Role of superdisintegrants in enhancing dissolution rate of valsartan

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(Received 2 / 6 / 2024. Accepted 9 / 7 / 2024)

□ ABSTRACT □

Bioavailability is greatly affected by the rate of drug dissolution and solubility. Low solubility is one of the most important challenges facing pharmaceutical manufacturing, as most marketed drugs have low aqueous solubility and therefore have poor bioavailability. Valsartan is an Angiotensin Receptor II Blocker, and one of the most common and effective drugs used in treating hypertension, but its bioavailability is low due to low solubility and dissolution rate.

This study aims to ameliorate Valsartan dissolution rate via superdisintegrants, thus enhancing its bioavailability, and therapeutic efficacy. Seven different formulations of Valsartan capsules were prepared using either crospovidone (4, 6 and 8% concentrations), or croscarmellose sodium (6, 8, 10 and 15% concentrations). These excipients were selected due to their good wicking and swelling effects, which grants them the ability to hasten Valsartan formulation capsule disintegration and thus improve dissolution rate. All formulations complied with the corresponding pharmacopoeia parameters including uniformity of weight, uniformity of content, disintegration time. Dissolution test showed that formulation containing 8% crospovidone and formulation containing 10% croscarmellose sodium exhibited the best results, releasing 99.932% and 99.468% respectively of their Valsartan content after 30 minutes.

Key words: solubility, dissolution rate, valsartan, superdisintegrants, capsules.

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دور المفتتات الفائقة في تحسين معدل انحلال الفالسارتان

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(تاريخ الإيداع 2 / 6 / 2024. قبل للنشر في 9 / 7 / 2024)

□ ملخّص □

يتأثر التوافر الحيوي بمعدّل انحلال الدواء وانحلاليته بشكل كبير. الانحلالية القليلة من أهم التحديات التي تواجه التصنيع الصيدلاني إذ أن معظم الأدوية المسوقة تمتلك انحلالية مائية منخفضة وبالتالي لها توافر حيوي ضعيف. يعدّ الفالسارتان أحد حاصرات مستقبلات الأنجيوتنسين II، وأحد أكثر الأدوية شيوعاً وفعالية في علاج ارتفاع ضغط الدم، لكن توافره الحيوي قليل نتيجة نقص الانحلالية ومعدل الانحلال. تهدف هذه الدراسة إلى تحسين معدل انحلال الفالسارتان باستخدام المفتتات الفائقة وبالتالي تحسين توافره الحيوي، وفعاليته العلاجية. تم تحضير 7 صيغ مختلفة من كبسولات الفالسارتان باستخدام إما الكروس بوفيدون بتركيز 4-6-8%، أو كروس كارميلوز الصوديوم بتركيز 6-8-10-15%، حيث تم اختيار هذه السواغات لامتلاكها خواص فتل وانتباج جيدة، وبالتالي تسرّع من تفتت صيغ كبسولات الفالسارتان ومنه تحسّن معدل الانحلال. حققت جميع الصيغ الشروط الدستورية من حيث تجانس الوزن، تجانس المحتوى، وزمن التفتت. أظهرت نتائج اختبار الانحلال أن الصيغة الحاوية على 8% من الكروس بوفيدون والصيغة الحاوية على 10% من كروس كارميلوز الصوديوم هي الصيغ الفضلى، حيث حررتا بعد 30 دقيقة 99.932% و99.468% على التوالي.

الكلمات المفتاحية: الانحلالية، معدل الانحلال، فالسارتان، مفتتات فائقة، كبسولات.

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Introduction

Active pharmaceutical ingredients (API) are not administered individually to patients, instead, therapeutically inactive ingredients called excipients are added to form pharmaceutical formulations, which are meticulously designed to achieve the required therapeutic efficacy, safety, and stability, in addition to patient convenience and compliance [1, 2].

Multiple drug administration methods are used for these pharmaceutical formulations, such as oral, rectal, injection, topical, etc. Among these, the oral route is considered the more commonly used[3], convenient, and tolerated method for drug administration, owing to it being non-invasive, economically viable, and oral formulations are amongst the easiest to mass produce [4]. Moreover, oral formulations are much more tolerated by patients and easier to use compared to other routes of administration [5]. Some of the most common oral formulations are: capsules, tablets, syrups, and others.

Unfortunately, however, a large portion of the currently marketed drugs exhibit relatively poor solubility, and thus are not sufficiently absorbed when administered orally, leading to poor oral bioavailability [1]. So, enhancing drug solubility - and thereby its bioavailability – is considered one of the most challenging aspects of drug formulation design, especially for oral formulations and administration methods [6].

Valsartan is considered one of the more prominent drugs used to treat and manage blood hypertension [7], as it works through selective inhibition of angiotensin II receptors, and it belongs to angiotensin II receptor blockers (ARBs) alongside Telmisartan, Candesartan, Losartan, Olmesartan, Irbesartan, and Eprosartan [8, 9].

It has the scientific name (2*S*)-3-Methyl-2-[pentanoyl[[2′-(1*H*-tetrazol-5-yl) biphenyl-4-yl] methyl] amino] butanoic acid, with the molecular formula $C_{24}H_{29}N_5O_3$, a chemical structure depicted in figure 1, and its molecular weight is 435.5 g\mol [10].

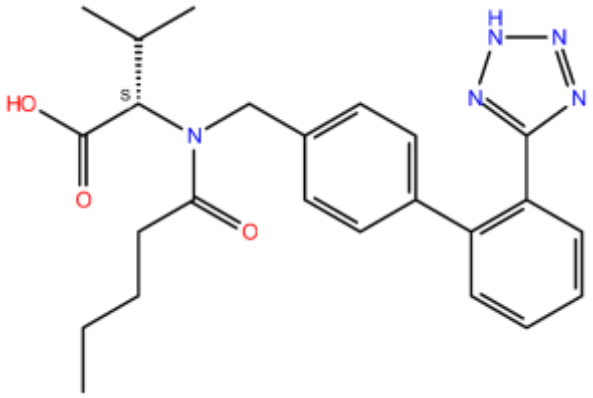

Figure 1: The chemical structure of valsartan

It is practically insoluble in water [10], belonging to group II or IV according to the Biopharmaceutics classification system (BCS) [11, 12], and in both cases it has poor solubility in water as mentioned and thus low bioavailability. It is freely soluble in anhydrous ethanol and sparingly soluble in methylene chloride. It appears as white or almost white hygroscopic powder. Valsartan solution has a peak absorbance wavelength λ_{max} = 250 nm [13].

This study aimed to improve the solubility and dissolution rate of Valsartan using superdisintegrants, which work mainly through two mechanisms, shown in figure 2, the first of which being wicking which includes liquid penetration of the formulation through

capillary action. The other mechanism is swelling, which includes the enlargement of particle size in all directions while pushing adjacent formulation ingredients, thus starting the disintegration process [14-16].

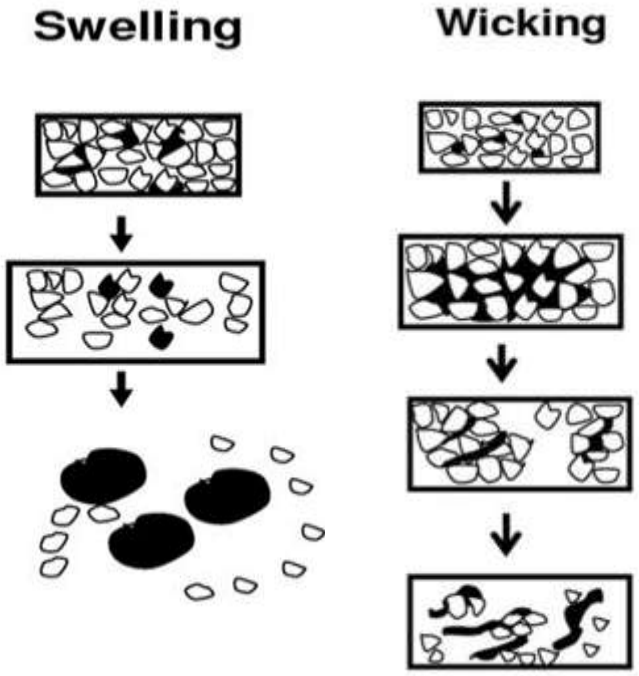

Figure 2: Swelling and wicking mechanisms

Materials and methods

The following materials were used to carry out this study:

Valsartan (Zein Pharma, Syria), Avicel (PH 102), Crospovidone (Kavya Pharma, India), Croscarmellose (Kavya Pharma, India), Povidone K-30 (TM-MEDIA, India), Magnesium Stearate (S.D. Fine Chem LTD, India), Colloidal Anhydrous Silica (Otokemi, India), Sodium Hydroxide (CHEM-LAB, Belgium), Monobasic Potassium Phosphate (SHAMLAB, Syria).

The following tests and preparations were conducted within the laboratories of the Faculty of Pharmacy, Tishreen University and Faculty of pharmacy, Manara University.

Preparation of phosphate buffer pH=6.8 (USP)

First, monobasic potassium phosphate solution was prepared by dissolving 27.22 grams of monobasic potassium phosphate in distilled water in a volumetric flask up to 1000 ml. Second, NaOH solution (0.2 M) was prepared by dissolving 8 grams of NaOH pellets in distilled water in a volumetric flask with up to 1000 ml.

Finally, 50 ml of monobasic potassium phosphate solution and 22.4 ml of NaOH solution were mixed and diluted with distilled water in a volumetric flask with up to 200 ml to obtain the buffer solution [17].

Valsartan optimal absorbance wavelength and standard curve

A valsartan standard solution was prepared by dissolving 20 mg of pure valsartan powder in the prepared phosphate buffer (pH = 6.8) in a volumetric flask, and filled up to 1000 ml. The prepared solution was subsequently scanned for light absorbance using a spectrophotometer to find the optimal absorbance wavelength (λ_{max}). Furthermore, a series of diluted solutions were prepared, and their light absorbance was determined using a

spectrophotometer measured at the previously determined λ_{max}. The results were used to obtain an Absorbance/Concentration standard curve and build an equation which will be used in further tests.

Capsule preparation

All capsules were prepared by precisely weighing all ingredients and mixing manually in a ceramic mortar using a stainless-steel spatula. The final mixture was filled by hand in hard gelatin capsules size #1, with the average empty capsule having the following characteristics: Volume: 0.48 ml, locked length: 19.4 (±0.76) mm, cap external diameter: 6.91 mm, body external diameter: 6.63, weight: 76 (±7.6) mg. Each capsule containing 140 mg of formulation powder mixture. Table 1 shows the prepared formulations.

Table 1: The contents of the prepared formulations

	F1	F2	F3	F4	F5	F6	F7
Valsartan (mg)	80	80	80	80	80	80	80
Crospovidon (%)	4	6	8	-	-	-	-
Croscarmellose Na (%)	-	-	-	6	8	10	15
Povidone-K30 (%)	2	2	2	2	2	2	2
Colloidal Anhydrous Silica (%)	3	3	3	3	3	3	3
Magnesium Stearate (%)	3	3	3	3	3	3	3
Avicel PH 102 (mg)	43.2	40.4	37.6	40.4	37.6	34.8	27.8
Total Weight (mg)	140	140	140	140	140	140	140

Powder flowability test

Bulk and tapped densities were calculated for powder mixtures before and after lubricant-glidant addition. Bulk density is defined as the ratio between the powder weight and its untapped volume measured in a graduated cylinder, as shown in the following equation:

$$Bulk\ density = \frac{Powder\ weight}{Untapped\ powder\ volume}$$

On the other hand, tapped density is defined as the ratio of powder weight over its tapped volume:

$$Tapped\ density = \frac{Powder\ weight}{Tapped\ powder\ volume}$$

The graduated cylinder was filled with the powder mixture, and placed in the tapper, and then subjected to 10 – 500 – 1250 taps subsequently, and the corresponding volumes (V_{10} – V_{500} – V_{1250}) were retrieved.

If the difference between V_{500} and V_{1250} is less than 2 ml then V_{500} will be set as the tapped density. However, if the difference is larger than 2 ml then the cylinder is subjected to 1250 more taps and the corresponding volume is retrieved until the difference is less than 2 ml between two consecutive runs.

Finally, the flowability profile of each powder mix was evaluated based on the Hausner Ratio and Carr's Compressibility Index which are calculated using the following equations [10].

$$Hausner\ Ratio = \frac{Tapped\ density}{Bulk\ density}$$

$$\text{Carr's Index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Bulk density}} \times 100$$

The flowability evaluation is based on the values shown in table 2.

Table 2: Powder flowability profiles based on Hausner Ratio and Carr's Index

Carr's compressibility Index (%)	Flow characteristics	Hausner Ratio
1-10	Excellent	**1-1.11**
11-15	Good	**1.12-1.18**
16-20	Fair	**1.19-1.25**
21-25	Passable	**1.26-1.34**
26-31	Poor	**1.35-1.45**
32-37	Very poor	**1.46-1.59**
>38	Very very poor	**> 1.6**

Quality assessment of formulated capsules

Uniformity of weight test

For each formulation, 20 capsules were selected at random. Each capsule was weighted individually, and was then completely emptied. Afterwards, each shell was weighted and the powder content weight was calculated by subtracting the shell weight from the total capsule weight obtained from the first step.

All formulation must adhere to the following conditions: No more than two masses are allowed to deviate from the average by more than the percent deviation shown in Table 3, and none are allowed to deviate beyond twice that percentage [10].

Table 3: Allowed weight deviation in uniformity of weight test based on capsule weight class

Average capsule weight (mg)	Percent standard deviation*
< 300	**± 10 %**
≥300	**± 7.5 %**

*Percent standard deviation = [(individual weight – average weight) / average weight] x 100

Uniformity of content test

10 capsules were randomly selected from each prepared formulation, and then the valsartan content of each was determined individually using the following method:

First, the capsule was dissolved in 500 ml of phosphate buffer (pH = 6.8), and then the solution was filtered through a micron filter (0.45 µM). Finally, the light absorbance of each solution was determined using a spectrophotometer at the optimal wavelength λ_{max} = 250 nm. The conditions for passing the test are as follows:

The formulation complies with the test if the content of each individual capsule lies in the range of 85-115% from the overall average content. On the other hand, the formulation fails the test if more than one capsule falls outside this range, or just one capsule falls outside 75-125% of the average content.

However, if only one capsule falls outside the 85-115% range, and none outside the 75-125% range, an additional 20 - also randomly selected - capsules are tested, in which case the formulation is compliant only if one capsule falls outside the 85-115% range and none outside the 75-125% range [10].

Capsule disintegration test

This test requires 6 capsules to be randomly selected, and then for each capsule to be placed in one of six tubes in the disintegration tester. A disk was used to prevent the capsules from floating during the test. The medium was filled with purified water and the temperature was maintained at 37±2^{o}C.

All capsules must disintegrate within the specified time of 30 minutes. However, in case one or two capsules fail to comply, the test must be applied to 12 more capsules, and a minimum of 16 out of the 18 total capsules must disintegrate within the specified time[10].

Dissolution test

The capsule dissolution test was conducted in conformance with the British Pharmacopoeia using Dissolution Apparatus 2 (paddle apparatus). 6 capsules were randomly selected for this test. Each capsule was put in a medium containing 900 ml of phosphate buffer (pH = 6.8), and the apparatus was set to rotate at a constant speed of 50 rpm, and a temperature of 37±0.5^{o}C for a total time of 30 minutes. Additionally, a sinker was used for each capsule to prevent floating.

During the test, 10 ml samples were withdrawn at equal intervals of 10 minutes in order to better analyze the dissolution curve. As such, samples were withdrawn at the 10, 20 and 30 minutes mark, while adding 10 ml of phosphate buffer after each withdrawal to compensate for the sample volume. The samples were then filtered using micron filters (0.45 µM).

Finally, the light absorbance of each sample was measured using a spectrophotometer at λ_{max} = 250 nm, and the corresponding concentrations were calculated using the following equation: y=0.033466x-0.0383 (R^2=0.9991)

As per the British pharmacopoeia, the acceptability criteria for each formulation is that the amount of valsartan released in 30 minutes is no less than 80% of the corresponding stated valsartan capsule content [13].

Results and Discussion

Valsartan optimal absorbance wavelength

The optimal absorbance wavelength was determined using a spectrophotometer and was found to be λ_{max} = 250 nm shown in figure 3.

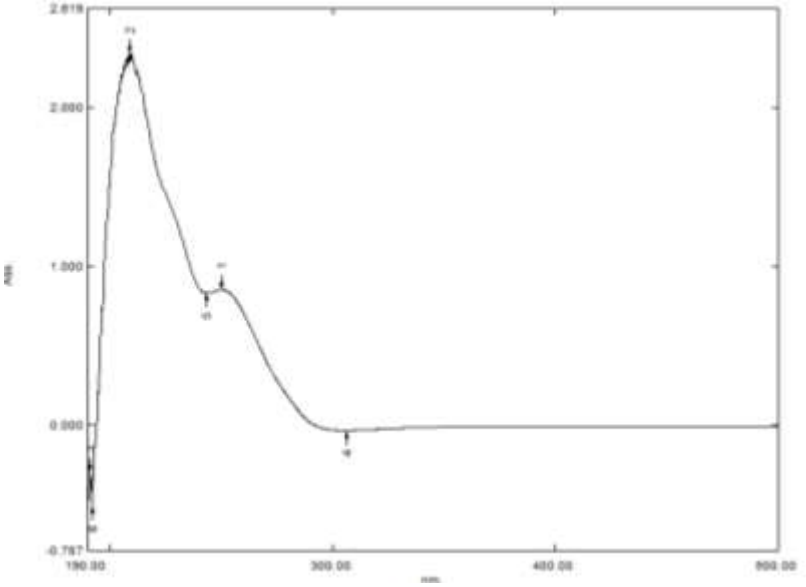

Figure 3: The absorbance spectrum of valsartan solution

Valsartan standard curve

Five solutions with different concentrations were prepared as shown in table 4. The absorbance of each of the solutions was determined using the spectrophotometer, and the resulting concentration-absorbance pairs were used to draw the corresponding standard curve shown in figure 4.

The minimum concentration (8 mg/L) was the lowest concentration corresponding to an absorbance higher than 0.2, thus remaining within the 0.2 to 0.8 absorbance range which is known to provide values with the highest precision [18]. As for the maximum concentration used (20 mg/L), it also corresponds to an absorbance within the aforementioned precision range, while providing good correlation between concentration and absorbance.

Table 4: Absorbance of the solutions used to plot the standard curve

Concentration (mg/L)	Absorbance (n=3)*
8	0.227±0.041
10	0.303±0.005
12	0.357±0.004
16	0.5±0.003
20	0.63±0.002

*n = number of readings per solution

The resulting linear equation y = 0.0335x - 0.0383 had a good regression factor R^2 = 0.9991, showing good correlation between concentration and its corresponding absorbance.

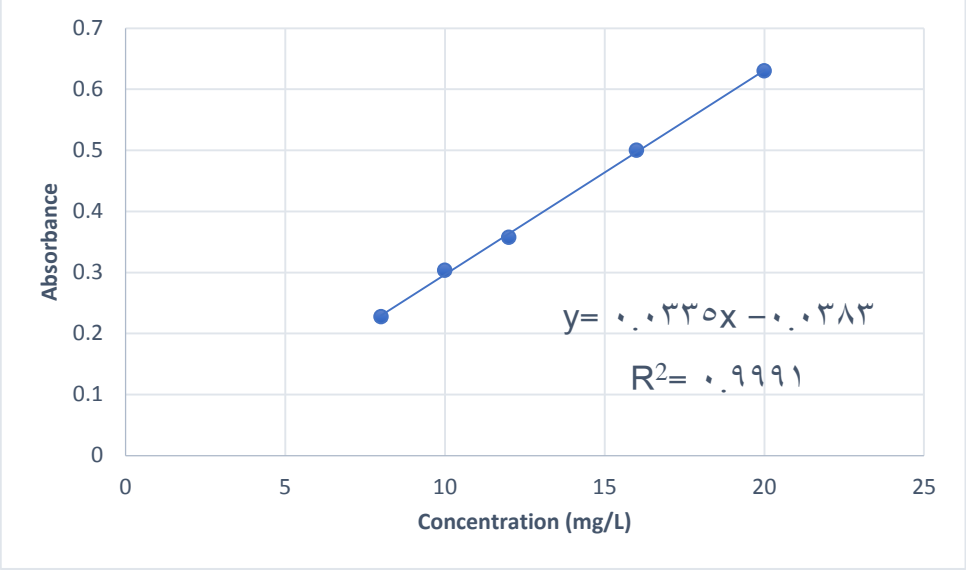

Figure 4: Standard curve of valsartan (R^2 = 0.9991)

Powder flowability test results

Bulk and tapped densities were calculated before and after lubricant-glidant addition for each formulation powder mixture, and then both the Hausner Ratio and Carr's Compressibility Index were calculated using the aforementioned equations. The results are shown in table 5. All formulations showed good flow characteristics after lubricant-glidant addition.

Table 5: Flowability profiles of powder mixtures before and after lubricant-glidant addition

Formulation		Bulk density (g/cm^3)	Tapped density (g/cm^3)	Hausner Ratio	Carr's Index (%)
F1	Before	0.411	0.560	1.363	**26.607**
	After	0.424	0.483	1.139	**12.215**
F2	Before	0.411	0.548	1.333	**25.000**
	After	0.431	0.500	1.160	**13.800**
F3	Before	0.425	0.560	1.318	**24.107**
	After	0.438	0.509	1.162	**13.949**
F4	Before	0.418	0.548	1.311	**23.723**
	After	0.438	0.500	1.142	**12.400**
F5	Before	0.418	0.585	1.400	**28.547**
	After	0.438	0.509	1.162	**13.949**
F6	Before	0.418	0.560	1.340	**25.357**
	After	0.431	0.500	1.160	**13.800**
F7	Before	0.418	0.598	1.431	**30.100**
	After	0.431	0.491	1.139	**12.220**

Capsule tests results

All prepared formulations were subjected to uniformity of weight, uniformity of content, and disintegration time tests, the results of which are shown in Table 6.

For the uniformity of weight test, the average powder weight for each capsule varied between 139.940 mg (F3) and 140.280 mg (F7), while the highest standard deviation percentage was 0,524%, which is well within the allowed deviation of ±10%. Thus, all formulations were in compliance with the test conditions of the corresponding weight class (<300 mg).

As for uniformity of content test, the results of all the formulations ranged from 99.755% (F2) to 101.333 (F6) with minimal deviation, which for both cases is within the acceptable range of 85-115%.

Capsule disintegration time for the formulations were <5 min which is lower than the maximum allowed time of 30 minutes, meaning all formulations passed the disintegration test.

Table 6: Results for uniformity of weight, uniformity of content, and disintegration time tests

Formulation	Powder weight average (mg)	Valsartan content (%)	Capsule Disintegration time (min:sec)
F1	140.080±0.334	99.926±1.246	02:30±4.899
F2	140.100±0.620	99.755±1.128	02:15±4.001
F3	139.940±0.290	99.794±0.759	02:00±7.348
F4	140.100±0.330	100.876±0.953	03:15±6.164
F5	140.235±0.251	99.878±0.836	02:30±8.832
F6	140.065±0.273	101.333±1.250	02:15±7.483
F7	140.280±0.303	100.522±0.777	03:00±7.348

Finally, the dissolution test was carried out for all formulations according to the British pharmacopoeia, the results of which are shown in table 7. The results were then used to

draw percent of valsartan released against time curves (figures 5 and 6) to better elucidate the effect of each super disintegrant on the solubility and dissolution of valsartan.

Table 7: The results of *in-vitro* dissolution test of valsartan capsules (F1 to F7)

Time (min)	10	20	30
F1	45.258±1.552	79.383±1.033	91.234±1.403
F2	59.996±1.590	91.947±0.892	98.441±1.113
F3	74.968±1.219	96.705±0.889	99.932±1.486
F4	46.755±2.611	74.937±2.413	86.771±1.059
F5	71.670±1.638	91.462±1.379	94.419±1.257
F6	73.849±1.607	93.418±1.962	99.468±1.942
F7	57.904±2.545	89.453±1.645	93.751±2.350

By comparing the first formulations F1, F2, and F3 (figure 5), containing 4%, 6%, and 8% crospovidone respectively, it is apparent that increasing crospovidone concentration is translated into an increase in dissolution rate ($P<0.05$), coupled with a lowered disintegration time, owing to the morphology of cospovidone particles which allow swift liquid absorption into the formulation through capillary action, in addition to fast expansion, and thus applying both the wicking and swelling effect to hasten disintegration and in turn dissolution of the formulation [15, 19, 20].

This result coincides with a previous study by Swamy et al. on Propranolol HCL, where fast disintegrating tablets were formulated using crospovidone 2%, 4%, and 6%, and it was noted that increasing crospovidone concentration lowered disintegration time and increased dissolution[21]. In another study by Gholve et al. conducted on instant release Fexofenadine HCL tablets, it was found that increasing crospovidone concentration to 8% had the optimal effect on enhancing dissolution rate [22].

As for formulation F4, F5, F6, and F7 (figure 6) containing 6%, 8%, 10%, and 15% croscarmellose respectively, it is noted that increasing croscarmellose concentration increases dissolution rate ($P<0.05$) and lowers disintegration time up to 10%. This can be explained by the good swelling properties of croscarmellose, as it can swiftly increase its size 4-8 times upon contact with water. Furthermore, it also exhibits good wicking properties which allow good absorption of water due to its high porosity [15, 23, 24]. However, using 15% croscarmellose had the opposite effect on valsartan dissolution.

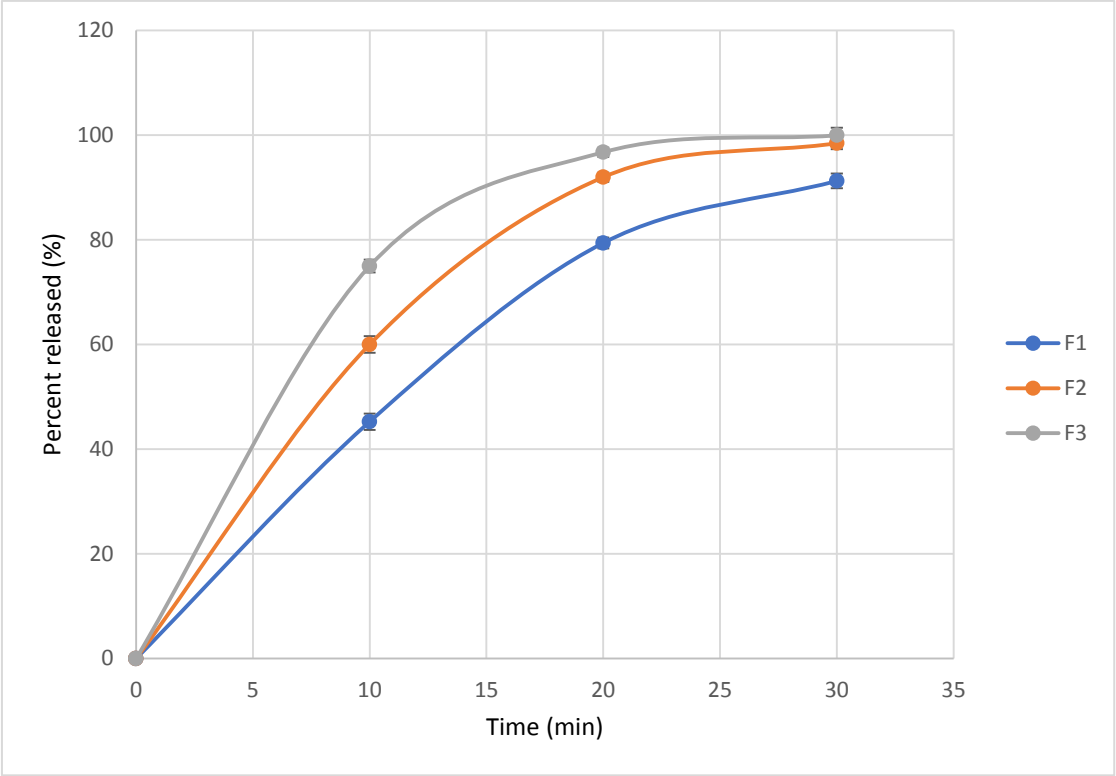

Figure 5: Percent of valsartan released throughout the dissolution test for F1, F2, and F3

This is in accordance with another study by Pandian et al. on Oseltamivir phosphate tablets, where increasing croscarmellose Na concentration led to decreasing disintegration time and improving dissolution rate [25]. Also, in another study by Nagathan et al. on orally disintegrating Bisoprolol fumarate tablets using various croscarmellose Na concentrations (4%-6%-8%), it was found that 8% croscarmellose had the best effect on dissolution [26].

However, when comparing F6 with F7 (10% and 15% croscarmellose), F7 exhibited lower dissolution rate ($P<0.05$). This can be attributed to the thickening effect of croscarmellose, as it can form a gel when used in high concentrations, which increases the medium's viscosity, lowering the surrounding liquid's penetrability into the formulation, which in turn leads to decreased dissolution [27].

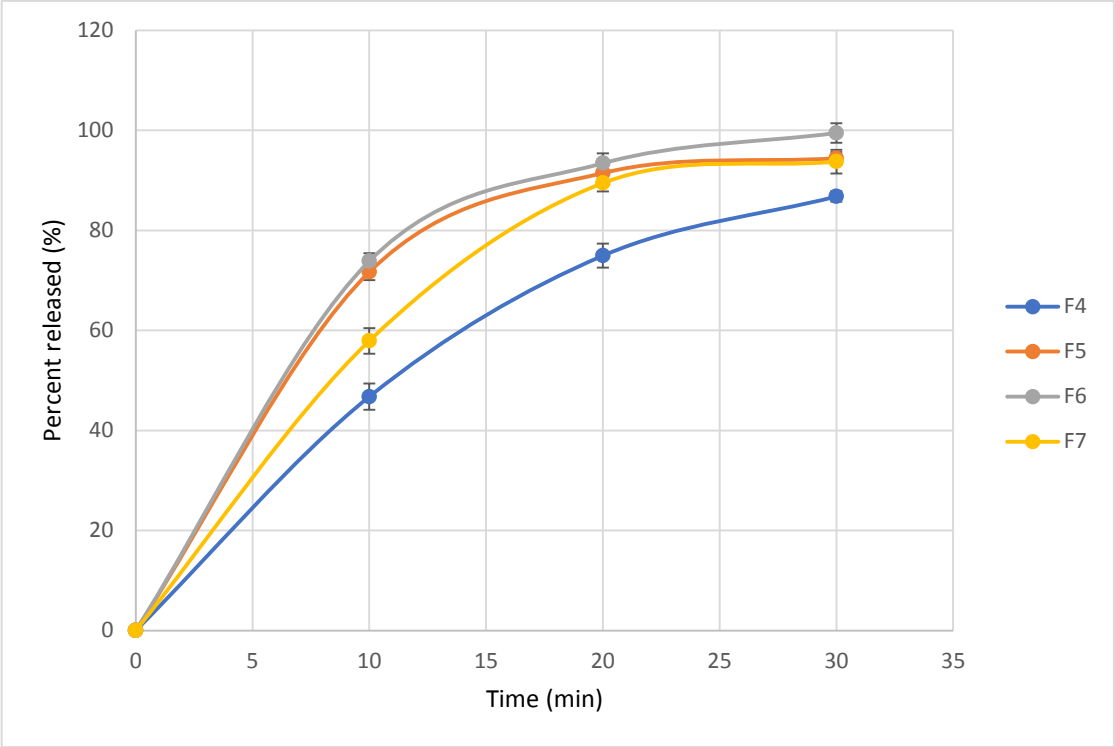

Figure 6: Percent of valsartan released throughout the dissolution test for F4, F5, F6 and F7

Conclusion

Valsartan is one of the most common and effective treatments for blood hypertension. However, it suffers from low solubility and dissolution, resulting in low oral bioavailability. This study aimed to circumvent this drawback through enhancing its dissolution rate. Super disintegrants were used in order to improve disintegration and dissolution rate of valsartan in capsule formulations. Crospovidone and croscarmellose were chosen as they exhibit good wicking and swelling properties. The resulting formulation were subjected to various quality tests, such as powder flowability, capsule uniformity of weight, content, and disintegration time, and finally concluding with the British pharmacopoeia dissolution test. Both superdisintegrants improved valsartan dissolution rate, with crospovidone having the better overall effect.

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