Original article

Formulation and Evaluation of Acyclovir Oral Disintegrating Tablets

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Abstract

Background: Orally disintegrating tablets (ODTs) have recently gained attention as the substitute of conventional dosage form. Superdisintegrants, the main component in the ODTs, render fast disintegrating properties and facilitate the dissolution of active drug. **Aims:** In the present study, the main aims were to prepare acyclovir ODTs using superdisintegrants (sodium starch glycolate and croscarmellose sodium) by direct compression method and investigate the outcome of using various concentrations of superdisintegrant in single and combination formulations. **Materials and Methods:** Superdisintegrants incorporated in the formulations were croscarmellose sodium and sodium starch glycolate in single (F1, F2, F3 and F4) and binary combination (F5 and F6) and acyclovir tablets were directly compressed. Critical quality attributes investigated were uniformity of weight, thickness, hardness, friability, wetting time and water absorption ratio, in vitro disintegration time and in vitro dissolution study. One-way statistical ANOVA test and post hoc test were conducted by using Statistical Package for the Social Science (SPSS) software version 21. **Results:** The maximum acyclovir release rate was achieved in formulations F5 (90.09 ± 0.43%) followed by F2 (70.29 ± 0.07%) and F1 (61.33 ± 1.15%). Among the 7 formulations investigated, 1% w/w SSG and 5% w/w CCS in formulation F5 demonstrated shortest disintegration time (7.33 ± 0.246 seconds) and greatest dissolution rate (90.09 ± 0.43%). Such combination ratio provided synergism between mechanisms of action of two superdisintegrants (swelling and

wicking) thus resulted in excellent wetting properties and water absorption ratio ($p < 0.05$). **Conclusion:** From the present study, combination of superdisintegrants in ratio 1:5 did result in better disintegration and dissolution rate compared to ratio 1:1 and other single superdisintegrant formulations in terms of critical quality attributes investigated.

Keywords: Orally disintegrating tablets, acyclovir, superdisintegrants, sodium starch glycolate, croscarmellose sodium

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Introduction

Oral disintegrating tablets (ODTs) encountered significant recognition and focus to provide a more convenient drug delivery system. United States Food and Drug Administration (FDA) defines it as 'a solid dosage form containing a medicinal substance or active ingredient which disintegrates rapidly usually within a matter of seconds when placed upon the tongue'[1].

Sodium starch glycolate (SSG) is a cross linked polymer of carboxymethyl starch. SSG is reported to undertake swelling mechanism where it can swell up to 7-12 folds in 3 dimensions within 30 seconds through fast water absorption. In a study of chlorpheniramine tablets formulated with different concentrations of SSG, it was found that when the concentration of superdisintegrant increased from 5% w/w and above, the disintegration time was reduced considerably[2]. However, it was reported that SSG of 8% w/w and above would lengthen disintegration time due to gel formation with increased viscosity[3].

Based on these studies, it is recommended to incorporate SSG at a concentration between 2-8%.

Croscarmellose sodium (CCS) is a cross linked polymer of carboxymethyl cellulose sodium. Cross linking in CCS makes it insoluble and hydrophilic hence rendering to the superior swelling properties[4]. Its fibrous nature assists the great uptake amount of water and disintegrating by capillary action[5]. CCS has both swelling and wicking mechanism for good disintegrating properties and its concentrations usually ranged between 1-5% w/w in tablet formulations[6].

Acyclovir is an antiviral drug used in the pharmacological management of Herpes simplex virus infections, Varicella zoster (chickenpox) and Herpes zoster (shingles). Acyclovir will be converted to acyclovir triphosphate, which actively blocks viral DNA polymerase and destroys the growing viral DNA chain. It is belongs to Class III Biopharmaceutics Classification System (BCS) as it has high solubility and low permeability[7]**.** Oral route is generally safer as compared to intravenous route in terms of adverse effects[8].

Materials and methods

Materials

Acyclovir was the active ingredient in the formulation. Microcrystalline cellulose acted as diluent and binder (COMPRECEL M102D+) and magnesium stearate was purchased from ACROS ORGANICS. Sodium starch glycolate and potassium dihydrogen phosphate anhydrous were purchased from CHEMSOLN. Parteck ODT® which contained 95% croscarmellose sodium and 5% mannitol were used as superdisintegrant.

Equipments

List of equipments involved Mettler Toledo Al204 Analytical Balance, Turbula Shaker Mixer, Mini Press-SF Tabletting Machine, Copley (TBF 1000) Tablet Hardness Tester, Electrolab EF-2 Friabilator, Electrolab ED-2AL Disintegration Tester, Electrolab TDT-08L Dissolution Tester and Beckman Coulter DU 730 Life Science UV/Vis Spectrophotometer

Methods

Formulation of acyclovir ODTs

Seven formulations containing acyclovir as active ingredient were formulated. Four formulations had single superdisintegrant (sodium starch glycolate) incorporated at 2% w/w, 4% w/w, 8% w/w and 10% w/w and one control formulation without superdisintegrant (F7). Two formulations had combination of superdisintegrants (sodium starch glycolate and crosscarmellose sodium) at the ratio of 1:5 and 1:1 as shown in Table 1. Acyclovir and the excipients were weighed and blended in turbula shaker mixer for 15 minutes at 45 rpm and accounted for pre-formulation studies. After that, the powder blends were tableted by direct compression using rotary punch tableting machine with compression force fixed at 600-800 N.

Table 1: Formulation composition of acyclovir ODTs

Ingredients (mg)	**Formulations (mg)**						
	F1	**F2**	**F3**	**F4**	**F5 (1:5)**	**F6 (1:1)**	**F7 (control)**
Acyclovir	50	50	50	50	50	50	50
Parteck ODT	-	-	-	-	10	10	-
MCC	144	140	132	128	136	128	148
SSG	4	8	16	20	2	10	-
Magnesium stearate	2	2	2	2	2	2	2
Total weight	200	200	200	200	200	200	200

Pre-formulation studies

Angle of repose

Angle of repose was employed to measure powder flow properties by using funnel method. The powder were poured and allowed to flow freely through the funnel onto the plane.

Angle of repose, $\tan \alpha = \frac{h}{r}$

h = Height (cm)

r = Radius (cm).

Carr's compressibility index and Hausner's ratio

$$\text{Bulk density} = \frac{\text{weight of sample (g)}}{\text{initial volume occupied by the sample (ml)}}$$

$$\text{Tapped density} = \frac{\text{weight of sample (g)}}{\text{volume occupied by the sample after tapping (ml)}}$$

Powder compressibility evaluates the ability of powder in forming a stable and intact compact mass after pressure is applied:

$$\text{Carr's compressibility index} = \frac{\text{tapped density} - \text{poured density}}{\text{tapped density}} \; x \; 100\%$$

$$\text{Hausner's ratio} = \frac{\text{tapped density}}{\text{poured density}}$$

Post-compression studies

Appearance

The appearance of the ODTs was recorded with respect to the components such as shape, colour, odour and surface texture.

Uniformity of weight

Twenty tablets were taken randomly from each formulation and weighed separately to determine the average mass by using Mettler Toledo Al204 Analytical Balance. The acceptance limit is no more than two tablets should be deviated by ± 7.5% and none of the tablets differ by exceeding two times of ± 7.5%.

Thickness

Ten tablets were chosen from each formulation and the average was reported in mm by using vernier calipers. Thickness of each tablet should be within ± 5% of variation.

Hardness

Ten tablets were picked from individual formulation at a random. Each tablet was positioned between the two plungers of the Copley (TBF-1000) Tablet Hardness Tester. The force needed to break down the tablet into two parts entirely was measured in terms of kg/cm^2.

Friability

For tablet with an individual weight equivalent to or lesser than 0.65 g, take a total mass as closely to 6.5 g. The tablets were rotated up to 100 revolutions in Electrolab Ef-2 Friabilator. After that, the tablets were removed for dedust and reweigh.

$$\% \text{ friability} = \frac{\text{initial weight} - \text{final weight}}{\text{initial weight}} \; x \; 100\%$$

Wetting time and water absorption ratio

A petri dish containing 10 mL of Rhodamine B solution was prepared by dissolving Rhodamine B dye in distilled water. A tablet was selected at random from every formulation and positioned in the centre of the petri dish. The test was carried out in triplicates. Time required for solution to reach top of the tablets was noted.

$$R = \frac{W_b - W_a}{W_a}$$

where R = water absorption ratio

W_a = weight before (g)

W_b = weight after (g)

In vitro disintegration time

The test was performed using a USP tablet disintegration test apparatus (Electrolab ED-2AL Disintegration Tester). Six tablets were employed from individual formulation in distilled water maintained at 37 ± 0.5 °C. The time needed for tablet to be complete disintegrated from large fragment into small fragments is recorded.

In vitro dissolution study

In vitro dissolution study for acyclovir ODTs were performed using United State Pharmacopoeia (USP) XXIV dissolution testing apparatus II (paddle method). The study was conducted at 50 rpm in 900 ml of phosphate buffer (pH 6.8) at 37 ^{0}C using Electrolab TDT-08L Dissolution Tester. Ten millilitre of the sample solution was withdrawn from every vessel at time intervals of 0, 1, 3, 5, 10, 15, 20, 30, and 40, 50 and 60 minutes. After each sampling, an equivalent volume of phosphate buffer was refilled into the medium to keep consistent volume. Amount of acyclovir release can be determined through regression equation (y= 0.0614x – 0.0139). Percentage of acyclovir release at every specific time was determined and plotted in graph. Dissolution studies were conducted in replicates of six. Tolerance requires not less than 80% of acyclovir should be released from the formulation at 45th minutes of dissolution study.

Analytical method validation

Linearity

Acyclovir stock solution was produced by dissolving 100 mg of acyclovir powder in 100 mL of phosphate buffer. Five different

concentrations (0.625, 1.25, 2.5, 5, 10 and 15 microgram per mL) were prepared from acyclovir stock solution to determine absorbance and plot calibration graph. When the square of the correlation coefficient, r^2 is equivalent to or greater than 0.98, linearity was fulfilled.

Specificity

Specificity test was conducted to determine the absorbance values of both placebo and active formulations. The maximum absorbance of acyclovir stock solution was determined at 250 nm using Beckman Coulter DU 730 Life Science UV/Vis spectrophotometer.

Accuracy

A tablet was dissolved in 100 mL of phosphate buffer. After that, the solution with dissolved tablet was tested by using Beckman Coulter DU 730 Life Science UV/Vis spectrophotometer at wavelength of 250 nm to get the readings of absorbance. The accuracy test was performed in triplicates for each formulation studied.

Precision

Intermediate precision was performed through dissolution test of the same formulation for 3 different days. Results were expressed as percentage of dissolution and the percentage of relative standard deviation (RSD) at the 60^{th} minutes of the study. Generally, a RSD of less than 2 % was required based on ICH guidelines.

$$\% \text{ RSD} = \frac{\text{Standard Deviation}}{\text{Mean}} \text{ x } 100\%$$

Robustness

Robustness test was performed by testing UV absorbance of standard stock acyclovir solution at 3 different wavelengths of 249 nm, 250 nm and 251 nm to obtain 6 replicates of readings for each wavelength by using Beckman Coulter DU 730 Life Science UV/Vis spectrophotometer.

Results and discussion

Pre-formulation studies

Table 2: Pre-formulation studies result of formulations F1 to F7.

Formulation	Angle of repose (°)	Bulk density (g/mL)	Tapped density (g/mL)	Carr's compressibility index (%)	Hausner's ratio
1	25.37	0.4387	0.5440	19.36	1.24
2	25.25	0.4508	0.5544	18.69	1.23
3	26.57	0.4495	0.5761	21.97	1.28
4	26.35	0.4389	0.5581	21.36	1.27
5	25.20	0.4262	0.5643	24.47	1.32
6	27.44	0.4464	0.5476	18.48	1.23
7	26.57	0.4447	0.5409	17.79	1.22

Angle of repose was in the range of 25° to 31°, showing powder blends suitable for manufacturing purposes. The compressibility index of all formulations was 17.79% to 24.47% while Hausner's ratio was observed to be between 1.22 to 1.32. With good powder flowabilty, the dies were filled with same amount every time during tableting process thereby the content uniformity for each tablet was assured.

FTIR Spectroscopy

Figure 1: FTIR results of formulations containing acyclovir, acyclovir with SSG, acyclovir with SSG and CCS and placebo

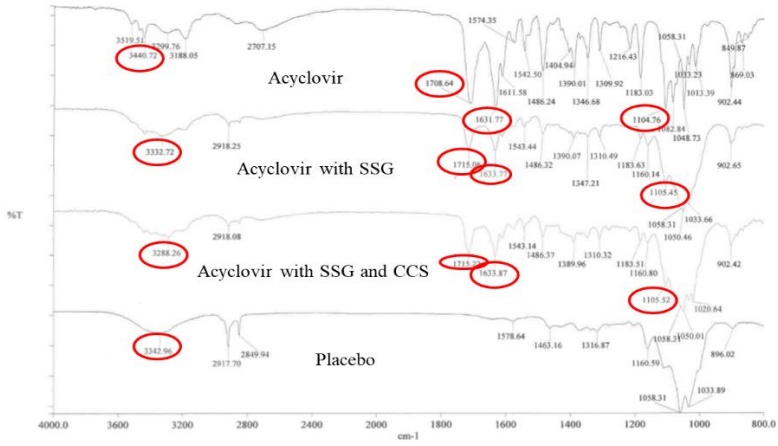

Table 3: FTIR results of formulations

Wave number	**Formulations**			
	Acyclovir alone	**Acyclovir with SSG (F2)**	**Acyclovir with SSG and CCS (F5)**	**Placebo (MCC and Mg stearate) (F7)**
N-H stretch	3440.72	3332.72	3288.26	3342.96
C=N stretch	1631.77	1633.77	1633.87	-
C=O stretch	1708.64	1715.06	1715.22	-
C-O-C stretch	1104.76	1105.45	1105.52	-

FTIR investigation of pure acyclovir, formulation F2 (acyclovir and SSG), formulation F5 containing (acyclovir, SSG and CCS) and control formulation F7 (MCC) were obtained. FTIR diagram of acyclovir demonstrated four particular peaks at 3440.72 cm^{-1} attributable to N-H stretch, 1631.77 cm^{-1} in view of C=N stretch, 1708.64 cm^{-1} owing to C=O stretch and 1104.76 cm^{-1} indicating C-O-C stretch. IR spectra of F2 and F5 demonstrated the characteristic pinnacles of the unadulterated drug acyclovir. Meanwhile, control formulation F7 showed peak at 3342.96 cm^{-1} which was possibly ascribed to the O-H bond in MCC structure. From the elucidation above, there was no shifting in the frequencies of functional groups mentioned earlier. Hence, there was no association between acyclovir and the excipients.

Post-compression studies

Physical evaluation of acyclovir ODTs

Figure 2: Physical appearance of acyclovir ODTs formulations F1-F7.

All the acyclovir ODTs were white, odourless and circular with smooth and shiny texture.

Performance evaluation of acyclovir ODTs

Table 4: Post compression evaluation results of acyclovir ODTs.

Formulation	Weight (g)	Thickness	Hardness	Friability (%)	Wetting time	Water absorption	In vitro disintegration

		(mm)	(kg/cm^2)		(sec)	ratio (%)	time (sec)
1	0.2304 ± 0.003	2.52 ± 0.012	6.70 ± 0.354	0.107	5.49 ± 0.176	75.46 ± 2.672	12.20 ± 0.243
2	0.2318 ± 0.003	2.52 ± 0.013	7.24 ± 0.325	0.117	2.80 ± 0.229	80.72 ± 1.843	9.07 ± 0.482
3	0.2420 ± 0.003	2.55 ± 0.020	6.66 ± 0.373	0.064	6.83 ± 0.405	63.81 ± 0.841	15.62 ± 0.816
4	0.2481 ± 0.003	2.63 ± 0.019	6.14 ± 0.332	0.549	6.74 ± 0.487	60.68 ± 0.508	20.80 ± 0.882
5	0.2422 ± 0.004	2.54 ± 0.011	6.50 ± 0.310	0.960	3.08 ± 0.772	82.13 ± 0.821	7.33 ± 0.246
6	0.2421 ± 0.007	2.57 ± 0.015	5.82 ± 0.120	0.170	8.99 ± 0.441	56.76 ± 0.569	17.66 ± 0.357
7	0.2337 ± 0.004	2.49 ± 0.016	7.51 ± 0.178	0.110	7.59 ± 0.331	41.14 ± 0.901	51.24 ± 0.993

All ODTs had complied with the uniformity of weight test as there was none of the single tablet which deviated from the average mass by ± 7.5% according to United State Pharmacopoeia (2014). The thickness for seven formulations was ranged 2.49 ± 0.016 mm to 2.63 ± 0.019 mm. Moving on to hardness, tablet hardness of all formulations was within the range of 5.82 ± 0.12 kg to 7.51 ± 0.178 kg. All formulations achieved the friability percentage in the range of 0.064% to 0.960 in accordance with the USP specifications which suggested that the tablets were mechanically stable and have the ability to resist abrasion in handling, packaging and transportation.

Formulation F5 showed the least wetting time followed by formulations F2, F1, F4, F3, F6 and F7 ($p < 0.05$). Control formulation F7 showed longest wetting time as it lacked of superdisintegrant in promoting the water uptake through swelling or wicking. The significantly longer wetting time observed in F3 and F4 was attributed to the disintegration mechanism of SSG which swells in contact with aqueous medium. Swelling in SSG was described to be occurred with gelling action and it may block the pores in the tablet to prevent water penetration into the tablet matrix thus wetting time increased. The incorporation of CSS to SSG formulations improved the wetting of the tablets due to its porous structure. However, formulation F6 comprising a binary superdisintegrants of SSG and CCS in ratio 1:1 had make an exemption as its wetting time was not critically shorter than formulations containing single superdisintegrant. It is possibly due to gelling effect of SSG contributing to the binding of tablet matrix and resulted in longer wetting time and limiting tablet disintegration[9].

Highest water absorption ratio was observed in formulation F5, which assumed to have swelled up to 82.13%. Formulations consisting superdisintegrants (F1-F6) showed greater water

absorption ratio than control F7 ($p < 0.05$). This was owing to the high water uptake and retention ability of superdisintegrants. Highly swelling materials (SSG and CCS) were able to absorb and maintain a larger amount of water whereas MCC showed low water uptake ability. Water uptake in MCC initiates in the pores accompanied by movement into the internal of the capillaries[10]. Without the incorporation of superdisintegrant, a tablet will not be able to retain the water after the maximum water uptake. Hence, the weight after wetting of a tablet is comparatively lower in formulation F7. Rojas et al. (2012) reported that SSG had high swelling ability and high water retention due to the amylopectin component of starch[10]. It was deduced that both SSG and CCS displayed swelling action and the capability of SSG to retain water depends on its concentration in the formulations. At optimal concentration of superdisintegrants, water uptake capacity improved with an increase in water absorption ratio.

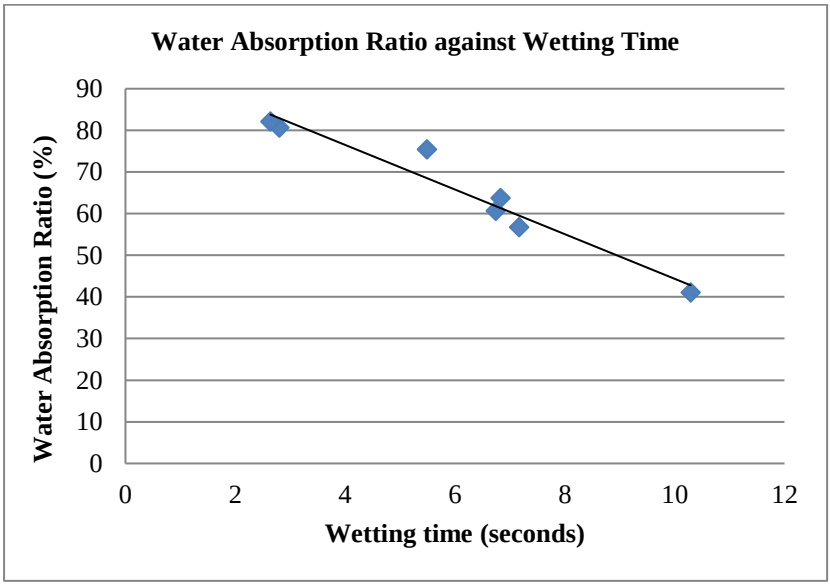

Figure 3: Correlation graph between wetting time and water absorption ratio.

F7 displayed longest disintegration time (51.24 ± 0.99 seconds) due to absence of superdisintegrant in the formulation. MCC did not replace the need for true superdisintegrants (SSG and CCS) in promoting fast disintegration[11]. Nevertheless, MCC lacks of swelling action which renders inadequate disintegration force and contributed to slower disintegration rate observed in formulation F7. In the matter of single superdisintegrant, both formulations F3 (8% w/w SSG) and F4 (10% w/w SSG) had longer disintegration time which indicated that SSG should not be used in the range of these concentrations. This was further supported by researches that reported when SSG concentration increases from and above 8% w/w of the formulation, it swells to a gel due to gelling and viscosity producing effect which blocks the pores in the tablet and prevent additional water uptake into the tablet[18]. According to the results, formulation F5 with combination of superdisintegrants had critically greater disintegration rate than F2 ($p < 0.05$). In formulation F5 comprised of a mixture of SSG and CCS, where water uptake was assisted by CCS and the swelling properties in SSG which promotes the disintegration rate with shortened disintegration time[12].

In vitro dissolution study of acyclovir ODTs (formulations F1, F2 and F5)

Table 5: Cumulative percentage of acyclovir release of formulations F1, F2 and F5.

Time (minutes)	**Cumulative percentage of acyclovir release (%)**		
	F1	**F2**	**F5**
1	9.63 ± 0.79	11.56 ± 2.22	17.35 ± 0.76

3	20.65 ± 1.43	22.62 ± 0.48	27.40 ± 0.68
5	27.22 ± 0.50	24.98 ± 0.90	30.13 ± 3.14
10	30.59 ± 1.26	30.70 ± 4.53	37.28 ± 3.28
15	35.46 ± 0.61	36.36 ± 4.37	51.34 ± 0.77
20	40.27 ± 0.56	45.97 ± 2.28	68.84 ± 2.64
30	45.04 ± 1.81	57.70 ± 1.00	78.93 ± 3.57
40	57.09 ± 2.23	65.69 ± 0.11	86.11 ± 0.67
50	60.45 ± 1.35	68.48 ± 1.00	87.99 ± 0.52
60	61.33 ± 1.15	70.29 ± 0.07	90.09 ± 0.43

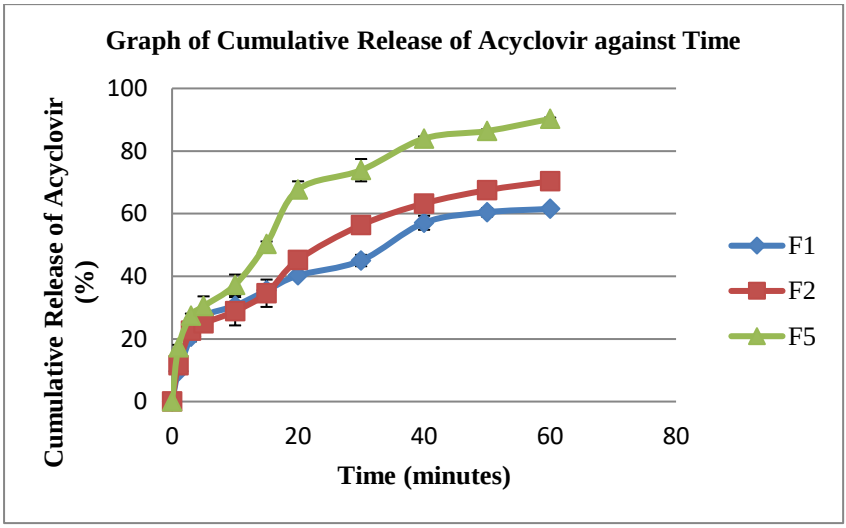

Figure 4: Graph of cumulative release of acyclovir against time.

Formulations F1, F2 and F5 were selected for dissolution study due to their performance in terms of critical quality attributes

investigated. Based on Table 5, formulation F5 has the highest acyclovir release rate of 90.09 ± 0.43%. Greatest cumulative percentage of acyclovir and fastest disintegration of acyclovir ODTs in formulation F5 was likely attributed to synergism in mechanism of action of two superdisintegrants (SSG and CCS). SSG was reported to have high swelling index accompanied by swelling and wicking action of CCS. The subsequent higher cumulative drug release was observed in formulation F2 which achieved 70.29 ± 0.07% and followed by 61.33 ± 1.15% in formulation F1. It can be explained by correlating the dissolution rate with the concentration of SSG in the formulations. When the SSG concentration increases, it swells rapidly upon contact with liquid hence dissolution rate will be greater provided the optimal concentration was not exceeded (< 8%).

Analytical method validation

Linearity

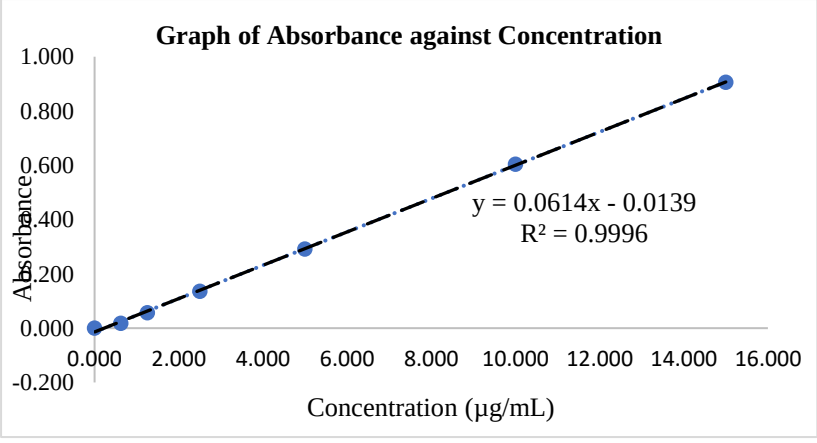

Figure 5: Calibration graph of acyclovir for linearity test.

The equation was determined as, y = 0.0614 + 0.0139x, where y is the absorbance, x is the concentrations of solution and y-intercept of 0.0614. The graph showed correlation coefficient, r^2

= 0.9996 which was greater than 0.98 hence linearity was established.

Specificity, Accuracy and Robustness

Table 6: Specificity, accuracy and robustness results of formulations F1, F2 and F5.

Formulation	**Specificity (absorbance)**		**Accuracy (Percentage of acyclovir released, %)**	**Precision (RSD, %)**		**Robustness (RSD, %)**
	Placebo	**Acyclovir**		**Intra-day**	**Inter-day**	
1	-0.001	0.614	91.33 ± 0.42	0.407	1.107	0.146
2	-0.078	0.601	98.13 ± 0.07	0.341	0.671	0.198
5	-0.002	0.748	98.87 ± 0.26	0.312	0.565	0.113

For specificity test, formulations F1, F2 and F5 containing acyclovir as active drug showed absorbance and peaks at wavelength of 250 nm. Meanwhile, placebo formulations showed no peak at wavelength of 250 nm which indicated the absence of acyclovir in placebo formulation. For accuracy test, the percentage of acyclovir released for formulations F1, F2 and F5 were 91.33%, 98.13% and 98.87% correspondingly hence formulations F2 and F5 were assumed to pass the accuracy test. The intra-day, inter-day precision and robustness results accomplished the acceptance limit as the (RSD) obtained were less than 2%.

Statistical Analysis

Data analysis was conducted by using the Statistical Package for the Social Science (SPSS) software version 21. One-way statistical ANOVA test and post hoc test were employed for analysis of data. A p-value of less than 0.05 was considered to be statistically significant.

Conclusion

In present study, acyclovir ODTs can be prepared using SSG and CCS as superdisintegrant through direct compression to enhance the disintegration and dissolution profile. All ODTs fulfilled the weight uniformity and friability test which complied with United States Pharmacopoeia (2014). All formulations had disintegrated within 51.24 seconds. Formulations F5 had shortest wetting time of 2.68 seconds which also showed shortest disintegration time of 7.33 seconds and greatest water absorption ratio of 82.13%. Formulation F5 containing 1% w/w SSG and 5% w/w CCS was the most preferred combination in formulating acyclovir ODTs. On account of its excellent wetting properties, it had the shortest disintegration time and greatest dissolution rate. In conclusion, the use of combination of superdisintegrants will fasten the onset of action and enhance the bioavailability of the drug.

Limitations of present study

Formulation F5 released more than 80% of acyclovir during 45 minutes of the dissolution test which complied with the acceptable limits. F1 and F2 containing SSG as the single superdisintegrant released only 61.33 ± 1.15% and 70.29 ± 0.07% of acyclovir. Such a low dissolution rate could be explained by the slower disintegration time of formulations F1 and F2. Despite the disintegration time obtained was lower than 12.20 ± 0.243 seconds, the tablets failed to disintegrate completely at the end of the dissolution test[27]. At 50 rpm, the

force of dissolution paddles was not as strong as the vertical movement of the disintegration apparatus to induce a whole breakdown of the tablets[28].

Recommendations for future study

In future study, it can be conducted by employing different combination ratio of superdisintegrants on the physical evaluation of acyclovir ODTs. Apart from that, flavour enhancers such as menthol and aspartame can be incorporated for taste masking. In contrast to MCC which was is insoluble in water, water soluble polyols such as mannitol and sorbitol are preferable as excipients for solid dosage forms that disintegrate in the oral cavity along with their pleasant mouth feeling, great mechanical properties and rapid dissolution[30].

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