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First step in the assessment of mechanical properties of pure API: production of tablet with minimum addition of excipient

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ABSTRACT

There are a number of challenges during tablet dosage form development like excipient selection, poor powder flow, poor tableting, lack of hardness, high friability, elevated disintegration time, low dissolution rate etc. Most of them are significantly influenced by the mechanical properties (like elasticity, plasticity, brittleness, powder compressibility, tensile strength, etc.) of the active pharmaceutical ingredient (API). Assessment of these properties of the pure actives is not always easy. Absence of lubrication may induce a lot of friction, causing capping, lamination or sticking or in many cases, combination of them, damaging the test tablet when taken out. Different approaches were studied to overcome this problem and a solution was found by compaction of a tablet of Sodium Starch Glycolate-Magnesium Stearate in a ratio of 2.75:1 before compressing each tablet of pure API.

Key words: Active pharmaceutical ingredient; Magnesium Stearate; Lubrication; Sodium Starch Glycolate.

INTRODUCTION

The science of drug discovery involves a series of complex steps (Streng and Lloyd, 1998). From finding out a suitable chemical entity to deliver it to the hand of the consumers, scientists have to overcome many hurdles (Stegemann et al., 2007). After completion of the lead selection and preformulation studies of a newly developed drug molecule, the challenge of formulation development comes on the way (Huang and Tong, 2004). Along with the chemical (molecular weight, partition coefficient, pKa etc.) and physical (crystallinity, melting point, surface area etc.) properties of the pure Active Pharmaceutical Ingredient (API) (Behl et al., 1998; Deák et al., 2008; Lau, 2001; Li and Zhao, 2007), mechanical properties have significant role in the success of formulation development (Mullarney et al., 2003). Mechanical properties are the properties of a material under an applied stress; this includes elasticity, plasticity, brittleness, powder compressibility, tensile strength, etc (Amidon et al., 2009; Jain, 1999). Despite of having good chemical & physical properties, poor mechanical properties of a drug can make it difficult to be formulated (He, 2009). A number of challenges during tablet dosage form development (such as excipient selection, powder flow, capping, lamination, sticking, tablet hardness, friability, disintegration, dissolution etc.) are influenced by the mechanical properties of the pure API (Amidon et al., 2009; He, 2009; Jain, 1999; Lau, 2001; Mullarney et al., 2003). This makes the testing of the mechanical properties of pure API a must for the formulation scientist. Manufacturing a tablet with only the API under test (without any excipient) would be an ideal approach to assess its mechanical properties. However, a pure active alone is usually very difficult

to compress and difficulties arise due to significant die wall frictions in the absence of lubricant. The tablets are very difficult to take out of the die because of the absence of lubricant (Wang et al., 2010). Aim of this study was to find out an easy way to formulate tablets of pure active pharmaceutical ingredients with minimum addition of excipient which can be used to carry out the tests of API mechanical properties. Paracetamol was used as the model drug.

MATERIALS AND METHODS

Materials

Sodium starch glycolate, magnesium stearate and paracetamol were purchased from Sigma-Aldrich.

Methods

The pure API was tried to compress using a 10mm IR tooling (Specac, UK) with a manual hydraulic press. But all the resulting tablets were deformed due to the absence of lubrication. To avoid these problems, lubrication for the pure actives was considered as lubrication masks the affinity between the pure active and the material from which the die is made. Moreover, it reduces the resistance to the compression process. Four different ways were considered for lubrication:

Method 1. The API was blended (2-4 minutes) with different concentrations of Magnesium stearate (Mg stearate) ranging from 0.5% to 5%, as recommended by the experts (Rowe et al., 2009). Study detail is tabulated in Table 1.

Method 2. The die was lubricated directly with Mg stearate loose powder before compressing pure API. The API tablets were taken out without any problem, but various results were obtained in the hardness test (tested by Pharma Test GmbH hardness tester, Germany) for the same sample tested, as the amount of lubricant cannot be controlled via this method (Table 2).

Method 3. A tablet of pure Mg stearate was compressed before each compaction of the pure active. The idea was to leave a thin film of the lubricant so that the subsequent API tablet would be ejected undamaged. But Magnesium stearate is not a very compressible material and most of the time either the tablet was damaged or a part of the tablet stuck to the disks.

Method 4. The compressibility problem of Mg stearate was aimed to avoid by blending it with another material, Sodium Starch Glycolate (SSG). A blend of SSG – Mg stearate at different ratio was tested (Table 3), as these two excipients are usually present in most tablet formulations. A tablet of 300 mg of this blend was compressed before each testing with the pure actives.

Additional tests were carried out with formulation F-61 as it seemed to be promising. The subsequent API tablets manufactured particularly after this formulation were taken out of the die without any problem and had most elegant appearance; there was no sign of capping, lamination, sticking or chipping at all observed in the tablets. 20 more tablets were produced to test the reproducibility of the formula.

RESULTS AND DISCUSSION

In the first method, the API was blended with variable concentrations of Mg stearate and different blending times. The idea was to provide sufficient lubrication to the API to reduce or eliminate friction between the die wall and the resulting tablet. Different blending time was considered as it showed variable results in the previous studies (Kikuta and Kitamori, 1994). However, all of the tablets produced by this method were damaged when taken out of the die due to friction and no further testing was possible.

Table 1. Test formulations with variable concentration of Mg stearate & different blending times.

Formulation	API (%)	Mg Stearate (%)	Blending Time (Min)
F-1	99.5	0.5	2
F-2	99	1	2
F-3	98.5	1.5	2
F-4	98	2	2
F-5	97.5	2.5	2
F-6	97	3	2
F-7	96.5	3.5	2
F-8	96	4	2
F-9	95.5	4.5	2
F-10	95	5	2
F-11	99.5	0.5	3
F-12	99	1	3
F-13	98.5	1.5	3
F-14	98	2	3
F-15	97.5	2.5	3
F-16	97	3	3
F-17	96.5	3.5	3
F-18	96	4	3
F-19	95.5	4.5	3
F-20	95	5	3
F-21	99.5	0.5	4
F-22	99	1	4
F-23	98.5	1.5	4
F-24	98	2	4
F-25	97.5	2.5	4
F-26	97	3	4
F-27	96.5	3.5	4
F-28	96	4	4
F-29	95.5	4.5	4
F-30	95	5	4

Table 2. Test formulations in which die was lubricated directly with Mg stearate loose powder.

Formulation	Weight of API (mg)	Method of lubrication	Hardness (Kg)
F-31	300	Die was lubricated directly with Magnesium stearate loose powder	0.71
F-32	300		0.61
F-33	300		1.22
F-34	300		0.65
F-35	300		0.67
F-36	300		0.89
F-37	300		1.14
F-38	300		1.11
F-39	300		0.85
F-40	300		0.69
F-41	300		1.05
F-42	300		1.21
F-43	300		0.82
F-44	300		0.60
F-45	300		1.20
F-46	300		0.63
F-47	300		0.66
F-48	300		0.83
F-49	300		0.71
F-50	300		0.85
		RSD =	**25.81%**

After lubricating the die directly with Mg stearate loose powder (Method 2), tablets were taken out without any problem, but variation in hardness was observed. This was probably because of the fact that the amount of lubricant could not be controlled via this method. Variable hardness of the products can be noticed (Table 2).

In the third attempt, a tablet of pure Mg stearate was tried to compress so that it would leave a thin layer of lubricant on the die surface. The idea was that, this left over lubricant would help the subsequent API tablet to eject without any problem. However, low compressibility of Mg stearate made this method unfeasible.

Final method was designed to overcome the compressibility problem of Mg stearate by blending it with SSG. Most promising formulation from this method (F-61) was further investigated. Less hardness variation of the final API products can be noticed from Table 4. The API tablets were taken out without any problem and hardness results showed low variability (RSD < 10%) for the same sample tested.

Table 3. Test formulations composed of SSG & Mg stearate in a different ratio. (*=Damaged tablet).

Formulation	Amount of SSG (mg)	Amount of Mg Stearate (mg)	Total weight of tablet (mg)	Hardness of API tablet (Kg)
F-51	20	280	300	0.82
F-52	40	260	300	0.84
F-53	60	240	300	0.63
F-54	80	220	300	0.72
F-55	100	200	300	0.99
F-56	120	180	300	0.93
F-57	140	160	300	0.69
F-58	160	140	300	1.00
F-59	180	120	300	0.98
F-60	200	100	300	1.21
F-61	220	80	300	1.22
F-62	240	60	300	1.02
F-63	260	40	300	*
F-64	280	20	300	*

Table 4. Reproducibility test of formula 61 using SSG and Mg stearate at a ratio of 2.75:1.

Formulation	Amount of SSG (mg)	Amount of Mg Stearate (mg)	Total weight of tablet (mg)	Hardness of API tablet (Kg)
F-61-1	220	80	300	1.16
F-61-2	220	80	300	1.09
F-61-3	220	80	300	1.05
F-61-4	220	80	300	1.17
F-61-5	220	80	300	0.81
F-61-6	220	80	300	1.07
F-61-7	220	80	300	1.14
F-61-8	220	80	300	1.08
F-61-9	220	80	300	1.04
F-61-10	220	80	300	1.21
F-61-11	220	80	300	1.01
F-61-12	220	80	300	1.13
F-61-13	220	80	300	1.08
F-61-14	220	80	300	1.01
F-61-15	220	80	300	1.19
F-61-16	220	80	300	1.04
F-61-17	220	80	300	1.11
F-61-18	220	80	300	1.08
F-61-19	220	80	300	1.18
F-61-20	220	80	300	1.11
			RSD =	**8.09%**

CONCLUSION

In our study, the tablets of pure API were damaged when being taken out of the die because of the absence of lubricant causing significant die wall friction. After careful consideration of several approaches, a feasible solution was found by compaction of a tablet of SSG-Mg stearate in a ratio of 2.75:1 before each test with the pure actives to lubricate the die wall. The findings from this work can be used for future research of determining mechanical properties of pure API.

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