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UTILITY OF NOVEL DUAL FUNCTIONALIZED COCRYSTALLIZED AND IONIC LIQUID BASED DRUGS FOR THE PAIN MANAGEMENT

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Abstract: Pain management requires a multi-pronged approach and concerted efforts from a team of healthcare providers. The symptom of pain often resolves once underlying issue is addressed. Depending on the intensity and duration, various classes of analgesics are used along with other medications such as anxiolytics, anticancer, antiviral, etc. For chronically ill patients, compliance with the treatment regimen is very common issue and a leading cause of preventable death. Thus combination drug formulations are very popular and in demand, whereby many drugs are present in one pill or capsule. However, when drugs are combined such that they alter each other physicochemical properties, without altering the chemical structure is extremely useful and subject of high importance in the pharmaceutical research and development sector. The cocrystallization and ionic liquids formation of the pharmaceuticals are relatively new and novel concepts. Both cocrystal and ionic liquid formation require the understanding of crystal engineering and acid base chemistry in terms of proton transfer (when applicable). There is limited literature available where multiple and often complementing drugs formed such systems and evaluated for potential therapeutic purposes. This review is specifically focused on analgesics (local and systemic) based on cocrystal and ionic liquid systems.

Keywords: Pain; Pill burden; Combination Drug; Cocrystals; Ionic Liquids

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INTRODUCTION

Pain is unpleasant feeling and a complex phenomenon to describe [1]. Currently most used definition of pain is: "An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" proposed by the International Association for the Study of Pain (IASP) [2]. The pain has been classified by Woolf [3], as, nociceptive pain (only when stimuli is present), inflammatory (due to the activation of immune system), and pathological pain (due to damage to the nervous system or it's abnormal function). Usually the symptoms of pain are temporary (acute pain) and go away when the underlying pathological stimulus is removed. However, in some disease states such as cancer, peripheral neuropathy and rheumatoid arthritis, the pain can last for years or life time (chronic pain). Chronic pain can cause feelings of hopelessness, anxiety and often leads to severe depression and suicidal thoughts [4]. Thus new strategies for pain management, including, developing new devices, new drugs, new formulation and novel systems are in demand and evaluated.

For chronically ill patients dealing with complex medication regimen, low compliance (talking pills on time or skipping) is a major issue. Reducing the "pill burden" by formulating two or more drugs in one dosage form has shown to increase the adherence to the treatment. It has become evident that for managing complex disorders, such as HIV infection, cancer, diabetes, neurological and cardiovascular disease, treatment with only one drug does not work. Combining multiple drugs into one caplet/tablet (ideally) is becoming more popular, however, formulating a tablet with one active pharmaceutical ingredient (API) is not an easy task, let along combing a few. It is important to note that, whether multiple APIs are formulated in one pill or each API formulated separately and many pills are taken together, this does not offer further advantage in terms of enhanced dissolution or permeation of the APIs, given no adverse drug-drug interaction is known. Altering the physicochemical properties (mainly solubility) of the active pharmaceutical ingredient (API) without significant chemical manipulation is of great value in pharmaceutical industry as majority of the new chemical entities (NCE) exhibit very low aqueous solubility. In this regard, cocrystallization and ionic liquid formation have gained much attention recently. Cocrystallization and ionic liquid formation (for ionic APIs only) offer many advantages including but not limited to, combination of multiple APIs, solubility and permeability enhancement, and cost reduction in the pharmaceutical industry.

One succinct definition of cocrystal is still in debates; however there seems to be agreement among solid state chemists that "cocrystals are crystalline single phase materials composed of two or more different molecular and/or ionic compounds generally in a stoichiometric ratio which are neither solvates nor simple salts [5]". Cocrystallization is attempted by combining API and a coformer (guest) molecule using various techniques such as sonic slurry method, neat

grinding and reaction crystallization [6] and monitored by various techniques (Raman, X-Ray, etc). Traditionally, nontoxic coformer have been chosen from the pool of those molecules, previously declared safe for human consumption and can be found in the collections, such as Generally Recognized as Safe (GRAS) by the U.S. Department of Health and Human Services and Everything Added to Food in the United States (EAFUS) [7-9]. While making cocrystals, pKa of the components must be considered, as complete proton transfer is possible resulting in salt formation, or some times, for compounds with similar pKa, the existence of a salt-cocrystal continuum has been suggested [10-12]. It is important to note that cocrystals of the salts can also be prepared and have been reported [12]. A major advantage of cocrystallized drugs is that it can increase the solubility of the API many fold that can translate into higher drug concentration in the blood (bioavailability) for Biopharmaceutics Classification System (BCS) II compounds. Although the examples of bioavailability enhancement via cocrystallization in animal studies are limited, based on available reports, it seems a very viable approach [13-15].

Recently, Ionic Liquid (IL), especially those are liquid at room temperature (RTIL), have found great applications in chemically green processes [14,17]. Usually ionic compounds are solid at room temperature and have very high melting point thus, Ionic Liquids (ILs) are defined as organic salts with Melting Points (MP) below 100°C [18-22]. Although, exact reasons for very low melting point of ILs are not evident, it has been suggested that bulky ions (could be either anion or cations) result in random molecular packing and prevent the formation of stable crystal [23]. Ionic liquids do not evaporate, can solubilize both polar and nonpolar species and recyclable thus are considered green solvents [24,25]. These unusual liquids (ILs) have found wide spread applications in liquid-liquid extractions [26], High Performance Liquid Chromatography (HPLC) [27], Capillary Electrophoresis (CE) [28,29]. Matrix Assisted Laser Desorption Ionization Time-Of-Flight Mass Spectrometry (MALDI-TOF MS) [30], Gas Chromatography (GC) [31], Micellar Electro Kinetic Chromatography (MEKC) [32,33], and as designer solvents in pharmaceutical synthesis.[34] About 50% of the marketed drugs are salts and thus, window of opportunity exist to select verity of counter ions to prepare multidrug salts, ionic liquids and cocrystals as well [35, 36]. Recently Rogers et al., have reported third generation of ionic liquids derived from active pharmaceutical ingredients (APIs) [37]. The pharmaceutical ionic compounds, liquid at room temperature, bypass the disintegration and dissolution phase in vivo as is the case with solid oral dosage forms. If the drug is hydrophobic enough, rapid dissolution can lead to potentially faster absorb and rapid onset of the drug action [38]. As stated earlier, for ionizable API, a counter ion can be chosen so as to enhance, complement and sustain it's biologically [39,40].

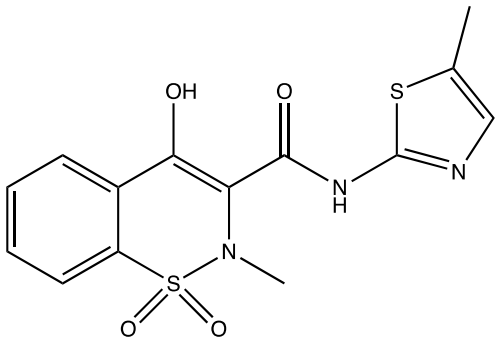
Both cocrystallization and ionic liquid formation are relatively new concepts in the pharmaceutical realm. However, combing multiple drugs for the treatment and management of

pain in this fashion is even more novel and potentially very useful. This review delves into the discussion of such systems.

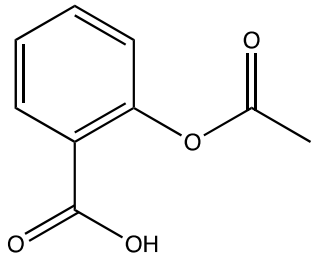
Dual Functional Cocrystals

Dual functional or two or more drugs containing cocrystals have gained much interest from the pharmaceutical industry due to the fact that, the new corystallized solids are patentable and could be considered as fixed dose combination [41]. Multidrug co-crystals are known to exhibit, better stability compared to co formulated drugs system [42], synergistic effects [43], enhanced dissolution [44], and enhanced bioavailability [45]. Multi drug cocsryal systems have not been explored as much as drug cocrystallized with non-API coformers [46], even though, possible benefits are enormous.

Meloxicam is a nonsteroidal anti-inflammatory drug (NSAID), belongs to BCS II category (low solubility, high permeability), it's low aqueous dissolution leads to slow onset, thus solubility enhancement could accelerate this process. Another NSAID, Aspirin was selected was evaluated as a possible coformer for meloxicam, this could not only help the increase in meloxicam solubility, but also compliment it's therapeutics action. The resulting cocrystal of meloxicam and aspirin exhibited faster kinetics and reduced the time required (twelve times) to reach the therapeutic level compared to the meloxicam itself and fourfold enhancement in bioavailability [47].

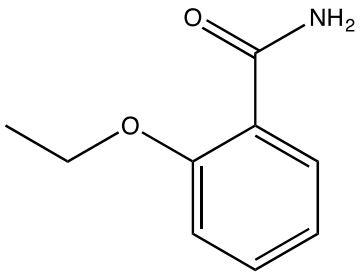


Meloxicam

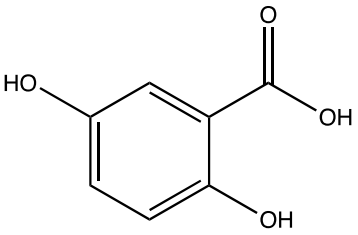


Aspirin

Srinivasulu et al. reported various cocrystals of ethenzamide with gentisic acid [48] and other bioactive molecules [49]. The ethenzamide is analgesic and anti-inflammatory drug, while gentisic acid is an active metabolite of salicylic acid biodegradation and has broad spectrum of biological activities, including anti-inflammatory, antirheumatic, antiarthritic, antioxidant and cytostatic agent [50]. The obtained cocrystals, exhibited enhanced intrinsic dissolution rate that could potentially lead to faster therapeutic onset and increased bioavailability.

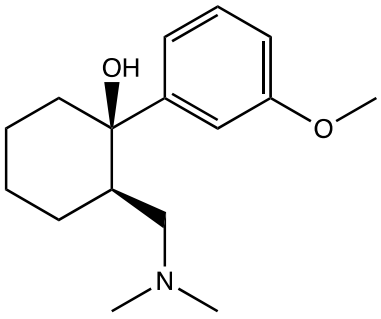


Ethenzamide

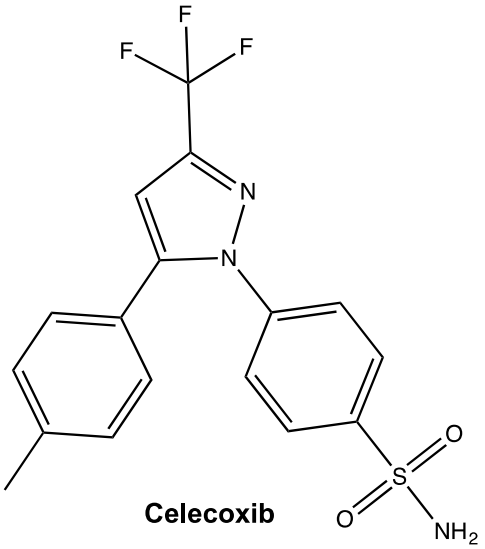


Gentisic acid

Tramadol is a BCS I synthetic morphinic derivative and weak opioid agonist with immense potential in analgesia. It is mainly absorbed in the upper part of the small intestine, has short biological half-life (6-8 hrs) and requires frequent. However, due to many side effects such as, pruritus, constipation, hallucination, vomiting, anxiety, tremor, diarrhea, and diaphoresis; it cannot be used for prolonged period of time for the treat of chronic pain. Thus often, opioids are supplemented with other analgesic agents, to lower the opioids dose. Co-administration of tramadol with NSAIDs has been a popular approach, thus Salaman, et. al., reported the synthesis of cocsrystal of tramadol and celecoxib with low solubility and high permeability (BCS class II). The results demonstrated that celecoxib was more available in the cocrystal form with tramadol, compared to celecoxib itself and to the physical mixture of tramadol and celecoxib. Furthermore, cocrystal of tramadol-celecoxib (1:1) was more successful in addressing the pain-induced gait changes in a rat model of acute monoarthritic pain compared to efficacy of each drug alone [51].

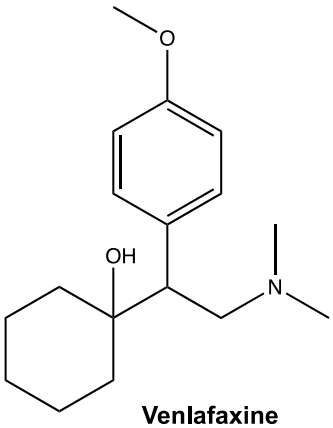


Tramadol

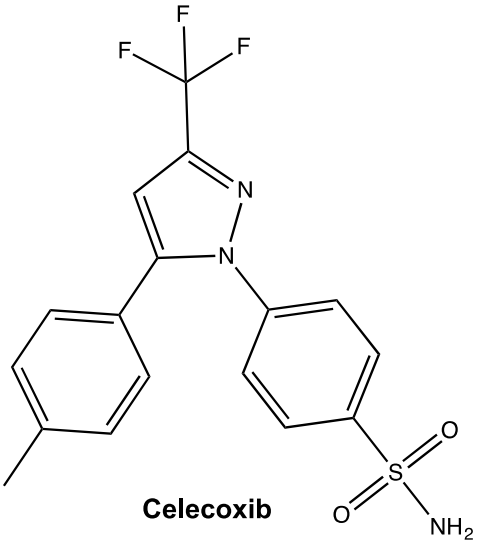


Celecoxib

Chronic pain could lead to depression, anxiety, and sleep disturbances, thus treating the pain in combination with depression often needed. In another report, Salaman, et. al., also reported the cocrystal system comprising of venlafaxine (BCS I drug) and in celecoxib (NSAID, BCS class II) [52]. Venlafaxine is an antidepressant from the serotonin-norepinephrine reuptake inhibitor (SNRI) class and is indicated in the treatment of major depressive disorder, generalized anxiety disorder, and social phobia [53]. The cocrystal of celecoxib and venlafaxine were shown to produce significant advantage over the equivalent doses for each drug tested in inhibiting mechanical allodynia in the paw incision postoperative pain model in the rats [52].



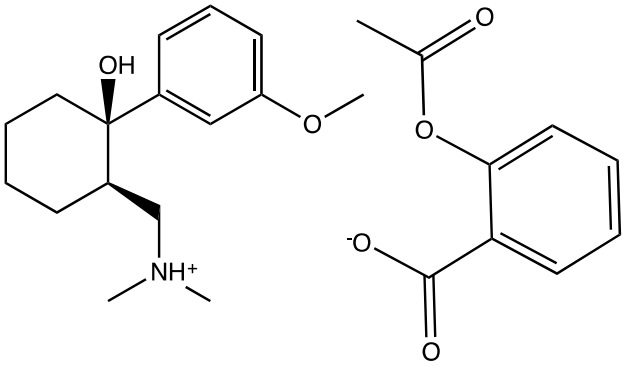
Venlafaxine



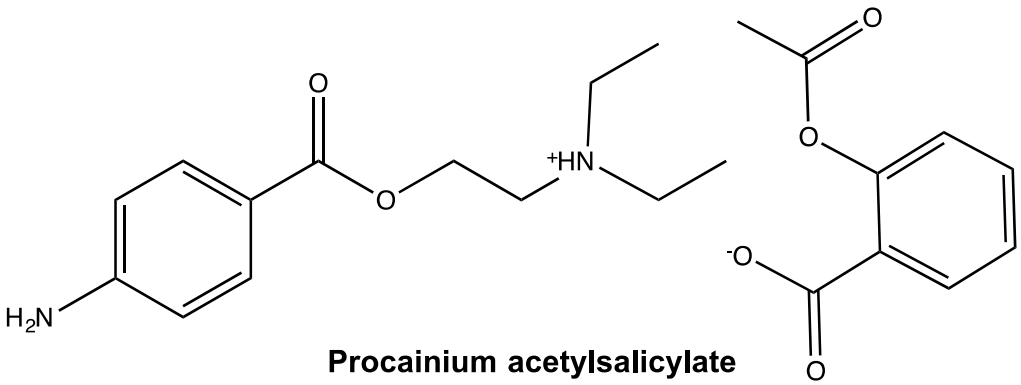
Celecoxib

Dual Functional Ionic Liquids

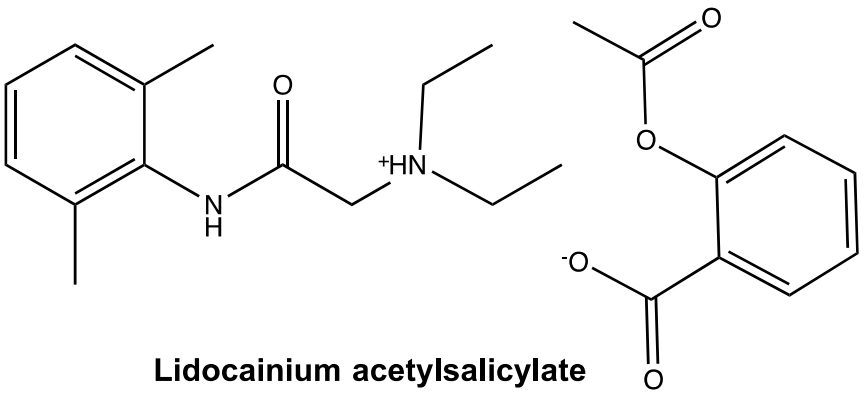
Ionizable drugs offer an added advantage that, anion-cation combination of various pharmaceuticals is possible. Due to the size and shape of the drug molecules, the resulting salts are very likely to be ionic liquids, thereby possessing enhanced solubility and absence of polymorphic forms [54, 55]. The research group of Professor Robin D. Rogers at the University of Alabama led the work for the third evolution of ionic liquids [56]. For example, oral (NSAID) acetylsalicylic acid generated dual functional pharmaceutical ionic liquid with tramadol, a potent opioid analgesic. The same group also reported, the synthesis and characterization of procainium acetylsalicylate and lidocanium acetylsalicylate [53]. Both procaine and lidocaine are well known and used clinical local anaesthetics. The skin permeability of most NSAIDs (due to ionizable carboxylic acid groups) is very poor. Therefore, ionic liquid of NSAIDs with these topical anesthetics will offer major advantages in terms of transdermal delivery.



Tramadolium acetylsalicylate

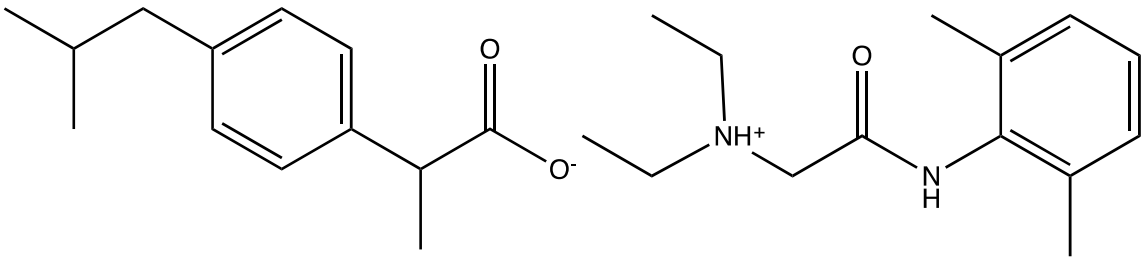


Procainium acetylsalicylate



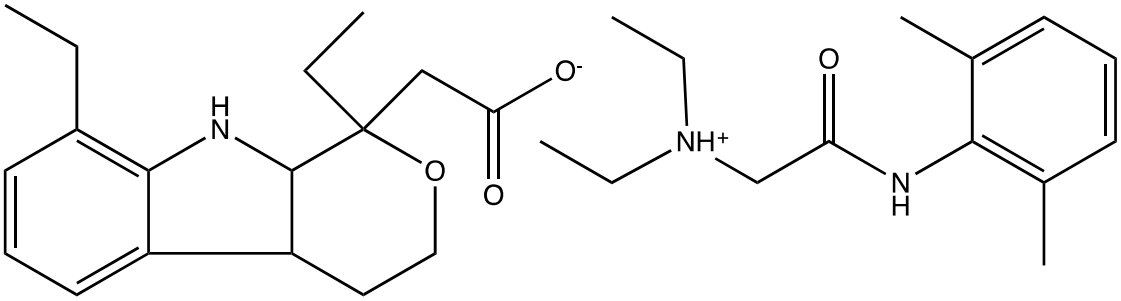
Lidocainium acetylsalicylate

Professor Mark Prausnitz group at the Georgia Institute of Technology reported the lidocaine ibuprofenate based room-temperature ionic liquid exhibiting rapid onset of local anesthesia, about 3-5 times faster, when compared with lidocaine alone in the rat's paw and tail with no apparent damage to the skin (histological analysis) [57].



Lidocainium ibuprofenate

Very recently, an etodolac-lidocaine topical patch (in the ionic liquid form) in the treatment of ankle sprains pain finished the phase III clinical trials [59-60], pending market launch. The in vitro studies (pig's skin) demonstrated that the permeation of etodolac was about 9-fold higher in the ionic liquid form when compared with an etodolac or lidocaine alone patch, given no change in the skin permeation of lidocaine itself [61].



Lidocainium etodolacate

CONCLUSION

Pain is one of the leading causes of disability worldwide having multi-billion dollars spent globally to address this issue. Owning to the fact that pain is symptom associated with many various acute and chronic illnesses, often patients have to take several medications many times a day. Combination drugs are one way to increase the patient's compliance and open the door for combining useful drugs. With the knowledge of supramolecular chemistry, scientists can design combination drugs having enhanced desirable properties (solubility, bioavailability, stability, etc). Solid-state dosage forms remained the most desired and produced formulations, however in case of crystalline substances polymorphic transformations are a nightmare. Cocrystals and ionic liquids offer solution to lot of aforementioned problems and design options.

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