Effect Of Amount Of Hydrophobic Lubricant And Mixing Time On Paracetamol Tablets Properties

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□ ABSTRACT □

Magnesium stearate (Mg-St) is a widely used lubricant in solid dosage forms. In this research, we examined the effect of the lubricant magnesium stearate at various concentrations, mixing times, and mixer's type on granule flowability and paracetamol tablets properties (hardness, friability, disintegration time, and dissolution rate). It was found that increasing the mixing time of MgSt improved granule flow and reduced hardness statistically significantly, while increasing the MgSt concentration and the type of mixer did not have a statistically significant effect on the flowability and hardness. On the other hand, the disintegration time increases and the dissolution rate decreases statistically with increasing MgSt concentration and mixing time.

Key words: Tablets, Lubricants, Paracetamol, Magnesium stearate, Mixing time

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تأثير كمية المزلق الكاره للماء وزمن مزجه على مواصفات مضغوطات الباراسيتامول

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□ ملخّص □

تعتبر شمعات المغنيزيوم (MgSt) أكثر المزلقات استخداماً لدى تحضير الأشكال الصيدلانية الصلبة، لذلك في هذا البحث قمنا بإضافة شمعات المغنيزيوم بتراكيز مختلفة والمزج لعدة أزمنة مختلفة باستخدام نوعين مختلفين من المازجات، ودراسة تأثير هذه المتغيرات على انسيابية الحثيرات أثناء التحضير وعلى خصائص مضغوطات الباراسيتامول الناتجة (القساوة، الهشاشة، زمن التفتت، الانحلال). حيث لاحظنا تحسن انسيابية الحثيرات وانخفاض قساوة مضغوطات الباراسيتامول بفارق هام احصائياً بزيادة زمن المزج مع شمعات المغنيزيوم، في حين أن زيادة تركيز MgSt واختلاف نوع المازج لم يكن له تأثير هام إحصائياً على الانسيابية والقساوة. من جهة أخرى لاحظنا زيادة زمن التفتت وانخفاض معدل انحلال مضغوطات الباراسيتامول المحضرة بفارق هام احصائياً بزيادة تركيز MgSt وزمن مزجه.

الكلمات المفتاحية: المضغوطات، المزلقات، الباراسيتامول، شمعات المغنيزيوم، زمن المزج.

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Introduction

The formulation of a solid dosage form requires precise processing control of the powder mixture to ensure volumetric delivery of a homogeneous aliquot.[1]

One of the most essential excipients in tablet formulation is lubricant[2], which has been commonly utilized in pharmaceutical formulations to improve the flowability of powder mixtures[3]. Pharmaceutical lubricants are substances that are added in very small amounts to tablet and capsule formulations to improve the powder processing characteristics of the formulations[4]. It is used to lower tablet ejection force during compression by decreasing friction between the tablet and the die wall, and it protects tablets from adhering to punch surfaces. Lubricants can enhance blend flowability and facilitate unit operation[4]. Most powder lubricants have these properties, albeit to varying degrees. Several properties of the manufactured tablets are affected by the type, concentration, technique of inclusion, time, and conditions of mixing, such as hardness, friability, and time for disintegration and dissolution[5].

Most lubricants are hydrophobic substances that can increase the hydrophobicity of a blend. The latter mix property influences the performance of post-lubrication processes in the tablet production process, such as compaction, as well as final product characteristics such as tablet disintegration and tablet strength.[6]

Lubricants work to reduce friction by forming a thin, continuous fluid layer between the tablet and the metal die surface or by forming a boundary layer on the formulation particles or metal die surfaces. Metallic salts, fatty acids, hydrocarbons, fats, esters, alkyl sulfates, polymers, and inorganic substances are the six main types of boundary lubricants used in pharmaceutical tableting.[7]

Magnesium stearate, a metallic salt boundary lubricant, is the most widely used lubricant in pharmaceutical tableting because it is relatively inexpensive, gives great lubrication, has a high melting point, and is chemically stable[7]. It is commonly added at a concentration of 0.5–2%. The lubricating effect of magnesium stearate, on the other hand, is impacted by industrial conditions and powder characteristics, which can produce unforeseen difficulties such as a lack of hardness, poor disintegration, and a delay in tablet dissolution.[8]

The research presented in this paper looks at the lubrication effectiveness of magnesium stearate at different concentrations and mixing times. Because variable degrees of magnesium stearate influence pharmaceutical bioavailability, it is critical to identify the right concentration that enables functional tablet manufacture while not interacting with the active ingredient's effects or limiting its bioavailability.

The influence of MgSt concentration and mixing time on the characteristics of paracetamol tablets is investigated in this research.

MATERIALS AND METHODS

1. Materials

Paracetamol is a pharmaceutical ingredient that is listed in the british pharmacopoeia and is used as an analgesic (it was obtained from loba chemie pvt. Ltd, India). Microcrystalline cellulose (avicel ph 102) is used as a binder, diluent, and disintegrant (it was obtained from otokemi mumbai, India). In tableting, povidone solution (pvp-k30, 15% w/v) is used as a binder in the wet granulation process (it was obtained from otokemi mumbai, India). Magnesium stearate is used as a hydrophobic lubricant (was obtained from otokemi mumbai, India **).**

2. Apparatus

- Sensitive balance (Radwag AS 220/X (Poland))
- Oscillates Granulator (Erweka AR 401, Germany)
- Convection oven (Memmert BE 200 Incubator, Germany)
- Cube mixer (ERWEKA D-63150 Heussenstamm UG, Germany)
- Planetary mixer (ERWEKA D-63150 Heussenstamm PRS, Germany)
- Rotary tableting machine (TIWIN INDUSTRY ZP130-7A)
- Tap density tester (SOTAX- TAP DENSITY TESTER (USP) - TD2V 230-315 Mat)
- Hardness tester (ERWEKA TBH200, Germany)
- Friability tester (Logan Instruments Inc., FAB-2A, Germany)
- Disintegration tester (ERWEKA ZT 52, Germany)
- Dissolution tester (Erweka DT 600, Germany)

3. METHODS

3.1 Granulation

The powders (Paracetamol and Avicel) were mixed in a manual, geometrical manner and then granulated with alcoholic PVP in a suitable amount using an oscillates granulator with a sieve of 1250 microns. Followed by drying at 50–55 °c for 12 hours. The dried granules were separated into six equal parts, each weighing 325 g.

3.2 Mixing Of Magnesium Stearate With The Granules

The granules and magnesium stearate were mixed using two types of mixers: cube and planetary, at a uniform rotational speed of 250 rpm, and the concentrations of magnesium stearate were 0.5–1–2 %. Furthermore, to observe the effect of mixing time, mixing for different periods was applied (5-10-20-30) min. The table (1) shows the formulas prepared according to the previous variables.

Table 1: Prepared paracetamol tablet formulations

Formula code	Paracetamol (mg)	AvicelPH102 (mg)	PVP 15%W\V	Magnesium stearate (%)	Mixer type	Mixing time (min)
F1	300	12	q.s	0.5%	cube	5
F2	300	12	q.s	0.5%	cube	10
F3	300	12	q.s	0.5%	cube	20
F4	300	12	q.s	0.5%	cube	30
F5	300	12	q.s	1%	cube	5
F6	300	12	q.s	1%	cube	10
F7	300	12	q.s	1%	cube	20
F8	300	12	q.s	1%	cube	30
F9	300	12	q.s	2%	cube	5
F10	300	12	q.s	2%	cube	10
F11	300	12	q.s	2%	cube	20
F12	300	12	q.s	2%	cube	30
F13	300	12	q.s	0.5%	Planetary	5
F14	300	12	q.s	0.5%	Planetary	10
F15	300	12	q.s	0.5%	Planetary	20
F16	300	12	q.s	0.5%	Planetary	30
F17	300	12	q.s	1%	Planetary	5

F18	300	12	q.s	1%	Planetary	10
F19	300	12	q.s	1%	Planetary	20
F20	300	12	q.s	1%	Planetary	30
F21	300	12	q.s	2%	Planetary	5
F22	300	12	q.s	2%	Planetary	10
F23	300	12	q.s	2%	Planetary	20
F24	300	12	q.s	2%	Planetary	30

3.3 Tableting

Tablets were compressed with a uniform compressive force on a rotary tableting machine (TIWIN INDUSTRY ZP130-7A) with a diameter of 8 mm (flat-faced punch).

3.4 Measurement Flowability of Granules

Tapped density tester was used to determine tapped and bulk density by taking random samples from the mixture, and the density of the powder sample within the cylinder was then determined as follows:

Bulk density (g/ml) = mass of sample /volume of sample

The sample within the cylinder was then vibrated/tapped until the resultant volume no longer changed, and the tapped density was determined:

Tapped density (g/ml) = mass of sample /tapped density volume (ml)

Density measurements were taken thrice. The bulk and tapped density measurements enabled the calculation of the Hausner ratio and Carr's index:

Hausner Ratio = tapped density / bulk density

Carr's Index = (tapped density-bulk density / tapped density) * 100%

3.5 Measurement of Tablet Properties

3.5.1 Hardness and Friability Tablets

The hardness of ten tablets was measured using a hardness tester (ERWEKA TBH200, Germany), For the determination of the tablets Friability Ten tablets were chosen at random, cleaned, with a cleaning brush and weighed using a balance (Radwag AS 220/X (Poland)). The tablets were rotated 100 times in four minutes in a Friability Tester (Logan Instruments Inc., FAB-2A, Germany). The tablets were cleaned and reweighed. Friability was then determined:

Tablet Friability (F) = $(W_0 - W / W_0) * 100$

Where W0 is original tablet weight (mg) and W is tablet weight after tumbling (mg).

If the tablet batch had less than 1% friability, it consider to satisfy the BP requirements.

3.5.2 Tablet Disintegration Test

A disintegration bath was filled with 800 mL of deionized water and heated to 37°C. Six tablets were placed in basket-rack tubes (ERWEKA ZT 52/Germany). The time taken for all tablets to fully disintegrate was recorded, and if all six disintegrated in less than fifteen minutes, the batch passed BP specifications.

3.5.3 Dissolution Test

Six tablets obtained for dissolution using a dissolution tester (Erweka DT 600/ Germany). The dissolution test was performed with the paddle method at 50 rpm in 900 mL of phosphate buffer (pH 5.8) at 37 ± 0.5°C. Samples of solution (5 mL) were collected at (30-60- 75) min and concentrations of paracetamol were measured by UV spectrophotometry (Jasco V-530/ Vis spectrophotometer/Japan) at 243 nm.

Results And Discussion

1. Effect of concentration, mixing time, and type of mixer on the granules flowability

The flowability test was carried out for paracetamol with Avicel PH102 powder (formula F00), as it showed poor flowability according to the Hausner ratio and Carr's index, so the wet granulation technique was used to improve the flowability (formula F0). We obtained the results shown in Table 2, which are considered poor to very poor according to the Pharmacopeia.

Table 2: Flowability test results for paracetamol powder and granules before adding the lubricant

Formula (before lubrication)	Hausner ratio	Carr's index (%)
F_{00}	1.5±0.01	33.38±0.288
F_0	1.32±0.03	24.14±1.745

The results (Table (3)) showed that the flowability has improved after the addition of magnesium stearates, but with a statistically insignificant difference. Increasing the duration for mixing the granules with the lubricant had a statistically significant effect and the flowability has reached a good to excellent, while the type of mixer had no significant effect.

Table 3: Carr's index and Hausner ratio for all formulations

Formula code	Hausner ratio	Carr's index (%)
F1	1.25±0.005	20.04±0.4
F2	1.19±0.003	16.46±0.3
F3	1.15±0.004	13.26±0.3
F4	1.15±0.01	14.40±0.2
F5	1.19±0.005	16.64±0.1
F6	1.19±0.002	16.73±0.3
F7	1.13±0.002	11.57±0.3
F8	1.10±0.004	8.88±0.4
F9	1.10±0.01	9.36±1.09
F10	1.10±0.004	9.20±0.2
F11	1.06±0.003	5.73±0.3
F12	1.05±0.002	4.80±0.2
F13	1.11±0.01	10.57±0.9
F14	1.10±0.01	9.30±1.03
F15	1.09±0.01	8.65±0.7
F16	1.05±0.002	5.22±0.1
F17	1.10±0.006	9.40±1.1
F18	1.10±0.006	8.73±1.09
F19	1.08±0.001	7.59±0.09
F20	1.05±0.001	4.86±0.1
F21	1.10±0.006	9.36±1.09
F22	1.04±0.01	4.26±1.05
F23	1.04±0.01	4.19±1.01
F24	1.01±0.001	1.68±0.8

2. Effect of concentration, mixing time, and type of mixer on the tablets' hardness

The results of the hardness measurement are presented in Table 4, which show a slight decrease in hardness with increasing MgSt concentration and no significant statistical changes. This could be because paracetamol is a brittle substance[9]. Brittle and fragmented materials generate new clean surfaces during compression, and the lubricant does not interfere as it does with plastic materials, resulting in a stronger tablet.[10]

The hardness of all tablets decreased statistically significantly as mixing time increased. It could be attributed to the tablet with coated particles of MgSt, and the ordered mixes had lower mechanical strength because the magnesium stearate particles situated between the granules disrupted particle bonding during composition with an increase in mixing time.[11]

As for the difference in the type of mixer used, the planetary mixer formulas showed a decrease in hardness than the cubic mixer formulas, but these differences did not have any significant statistical significance.

Table 4: Tablet hardness and Friability values

Formula code	Hardness Average % ± SD	Friability% (n =10)
F1	6.53±1.03	0.65
F2	6.51±1.6	0.65
F3	5.45±0.5	0.71
F4	4.91±1.3	0.78
F5	6.45±1.01	0.80
F6	5.47±0.7	0.812
F7	4.79±0.8	0.9
F8	4.59±0.8	0.989
F9	5.76±1.1	0.8
F10	4.98±0.9	0.842
F11	4.65±0.8	0.85
F12	3.89±0.7	0.86
F13	6.15±1.6	0.59
F14	5.74±0.6	0.6
F15	4.82±0.9	0.623
F16	4.40±0.7	0.63
F17	5.94±1.05	0.68
F18	5.28±0.6	0.713
F19	4.67±0.7	0.77
F20	4.32±0.9	0.8
F21	5.44±0.7	0.7
F22	4.93±1.08	0.716
F23	4.51±0.6	0.78
F24	4.24±0.9	0.89

3. Effect of concentration, mixing time, and type of mixer on the tablets' friability

The friability test results showed that all of the tested formulas tablets passed constitutional specifications, with all formulations having a friability of less than 1%, as shown in Table 4. Lubrication causes increased friability by reducing interactions at the particle-particle bonding interface.**[12]**

4. Effect of concentration, mixing time, and type of mixer on tablet disintegration time

The results of the disintegration test showed the tablet disintegration time was significantly prolonged as the concentration of MgSt increased. When MgSt was mixed into granules at a concentration of 0.5–2%, F1 and F9, the disintegration times were 1.50 and 9.80 min, respectively, as shown in Table 5. In addition, the disintegration time versus the mixing time showed that while the tablets disintegrated within 1.50 min after mixing with MgSt for 5 min (F1), it took 4.11 min after mixing for 30 min (F4), and the disintegration time was significantly prolonged. Because MgSt has high water insulative properties, increasing the concentration and/or prolonging the mixing time of MgSt allows for the formation of a hydrophobic coating on the granular surface and tablet surface, resulting in a longer disintegration time.[13]

The type of mixer also had a statistically significant effect, as the planetary mixer formulas showed a longer disintegration time compared to the cube mixer formulas, and this is due to the lower shear forces of the cube mixer compared to the planetary mixer, and therefore a lower mixing efficiency.[14]

Table 5: Tablet disintegration time test results

Formula code	Average (min) ± SD
F1	1.5±0.4
F2	2.8±0.5
F3	3.7±0.3
F4	4.11±0.4
F5	6.48±0.6
F6	6.88±0.2
F7	7.33±0.4
F8	8.51±0.4
F9	9.8±0.4
F10	11.13±0.4
F11	14.5±0.6
F12	16.18±0.5
F13	2.01±0.3
F14	3.46±0.5
F15	4.75±0.3
F16	5.11±0.3
F17	7.08±0.5
F18	7.75±0.3
F19	8.08±0.4
F20	9.03±0.3
F21	16.01±0.6
F22	16.51±0.5

F23	18.01±0.6
F24	20.08±1.2

5. Effect of concentration, mixing time, and type of mixer on tablet dissolution

5.1 Effect of MgSt concentration on paracetamol dissolution rate

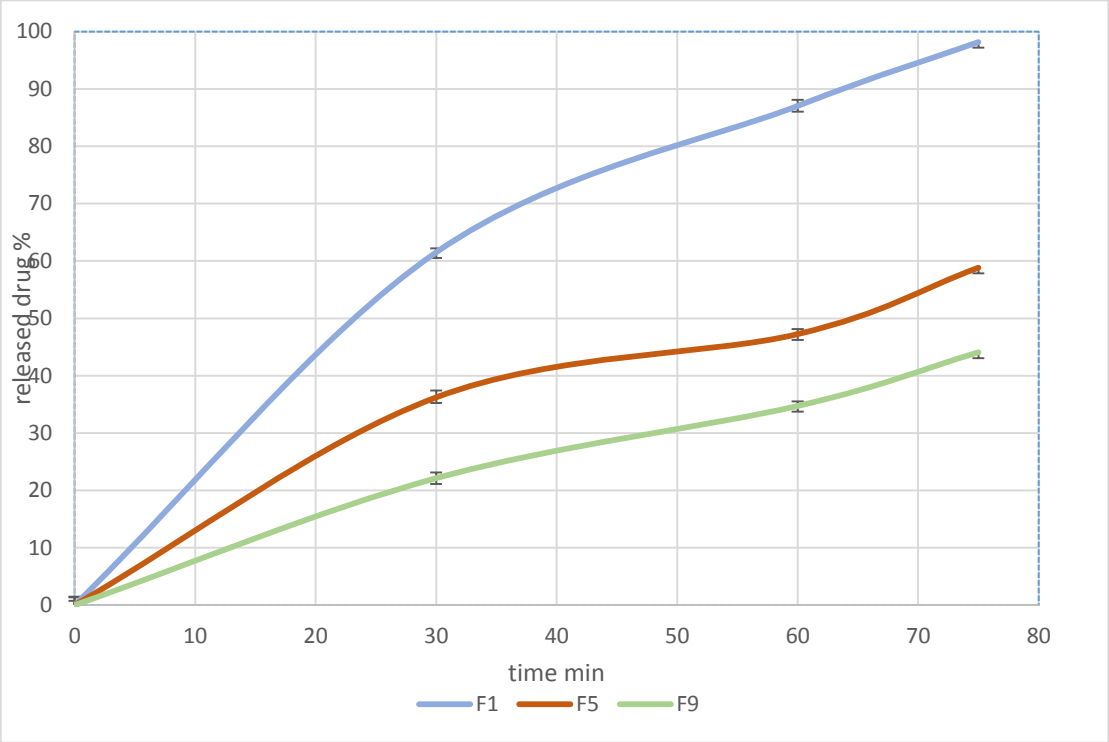
Tablet dissolution rates decreased as MgSt concentration increased by a statistically significant difference. After 30 minutes, F1 (0.50% MgSt) has released more than 60% of the drug, whereas the other two concentrations, F5 (1% MgSt) and F9 (2% MgSt), are closer to 30%–20% dissolution, as indicated in Table 6 and Figure 1. As a result, paracetamol must be released over a longer period of time when the tablet contains higher amounts of MgSt lubricant. This result, as explained previously, has been attributed to the formation of a hydrophobic layer on the surface of the granulation particles.[15]

Table 6: Released amount of paracetamol (%) as a function of time

Formula code	The amount released% after 30 min	The amount released% after 60 min	The amount released% after 75 min
F1	61.5±1.04	87.03±0.6	98.16±0.7
F2	56.3±0.7	80.58±1.02	91.61±1.02
F3	54.68±0.6	74.71±1.05	84.93±1.3
F4	46.01±0.7	63.18±0.7	74.83±0.7
F5	36.21±0.8	47.25±1.1	58.83±1.4
F6	32.83±0.8	44.08±0.6	56.03±0.3
F7	29.96±0.7	41.58±0.6	53.68±0.6
F8	25.03±1.04	36.45±0.8	47.3±0.8
F9	22.13±0.7	34.71±0.9	44.08±1.3
F10	20.13±0.7	32.16±1.2	40.91±1.2
F11	18.2±0.5	30.38±0.4	38.11±0.7
F12	16.85±0.5	29.11±0.7	37.5±0.7
F13	64.66±1.08	82.75±1.4	93.33±1.1
F14	56.61±1.05	75.83±0.9	86.56±0.9
F15	54.75±0.9	73.91±0.8	85.71±0.9
F16	52.3±1.01	66.88±1.4	77.8±1.1
F17	31.78±0.5	47.8±0.6	58.61±1.1
F18	30.96±0.7	46.8±1.6	58.08±1.2
F19	30.3±0.5	42.31±0.5	57.61±0.3
F20	27.68±1.09	43.11±1.1	54.46±0.9
F21	18.55±0.7	28.63±0.8	37.8±0.8
F22	17.51±0.5	27.46±0.7	35.78±0.9
F23	17.08±0.5	26.35±0.7	34.58±0.5
F24	15.93±0.6	24.45±0.8	32.68±0.7

5.2 Effect of MgSt-mixing time on paracetamol dissolution rate

When the mixing time with the MgSt was increased, the dissolution rate decreased statistically significantly, as shown in Figure 2. The percentage of paracetamol dissolved decreased with increasing mixing time, from 64% F13 (5 minutes of mixing time) to 52% F16 (30 minutes of mixing time), as shown in Table 6. After material mixing, the Mg-St coated the surface of each granule particle. This coating effect may reduce particle wettability and cause the dissolving time to be prolonged..[13]



Figuer 1 shows the impact of MgSt-concentration on the average dissolution profiles of formulations (F1 –F5 –F9).

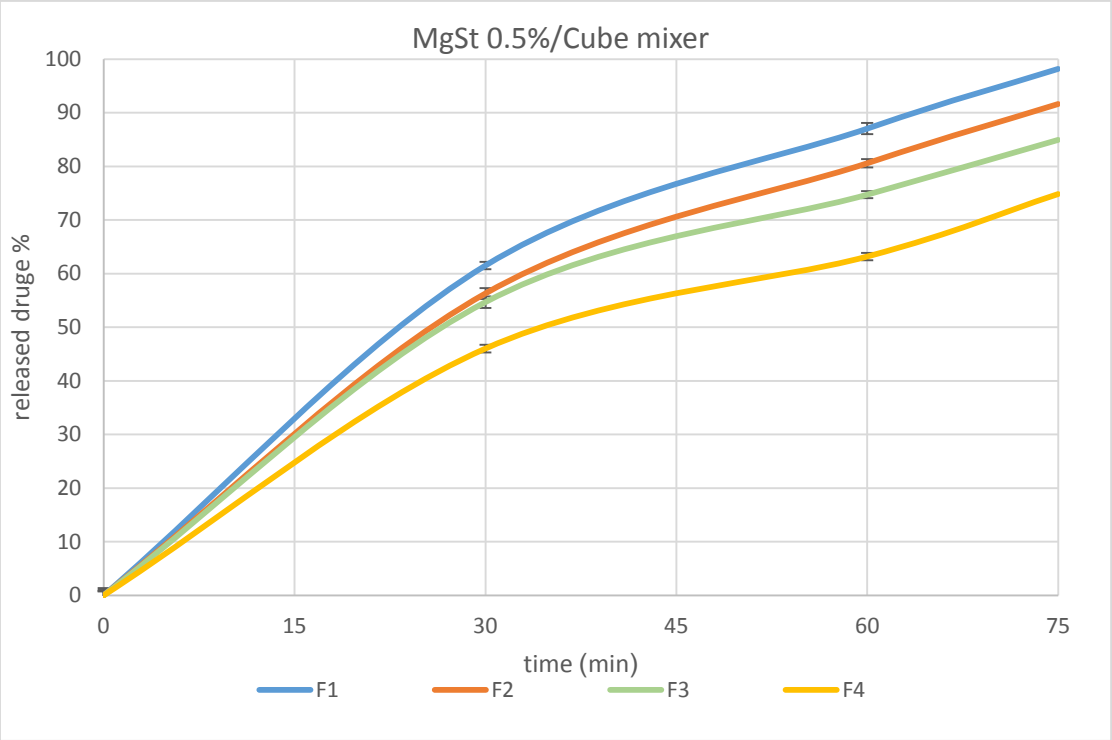


Figure 2 shows the impact of MgSt-mixing time on the average dissolution profiles of formulations (F1 -F2 -F3 -F4).

5.3 Effect of mixer type on paracetamol dissolution rate

The difference in the type of mixer showed a statistically significant effect for most of the prepared formulations, where the percentage of the amount of paracetamol released in the planetary mixer formulas was less than that in the cube mixer formulas. As it becomes clear when comparing F1 with F13 in Figure 3, this is due to the high shear rate compared to the low shear rate of the cube mixer.[14]

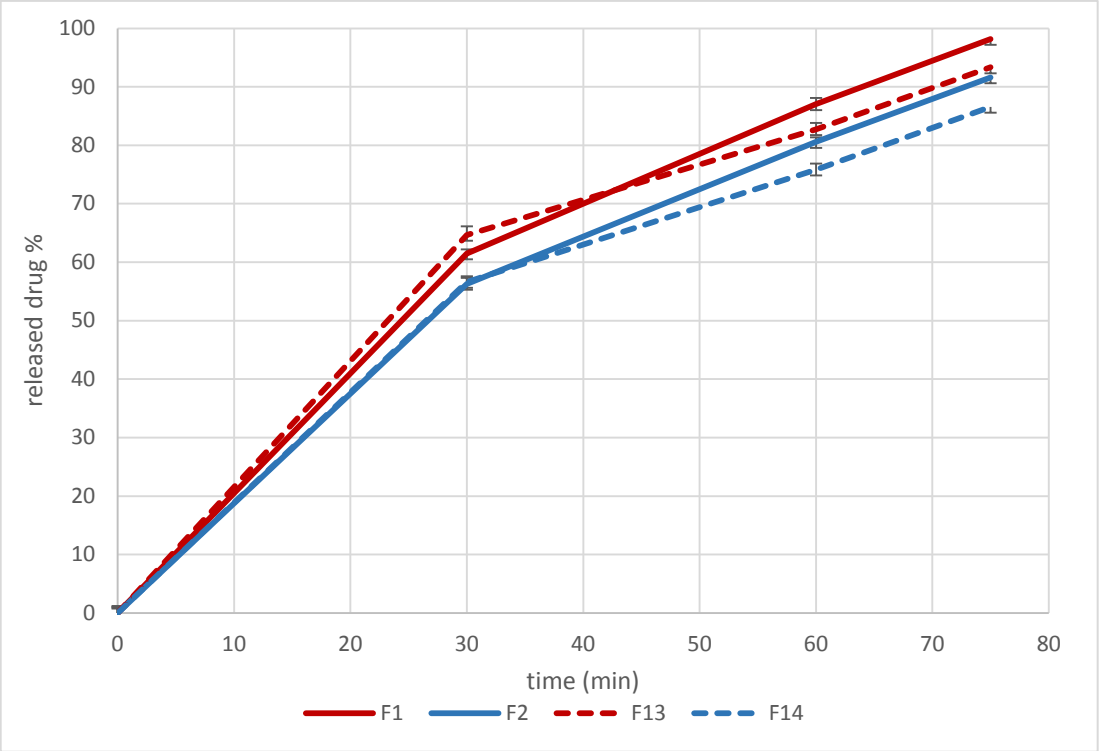


Figure 3 shows the effect of mixer type on the average dissolution profiles of formulations (F1 –F2 –F13 –F14).

CONCLUSION

The aims of this study were to look into the effect of MgSt concentration, mixing time, and type of mixer on granule flowability and paracetamol tablet properties. The results showed that increasing the mixing time and adding magnesium stearate enhanced granule flow.

All tablets' hardness decreased as mixing time and MgSt concentration increased, although differences in mixers had no statistical significance. The friability of all the manufactured tablets was less than 1%. Hydrophobic Mg-St films formed simply during mixing in this study as Mg-St concentration and mixing time were increased, and this most likely interfered with water penetration into the tablets. As a result, the disintegration and dissolution rates of the tablet decreased, and the type of mixer had a statistically significant influence, with planetary mixer formulations having a longer disintegration time than cube mixer formulations.

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