Study of the Impact on Physicochemical Properties of Inhaled Products in several Simulated Lung Fluid media

T3057

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Purpose

The aim of this poster was to study the impact of several simulated lung fluid (SLF) media on the physicochemical properties of a selected group of inhaled drugs. Physicochemical properties such as pK_a, log P, solubility and dissolution rates were measured at different conditions using protic and aprotic salts in phospholipid and surfactant systems to observe the impact of the media on the physicochemical properties of the drug. Sample properties were also compared with a standard phosphate buffer medium system.

Method

Four samples used in inhalation products (zafirlukast, amlexanox, viozan and epinephrine) were selected in this study (Fig. 1).

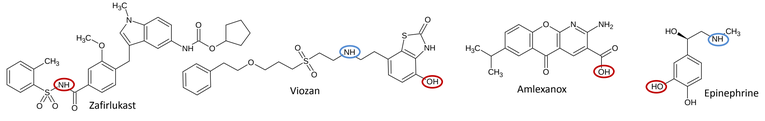

Fig. 1: Structures of the four drugs studied. Blue circles denote basic ionizable groups and red circles acidic ionizable groups.

SLFs Phosphate Buffer Conditions				
	Concentration (mM)	pH	Ionic Strength (M)	Temperature (°C)
Aqueous	50	7.4	0.17	37
0.5% SDS	10	7.4	0.15	37
0.025% DPPC	10	7.4	0.15	37
0.003% Curosurf®	10	7.4	0.15	37

Table 1: Properties of the solutions used in this study.

Physicochemical properties for the four selected drugs were compared using standard phosphate buffer and three different simulated lung fluid (SLF) media: 0.5% sodium dodecyl sulphate (SDS), 0.025% 1,2-dipalmitoyl-*ns*-glycero-3-phosphocholine (DPPC) and 0.003% Curosurf® (table 1). All three were made in phosphate buffer solution.

Aprotic salts were added to the different media to study their impact on pK_a and solubility of epinephrine. Moreover, aprotic + protic salts were studied in the same way for the dissolution experiments on zafirlukast (table 2).

All experiments were performed on SiriusT3, an automated titration platform with in-situ UV fibre-optic spectroscopy. Small quantities of drug material were used in 1 to 3 mL volumes to determine pK_a, log P, solubility and dissolution behavior at 0.15 M ionic strength and 37°C. Dissolution experiments were carried out at pH 7.4.

SLFs Salts	
Aprotic salts	**Protic salts**
$MgCl_2$	$NaCH_3COO$
NaCl	$NaHCO_3$
KCl	Na_3Cit
Na_2SO_4	Na_2HPO_4
CaCl2	

Table 2: Aprotic and protic salts selected in this study for the different SLF media

Experimental and Results

Physicochemical properties

SLFs Phosphate Buffer Conditions				
	pK_{a1}	pK_{a2}	log P	Solubility
Zafirlukast	acidic			
Aqueous	3.75 ± 0.02	-	4.54 ± 0.02	903 pg/mL
0.5% SDS	5.24 ± 0.01	-	2.28 ± 0.01	1.25 µg/mL
0.025% DPPC	4.55 ± 0.04	-	3.27 ± 0.02	#
0.003% Curosurf®	3.78 ± 0.01	-	4.36 ± 0.05	1.04 µg/mL
Amlexanox	acidic			
Aqueous	3.39 ± 0.01	-	4.16 ± 0.02	525 ng/mL
0.5% SDS	4.54 ± 0.01	-	2.51 ± 0.06	2.32 µg/mL
0.025% DPPC	3.49 ± 0.08	-	4.00 ± 0.01	320 ng/mL
0.003% Curosurf®	3.51 ± 0.06	-	3.83 ± 0.02	155 ng/mL
Viozan HCl	basic	acidic		
Aqueous	6.49 ± 0.03	8.35 ± 0.02	2.25 ± 0.01	117 µg/mL
0.5% SDS	7.50 ± 0.15	9.45 ± 0.01	0.66 ± 0.04	¥
0.025% DPPC	6.20 ± 0.01	8.50 ± 0.02	2.33 ± 0.06	321 µg/mL
0.003% Curosurf®	6.14 ± 0.02	8.51 ± 0.02	2.33 ± 0.02	325 µg/mL
Epinephrine	basic	acidic		
Aqueous	8.49 ± 0.01	9.67 ± 0.01	*	114 µg/mL
0.5% SDS	8.46 ± 0.01	9.67 ± 0.01	*	82.5 µg/mL
0.025% DPPC	8.43 ± 0.01	9.69 ± 0.01	*	115 µg/mL
0.003% Curosurf®	8.45 ± 0.01	9.70 ± 0.01	*	131 µg/mL

#Drug too insoluble to be measured in aqueous media. Cosolvent media is required
¥Possible decomposition
**logP<1 below measurable range of the technique*

Table 3: physicochemical properties of zafirlukast, amlexanox, viozan and epinephrine, in several SLF (phosphate buffer) media.

Table 3 shows the physicochemical properties of the four drugs displayed in figure 2.

pK_a: For acidic groups, the ionization constant increased in the three media selected, compared to phosphate buffer (aqueous). Conversely, pK_a decreased for bases. Viozan (SDS, basic pK_a = 7.50) had a high standard deviation attributed to a poor UV-signal observed. There were no significant differences between pK_a values for epinephrine in the four different media compared to the other drugs. Epinephrine was the only drug studied with no surface activity.

Log $P_{(oct/water)}$: measurements showed a decrease of the log P value for all the drugs studied in the three SLF media compared to the aqueous conditions. The biggest impact was observed in the presence of SDS with a decrease between 1.6 and 2.3 log units for all drugs. There were no significant differences observed in log P values between aqueous, DPPC and Curosurf® for viozan.

Intrinsic solubility: SDS SLF media showed an increase in the solubility for acidic compounds and Curosurf® for the ampholyte compounds.

Epinephrine

pK_a increased with the addition of salts for the two media studied (table 4).

Intrinsic solubility measurements showed that Curosurf® slightly increased the solubility of epinephrine from 114 µg/mL (aqueous) to 131 µg/mL (Curosurf®). However, the addition of salts decreased the solubility in both media.

Epinephrine: SLFs (± aprotic salts) Conditions			
	pK_{a1}	pK_{a2}	Solubility
Aqueous	8.49 ± 0.01	9.67 ± 0.01	114 µg/mL
0.003% Curosurf®	8.45 ± 0.01	9.70 ± 0.01	131 µg/mL
Aqueous + salts	8.53 ± 0.01	9.94 ± 0.02	87.6 µg/mL
0.003% Curosurf®+ salts	8.53 ± 0.01	9.88 ± 0.01	113 µg/mL

Table 4: physicochemical properties of epinephrine in aqueous and Curosurf® conditions. Comparison with and without aprotic salts.

Dissolution

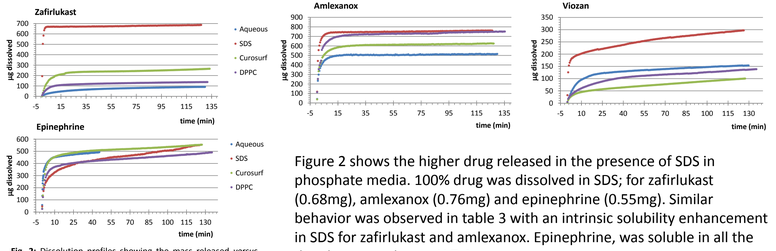

Fig. 2: Dissolution profiles showing the mass released *versus* time for the four drugs studied in the SLFs described in table 1.

Figure 2 shows the higher drug released in the presence of SDS in phosphate media. 100% drug was dissolved in SDS; for zafirlukast (0.68mg), amlexanox (0.76mg) and epinephrine (0.55mg). Similar behavior was observed in table 3 with an intrinsic solubility enhancement in SDS for zafirlukast and amlexanox. Epinephrine, was soluble in all the dissolution media at pH 7.4.

Zafirlukast

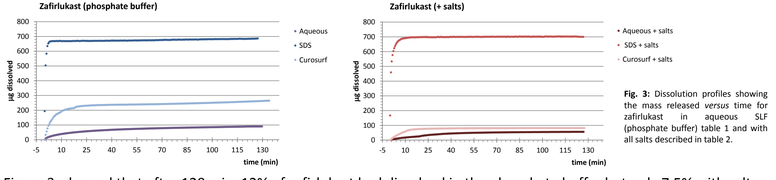

Fig. 3: Dissolution profiles showing the mass released *versus* time for zafirlukast in aqueous SLF (phosphate buffer) table 1 and with all salts described in table 2.

Figure 3, showed that after 120 min, 12% of zafirlukast had dissolved in the phosphate buffer but only 7.5% with salts. In Curosurf®, 49% had dissolved in phosphate buffer and 14% with salts. There was a marked increase in dissolution performance of zafirlukast with SDS which dissolved the entire drug (100%), both with and without the presence of the salts. However, it was observed that the dissolution rate was slower in the presence of the salts.

Conclusion

The physicochemical properties of inhaled drugs were measured in various simulated lung fluid media. The addition of SDS revealed the biggest impact on log P, solubility and dissolution measurements, whilst Curosurf® also increased solubility and dissolution rate compared to the pure phosphate system. The addition of salts, however, decreased solubility and retarded dissolution performance.

References

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Marques, M. et al; Dissolution Technol., 2011, 18(3),18-28

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