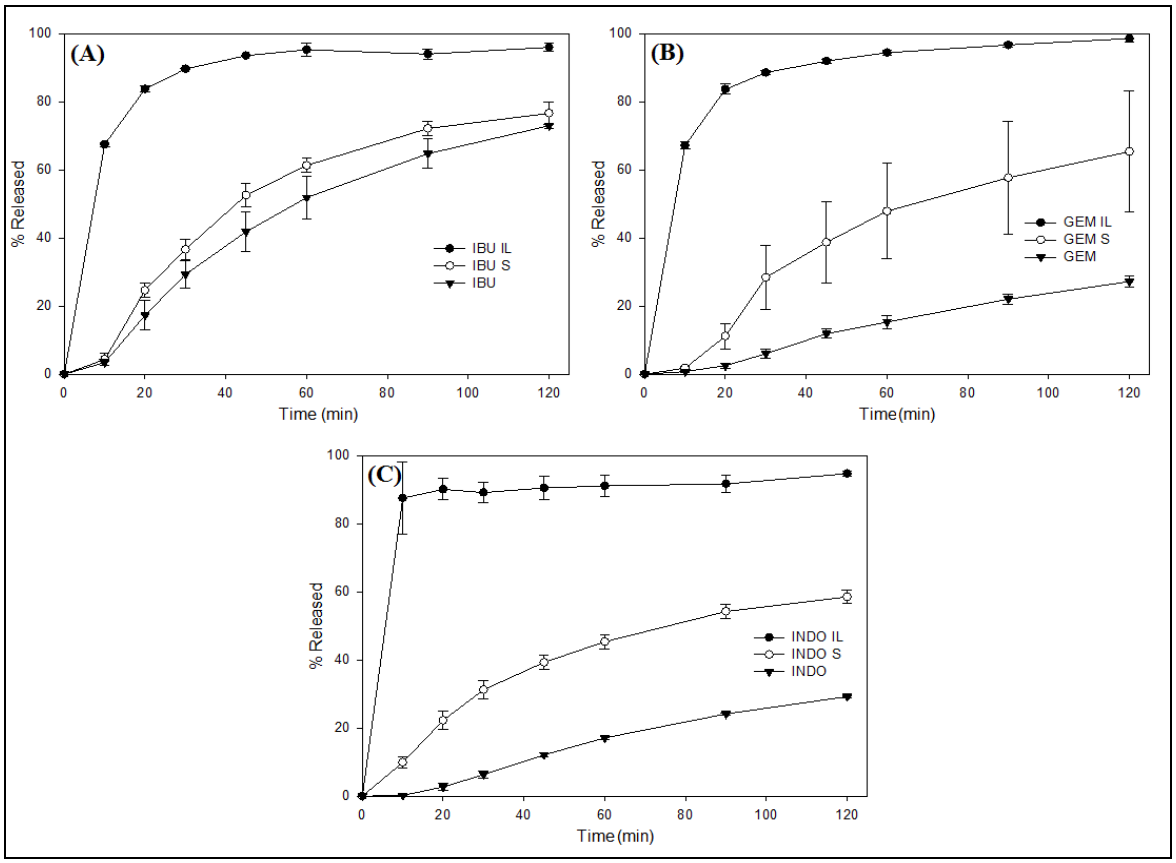


FIG.5: *IN VITRO* RELEASE OF IBUPROFEN, GEMFIBROZIL AND INDOMETHACIN FROM (A) IBU IL, (B) GEM IL AND (C) INDO IL IN PHOSPHATE BUFFER AT PH 6 USING USP APPARATUS 2 AT 50 RPM. IBU S, GEM S AND INDO S REPRESENTS PHYSICAL MIXTURE WITHOUT LIQUID SALT.

In order to verify significance of liquid salt in formulation, physical mixture containing everything but liquid salt was evaluated for dissolution behavior. The physical mixtures IBU S, GEM S and INDO S showed comparatively better dissolution when compared to pure drugs. More likely, polysorbate 20 in the physical mixture, lowered surface tension and favored wetting and subsequent dissolution. However, the dissolution from physical mixtures was significantly low compare to liquid salt formulations. This justifies that the liquid salt contributed significantly to enhance dissolution by keeping drug in solution state and readily available upon contact with dissolution media. Moreover, polysorbate 20 provides favorable microenvironment at interface between liquid medication and dissolution media, which further facilitate dissolution.

CONCLUSIONS: The development of stable formulation of poorly soluble drugs with relatively very low glass transitions, could be challenging with conventional formulation techniques. Hence, the liquid salt formulation technique was developed to overcome challenges associated with amorphous systems.

The liquid salt EMIM ES served as eco-friendly substitute to the environmentally alarming organic solvents. In addition, EMIM ES exhibited great solvation ability for all three model compounds and contributed to higher drug loading in the formulations. The dissolution profiles demonstrated significantly faster and higher dissolution from LSF compared with crystalline pure drugs. The LSF exhibited superior physical stability even on exposure to high temperature and relative humidity. EMIM ES displayed superior ability to keep drug

molecules in a solution state and to prevent crystallization on storage, which contributed to higher dissolution rate and good stability. The presence of drugs in solution state was confirmed by pXRD and DSC analysis. Neusilin US2 showed high liquid adsorption capability and helped to convert liquid medication to a solid state for easy handling in further development. The findings of this innovative technique suggest that liquid salt formulations could serve as compelling alternate for the future formulation development of poorly soluble compounds.

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