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Application of an Aqueous Ethylcellulose Dispersion in Multiple-Unit Pellet Systems.

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Abstract Summary

The objective of this work was to investigate drug release from compressed multiple-unit pellet systems, coated with an aqueous ethylcellulose dispersion (Surelease® E-7-19040). Damage during compression, a major challenge in the compaction of coated pellets, was minimized through the use of protective excipients.

Introduction

Compressed multi-unit pellet systems (MUPS) combine the clinical advantages of a multi-unit system with the cost-effectiveness of a tablet dosage form. Several reports on such systems exist, the majority of which are based on pellets organically coated with ethylcellulose. Environment, health and safety concerns require an evaluation of aqueously coated pellets in such systems.

Compression of coated pellets into disintegrating tablets may lead to damage of the film coating, resulting in altered drug release characteristics as compared to non-compressed pellets. In order to protect the integrity of coated pellets, excipients with protective (cushioning) properties are incorporated into tablet formulations. This study examines the compression of pellets coated with an ethylcellulose aqueous dispersion (Surelease E-7-19040), and the impact of cushioning materials on drug release.

Experimental Methods

Preparation of Drug Pellets

One hundred grams of microcrystalline cellulose (MCC) spheres (Celphere® CP-203, Asahi Kasei) were layered with a metoprolol succinate (MS)-binder solution in an Aeromatic Strea-1™, fluid-bed coater (Aeromatic-Fielder). Drug layered pellets were then seal coated (1% weight gain), barrier coated (26% weight gain), and then top coated (3% weight gain). The composition of all coating solutions is shown in Table 1.

Table 1: Coating Compositions

Layer	Ingredient	g
Drug-binder solution	Metoprolol succinate (IPCA)	300.0
	Opadry® 03F59040 (Colorcon)	15.0
	Kollidon® 30 (BASF)	9.0
	Purified water	1412.0
Seal coat	Opadry 03F59040	4.2
	Purified water	137.0
Barrier coat	Surelease E-7-19040 (Colorcon)	445.0
	Purified water	297.0
Top coat	Opadry 03F59040	16.8
	Purified water	523.0

Protective Particles
Partially pre-gelatinized maize starch (Starch® 1500, Colorcon), microcrystalline cellulose or MCC (Avicel® PH102, FMC), and spray-dried lactose (Lactopress®, Borculo Domo Ingredients) were each evaluated as cushioning agents at 70% w/w level.

Additionally, each of these materials was modified using a melt granulation process and further evaluated as cushioning agents. For example, Avicel PH102, low viscosity hypromellose (Methocel™ E3 LV, Dow) and polyplasdone XL® (crospovidone, ISP) were blended together and granulated using melted cetyl alcohol in a food processor (Grinderman, Sumeet machines). Aerosil® 200 (degussa) was then added to the granules. A similar procedure was followed using Starch 1500 or Lactopress in place of Avicel.

These three different granulate materials were then evaluated for their cushioning ability.

Tableting
Blends containing neat excipients (70%) and coated pellets (30%) were compressed. In the case of the modified excipients, the formulation contained the modified excipient (39-69%), Avicel PH102 (1%) and drug pellets (30-60%). Blending was carried out in a V-blender (Karnawati). Tablets weighing 330 mg were compressed on an instrumented 8 station rotary tablet press (Rimek) fitted with 10 mm standard concave tooling. Tablets were compressed at compaction forces of 3, 4, 5 and 7 kN.

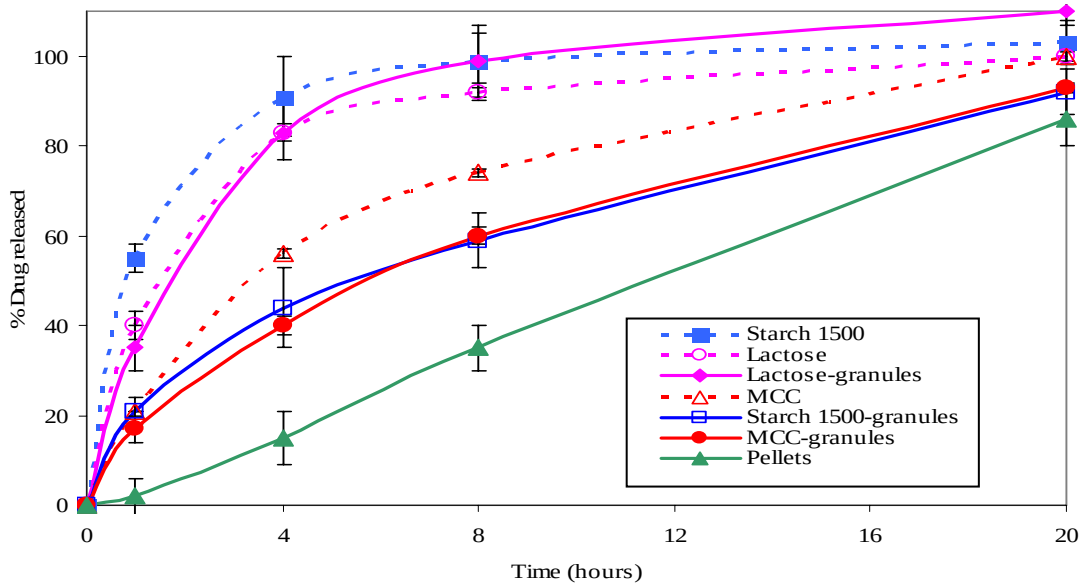
Tablet Testing
Diametrical crushing strength and friability of the tablets were determined using a PTB 311E hardness tester (PharmaTest) and a USP compliant Friabilator (Electrolab), respectively. Disintegration time was measured in an ED-2L (Electrolab) disintegration tester using water maintained at 37°C (±0.5°C). Dissolution testing was performed in a USP apparatus II, paddles (Electrolab) at 50 rpm. The dissolution medium was 500 ml of pH 6.8 phosphate buffer. Samples were withdrawn at 1, 4, 8 and 20 hours and an equivalent amount replaced with fresh dissolution medium. Samples were analyzed chromatographically using the USP test method for metoprolol succinate extended release (ER) tablets.

Results and Discussion

Figure 1 shows drug release profiles from MUPS compressed using neat excipients or granulated excipients. As expected, when neat MCC was used, it provided better protection to the coated pellets than when either partially pregelatinized starch or lactose was used.

It has been reported that, plastically deforming excipients are more effective in protecting the coated pellets during compression (Beckert et al 1996; Torrado and Augsburger, 1994). As MCC undergoes plastic deformation as compared to lactose which undergoes fragmentation and partially pregelatinized starch generally deforms by both mechanisms, it provides a better protection to the coated pellets. With respect to the granulated materials, MCC and partially pregelatinized starch afforded a similar protective effect to the pellets. Lactose however, provided no protection even after granulation.

Figure 1: The Influence of Type of Cushioning Agent Used on Metroprolol Succinate Release Profiles from MUPS



The term “protective excipient” through the remainder of this work will refer to the MCC granules prepared using the melt granulation process.

Figure 2: The Influence of Proportion of Coated Pellets Used in MUPS on Drug Release

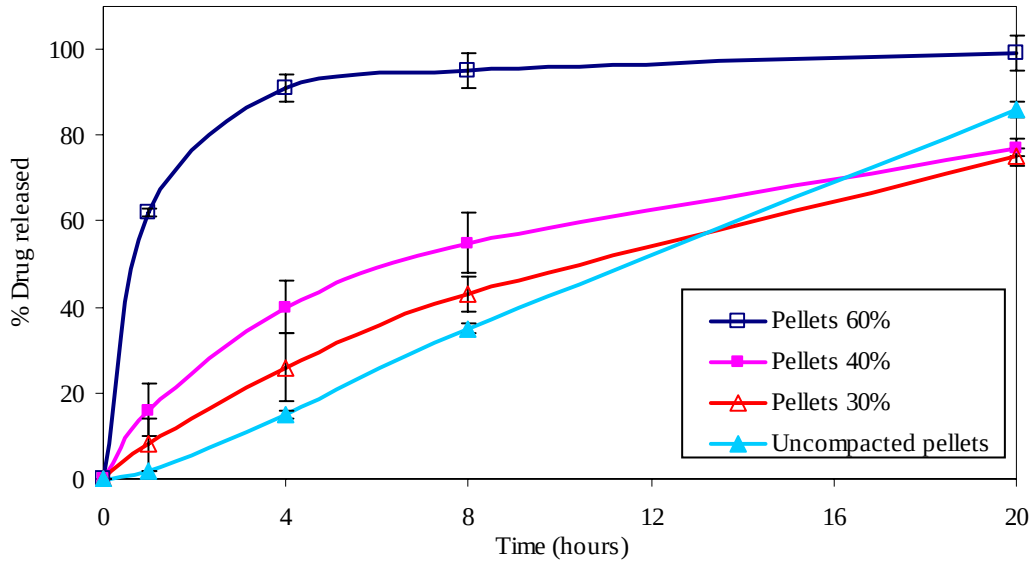


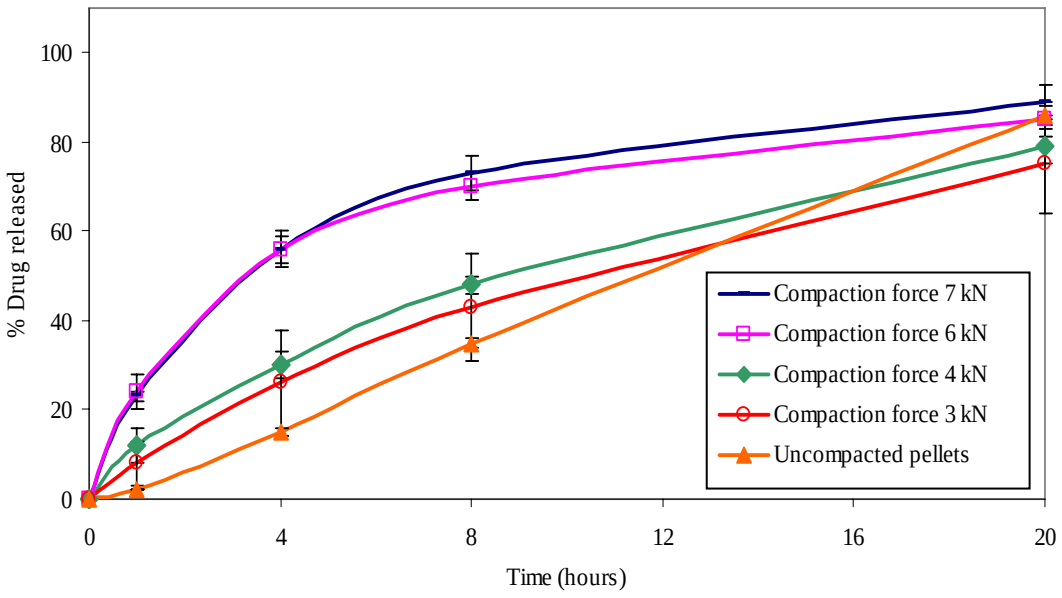
Figure 2 shows that the uncompressed coated drug pellets had an extended drug release profile. Compressing coated pellets (60% peletts) with 40% protective granulated excipient resulted in the loss of their ER properties.

Increasing the protective excipient to 70% ($t_{50\%}$ ~ 10.4 hr) minimized damage to the compressed drug pellets, with the f_2 between compressed and uncompressed pellets being 60.9. Values for f_2 between 50 and 100 indicate that the two profiles are similar (Federal Register, 1995).

This is explained by the lower yield pressure of the soft granulated material which absorbs the energy of compaction and preferentially deforms under pressure, thus protecting the pellets. A higher level of the cushioning excipient also reduces the number of pellets coming in direct contact with each other or with the punch surfaces during the compression cycle which can cause pellets to rupture (Beckert et al, 1996).

Increasing compaction force results in faster drug release (Figure 3) indicating damage to the film coating. The f_2 values for tablets compressed at compression forces of 3 kN and 4 kN were 60.2 and 55.3 respectively, Low friability values of less than 0.5% were achieved, due to the excellent binding and compressibility properties of the granulated excipient.

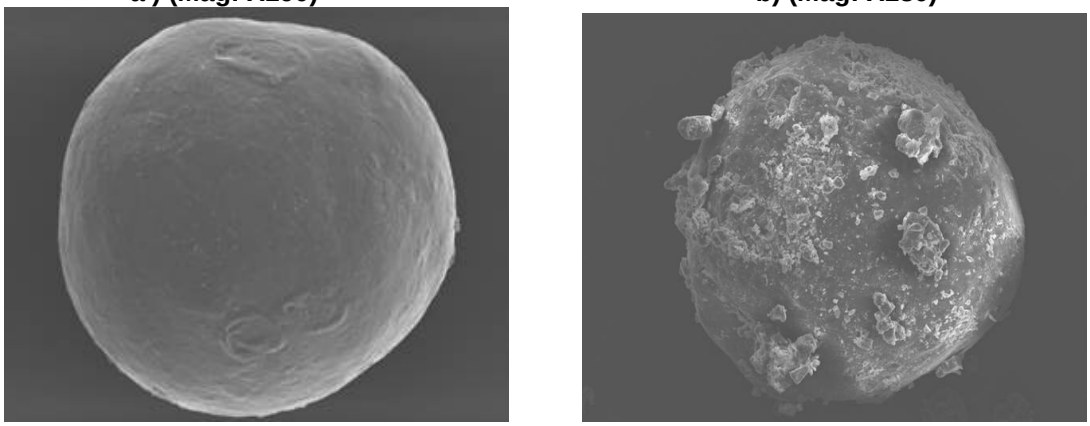
Figure 3: Influence of Compression Force on Drug Release Profiles (MUPS Containing 70%w/w Granulated Excipient)



Increasing the tablet compaction force produced tablets of greater strength. However, an increase in tablet disintegration time was also observed (>15 minutes for compaction forces above 7 kN). Higher disintegration times could be attributed to a lower penetration of the disintegration test media into the tablet, due to the presence of the cetyl alcohol in the granules.

Figure 4: SEM Images a) Coated Pellet; b) Deaggregated Pellet after Compression

a) (Mag: X190) **b) (Mag: X180)**



SEM images of coated pellets (Figure 4a) reveal a smooth surface. Pellets de-aggregated from the cushioning material after compression (at 3 kN) indicate that the pellets were sufficiently protected during tableting (Figure 4b). No cracks or indentations on the pellet surface were visible.

Conclusion

Pellets coated with an aqueous ethylcellulose dispersion (Surelease E-7-19040) were incorporated into a multiple unit pellet system, with minimal changes in drug release. Inclusion of 60-70% cushioning granules into the MUPS resulted in hard tablets with low friability and consistent drug release profiles.

References

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