NSAIDs Taste Masking by New Maltodextrins (KLEPTOSE® Linecaps)

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INTRODUCTION

API's undesirable taste is one of the most challenging parameters when addressing patient compliance for oral drug delivery systems. This issue is even more critical in the case of pediatric and geriatric populations. The ability to mask taste impacts the commercial success of the final product by increasing patient compliance and business profitability. Various formulation strategies have been used to mask the taste of drugs, including using sweeteners, coatings, microencapsulation, and cyclodextrin complexes [1, 3].

MATERIALS & METHODS

OBJECTIVES:

1. The purpose of this project was to evaluate NSAIDs (Ibuprofen (IBU), Ketoprofen (KET), Naproxen (NAP), and Flurbiprofen (FLUR)) complexing capability with two new maltodextrins with high amylose content (KLEPTOSE® Linecaps 17 with 17 Dextrose Equivalent and LPDE 12, a Laboratory Prototype with 12 Dextrose Equivalent).
2. To evaluate the taste masking performance of these two new maltodextrins with high amylose content by an Alpha MOS Astree electronic tongue system (AeT).

MATERIALS: Ibuprofen (IBU), Ketoprofen (KET), and Naproxen (NAP) were purchased from Spectrum Chemical Company (Gardena, CA). Flurbiprofen (FLUR) was obtained from Sigma Aldrich (St. Louis, MO). DE 17 (KLEPTOSE® Linecaps 17 with 17 Dextrose Equivalent) and DE 12 (LPDE 12 , a Laboratory Prototype with 12 Dextrose Equivalent) were supplied by Roquette America, Inc. (Geneva, IL).

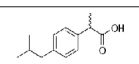
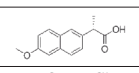
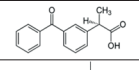
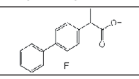
METHODS:

Solution Preparation: Aqueous solutions of DE12 (10, 20, and 30% w/w, equivalent to 0.007mM, 0.0142mM, and 0.021mM) and DE 17 (10, 20, 30, and 40% w/w, equivalent to 0.008mM, 0.016mM, 0.025mM, and 0.033mM) in deionized water were prepared. Excess amounts of four model nonsteroidal antiinflammatory compounds (NSAIDs), including Flurbiprofen, Ibuprofen, Ketoprofen and Naproxen, were added to the DE solutions and mixed for 7 days at ambient conditions to insure a saturated solution. Filtered aliquots of each sample were then analyzed for drug content by high-pressure liquid chromatography (Model 1260 Infinity series, Agilent Technologies, Santa Clara, CA). Aliquots of the same samples were lyophilized and then evaluated after reconstitution in water.

Taste Masking Effects: Taste masking of the model drugs by the high amylose maltodextrins was assessed using an Alpha MOS Astree electronic tongue system (AeT). The distance value between fresh formulations and their respective placebo (water) were calculated using a program based on Euclidean algorithm. These values are indicative of the taste proximity of each solution. Moreover, a Discrimination Index (DI, in %) was determined for each solution. This indicator takes into account the average difference between the pairs, as well as the dispersion of each sample. The closer to 100%, the longer the distance between groups and the lower the dispersion.

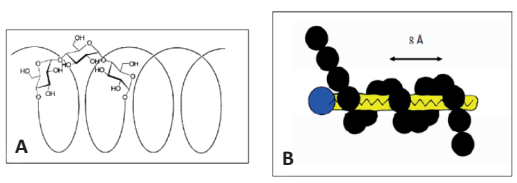
RESULTS & DISCUSSION

Table 1. NSAIDs Chemical Structure and Pharmaceutical Properties.

Drug	Chemical Structure	Log P	Solubility (M)*
IBU		4.2	3.86 x 10^{-4}
NAP		3.2	2.88 x10^{-4}
KET		3.1	6.73 x 10^{-4}
FLUR		4.2	2.23 x 10^{-4}

*Determined experimentally

Figure 1. Amylose (A) and Amylose-Drug Complex (B).



NSAID Phase Solubility Diagram

Figure 2. Phase Solubilization Diagram.

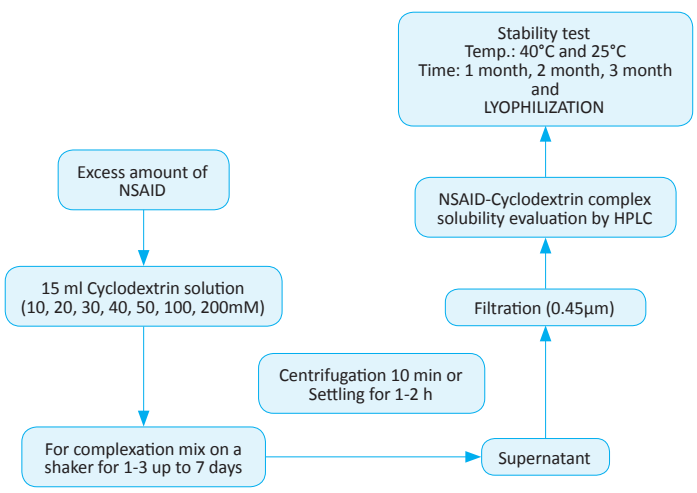


Figure 3. Taste Masking Efficiency as Measured By the E-Tongue System.

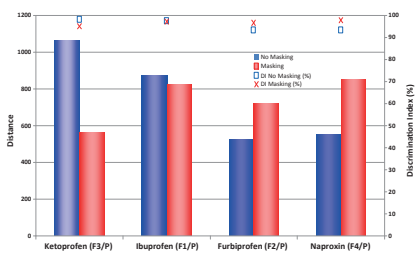


Figure 4. NSAID Solubility as a Function of DE Concentration.

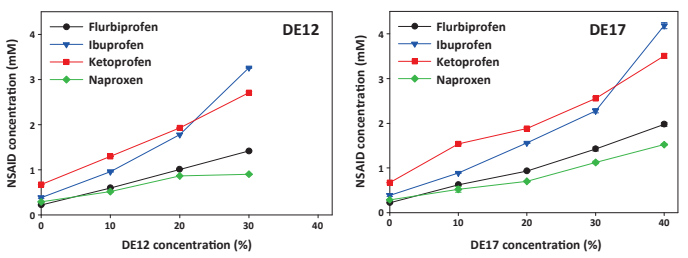


Table 2. NSAID Solubility as a Function of DE12 and DE17 Concentration.

NSAID	DE Conc (%)	DE12 Drug Conc (mg/ml)	DE12 Drug Conc (mM)	DE12 Solubility Increase Ratio (S/S_0)	DE17 Drug Conc (mg/ml)	DE17 Drug Conc (mM)	DE17 Solubility Increase Ratio (S/S_0)
FLUR	10	0.15	0.6	2.68	0.15	0.62	2.79
	20	0.25	1.01	4.52	0.23	0.93	4.18
	30	0.35	1.42	6.35	0.35	1.42	6.38
	40	-	-	-	0.48	1.98	8.85
IBU	10	0.2	0.96	2.49	0.18	0.89	2.29
	20	0.37	1.78	4.61	0.32	1.56	4.04
	30	0.67	3.26	8.44	0.47	2.28	5.9
	40	-	-	-	0.86	4.19	10.84
KET	10	0.33	1.3	1.93	0.39	1.54	2.28
	20	0.49	1.93	2.86	0.48	1.88	2.79
	30	0.69	2.71	4.02	0.65	2.55	3.79
	40	-	-	-	0.89	3.51	5.21
NAP	10	0.12	0.52	1.79	0.12	0.52	1.81
	20	0.2	0.87	3.01	0.16	0.7	2.42
	30	0.21	0.9	3.13	0.26	1.12	3.9
	40	-	-	-	0.35	1.52	5.27

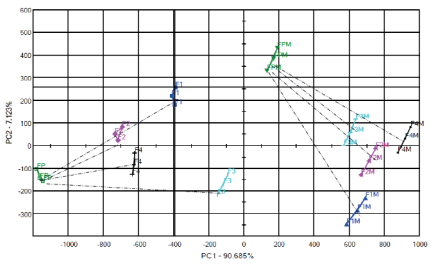
Table 3. Sample Preparation for the E-Tongue System.

Labels	Type	IBU API (mg/ml)	FLUR API (mg/ml)	KET API (mg/ml)	NAP API (mg/ml)	DE17 mM	ALL OTHER COMPONENTS	Description
F1	Active, no masking	1	0	0	0	0	QS to 100%	Ibuprofen, no masking
F2	Active, no masking	0	1	0	0	0	QS to 100%	Flurbiprofen, no masking
F3	Active, no masking	0	0	1	0	0	QS to 100%	Ketoprofen, no masking
F4	Active, no masking	0	0	0	1	0	QS to 100%	Naproxen, no masking
FP	Placebo, no masking	0	0	0	0	0	QS to 100%	No Active, no masking
F1-M	Active, with masking	1	0	0	0	0.033	QS to 100%	Ibuprofen, with masking
F2-M	Active, with masking	0	1	0	0	0.033	QS to 100%	Flurbiprofen, with masking
F3-M	Active, with masking	0	0	1	0	0.033	QS to 100%	Ketoprofen, with masking
F4-M	Active, with masking	0	0	0	1	0.033	QS to 100%	Naproxen, with masking
FPM	Placebo, with masking	0	0	0	0	0.033	QS to 100%	No Active, with masking

Table 4. Taste Masking Efficiency Measured by Placebo - API Distance.

	Ketoprofen (F3 / P)	Ibuprofen (F1 / P)	Flurbiprofen (F2 /P)	Naproxen (F4 / P)
No Masking	1065	873	522	554
DI No Masking (%)	98.14	97.51	93.37	93.42
Masking	565	827	722	851
DI Masking (%)	95.06	97.33	96.71	97.76

Figure 5. Taste Map Based on E-Tongue Data on Placebo, NSAIDs with no DE17, and NSAIDs with DE17.



CONCLUSION

- DE12 and DE17, maltodextrins which contain a high ratio of amylose flexible helixes, enable the entrapment of API molecules and ensemble stability (**Fig 1**).
- The aqueous solubility of all four model NSAIDs used in the current study increased with increasing concentrations of both DE12 and DE17 (**Table 2**, **Fig 4**). The greatest solubility enhancement was observed for IBU and KET.
- Taste masking HYPOTHESIS: If masking is occurring, the distance between the active/placebo pair with masking will be smaller than the active/placebo pair without masking (**Fig 5**).
- Figures 3 and 5 show a clear discrimination between the different formulations (**Table 3:** Placebo (FP), NSAIDs formulation without masking (F), NSAIDs formulation with Masking (FM)).
- Table 4 ranks taste masking efficiency measured by Placebo - NSAIDs distance on AeT from the best taste masking to the worst as follows: Ketoprofen > Ibuprofen > Flurbiprofen > Naproxen.

ACKNOWLEGEMENTS

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