RESEARCH ARTICLE

Effect of Disintegrants on Spironolactone Tablet Stability

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ABSTRACT

Introduction: Spironolactone is a potassium-sparing diuretic, marketed as a tablet dosage form. Because of high lipophilicity, the bioavailability of spironolactone is affected by the type of excipients used in the formulation. The physical properties of the tablets, including disintegration and dissolution time, have a direct relationship with the bioavailability of spironolactone and its therapeutic activity. The current study aims to formulate a spironolactone tablet dosage form using different disintegrants and assess the disintegration and dissolution behavior upon storage at high temperatures and humidity.

Materials and methods: Spironolactone tablets were prepared by the wet granulation method in two doses (25 and 50 mg) using two disintegrants (starch 1500 and croscarmellose sodium). The resultant tablets were stored at 30°C ± 2°C and 65% ± 5% RH. The disintegration time and dissolution after 45 minutes (D45) were used to assess the stability.

Results: The prepared formulas were within the pharmacopeial specifications of spironolactone tablet. The disintegration time and dissolution of formulas prepared with croscarmellose were faster than those prepared with starch 1500.

Additionally, disintegration time and D45 for formulas prepared with starch 1500 showed significant change upon storage, whereas formulas prepared with croscarmellose did not show such changes.

Conclusion: Selection of the proper disintegrant is crucial in designing the formula for lipophilic drugs as it affects the disintegration and subsequently affects dissolution and bioavailability. Furthermore, it is necessary to study the behavior of disintegrants upon storage at stress condition to examine the ability to disintegrate tablet after exposure to environmental conditions.

Keywords: Disintegration, Dissolution, Spironolactone.

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INTRODUCTION

The oral route of administration is preferred over other routes because of its convenience and ease of administration. Tablet dosage form contains active ingredients and excipients that serve different functions such as causing bulkiness and altering the shape of the tablet, taste masking and enhancing palatability, facilitating disintegration, and improving the release of the drug from the dosage form. Therefore, optimizing the type and proportion of these excipients will play a critical role in the *in-vivo* performance of the dosage form.[1]

For the drug to be effective and has an acceptable bioavailability, it should be released at a reasonable rate from the formulation at the site of absorption, if the drug is not released or is released only slowly, bioavailability will be considered to be poor which makes it ineffective therapeutically.[2] In the absorption site inside the gastrointestinal tract (GIT), tablets disintegrate to produce smaller granules with a larger surface area allowing more contact with the dissolution medium, which is the GIT fluid; tablet disintegration is enhanced by the addition of some excipients called disintegration agents to the tablet formulation.[3]

Medicines are generally exposed to deterioration and change in properties under storage conditions like elevated temperature and moisture. Changes in properties might include chemical, physical, and microbial change.[4]

Spironolactone is a potassium-sparing diuretic. It is used for the treatment of fluid accumulation due to heart failure, renal diseases, and hepatic scarring. It is also used for hypertension, hypokalemia, premature male puberty, and for acne , and unnecessary hair development in females.[5] Its chemical name is 7α-acetylthiospirolactone, it is a steroidal 17α-spirolactone[6] (Figure 1).

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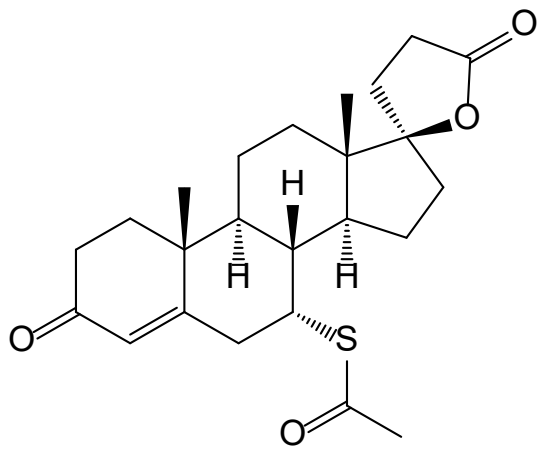

Figure 1: Spironolactone chemical structure.

Table 1: The composition (in mg/tablet) of the prepared tablets spironolactone tablet by wet granulation method.

Component	*S1*	*S2*	*S3*	*S4*
Spironolactone	25	50	25	50
Calcium sulfate	112.7	87.7	112.7	112.7
Avicel ph 102	20	20	20	20
Starch 1500	10	10	-	-
Croscarmellose sodium	-	-	10	10
Povidone K30	10	10	10	10
Magnesium stearate	1	1	1	1
Aerosil 200	1	1	1	1
Peppermint oil	0.3	0.3	0.3	0.3
Tablet weight	180	180	180	180

Spironolactone has two ionizable groups with pKa of -4.9 and 18, respectively. It is a lipophilic (log Ko/w = 2.78) that appears as a crystalline powder. The solubility of spironolactone graduated from very soluble in chloroform and benzene, soluble in ethyl acetate and ethanol, and slightly soluble in methanol, whereas it is practically insoluble in water.[7]

In the current study, spironolactone tablet was formulated using different excipients having variable disintegrant effects. The various formulas were evaluated according to the official testing methods of the pharmacopeias. Active ingredient concentration and size of the tablet were also considered important factors affecting the physical properties of the tablets, most importantly, disintegration and dissolution time, which have a direct relationship with the bioavailability of spironolactone and its therapeutic activity. The present study aims to evaluate the effect of different excipients on the disintegration, dissolution, and stability of spironolactone immediate release spironolactone tablets.

MATERIALS AND METHODS

Materials

The materials used in the current study with their companies were: Spironolactone (Zhejiang Langhua Pharmaceutical), calcium sulfate, Avicel ph 102, and croscarmellose sodium (JRS), Starch 1500 (Prachin Chemical), Povidone k 30 (BASF), Magnesium stearate (Sunshine Organic), Aerosil 200 (Evonic), Peppermint oil (Nectar Lifesciences). All other solvents and reagents were of 99% analytical grade.

Blend and Tablet Formulation

In a 500 mL beaker, 200 mL of ethanol was added, then spironolactone, PVP K30, and peppermint oil were added with continuous mixing for 15 minutes. The resultant solution was then added to calcium sulfate in a high shear mixer granulator and granulation was carried out for 30 minutes, the wet granules were dried after that in the oven at 50°C. The resultant granules were then sieved on mesh 20 and then mixed with different disintegrant(s) for 5 minutes. Magnesium stearate was added to the mixture and final sieving was carried out for another 5 minutes. The final mixture was compressed by tableting machine. the composition of the prepared tablets is shown in Table 1. The resultant tablets were stored for evaluation.

HPLC Assay of Spironolactone

The assay of spironolactone was determined by high-pressure liquid chromatography (HPLC) method according to the following conditions using Shimadzu HPLC (Japan):

- Column: L1 (150 x 4.6 mm, 5 µm).
- Mobile phase: de-gassed solution of methanol in water (60:40 v/v).
- Flow rate: 1 mL/minute.
- Detection: UV, 238 nm
- Standard stock solution: concentration of 0.5 mg/mL of the reference standard of spironolactone in a solution of acetonitrile and water (50:50 v/v).
- Test solution: around 0.5 mg/mL of a tested sample of spironolactone in a mixture of acetonitrile and water (50:50 v/v).
- Injection volume: 20 µL of each solution.
- Chromatography time: 3.5 minutes.
- Assessment: The peak area in each chromatogram of both standard and test solutions was proportionated to get the amount of spironolactone in the test solution.

Content Uniformity Test

The content uniformity of spironolactone tablet was assayed by crushing and grinding 10 tablets. Then, a sufficient quantity of the resultant powder was dispersed in diluent (mixture of water and acetonitrile, 50:50 v/v) under sonication. As mentioned earlier in the HPLC method, the final solution with a target concentration of 0.5 mg/mL was filtered and assayed.

Assessment of spironolactone Tablet (Weight Variation Test, Hardness, and Dimensions)

The physical characterizations of the prepared tablets were conducted according to USP. The weight variation test was performed by recording the mean weight of 20 tablets ± standard deviation.[8] The mechanical strength in terms of hardness was studied by taking the average force required to crack the tablet in Kg (mean of individual three tablets ± standard deviation)

using Erweka manual hardness tester (Germany).[9] For tablet dimensions, five tablets individually were placed in micrometer Vernier caliper. The mean of tablet diameter and thickness (in mm) were recorded ± standard deviation.[10]

Disintegration Tests

A pharma-test disintegration tester (Germany) was used to evaluate the disintegration time of the prepared spironolactone tablet. According to USP, the average disintegration time of six tablets for each patch was determined in distilled water at 37°C ± 1°C.[8]

Dissolution Tests

Caleva dissolution tester, basket type (Germany), was used to study cumulative spironolactone release profile. According to USP, one tablet was placed in a dissolution jar containing one liter of 0.1N HCl (pH = 1.2, with 0.1% sodium lauryl sulfate) with the rotation speed of 75 rpm and at a temperature of 37 ± 0.5°C.[8] A sample of 5 mL was collected at 0, 10, 15, 30, and 45 minutes of experiment and then replaced by equal volume of fresh media to maintain sink conditions. The collected samples were filtered and analyzed for spironolactone content as in the HPLC method mentioned earlier. In addition to dissolution profile, the percentage of cumulative amount released after 45 minutes (D45) was also used to compare the prepared formulas. The dissolution experiment was conducted for 6 tablets for each prepared batch.

Stability Study

The prepared formulas of spironolactone tablet were stored for 12 months in a stability cabinet at 30 C ± 2°C and 65% ± 5% RH (as stated for Iraqi climatic zone) in order to assess the effect of using different disintegrants on the disintegration and dissolution behavior of spironolactone upon storage. The analysis time points were in three months' basis.[11]

Statistical Analysis

The results data are presented as mean ± standard deviation, and one-way ANOVA was used to study the significant level of differences at $p < 0.05$ among the prepared formulas of spironolactone tablets.

RESULTS AND DISCUSSIONS

HPLC Chromatogram

The content of prepared spironolactone tablets and the amount released in the dissolution experiments were calculated based on the area under the spironolactone standard solution chromatogram (Figure 2). According to British Pharmacopeia (BP), the acceptance criteria of spironolactone assay in tablet dosage form range from 95 to 105%, and not less than 70% of spironolactone should be dissolved after 45 min of dissolution experiment.[12]

Physical Characterization of the Prepared Formula

In the current study, spironolactone tablets were prepared in two doses (25 and 50 mg) using calcium sulfate and Avicel ph 102 as diluents, povidone K30 as binder, mg stearate as lubricant, aerosel 200 as gliding, and peppermint oil as a flavoring agent. Two different disintegrants (Starch 1500, and croscarmellose sodium) were used to evaluate the effect of disintegrant type on the prepared formulas. Table 2 shows the physical characterization of the prepared tablets of spironolactone.

According to USP and BP, the content assay of spironolactone tablets is within the accepted limits (95–105%).[8,12] The hardness of the prepared tablets was found to be in the range of 3.4 to 7.2 Kg. A slight variation was observed in tablet thickness and diameter as a result of variation in the type of disintegrants.

Disintegration Tests

All the tablets of this formulation were disintegrated in less than 6 minutes (Figure 3) which is much shorter than the time allowed by British Pharmacopeia (for uncoated tablets), which is 15 minutes.[12]

Avicel ph 102 (microcrystalline cellulose) was added with calcium sulfate in all formulas. It was added as a co-diluent, but it has a disintegrating effect and further facilitated the disintegration by shortening the time required to break up the tablet into smaller fragments.[13]

The first set of the prepared tablets (S1 and S2) using different potencies of spironolactone and starch 1500 as disintegrant showed a longer disintegration than set 2 formulas (S3 and S4) which employs croscarmellose as disintegrant. This could be explained by the fact that croscarmellose acts by

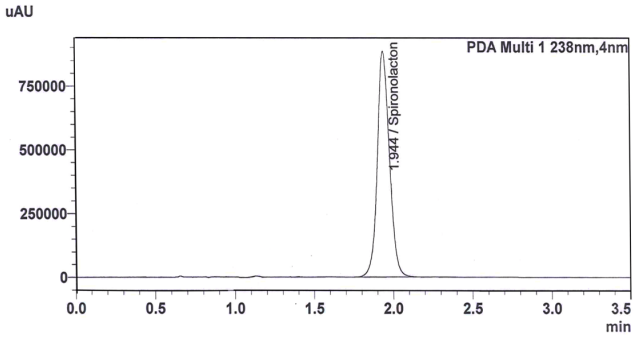

Figure 2: HPLC chromatogram of spironolactone (0.5 mg/mL) at 238nm

Table 2: Physicochemical properties of the prepared formulas of spironolactone tablets.

Formula	*Chemical assay %*	*Hardness*	*Thickness (mm)*	*Diameter (mm)*	*Average weight (mg)*
S1	101.1 ± 0.9	3.4 ± 0.2	3.17 ± 0.04	6.90 ± 0.62	183.9 ± 1.1
S2	96.6 ± 0.6	5.1 ± 0.3	3.25 ± 0.04	7.08 ± 0.04	178.7±3.4
S3	96.4 ± 1	6.5 ± 0.1	5.09 ± 0.06	7.09 ± 0.06	185.6 ± 1.8
S4	97.9 ± 0.9	7.2 ± 0.3	5.96 ± 0.03	7.06 ± 0.06	177.2 ± 2.2

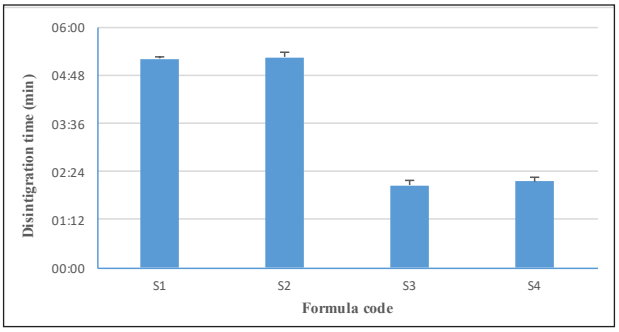

Figure 3: The disintegration time of the prepared formulas

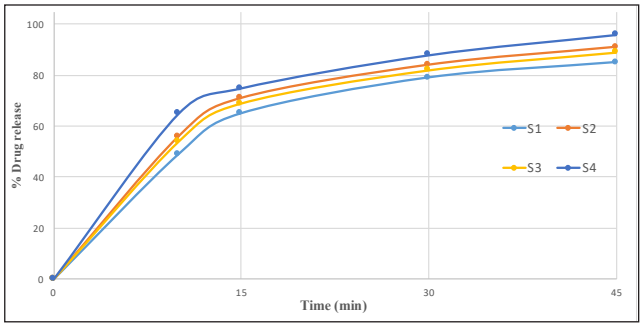

Figure 4: Dissolution profile of prepared spironolactone tablets.

two mechanisms based on swelling and wicking[14] in contrast to starch which acts only by swelling.[15] Croscarmellose is crossed linked carboxymethyl cellulose well known for its strong disintegrant activity. It acts by absorbing water inside the gastrointestinal tract, which leads to swelling and rupture of the tablet to form smaller granules, increasing the surface area of the formulation exposed to gastric fluid.[16] During the current experiment, the use of croscarmellose has reduced the disintegration time by more than double when comparing two the other formulas. This substance was the primary influencer when it comes to decreasing the disintegration time of spironolactone tablet.

The disintegration agents are generally divided into two types according to how they trigger tablet disintegration and rupture into small granules. The first type of these excipients is called swelling agents, and they act by causing swelling of the tablet structurer upon entrance of water from the GIT fluid, increasing pressure between tablet particles pushing apart the adherent granules and molecules which have initially been bound together by the addition of binder and compression force effects. Examples of such disintegrants are cellulose derivatives like carboxymethyl cellulose and microcrystalline cellulose.[17] The second well-known mechanism is called strain or shape recovery, which happens because of the metastable configuration of macromolecules either due to interlocking of the polymers chains, or crystallization upon tablet compaction. The release of energy occurs immediately after compaction in the form of heat. Upon entering the water and its contact with the polymer, entropy is regained, leading to the recovery of the polymer's original shape; starch derivatives are famous examples of such excipients.[18]

Dissolution Tests

The factors affecting the dissolution rate of the drug from a tablet or solid dosage form are defined by Noyes-Whitney equation.[19]

$$\frac{dC}{dT} = \frac{DS(Cs-C)}{h}$$

where dC/dT represents the rate of dissolution of drug molecules, D is the drug diffusion coefficient, and S is the surface area of the dissolved solid molecules exposed to the dissolution medium. Cs-C is the driving force of dissolution, where Cs is drug concentration in the dissolution layer (the saturation solubility), whereas C is the drug concentration at the bulk of the dissolution medium. Noyes-Whitney suggested a thick diffusion layer with a thickness of h that surrounds the dissolving drug particles.[19]

As a general concept, it is fair to assume that the D (coefficient of diffusion of a particular drug) and h (diffusion layer thickness) are the same in a dissolution experiment. The reason for such assumption is that the speed of rotation and the dissolution media are held constant for each experiment in dissolution apparatus. Accordingly, concentration gradient through the diffusion layer and the exposed surface area of the dissolving particles are the main factors affecting the drug release from immediate-release dosage form during the *in vitro* dissolution studies.[20]

The results of dissolution experiments (Figure 4) were harmonious with the principles of the Noyes-Whitney equation, where tablets in S2 and S4 containing 50 mg of spironolactone showed a faster rate of dissolution than with lower potencies because of high Cs and increased the Cs-C fraction.[21]

Furthermore, Noyes-Whitney equation stated that the drug dissolution rate is directly proportional to the total exposed surface area of the dissolving drug molecules (S). Although S2 and S4 had the same amount of active ingredient (50 mg of spironolactone), Formula S4 had a higher dissolution rate because the shorter disintegration time ensures fast conversion into smaller particles with a larger surface area allowing more contact between the drug and dissolution medium.[22]

Stability Study

The stability study was carried out under elevated temperature and humidity conditions to evaluate the effect of storage conditions on the prepared tablets over time (Figures 5 and 6).

Disintegration time is one of the physical properties that could change upon exposure to environmental conditions. An essential part of the physical stability of tablets is that disintegration time does not change significantly when the dosage form is stored for a long time under harsh conditions. Any increase or even decrease in disintegration time might affect the therapeutic value of medicines because disintegration directly affects the dissolution of the drug and thus, the bioavailability can be affected.[23]

It is noticeable from Figure 5 that the disintegration time increases in all test formula with time causing prolongation in the dissolution time as well (Figure 6).

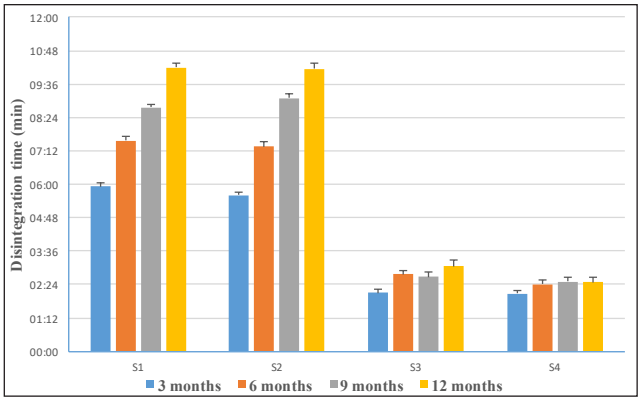

Figure 5: Effect of storage on disintegration time of spironolactone tablets

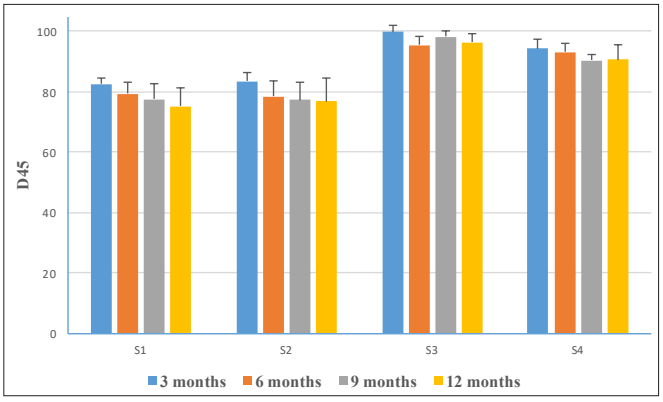

Figure 6: Effect of storage on the dissolution of spironolactone tablet

The most apparent change in the disintegration time is noted S1 and S2 as the disintegration time changed from 5 min before storage to about 10 min after one year of storage. The results of the dissolution experiment on the stored tablets are following the disintegration study. S1 and S2 showed a significant reduction in D45 compared to the freshly prepared formulas as only less than 80% of spironolactone were released after one year of storage. In S3 and S4 more than 90% of the drug was released at the end of the stability study. This might be explained based on the type on disintegrant employed as the starch derivative loss some of their disintegrating activity upon storage.[24] The case is contradictory with cellulose derivatives which are minimally affected by storage. The importance of change in disintegration time is that it is a major determinant of dissolution rate, especially of drugs with poor water solubility, which, in turn, can decrease the bioavailability of drugs. The above makes it important to choose excipients that could reserve the disintegration capability over time and upon exposure to various stressful storage conditions.

CONCLUSIONS

As disintegration agents are polymeric excipients with hydrophilic and amorphous nature, they are susceptible to change upon exposure to storage conditions such as moisture and elevated temperature, which could weaken their ability to induce disintegration of the tablet, and in turn, affecting the drug dissolution rate. Spironolactone tablets were successfully prepared in two doses (25 and 50 mg) using croscarmellose sodium as a disintegrating agent. One year storing of spironolactone tablets (with croscarmellose sodium) at high temperature and humidity did not change the disintegration and dissolution of the prepared formulas. At the same time, disintegration and dissolution of tablet prepared with starch 1500 as disintegrant were significantly affected.

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