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The Effect of Concentration Variable of Croscarmellose Superdisintegrant on Tablet Properties

Zhehat Abdulwahed Yaseen[1] *, Mohanad Alfahad[2]

[1] *Pharmaceutics Department, College of Pharmacy, University of Duhok, Duhok City, Iraq.*
[2] *Pharmaceutics department, College of pharmacy, University of Mosul, Mosul ,*

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***CORRESPONDING AUTHOR:**
Zhehat Abdulwahed Yaseen
e-mail: zhehatyaseen@gmail.com

ABSTRACT

Background: The incorporation of superdisintegrating agents in tablet formulations is to accelerate the disintegration time by affecting the release of the active ingredient from the tablet dosage form which in turn affects the drug onset of action in the body. Croscarmellose sodium possess characteristics which fulfill its action as a superdisintegrating agent with effects on other parameters including hardness and friability. **Aims:** The aim of this research is to determine the effects of concentration variable of Croscarmellose sodium as a superdisintegrating agent on tablet dosage form critical quality attributes (CQA's) including Disintegration time, Hardness and friability. **Material and methods:** Three powder blends were prepared. Each blend constituting from poorly water soluble active pharmaceutical ingredient(API) in solid dispersion form, a filler, a Disintegrant and a lubricant. Three different tablet dosage form formulations were prepared (F1 (0.5% CCS), F2 (3% CCS), F3 (5% CCS)) as three test group formulations using the direct compression method. The prepared tablets then were tested for three Critical quality attributes (CQA's) including Disintegration time, Hardness and friability in accordance to the United States pharmacopeia. **Results**: The results of this study have shown that variations in the concentration of disintegrating agents have a different influence on the tested parameters of the tablets produced. The best disintegration time results were obtained in Formula 3, whereas highest tablet hardness and lowest friability percentage were obtained with Formula1. **Conclusion:** Increasing the concentration of Croscarmellose sodium in the tablet dosage form results in decreasing tablet disintegration time and hardness while increasing tablet friability.

1. Introduction

Oral tablet dosage form is the most common and preferred dosage form for delivering medication to the patients [1,2].

Immediate release tablet dosage forms are designed to rapidly break up into smaller particles upon exposure to aqueous and body fluids by a process called disintegration. Once a tablet is ingested, it disintegrates into small fragments in the gastrointestinal fluids which guarantee an increase in the surface area favoring rapid drug dissolution which increases bioavailability. As disintegration process is considered the first step in the cascade of bioavailability. therefore, Formulators primarily ensure efficient disintegration process as a first integral step[3].

The mechanism of a tablet dosage form disintegration involves a two-staged process which is: (1) initial breakage into coarse aggregates and (2) the ensuing disaggregation of aggregates in order to form the primary particles[4].

Disintegration time is considered one of the required compendial quality-control tests and is frequently performed to ensure reproducibility within a manufacturing process[4].

The three most commonly used superdisintegrants in pharmaceutical formulations are sodium starch glycolate (SSG), croscarmellose sodium (CCS) and crospovidone (XPVP) which incorporated in formulation at concentrations of 2-8%, 0.5-5% and 2-5% respectively[5–7].

CCS is a sodium salt which remains in its neutral state under acidic conditions and in its ionized state under alkaline conditions. CCS is obtained in two steps (carboxymethylation and crosslinking to natural polymer chains) which act used to maximize the functionality of the CCS [8].

CCS acts by two main mechanisms, (1) increased rate of water uptake, or water wicking, and (2) high rates of expansive swelling (omni-directional) [9]. CCS has favorable dissolution and disintegration characteristics, which provide a reduced disintegration time of tablet formulations [10].

Various approaches were proposed for assessing the effect of superdisintegrants including the testing of disintegration time of formulations, Tablet hardness and friability[8,11,12].

While tablet hardness used to measure crushing strength required to break a tablet across its diameter, Friability refers to a material's tendency to crumble or break into smaller pieces under mechanical stress[13]. Both tests are required to ensure tablet resistance against handling, shipping, and packaging, while allowing proper disintegration and dissolution once ingested[14–16].

The aim of this study was to investigate the effect of various concentrations of CCS on critical quality attributes (CQA's) (Disintegration time, Hardness and Friability) in the formulated tablet dosage forms of Sildenafil citrate. Moreover, a relationship will be established between the three parameters in relation to the resultant effect of CCS Concentration on such parameters. Sildenafil citrate was chosen as it is a BCS Class II drug with low aqueous solubility which limits its dissolution and bioavailability[1].

2. Materials and Methods

2.1. Materials

The Active Pharmaceutical ingredient, Croscarmellose sodium, Magnesium stearate and lactose were kindly provided by Awamedica pharmaceutical company (Erbil, Iraq). All other laboratory equipment and chemicals were of laboratory grade.

2.2. Methods

2.2.1. Content of tablets

In the production of the tablet dosage form, 300mg of a poorly water soluble active pharmaceutical ingredient containing Sildenafil citrate (50 mg) and urea (250mg) formulated as a solid dispersion were incorporated as a non-variable combination, Croscarmellose sodium (CCS) as a superdisintegrant which is incorporated as a variable in the ratios of (0.5%,3%,5%)[17,18] , and a Lubricant (Magnesium stearate) which is incorporated as a non-variable in the ratio of (0.5%)[19,20], Lactose monohydrate was in-

Table 1. Formulation content of the tablet dosage forms

Formulation	CCS (%)	Lubricant (%)	API (mg)	Diluent (mg)	Total Tablet Weight (mg)
F1	0.5	0.5	300	294	600
F2	3	0.5	300	279	600
F3	5	0.5	300	267	600

corporated as a diluent to fill the remained gap of the total weight of the tablet up to 600mg.[21].

2.2.2. Design of experiment

Based on the data from the literature, among the contents of the tablet dosage form used in this study, only croscarmellose sodium (CCS) Was regarded as a variable yielding three formulations as shown in table 1[22].

2.2.3. Formulation process of the tablets

To obtain the powder mixture for tablet compression for each of the formulations, known amounts of the API were first mixed with Diluent to obtain a homogenous mixture. then croscarmellose sodium was added and mixed for 3 minutes[23]. Then Lubricant was added to the mixture in final stage with a mixing time of 1 minute.[24]. After the mixture was ready, equal amounts of the resultant powder (600mg) were weighed and placed in 12mm Dies in the single-die punching machine operating at the rate of 20 rpm and the force of 10 kilonewtons to produce the tablets of 12mm diameter, 5mm thickness and a hardness of around 100 Newtons(N)[25] using direct compression method[26]. The formulated tablets were stored for further evaluation.

2.2.4. Disintegration test

To test the disintegration time of the tablets, 6 tablets were individually placed in a disintegration basket rack assembly (USP apparatus 1) (HM L-TT-DI1, China). the basket rack was placed in a 1000 ml vessel containing 900 ml of media with a maintained temperature at 37 ± 2 °C with sink conditions, ensuring the tablets remain 2.5 cm below the surface of the liquid on their movement upward and descent not closer than 2.5 cm from the bottom of the beaker. A standard motor driven device was used to move the basket assembly up and down through a distance of 5–6 cm at the rotational speed of 30 cycles per minute. The mediums that were used were acid buffer (0.1 N Hydrochloric Acid (HCl) (pH 1.2). the tablets were observed for complete disintegration of the 6 tablets within 30 minutes in accordance to the acceptance criteria[12,27].

2.2.5. Tablet breaking force (Hardness test)

The hardness test of the tablets is used to measure the tablet's resistance to breakage and withstand ability to outside forces during handling, packaging and transportation. The test was carried on by randomly selecting 10 tablets from each Formulation batch (F1, F2, F3) and individually placing them in a tablet hardness tester (HM L-TT-M6, China) along their long diameter. the breaking force for each tablet was recorded and the mean breaking force of the batch was evaluated against the acceptance criteria (28). while there are no strict requirements for hardness results. However, A typical range for standard oral tablets is approximately 4 to 10 kg, which is equivalent to 39.2 to 100 newtons (N) is acceptable in the pharmaceutical industry [11,28,29].

2.2.6. Friability test

The friability test of the tablets was carried on by randomly selecting 11 tablets and placing them in a friabilator (HM L-TT-FR1, China). The friabilator was

set at the rotation speed of 24rpm for 4 minutes. After the rotation time is ended, the tablets were then dedusted and re-weighed. The difference in the two weights was used to calculate friability by using the following formula

Friability % =

$$[(I_w - F_w) / I_w] \times 100 [(I_w - F_w) / I_w] \times 100$$

Where $I_w I_w$ is the total initial weight of the tablets,

$F_w F_w$ is the total final weight of the tablets after friability testing.

The results were evaluated against the acceptance criteria which according to USP-NF, the tablets comply with the criteria if tablets loss less than 1% of their initial weight. [12,30,31]

2.0.7. Statistical analysis

Descriptive statistics: Means & standard deviations, tables and charts were used. One-way analysis of variance (ANOVA) and Tukey's post hoc tests were used for comparison of disintegration time, hardness and friability between the experimental groups. All the results were analysed utilizing IBM SPSS Statistic software (v.25.0; IBM Corp).

3. Results

Effectiveness of oral tablet dosage forms lies in their ability to disintegrate quickly, thus enabling the subsequent dissolution and biological activity. This requirement is usually met by the addition of a superdisintegrant that allows a disintegration in low volumes of physiological liquids. At the same time, the tablets should be resistant to breaking, capping and fragmentation at the time of transportation and handling. The pharmaceutical industry, thus, aims to utilize superdisintegrants with minimal variations in the hardness or the friability of tablets[32].

This study has been conducted in order to evaluate the effect of Croscarmellose sodium concentration on the Tablet critical quality attributes (CQAs), Mainly Hardness, Friability and disintegration properties.

3.1. Disintegration time

The disintegration times of all three formulations are depicted in table 2.

Table 2. Descriptive and statistical analysis (ANOVA, Tukey post hoc) of the Disintegration time values for the tablets in 3 formulations

	Disintegration Time (seconds)		
Tablet No.	Formulation 1 0.5% CCS	Formulation 2 3% CCS	Formulation 3 5% CCS
1	115	92	68
2	113	88	67
3	120	93	67
4	115	91	72
5	113	88	73
6	114	88	73
Mean	115	90	70
Standard deviation	2.61	2.28	2.97
P-value	P<0.001		

The mean disintegration times for the three tested formulations (F1, F2, F3) reveals that F1 has the highest disintegration time, while F3 has the lowest. Those results indicate a trend of a decrease in disintegration time that aligns with the increase in the concentration of Superdisintegrant (CCS)

ANOVA & Tukey's post hoc test analysis revealed significant differences between all formulations. The variations in the concentration of the super disintegrating agent have a significant effect on the disintegration time of the produced tablets due to the high-water absorption ability of CCS leading to the enhancement in compact wetting or compact disintegration due to the hydrophilicity and omnidirectional swelling of CCS which is more influential in breaking the formation of the tablet[8,33,34]. All formu-

Table 3. Descriptive and statistical analysis (ANOVA, Tukey post hoc) of hardness test results for 10 tablets from each formulation (F1, F2, F3)

	Fracture load (N)		
Tablet No	**Formulation 1 (0.5% CCS)**	**Formulation 2 (3% CCS)**	**Formulation 3 (5% CCS)**
1	**200**	**125**	**107**
2	**189**	**128**	**108**
3	**185**	**136**	**115**
4	**190**	**136**	**117**
5	**200**	**135**	**116**
6	**194**	**138**	**118**
7	**184**	**134**	**120**
8	**185**	**136**	**112**
9	**198**	**130**	**114**
10	**195**	**130**	**121**
Mean	**190**	**132**	**114.8**
Standard deviation	**6.25**	**4.26**	**4.69**
P-value	**P < 0.05**		

lations met the USP disintegration time test requirements, namely not more than 115 seconds. Also, our study results were consistent with the results of the studies conducted by Late & Banga, 2010; Quodbach & Kleinebudde, 2016; Yavari et al., 2022 [8,35,36].while they were different from those reported by Adane et al. in 2007, Gordon & Chowhan in 1987, Lee et al. in 2025, López-Solís and Villafuerte-Robles in 2001 (37–40). According to the latter the increase in CCS Concentration led to the increase in Disintegration time. Such an increase could be attributed to CCS gelation in water which slows down water penetration into the tablet matrix, to the increase in magnesium stearate in the tablets or to the presence of soluble excipients which compete with CCS for the locally available water; thus, inhibiting the action of super-disintegrating agent[38,39].

3.2. Hardness

The hardness values of all three formulations are depicted in table 3.

Table 3 shows the change in the hardness of the formulated tablets between the three formulations (F1, F2 and F3) showing that F3 has the lowest mean hardness value while F1 has the highest. Those results indicate a trend of an increase in hardness that aligns with the decrease in the concentration of Superdisintegrant (CCS due to the fibrous, insoluble, and crosslinked polymer nature of CCS, causing disruption of interparticulate bonds during compression[41]. Moreover, this can also be attributed to the reason that the increase in CCS concentration resulted in a better compressibility and more interparticulate spaces and in turn less hardness and more friability[42].

Moreover, ANOVA tests followed by Tukey Post hoc has revealed highly significant differences of tablet hardness means between the three groups of the tablets ($P<0.05$) indicating distinctive hardness properties among each of the groups. According to USP Desired hardness values for tablet dosage forms, F3 was considered the best formulation in

Table 4. Descriptive and statistical analysis (ANOVA, Tukey post hoc) of Friability test results for each of the three formulations (F1, F2, F3)

Formulations	Initial weight(Iw)(in g)	Final weight (Fw) (in g)	Friability percentage (Must be Less than 1%)
F1	6.5662	6.546	0.30
F2	6.5861	6.557	0.44
F3	6.5715	6.54	0.48
P-Value	P< 0.05		

terms of hardness with a mean hardness value of 114.8 N.[11,28,29]

The results of our study were consistent with the studies conducted by Ikasari in 2025; Late & Banga in 2010; Lee et al. in 2025[33,36,37] while our study results contradicted the results of the studies conducted by Adane et al. in 2007, Parfati & Rani in 2018 [40,42].

3.3. Friability

The results of the friability test for the three formulations are presented in table 4.

The results of friability testing for the three formulations (F1, F2, F3) show that F3 has the highest friability while F1 has the lowest. Those results indicate a trend of an increase in friability that aligns with the increase in the concentration of Superdisintegrant (CCS)[43].

Moreover, ANOVA & Tukey's post hoc test analysis revealed significant differences in friability values between the formulations. According to USP Desired Friability values for tablet dosage forms, all formulas were in the accepted range of friability limit [12,30,31].

The results of this study were in agreement with the studies conducted by Yousaf et al. in 2019 [32] as evidenced by the dominant influence of CCS concentration in increasing the percentage of tablet Friability because of the hygroscopic properties of CCS [33].

4. Discussion

The test results of the three Critical quality attributes (CQA) show a close relationship between the three parameters. There is a direct relationship between hardness and disintegration time, meaning the higher the hardness of a tablet, the higher the disintegration time. On the other hand an inverse relationship between tablet hardness and friability is confirmed, meaning the higher the hardness the tablet, the less the tablet will be prone to friability. In a similar manner, the relationship between Friability and Disintegration time is inverse, meaning that the disintegration time of a tablet decreases with the increase in friability percentage. The overall results agreed to what is reported in the literature [13,33,36,44,45].

One of the drawbacks of this study is that in accordance to the change in croscarmellose concentration among each of the three formulations, the concentration of lactose also changed in correspondence. This leads to some degree of uncertainty regarding the extent of the effect of Croscarmellose concentration on the tested tablet properties. Therefore, further study is required in this regard as lactose is known to exert no swelling force while acting as disintegrant by a passive mechanism [46]

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5. Conclusion

The use of the disintegrating agent Croscarmellose Sodium with varying concentrations of 0.5%, 3% and 5% has a different influence on the tested Critical quality attributes of the tablet dosage form including disintegration time, hardness and friability. The observed trend indicated that increasing the concentration of the superdisintegrant (CCS) in the tablet dosage form has resulted in decreasing the tablet disintegration time and hardness while tablet friability has increased in a direct relationship manner. To ensure CCS effect on improving tablet dosage form dissolution and bioavailability, further in vitro

and in vivo tests are required in this regard. Moreover, since the prepared tablets contain other ingredients as well, stability studies and more extensive tests are required to determine the degree of their interaction and effect on the tested parameters of the current tablet dosage form.

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