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Drug Discovery—Development Interface

Application of ion-exchange chromatographic technique using resins to prepare the salts of polar unstable prodrugs and new chemical entities (NCEs)

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ABSTRACT

Prodrugs are inactive and bio-reversible derivatives of drugs or clinical candidates. Prodrugs and New Chemical Entities (NCEs) often do not show good bioavailability primarily due to poor solubility. One of the strategies to overcome this challenge is to use their salt forms. Conventional salt preparation techniques fail when applied to polar unstable prodrugs and NCEs. Herein, we have developed a simple efficient salt preparation technique using ion exchange resin chromatography. This technique involves the exchange of cations on sulfonic acid-based resin that could be applied successfully to prepare the salts of acidic prodrugs and NCEs. In this current work, phosphate/sulfate/carboxylate-prodrugs were prepared in the form of their inorganic (e.g. Na^+, K^+) and organic amine (e.g. erbumine, trizma, meglumine, arginine) salts with excellent control. The resin cartridge was reused for the preparation of different salts without any significant compromise in yields. Moreover, this protocol was employed to quickly switch the counterions for the pH-sensitive prodrugs, which is very useful in pharmaceutical development. This method is cost effective, operationally simple and presents a broad substrate scope. We wish this technique would help organic and pharmaceutical chemists to prepare various salt forms of prodrugs or NCEs in an efficient and controlled manner.

Introduction

Salification of drugs is often employed to improve biopharmaceutical properties, such as solubility, bioavailability, hygroscopicity, etc.[1-3] Therefore, the preparation of salts of active drugs or clinical candidates is always of great interest to medicinal/pharmaceutical chemist and formulation researchers. Traditionally, salt of drug molecules is prepared by acid-base neutralization reaction (acidic drug with basic counter anion or basic drug with acidic counter cation) followed by crystallization.[4-6] This method is broadly successful for chemically robust drugs. However, this method poses significant challenges while preparing the salt of labile prodrugs, due to its inherent instability in slightly acidic or basic reaction media. In addition, controlling the stoichiometry of corresponding counterion in the resulting salts, removal of metal impurities, etc. are crucial from pharmaceutical development perspective of the drug.[7] Therefore, development of a unified, predictable, and operationally simple method for the preparation of the salt of prodrug and polar NCEs is highly desirable. FDA, over the years, has approved various ammonium and metal salts for marketed acidic drugs and prodrugs for different therapeutic indication.[2,8]

Ion exchange chromatography is conventionally used for the purification or separation of organic molecules like proteins/amino acids, metal separation, water softening, catalysis, etc.[9] In this context, Dowex resin was widely used as a stationary phase for ion-exchange chromatography for the treatment of contaminated water,[10,11] in the chlor-alkali industry as brine-decalcifying agent,[12] catalyzing organic reactions, etc.[13] Dowex resins act on exchanging the cations/hydrogen-ion with suitable ions of same charge and used in the preparation of salt of drug molecules.[14]

Despite the proven utility of ion exchange resin in organic synthesis, its use was scarcely explored in pharmaceutical chemistry for the preparation of the salt of polar unstable prodrugs.[15] Furthermore, the lack of a systematic and unified methodology for the preparation of salt of polar unstable prodrugs/NCEs limit its use in the drug-development laboratory. Herein, in this publication we have systematically studied the salt formation of polar unstable prodrugs/NCEs using ion exchange resin. The application of this methodology is showcased preparing various inorganic (e.g. Na^+, K^+) and organic amine (e.g. erbumine, trizma, meglumine, arginine) salts with controlled stoichiometry (Fig. 1). A unified and operationally simple protocol has been set to execute salt preparation of drug molecules.

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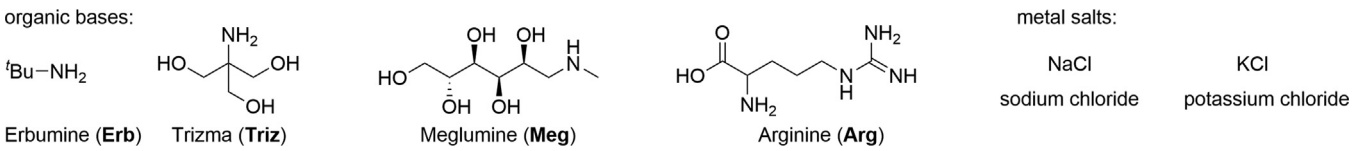


Fig. 1. Amine base and metal chloride used in this study.

Technical background, material, and methodology

Ion exchange is a reversible interchange of one species of ion present in an insoluble solid with another of like charge present in a solution surrounding the solid. Herein an exemplary graphical representation of our current work is described (Fig. 2). Resin's sulfonic acid motif reacts with the amine to form ammonium salt of sulfonate and becomes ready for ion exchange with acid/conjugate base. Now, when a solution of free phosphoric acid/phosphate salt of prodrugs/NCEs meets the resin, it exchanges the cation to form the desired ammonium salt of phosphate. Finally, elution with appropriate solvent brings the salt out and leave sulfonic acid resin.

Step wise protocol: Following this step wise protocol all the salt preparation and salt exchanges were performed [at 50-100 mg scale]:

Step-1: A fitted chromatographic glass column (sintered or glass-wool) was packed with 2 g of Dowex resin (50WX8) and allowed to swell in water (10 mL) for 20-30 min.

Step-2: The column was washed with water (10 mL) till neutral (checked with universal pH paper).

Step-3: a) For Organic amine exchange: Eluted with a solution of organic amine (1 mL or 1 g) in MeCN/H_2O (10 mL; 1:1); b) For inorganic metal salt exchange: Eluted with a solution of metal chloride salt (1 g) in H_2O (10 mL).

Step-4: Washed the excess amine/metal-chloride by eluting MeCN/H_2O (1:1) or H_2O till neutral (checked with universal pH paper).

Step-5: A solution of phosphate/sulfate/carboxylate-prodrugs/NCEs (50-100 mg) in MeCN/H_2O (10 mL; 1:1) was added and allowed to elute through the resin column by gravity.

Step-6: The column was eluted with additional MeCN/H_2O (1:1; 30-40 mL).

Step-7: Combined fraction was lyophilized to obtain the desired salt.

Note: Average time for one complete cycle of the salification process [*step-1* to *step-6*] is ~2.5 h.

Result and discussion

The exploration of the preparation of salt of prodrugs/polar NCEs began by synthesizing various prodrugs of paracetamol (**S1**), being a model drug.[1] Various prodrugs of paracetamol [phosphate (**1**), carbonate-phosphate (**2**), carbonate-sulfate (**3**), carbamate-carboxylate (**4**)] and adenylic acid (**5**) [polar NCE] were chosen to demonstrate the applicability of this method [Fig. 3].

Following the general procedure, organic ammonium and sodium salt of paracetamol prodrugs **1-4** were prepared; the results are sum-

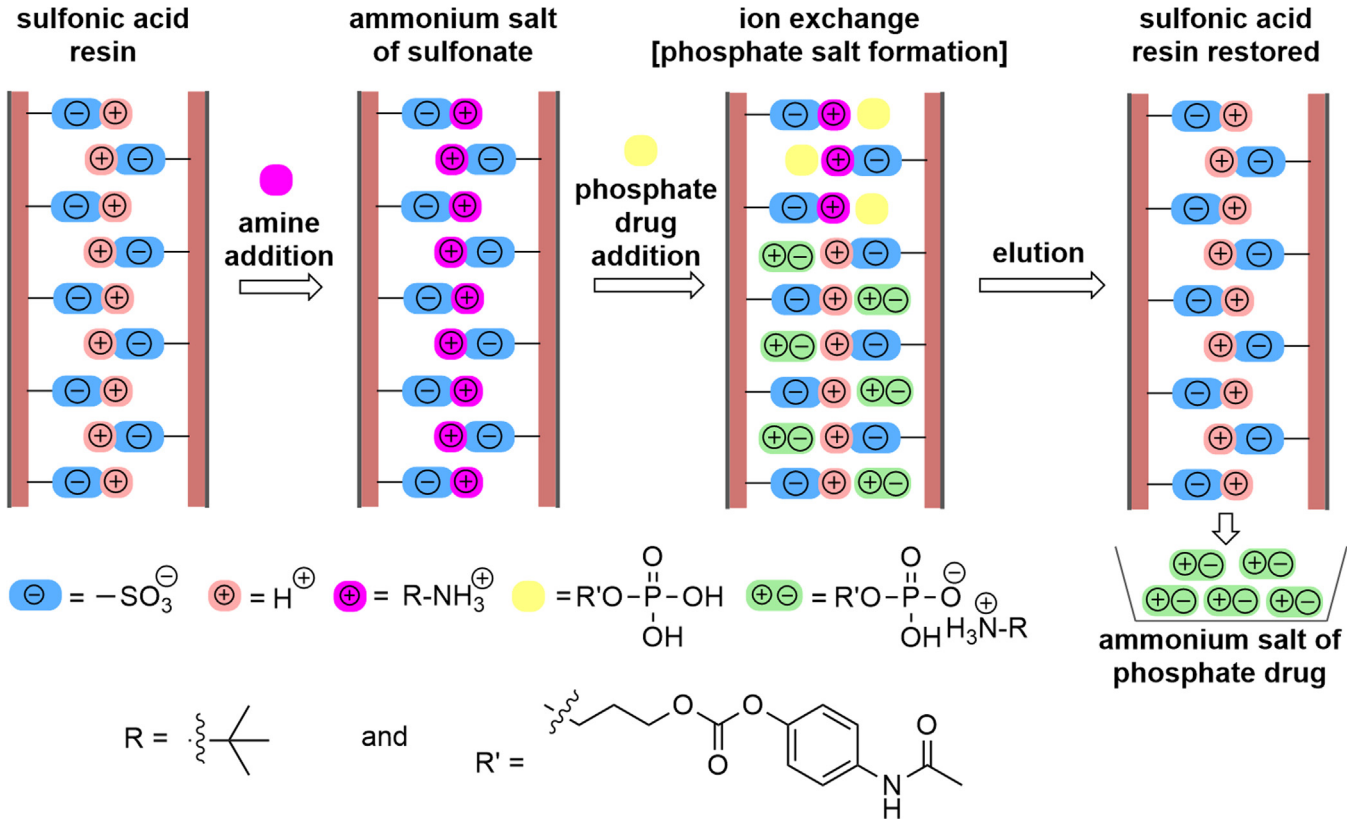


Fig. 2. Exemplary working flowchart of salt exchange on ion exchange resin with phosphate drug (2, Fig. 3) and amine (Erbumine).

[1] See Supporting Information for more details.

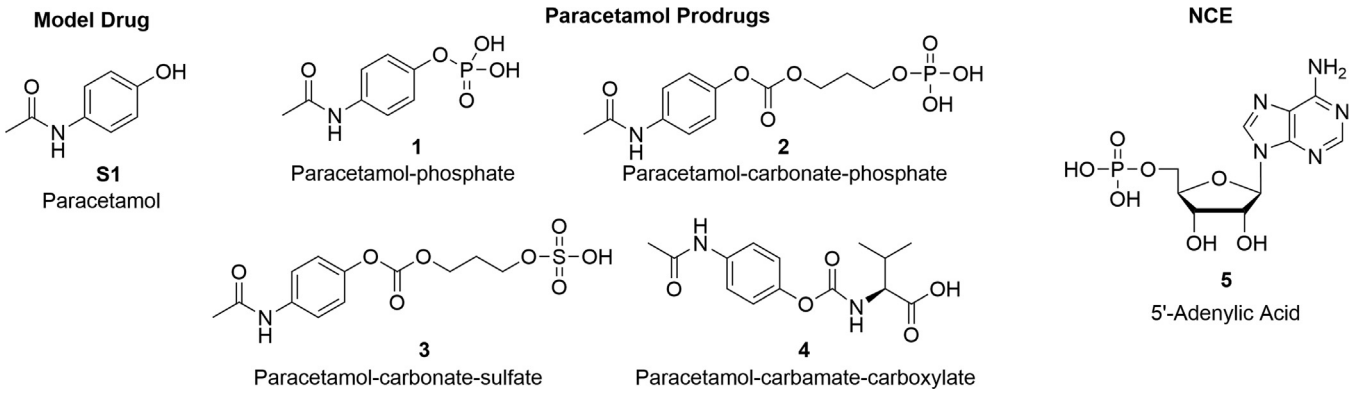
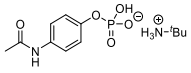
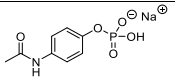
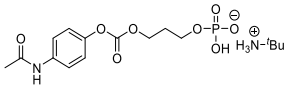
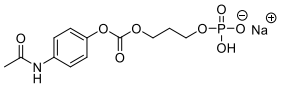
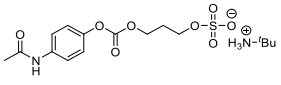
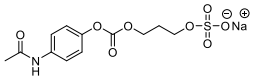
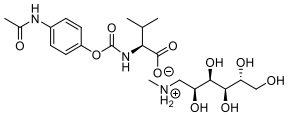
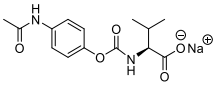


Fig. 3. Paracetamol, paracetamol prodrugs, and adenylic acid as NCE.

marized in Table 1. Erbumine and Na-salts of paracetamol-phosphate **1** were isolated in 82% and 87% yield, respectively (entry 1-2). The stoichiometry of cation(s) in phosphate ammonium-salt was determined by ^{1}H-NMR spectra, whereas IC-analysis was used for corresponding Na-salts.[16,2] Carbonate pro-moieties, used in numerous prodrugs, are at large chemically labile in the basic pH. Additionally, longer crystallization or precipitation time in the formulation development could lead to decomposition to their parent drug. To testify this, an attempt was made to prepare an erbumine salt of **2** via a classical acid-base reaction of carbonate-phosphate prodrug **2** with erbumine. This resulted into a significant decomposition of prodrug **2** to form its corresponding parent – paracetamol (**S1**).[1] However, these issues were circumvented when the carbonate-bearing phosphate as well as sulfate prodrug salts (Table 1, entry 3-6) were realized in high chemical purity, using our ion-exchange strategy. Similarly, paracetamol carbamate-carboxylate salt **12** and **13** were prepared from the carboxylate prodrug **4** using meglumine and NaCl, respectively (entry 7-8). All these salts isolated via ion exchange method were in high

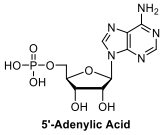
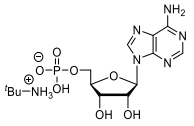
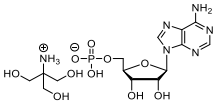
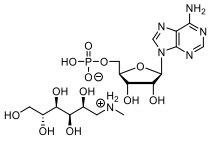
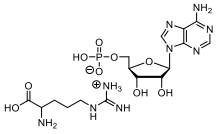
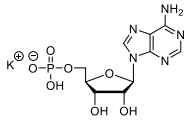
Table 1
Preparation of salts of paracetamol prodrugs.

Entry	Prodrug	Amine/MCl	Prodrug-salt	Salt No	Yield (%)[a,b]
1	Paracetamol-phosphate (**1**)	Erbumine		**6**	82 (100 → 108 mg)
2		NaCl		**7**	87 (50 → 48 mg)
3	Paracetamol-carbonate-phosphate (**2**)	Erbumine		**8**	90 (100 → 110 mg)
4		NaCl		**9**	80 (100 → 85 mg)
5	Paracetamol-carbonate-sulfate (**3**)	Erbumine		**10**	62 (50 → 38 mg)
6		NaCl		**11**	88 (50 → 47 mg)
7	Paracetamol-carbamate-carboxylate (**4**)	Meglumine		**12**	75 (50 → 63 mg)
8		NaCl		**13**	90 (50 → 48 mg)

[a]Isolated yield. [b]Conversion in absolute weight is given in parenthesis.

[2] The IC analysis confirms the formation of mono-Na salt for **7** & **9** and mono-K salt for **18**. Based on these results, the stoichiometry of other Na- or K-salts were predicted. The qualitative conversion of phosphate prodrug to their salt was unambiguously confirmed via 31P-NMR (please see SI).

Table 2
Preparation of salts of NCE (adenylic acid).

Entry	NCE	Amine/MCl	NCE-salt	Salt No	Yield (%)[a,b]
1	 5'-Adenylic Acid	Erbumine		**14**	87 (100 → 105 mg)
2		Trizma		**15**	93 (100 → 126 mg)
3		Meglumine		**16**	77 (100 → 120 mg)
4		Arginine		**17**	81 (100 → 122 mg)
5		KCl		**18**	72 (100 → 80 mg)

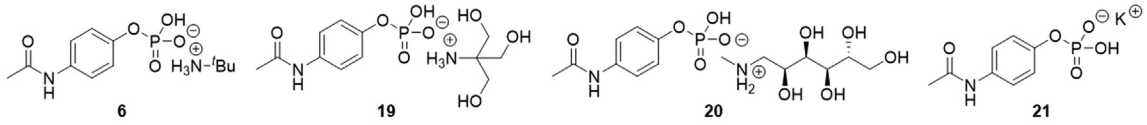
[a]Isolated yield. [b]Conversion in absolute weight is given in parenthesis.

purity, an essential requirement for the formulation development of prodrugs and NCEs. This process leads to the formation of mono-selective phosphate salts. Di-salt of phosphate did not form presumably due to the weak acidity (pKa_3 = ~6-7) of second P-OH moiety of phosphate prodrugs.[17]

Adenylic acid, a building block of RNA and an energy carrier in cells, is composed of adenine base, ribose, and phosphate group. This highly polar phosphate NCE was used for the preparation of various ammonium and metal salts using ion-exchange strategy; the result is summarized in Table 2. Mono-ammonium salts of adenylic acid (**5**), such as: erbumine (**14**), trizma (**15**), meglumine (**16**), and arginine (**17**), were prepared in good to excellent yields (Table 2, entry 1-4). Similarly, K salt of **5** were prepared in 72% yield (entry 5). These results demonstrate the efficiency of the current protocol in the salification of polar NCEs.

Reusability of the column

Ion exchange cartridge/column, after regeneration of its sulfonate functionality by acid treatment, could be repeatedly used for salt



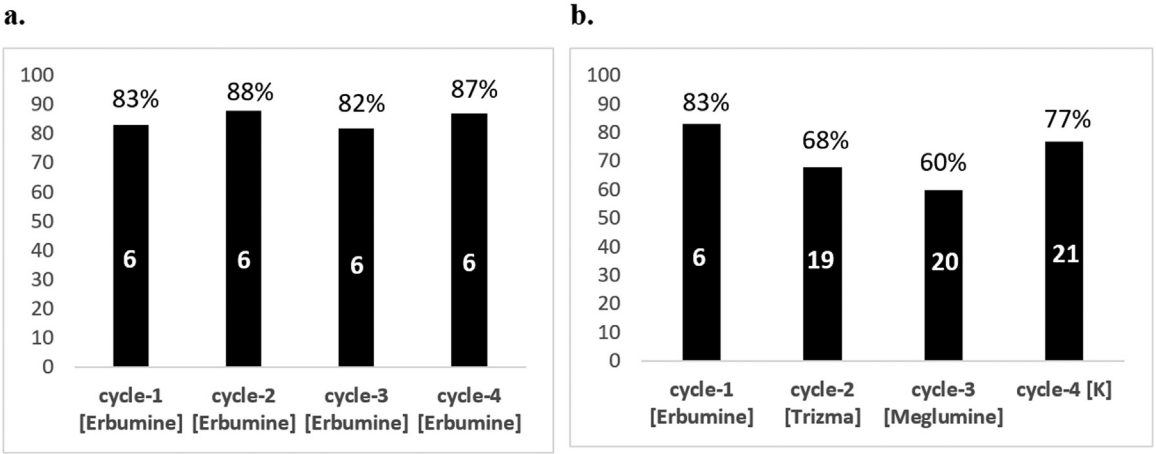
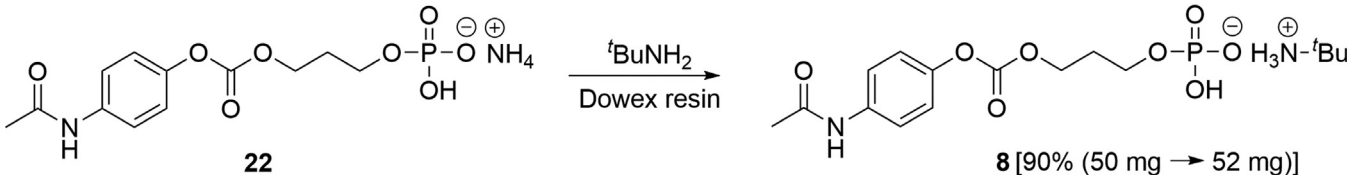


Fig. 4. Reusability of resin column; [a] Isolated yields of Erbumine salt 6 using same resin column (up to 4-cycles) and [b] Isolated yields of various salts of 1 using same resin column.



Scheme 1. Salt exchange of ammonium salt 22.

Scheme 2. De-saltification of ammonium salt 22.

preparation. Herein we have demonstrated the use of a single resin column in multiple salt preparation, which in turn reflects the cost effective and greener aspect of this salt preparation in pharmaceutical development. Initially, erbumine salt **6** (83%) was isolated from paracetamol phosphate **1** (Fig. 4a, cycle 1). Once completed, the column was washed with aq. HCl to activate the resin and used for the next salt preparation.[1] This protocol was repeated thrice using the same resin column to make the erbumine salt **6** [yield = 82-88%] (Fig. 4a, cycle 2-4) without compromising the yield in each cycle. Furthermore, this strategy could also be used to make different salts of prodrug using same resin column. Accordingly, different ammonium (e.g. erbumine, trizma, meglumine) and metal salt (e.g. potassium) of phosphate **1** were prepared using a single column (Fig. 4b, cycle 1-4). These results truly demonstrate the reusable aspect of the resin cartridge in this salt preparation strategy.

Salt exchange of prodrug via ion-exchange chromatography

In prodrug chemistry, free phosphate prodrugs having an acid-sensitive functionality in the linker or parent-drug are observed unstable, due to the inherent acidity arising from phosphate group. Often these phosphate prodrugs are isolated as ammonium salt via reverse phase purification using aq. ammonium bicarbonate as an eluent. However, simple ammonium salt of acidic prodrugs is undesirable in the formulation development of a drug. Therefore, the exchange of this simple ammonium salt to its FDA approved higher organic amine salt or inorganic metal salt would be beneficial. Notably, this methodology was successfully used to exchange the ammonium salt **22** to erbumine salt (**8**) with excellent efficiency (Scheme 1).

De-salification of prodrug via ion-exchange chromatography

In some instances, a free phosphate prodrug is required from its ammonium salt which is obtained via prep-HPLC purification. We established that using this strategy, de-salification of phosphate ammonium salt to its free phosphate analog could be achieved. Towards this the ammonium phosphate prodrug **2** was prepared from **22** (Scheme 2).

Conclusion

A chromatographic method has been developed to prepare salts of chemically labile prodrugs and highly polar NCEs via ion exchange on resin column. Both organic ammonium and metal salts [approved by the FDA for various marketed drugs] of prodrugs were prepared in appreciable yields with excellent purity. The reusability of the resin column was demonstrated by generating various salts of paracetamol prodrug **1**. This methodology is operationally simple, highly reliable, and cost effective. Furthermore, the ability to work near neutral pH (~7.0) broadens the scope of acid/base sensitive prodrugs in this methodology. This protocol was employed to quickly switch the counterions on pH-sensitive prodrug, which is very useful in the pharmaceutical development. The utilization of this salt preparation strategy to more complex polar compound classes like PROTACs, peptides, oligonucleotides, etc. would be the future scope of the work.

Declaration of competing interest

The authors declare that they have no known conflict of interest that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.xphs.2026.104152.

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