

Influence Of Protective Coating on Extended-release Pellets and Maintaining Desired Drug Release from MUPS Tablets

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Introduction

Multi-unit particulate systems (MUPS) are filled into a capsule or compacted with excipients to form a tablet. Recently, MUPS tablets have gained more popularity due to several advantages. Compared to capsules, tablets are the preferred oral solid dosage form due to the convenience of use by patients, lower manufacturing costs and higher production rates. Additionally, MUPS tablets offer divisible dosage form without compromising the drug release characteristics of the individual units. To date, only a few pharmaceutical MUPS tablets are commercially available, due to several challenges associated with the formulation and manufacture of MUPS tablets. Ideally, compressed MUPS should disintegrate rapidly in the gastrointestinal tract after oral administration, resulting in the same drug release pattern as uncompressed multiparticulates. The main challenge in MUPS tablet production is that compression can damage the functional barrier membrane coating, leading to subsequent loss of the intended modified-release functionality of the dosage form. The purpose of this study was to evaluate the potential of a protective coating of multiparticulates on drug release for extended release compressed MUPS.

Methods

Sugar pellets, (Suglets® PF053, Colorcon) were used as starting substrate, seal-coated with formulated ethyl cellulose organic coating system (Corelease EC™, Colorcon) with the aim to circumvent osmotic effect of sugar and its potential impact on drug release. Metoprolol succinate (Zhejiang Haixiang) was then loaded onto the seal-coated beads using Hypromellose based Opadry® (Colorcon) as a binder. Corelease EC was then applied on the drug layered pellets to achieve extended-release functionality. A protective coating layer, composed of a Hypromellose based Opadry with additional polyethylene glycol (PEG 3350, Dow) was subsequently applied on half of the pellets. All coating systems were applied using a bottom spray fluid bed coater (Strea-1, Aeromatic fielder, GEA). Pellets with

and without protective coating were separately blended with a mix of microcrystalline cellulose (Avicel® PH101, IFF), directly compressible starch (StarTab®, Colorcon) and crospovidone (Kollidon® CL, BASF) for 5 minutes. Sodium stearyl fumarate (PRUV®, JRS) was then added into the mixture and blended for another minute. Both mixtures were compressed into tablets individually using a rotary tablet press (Remik). Dissolution testing was conducted on both tablet formulations and on uncompressed pellets (with/without protective coating), in 750 mL phosphate buffer, pH6.8 or water at a paddle speed of 100 rpm. Drug release was determined via UV detection (Cary 50, Varian) at 274 nm. Tablets containing pellets with protective coating were finally coated with Opadry QX (Colorcon) in a traditional coating pan (BY-300, Bojing Pharma), and subjected to drug release testing using the same criteria as above. Additionally, scanning electron microscopy (SEM, TM4000, Hitachi) was used to capture images of the tablet's cross sections.

Table 1. Seal coating formulations and parameters

Item	Value
Suglets® PF053 (g)	200
Corelease EC™ (g)	20
90% ethanol: 10% water (g)	380
Solids (%)	5
Inlet Air Temperature (°C)	39-40
Product Temperature (°C)	31-34
Fluid Delivery Rate (g/min)	2.2-2.3
Atomizing Pressure (bar)	1.8
Airflow (m³/hr)	70
Theoretical Weight Gain (%)	10%

Table 2. Drug layering coating formulations and parameters

Item	Value
Seal coated pellets (g)	200
Metoprolol Succinate (g)	284
Opadry® (g)	19
Purified water (g)	1945
Solid (%)	16
Inlet Air Temperature (°C)	44-45
Product Temperature (°C)	34-35
Fluid Delivery Rate (g/min)	2.7-2.8
Airflow (m ³ /hr)	70
Atomizing Pressure (bar)	1.8-2.0
Practical Weight Gain (%)	~151.5%

Table 3. Drug layering coating formulations and parameters (2)

Item	Value
½ drug layering pellets (g)	242
Metoprolol Succinate (g)	238
Opadry® (g)	15.87
Purified water (g)	1333
Solid (%)	16
Inlet Air Temperature (°C)	44-45
Product Temperature (°C)	34-35
Fluid Delivery Rate (g/min)	2.7-2.8
Airflow (m ³ /hr)	70
Atomizing Pressure (bar)	1.8-2.0
Practical Weight Gain (%)	~98.4%

Table 6. MUPS Tablet formulations

Item	Percentage	Function
Protective coated pellets	About 58.5% (based on assay)	ER Pellets
Microcrystalline cellulose	31.0%	Cushioning agent
StarTab®	7.0%	Filler and disintegrant
Super disintegrant (PVPP)	3%	Disintegrant
Sodium stearyl fumarate	0.5%	Lubricant
Total (360mg/Tablet)	100%	Hardness>60N

Table 4. Extended-release coating formulations and parameters

Item	Value
Drug layering pellets (g)	200
Corelease EC™ (g)	80
90% ethanol: 10% water (g)	1520
Solids (%)	5
Inlet Air Temperature (°C)	40-43
Product Temperature (°C)	32-34
Fluid Delivery Rate (g/min)	2.2-2.3
Airflow (m ³ /hr)	70
Atomizing Pressure (bar)	1.8-2.0
Theoretical Weight Gain (%)	36%

Table 5. Protective coating formulations and parameters

Item	Value
Corelease EC™ coated pellets (g)	200
1st layer: Opadry® (g)	60
Water (g)	1140
Solids (%)	5
2nd layer: PEG 3350 (g)	26
Water (g)	494
Solids (%)	5
Inlet Air Temperature (°C)	55-65
Product Temperature (°C)	38-42
Fluid Delivery Rate (g/min)	1.5-1.7
Airflow (m ³ /hr)	70
Atomizing Pressure (bar)	1.8-2.2
Theoretical Weight Gain (%)	Opadry: 36%/PEG: 10%

Table 7. Top Coating formulations and parameters

Item	Value
Core Tablet (g)	300
Opadry® QX (g)	12
Water (g)	36
Solids (%)	25
Inlet Air Temperature (°C)	105-115
Product Temperature (°C)	38-42
Fluid Delivery Rate (g/min)	2.0-2.5
Atomizing Pressure (bar)	1.2-1.4
Theoretical Weight Gain (%)	4%

Results

Dissolution results showed that drug release profiles from pellets with/ without protective coating were similar ($f_2=83.4$). After compression, drug release from MUPS tablets containing protective coated pellets was similar to the pellets before tableting ($f_2=80.9$), but significantly different from the tablets that contained pellets without protective coating ($f_2=24.1$). SEM result showed the use of a protective coating resulted in round pellets that kept their integrity throughout the process after compression into a MUPS tablet, but the film of some pellets on the surface of the tablet without protective coating was cracked. Furthermore, drug release from MUPS tablets coated with Opadry QX was similar to that of uncoated MUPS tablets ($f_2=80.5$). Compression force (9-19KN) has no influence on drug release from MUPS tablets containing protective coated pellets ($f_2>80$).

Figure 1. Drug release from metoprolol succinate ER pellets with/without protective coating

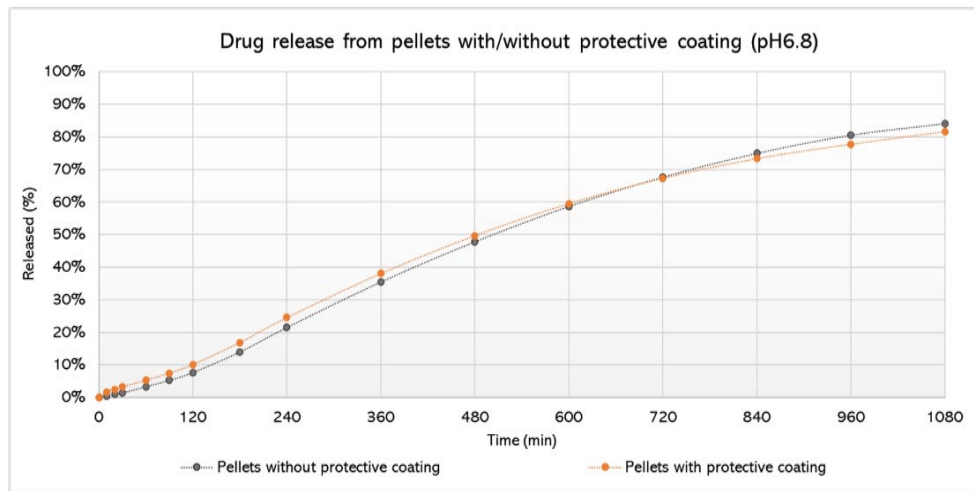


Figure 2. Drug release from metoprolol succinate ER pellets before/after compression

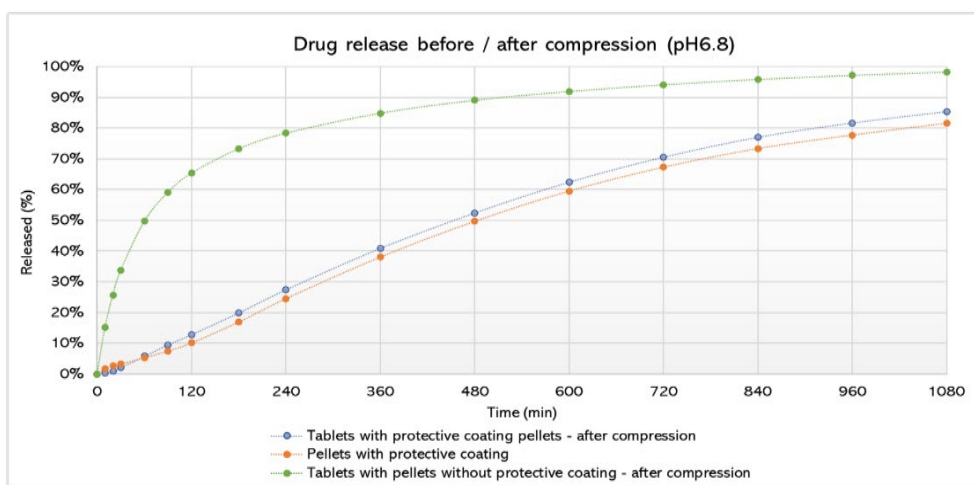


Figure 3. Drug release from tablets with/without top coating

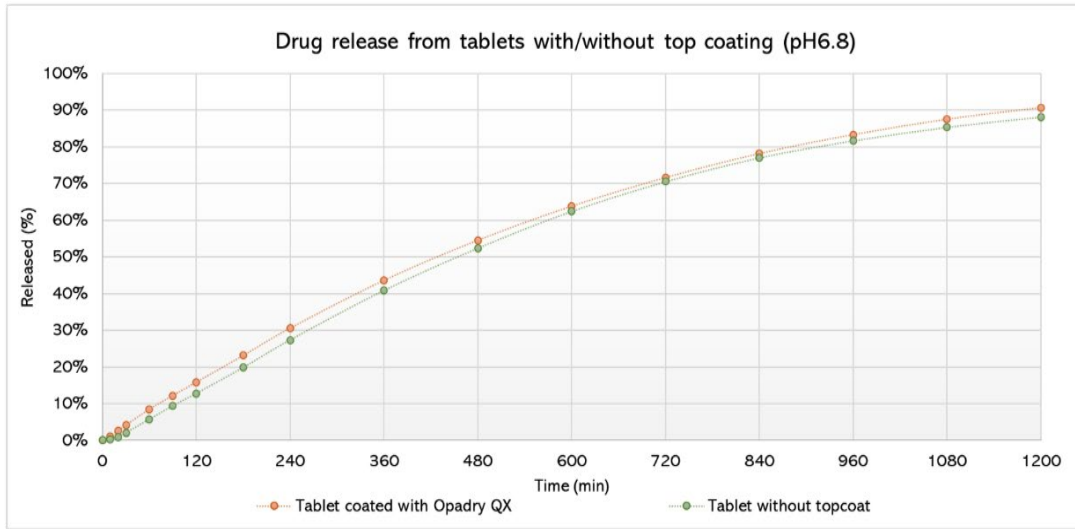


Figure 4. Influence of compression force on drug release from MUPS tablets with protective coated pellets

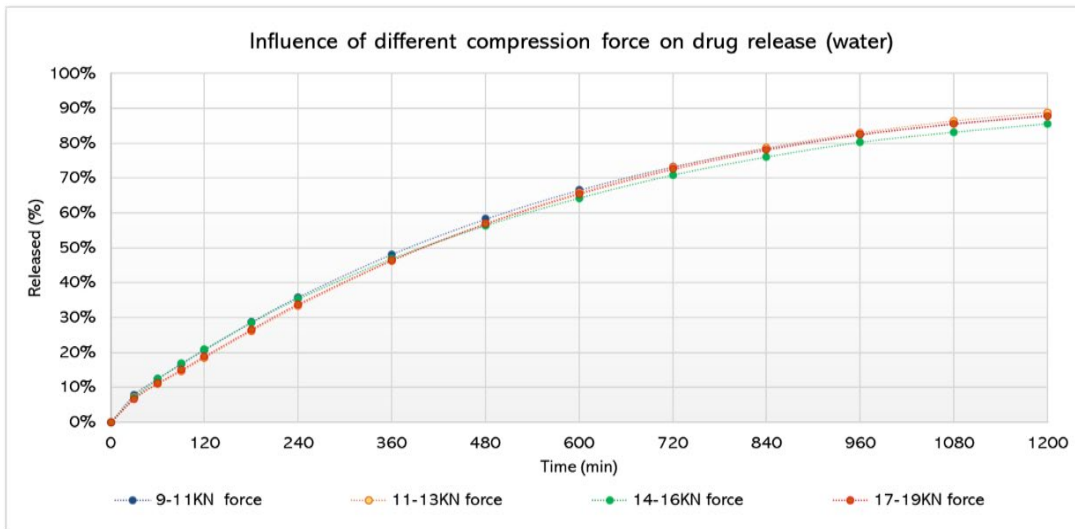


Figure 5. Cross section of MUPS tablet with protective coating pellets

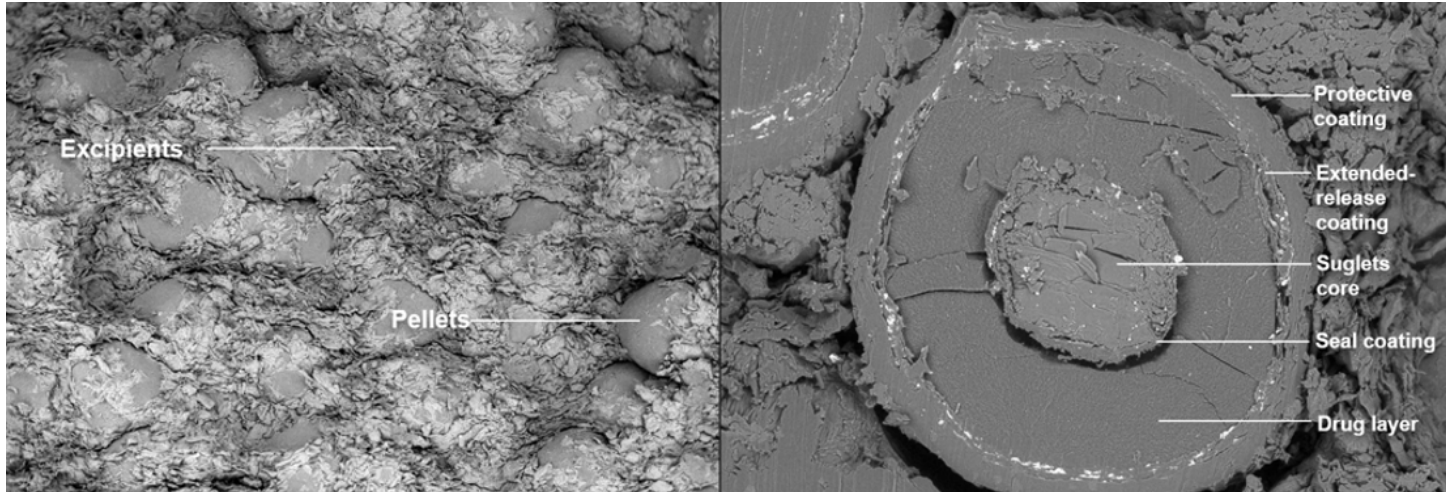
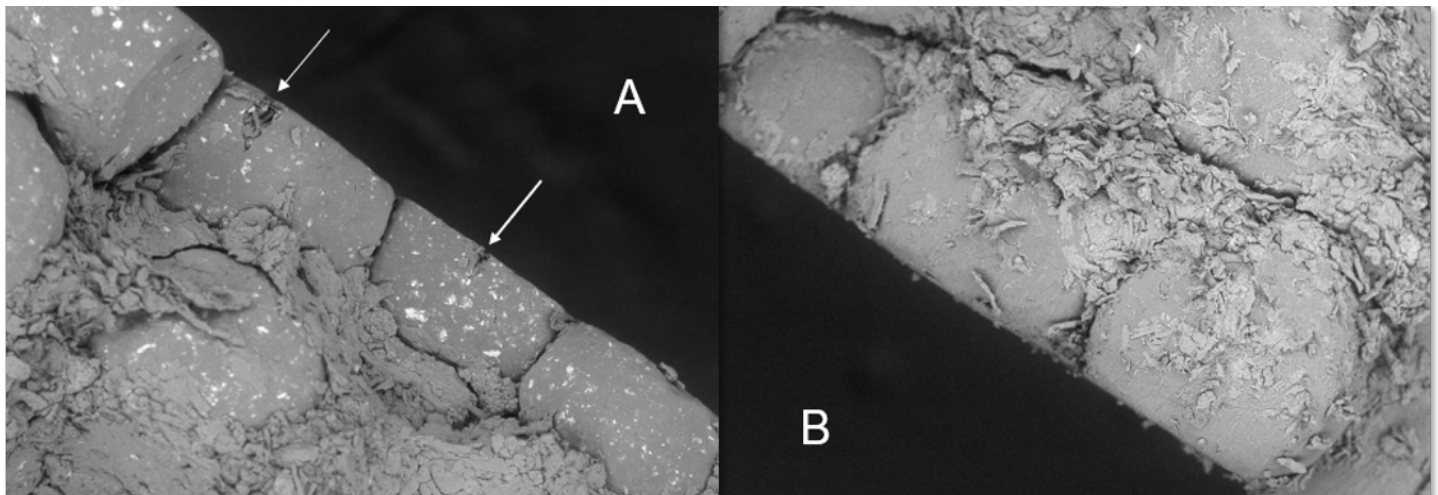


Figure 6. Pellets on surface of tablet (A: without protective coating, B: with protective coating)



Conclusions

After compression, tablets containing the extended-release pellets without protective coating showed faster drug release compared to uncompressed pellets. A protective coating with Opadry (with additional polyethylene glycol) had no influence on drug release from the Corelease EC™ coated pellets but resulted in enhanced protection of the extended-release pellets upon compression into MUPS tablets with comparable drug release profiles to the uncompressed pellets. Application of a protective coating is an easy way to overcome the challenge of formulation development of MUPS tablets and achieve desired tablet properties and drug release without compromising the characteristics of the individual units.

References

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