Efficient taste masking through high shear coating with lipid excipients

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Rosiaux Y., Forest A., Girard J.M., Deleglise C., Marchaud D.
Gattefossé SAS, 36 chemin de Genas, 69804 Saint-Priest, France, yrosiaux@gattefosse.com

INTRODUCTION

Solid lipid excipients can be used as taste masking agents in **hot melt coating** in a fluid bed coater. The lipid is melted and sprayed onto the drug particles forming a tasteless film which acts as a physical barrier between the bitter drug and the taste receptors in the oral cavity. The process can be considered time and material efficient and 'green' since the coating time is short, 100% of the coating material is applied and solvents are not required. However, heating protocols for the feeding tubes and spray nozzle may be considered complicated. In this study we evaluated an alternative and more simple taste masking process using a high shear mixer.

Glyceryl distearate is a solid lipid excipient with precedence of use in pediatric dosage forms. Upon **high shear mixing** inter-particulate frictions and frictions between the particles and the mixing bowl are generated which induces sufficient heat to partially melt the lipid at about 48 °C and to coat individual drug particles. Upon cooling below its melting point glyceryl distearate recrystallizes instantly providing a solid film that is neutral in taste and perfectly suitable for taste masking approaches or drug protection. No complicated heating protocol is required meaning the process is straightforward to execute and control.

Potassium chloride is prescribed for use in pediatric patients for the treatment of compensation of potassium loss. It is a bitter salt and a good candidate for taste masking with a view to improve acceptability.

EXPERIMENTAL METHODS

A binary mixture of 80% potassium chloride (KCl, 280 g) and 20% glyceryl distearate (Precirol® ATO 5, 70 g) was placed into a 1 L high shear mixer (Diosna P1) and homogenized at 50 rpm for 3 min. The impeller was set to 900 rpm until the mixture reached 45 °C. The impeller speed was then reduced to 450, 600 or 750 rpm whilst setting the chopper speed to 500, 1000 or 1500 rpm referring to the parameter combinations determined in the surface response experimental design (Figure 1). The blend was coated for 1, 3 or 5 min once the product temperature reached 48 °C. Post-process the blend was gently cooled down to 35 °C with a reduced impeller speed of 50 rpm and chopper speed of 100 rpm. After 30 min at room temperature the coated powder blend was sieved through 1250 µm. Only the sieved fraction herein referred to as process yield was retained for further investigation.

The efficiency of the coating process was evaluated with *in-vitro* drug release measurements. The drug was considered successfully coated when the release of the processed KCl particles was within the reported taste perception range from 0.005[1] to 0.03 M[2] corresponding to 0.3 and 2.2 mg/mL KCl. Drug release was conducted for 5 min in 3 mL of demineralized water using an electrical conductivity meter (37 °C, gentle stirring). Binocular loupe and microscope were used for visual inspection. Particle size measurement provided additional information on the film coating thickness.

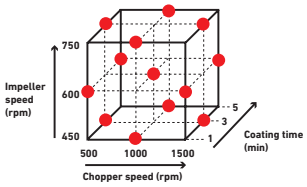

Figure 1. Box-Behnken response surface design for the investigation of effective lipid coating parameters .

RESULTS

KCl is a colorless crystalline powder with cubic shape as displayed in Figure 2a and 2b. After processing in the high shear mixer with glyceryl distearate the crystals became opaque (Figure 2c) and light refraction changed (Figure 2d), indicating that film coating was achieved - at least partially.

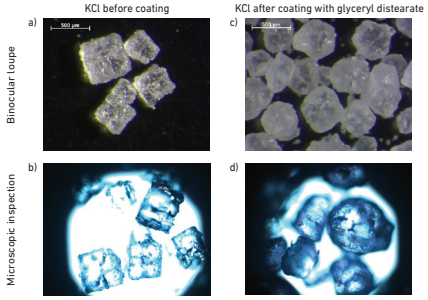

Figure 2. Aspect of KCl before and after coating with glyceryl distearate using binocular loupe and microscope.

The initial mean particle size of KCl was 369 ± 151 µm with d_{10}, d_{50} and d_{90} of 179, 362 and 572 µm respectively. The particle diameter increased post-coating as indicated in Table 1. This increase can be attributed to the adsorption of melted glyceryl distearate on the surface of individual KCl particles forming a film coat of a specific thickness. However, some of the tested process parameter combinations induced particle granulation. For both, coated and granulated particles, taste masking could be achieved.

Efficient coating of individual particles was suggested when a process yield of > 80% was obtained and when drug release was below the upper perception threshold of 2.2 mg/mL. For a process yield ≤ 80% we assumed that particle granulation took place. For drug release greater the threshold value efficient taste masking was not concluded. For example, KCl was considered individually coated and taste masked using the process parameter combinations of Run 6, 9 and 10. Drug release was below 2.2 mg/mL and the process yield greater 80% (Table 1, Figure 3). Since less than 80% of the particles passed the sieve of 1250 µm using the parameter combination of Run 4 taste masking of KCl was assumed to be obtained by granulation (Table 2, Figure 4). Run 3 was supposed to provide individually coated KCl particles with a process yield of > 80%, however coating was considered inefficient as drug release beyond 30 sec was above 2.2 mg/mL (Figure 3). It is likely that the lipid coat was too thin to prevent the dissolution of the drug. Particle growth expressed by d_{10}, d_{50} and d_{90} was less than that obtained from the other parameter combinations (Table 1). KCl obtained from Run 7 and 8 was considered granulated with inefficient taste masking (Table 2, Figure 4). It can be considered that glyceryl distearate acted as a binder between the KCl particles rather than a coating agent.

Table 1. Process parameters, drug release, process yield and particle size of KCl **coated** with glyceryl distearate.

Run n°	Process parameters			Process yield (%)	Drug release (mg/mL)				Particle size growth (µm)		
	Impeller speed (rpm)	Chopper speed (rpm)	Coating time (min)		30sec	1min	2min	5min	d_{10}	d_{50}	d_{90}
10	450	1500	3	94	0.1 ± 0.0	0.2 ± 0.0	0.4 ± 0.1	1.3 ± 0.1	100	99	114
9	600	500	1	94	0.2 ± 0.1	0.3 ± 0.1	0.7 ± 0.2	1.7 ± 0.6	68	66	52
6	450	500	3	88	0.2 ± 0.1	0.3 ± 0.1	0.7 ± 0.2	1.9 ± 0.6	15	46	105
5	450	1000	5	89	0.2 ± 0.0	0.5 ± 0.1	1.5 ± 0.4	4.3 ± 1.9	23	60	163
12	600	1000	3	89	0.9 ± 0.7	1.4 ± 0.5	2.7 ± 0.4	6.0 ± 0.1	81	107	164
3	450	1000	1	97	1.6 ± 0.7	3.2 ± 0.7	6.1 ± 1.1	14.9 ± 6.2	-10	37	55

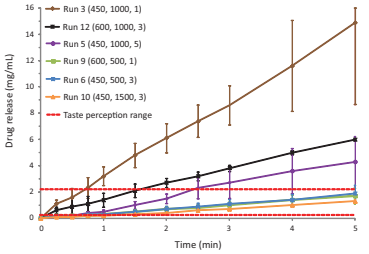

Figure 3. Release kinetics of KCl **coated** with glyceryl distearate at different process parameter combinations (impeller speed in rpm, chopper speed in rpm, coating time in min).

Table 2. Process parameters, drug release, process yield and particle size of KCl **granulated** with glyceryl distearate.

Run n°	Process parameters			Process yield (%)	Drug release (mg/mL)				Increase in particle size (µm)		
	Impeller speed (rpm)	Chopper speed (rpm)	Coating time (min)		30sec	1min	2min	5min	d_{10}	d_{50}	d_{90}
4	750	1000	1	76	0.1 ± 0.0	0.2 ± 0.0	0.5 ± 0.2	1.6 ± 0.3	20	83	174
13	600	1500	5	76	0.1 ± 0.0	0.3 ± 0.0	0.8 ± 0.3	3.4 ± 2.3	93	111	215
1	750	1500	3	80	0.4 ± 0.2	0.8 ± 0.6	1.6 ± 0.9	7.4 ± 7.1	42	101	225
11	750	1000	5	67	0.5 ± 0.5	1.0 ± 0.4	2.5 ± 0.2	6.7 ± 1.7	74	119	283
2	600	500	5	79	0.8 ± 0.5	1.4 ± 0.6	2.7 ± 0.6	9.4 ± 5.7	32	98	207
7	600	1500	1	74	1.3 ± 0.7	2.7 ± 0.4	4.4 ± 0.6	10.4 ± 5.3	78	117	252
8	750	500	3	80	3.1 ± 1.5	4.2 ± 1.2	6.5 ± 0.9	13.6 ± 3.8	99	145	288

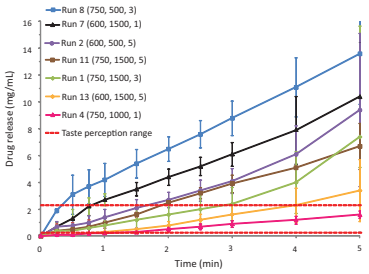

Figure 4. Release kinetics of KCl **granulated** with glyceryl distearate at different process parameter combinations (impeller speed in rpm, chopper speed in rpm, coating time in min).

CONCLUSION

KCl, a bitter salt with need for oral age appropriate formulations[3], was coated with glyceryl distearate, a lipid excipient with precedence of use in pediatric hard gelatin capsules of acetaminophen and plant extracts. The study showed that lipid coating in a conventional high shear mixer provides a straightforward approach to mask the unpleasant taste of pediatric drugs without the need of complex heating protocols and solvents.

Coating efficiency depended on all three process parameters: impeller speed, chopper speed and coating time. Low impeller speed with longer coating times or faster mixing for short times seems to be the best combinations. The use of low impeller speed favored coating of individual particles whereas higher impeller speed rather induced granulation. The effect of the chopper depended on mixing speed and time.

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