Bulletin of Health,
Science and Technology
BHST
ISSN 0858-7531
Volume 12, Number 1, 2014 : 33-43

APPLICATION OF POLYVINYLPYRROLIDONE K30 AND CHITOSAN AS CO-BINDERS IN PREPARING FUROSEMIDE TABLET BY WET GRANULATION METHOD

Pienkit Dangprasirt[1,*], Sansanee Pongwai[1], Vasinee Limwong[1], Saraporn Harigarnpakdi[1], Kanokporn Burapapat[1] and Moleephan Dangprasirt[2]

[1] Faculty of Pharmacy, Rangsit University, Patumtani 12000, Thailand
[2]Research and Development Division, Thailand Institute of Nuclear Technology (Public Organization), Nakornnayok 26120, Thailand

*Corresponding author : E-mail : pienkitd@yahoo.com

Abstract: Furosemide tablets were prepared by wet granulation using polyvinylpyrrolidone K 30 (PVP) alone, as single binder, and PVP with chitosan (CS), as co-binders. Spray-dried rice starch (Era-Tab®) and croscarmellose sodium (Ac-Di-Sol®) were employed as tablet diluent and disintegrant, respectively. The prepared tablets were tested for tablet physical properties, disintegration and dissolution. The effects of PVP, CS and Ac-Di-Sol® contents on tablet friability, disintegration time and dissolution were studied using a two-level full factorial experimental design. The tested properties of furosemide tablets prepared by using the single binder were compared to those prepared by using the co-binders. The usage of co-binders, PVP and CS, was found to significantly decrease the tablet friability without considerable change in disintegration time. The furosemide tablet of good physical properties and fast drug dissolution was prepared by using low content of Ac-Di-Sol® and optimum amounts of the co-binders, PVP and CS. Inclusion of a surfactant, sodium lauryl sulfate (SLS), in the furosemide tablets did not improve the tablet dissolution. No significant change in tablet dissolution profile was observed when sodium starch glycolate (Explotab®) was used as disintegrant, instead of Ac-Di-Sol®, in the furosemide tablets prepared by using co-binders. However, the usage of proper content of SLS in the furosemide tablet formulation consisting of Explotab® was found to provide the tablet of improved dissolution.

Keywords: Chitosan, Co-binders, Furosemide tablet, Polyvinylpyrrolidone

บทคัดย่อ: เตรียมยาเม็ดฟูโรซีไมด์โดยวิธีการทำแกรนูลเปียกโดยใช้โพลีไวนิลไพโรลิโดน (PVP) เป็นสารยึดเกาะเดี่ยว และใช้ PVP ร่วมกับไคโตซาน (CS) เป็นสารยึดเกาะร่วม ใช้แป้งข้าวเจ้าที่ทำให้แห้งโดยการพ่นแห้ง (Era-Tab®) และครอสคาเมลโลสโซเดียม (Ac-Di-Sol®) เป็นสารเพิ่มปริมาณและสารช่วยแตกตัวตามลำดับ นำยาเม็ดที่เตรียมไปทดสอบหาคุณสมบัติทางกายภาพ เวลาในการแตกตัว และการละลายของยาเม็ด ศึกษาผลของปริมาณของ PVP, CS และ Ac-Di-Sol® ที่มีต่อความกร่อน เวลาในการแตกตัวและการละลายของยาเม็ดโดยใช้การออกแบบการทดลองแบบฟูลแฟคตอเรียลที่สองระดับ เปรียบเทียบคุณสมบัติต่าง ๆ ของยาเม็ดที่เตรียมจากสารยึดเกาะเดี่ยวและคุณสมบัติดังกล่าวของยาเม็ดที่เตรียมจากสารยึดเกาะร่วม พบว่าการใช้สารยึดเกาะร่วมคือ PVP และ CS ทำให้ความกร่อนของยาเม็ดลดลงอย่างมีนัยสำคัญโดยไม่มีผลต่อเวลาในการแตกตัวของยาเม็ดอย่างมีนัยสำคัญ ยาเม็ดฟูโรซีไมด์ที่มีคุณสมบัติทางกายภาพที่ดีและมีการละลายของยาที่เร็วสามารถเตรียมได้โดยใช้ Ac-Di-Sol® ในปริมาณต่ำและใช้สารยึดเกาะร่วมคือ PVP และ CS ในปริมาณที่เหมาะสม การเติมสารลดแรงตึงผิวคือโซเดียมลอริลซัลเฟตในยาเม็ดฟูโรซีไมด์ไม่ช่วยในการเพิ่มการละลายของยาเม็ด พบว่าการเปลี่ยนสารช่วยแตกตัวจาก Ac-Di-Sol® เป็นโซเดียมสตาร์ชไกลโคเลต (Explotab®) ในยาเม็ดฟูโรซีไมด์ที่เตรียมจากสารยึดเกาะร่วมไม่ทำให้การละลายของยาเม็ดมีการเปลี่ยนแปลงอย่างมีนัยสำคัญ อย่างไรก็ตามการเติม SLS ในปริมาณที่เหมาะสมในตำรับยาเม็ดฟูโรซีไมด์ที่ใช้ Explotab® สามารถเพิ่มการละลายของยาเม็ดได้

คำสำคัญ ไคโตแซน สารยึดเกาะร่วม ยาเม็ดฟูโรซีไมด์ โพลีไวนิลไพโรลิโดน

INTRODUCTION

Chitosan (CS) is a natural polymer obtained by deacetylation of chitin. After cellulose, chitin is the second most abundant polysaccharide in nature (Sandford, 1989). Chitosan, which is soluble in acidic aqueous media, is used in many applications such as food, cosmetics, biomedical and pharmaceutical applications. (Rinaudo, 2006). Chitosan dissolves in acid medium resulting in solution of high viscosity. Therefore, it is interesting to study the use of chitosan solution as binding liquid in preparing tablets by wet granulation method. Chitosan has been studied as binder in controlling drug release from tablets prepared by wet granulation method (Kepsutlu et al, 1999; Brine, 1989). However, the usage of chitosan as binder in preparing fast release tablet still gets less intension. Since the chitosan solution is very viscous and consequently the high concentration of chitosan solution is difficult to prepare. Thereby, the usage of chitosan solution alone in low concentration as a binding solution is doubtful due to its lack of sufficient binding property.

Polyvinylpyrrolidone (PVP) is a widely applied binder utilized in preparing tablets by wet granulation process (Rowe, Sheskey, Quinn 2009). PVP K30 and PVP K90 are the two commonly employed binders. PVP K30 solution is less viscous than PVP K90 solution, therefore, it provides less binding effect. However, it is easier to prepare as solution. Incorporation of low concentration of chitosan solution into PVP K30 solution in order to be used as co-binders is an alternative way to improve binding ability of PVP K30 solution. The obtained co-binders may be useful to prepare wet granulation tablets with satisfied physical properties.

In this investigation, chitosan and PVP K30 were studied as co-binders in preparing furosemide tablets by wet granulation method. A poorly water-soluble drug, furosemide (FS), was used as a model drug in order to study the effects of the co-binders on the dissolution of the poorly water-soluble drug from the prepared tablets and on the tablet physical properties. The effects of a solubilizer, sodium lauryl sulfate (SLS), and a superdisintegrant, Ac-Di-Sol®, employed in the FS tablets on tablet dissolution were also studied.

MATERIALS AND METHODS

The following materials were obtained from commercial sources. Furosemide (Lot No. 897657) was obtained from Asia Drug & Chemical Ltd. Part., Thailand. Chitosan was obtained from Unicord PCL Ltd., Thailand. Polyvinylpyrrolidone K30, spray-dried rice starch (Era-Tab®), magnesium stearate, colloidal silicon dioxide (Aerosil®), croscarmellose sodium (Ac-Di-Sol®) and sodium starch glycolate (Explotab®) were supplied by Pharmaceutical Science Ltd., Part., Thailand.

Preparation of furosemide tablets

Furosemide tablets were prepared by wet granulation process using spray dried rice starch (Era-Tab®) as diluent. A single binder, polyvinylpyrrolideone K30 (PVP), and co-binders, PVP and chitosan (CS), were used as granulating agents. Croscarmellose sodium (Ac-Di-Sol®) was employed as tablet disintegrant. Silicon dioxide (Aerosil®) and magnesium stearate were also used as glidant and lubricant, respectively. A two level full factorial experimental design was applied to study the effects of PVP, chitosan and Ac-Di-Sol® contents on the dissolution and physical properties of the prepared furosemide tablets. According to the experimental design (Table 1), the total of eight tablet formulations (F1-F8) was obtained as listed in Table 2. The FS tablet formulation using CS alone in the amount of 0.1 mg per tablet (F0) was also prepared. However, this formulation was not successfully

prepared due to the lack of sufficient compressibility of the granules that obtained by using CS alone as binder.

In order to prepare the furosemide tablets, the required amounts of furosemide, Era-Tab® and Ac-Di-Sol® were weighed and screened through a 40 mesh sieve. For the FS tablets prepared by using PVP as binder, the mixture of FS, Era-Tab® and a half amount of the required Ac-Di-Sol® content was mixed thoroughly and the required amount of 10% w/w PVP aqueous solution was added as granulating agent. For the FS tablets prepared by using PVP and CS as co-binders, the required amount of 10% w/w PVP aqueous solution was added firstly to the mixtures of FS, Era-Tab® and Ac-Di-Sol® then the required amount of 1% w/v CS solution in 1% acetic acid was incorporated. The obtained wet mass was sieved through a 14 mesh sieve and dried in a hot air oven (Viuhang Engineering, Thailand) at 60°C for 2 hours. The dried granules were screened through an 18 mesh sieve and mixed with remaining half amount of the required Ac-Di-Sol® content and the predetermined amounts of Aerosil® and magnesium stearate. The obtained mixture was compressed into tablets of 3/8 inch in diameter by a single stroke tabletting machine (Viuhang Engineering, Thailand) with the hardness between 6 to 8 kg.

Table 1. Levels of PVP, CS and Ac-Di-Sol® contents employed in various furosemide tablet formulations according to a two-level full factorial experimental design for 3 variables.

Formulation	Level (content) of independent variable used		
	Polyvinylpyrrolidone K30 (X_1)	Chitosan (X_2)	Ac-Di-Sol® (X_3)
F1	-1 (5 mg)	-1 (0 mg)	-1 (1.6 mg)
F2	-1 (5 mg)	1 (0.1 mg)	-1 (1.6 mg)
F3	1 (10 mg)	-1 (0 mg)	-1 (1.6 mg)
F4	1 (10 mg)	1 (0.1 mg)	-1 (1.6 mg)
F5	-1 (5 mg)	-1 (0 mg)	1 (3.2 mg)
F6	-1 (5 mg)	1 (0.1 mg)	1 (3.2 mg)
F7	1 (10 mg)	-1 (0 mg)	1 (3.2 mg)
F8	1 (10 mg)	1 (0.1 mg)	1 (3.2 mg)

Table 2. Formulations of prepared furosemide tablets

Ingredient (per tablet)	**Formulation (mg)**								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F0**
FS	40	40	40	40	40	40	40	40	40
Era-Tab®	100	100	100	100	100	100	100	100	100
PVP K30	5	5	10	10	5	5	10	10	0
CS	-	0.1	-	0.1	-	0.1	-	0.1	0.1
Ac-Di-Sol®	1.6	1.6	1.6	1.6	3.2	3.2	3.2	3.2	3.2
Magnesium stearate	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8
Aerosil®	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8
Total	148.2	148.3	153.2	153.3	149.8	149.9	154.8	154.9	144.9

Table 3. Formulations of furosemide tablet prepared in the latter stage of experiment**.**

Ingredient (per tablet)	**Formulation (mg)**					
	F9	**F10**	**F11**	**F12**	**F13**	**F14**
FS	40	40	40	40	40	40
Era-Tab®	100	100	100	100	100	100
PVP K30	10	10	10	10	10	10
CS	0.1	0.1	0.1	0.1	0.1	0.1
Ac-Di-Sol®	1.6	3.2	1.6	-	-	-
Explotab®	-	-	-	6.0	6.0	6.0
Sodium lauryl sulfate	1.4	1.4	2.8	-	1.4	2.8
Magnesium stearate	0.8	0.8	0.8	0.8	0.8	0.8
Aerosil®	0.8	0.8	0.8	0.8	0.8	0.8
Total	154.7	156.3	155.5	157.7	159.1	160.5

Test for tablet properties

Each tablet formulation was tested for hardness, friability, weight variation, disintegration time and dissolution. Ten tablets from each formulation were tested for tablet hardness (Dr.Schleuniger Co., Type THP-4M hardness tester, Switzerland). Tablet friability of each formulation was tested on 20 tablets using a Roche friabilator for 4 minutes at the speed of 25 rpm. Tablet weight variation was tested on 20 tablets using an analytical balance (Sartorius, Model A200S analytical balance, Germany) according to BP 2008 on the test for uniformity of weight (The Department of Health, Great Britain, 2008). Disintegration test was performed on 6 tablets per formulation by USP type disintegrator (K.S.L. Engineering Co., Ltd., Thailand) using distilled water ($37\pm2^{o}C$) as medium according to USP 32 and NF 27 (The United States Pharmacopeia, 2009). Dissolution studies of the prepared FS tablets were also performed according to USP 32 and NF 27 (The United States Pharmacopeia, 2009) using a type II dissolution apparatus (Pharma Test Co., Model TW II, Hamburg, Germany). The paddle was adjusted to rotate at 50 rpm. Nine hundred milliliters of pH 5.8 phosphate buffer was employed as dissolution medium. Six tablets from each formulation were tested for dissolution at $37\pm0.5^{o}C$. Five milliliters of dissolution medium was withdrawn at predetermined time intervals up to 1.5 hours and assayed for drug content by UV spectrophotometer (Spectronic Instruments, Inc., Spectronic® Genesys™, Rochester, NY, U.S.A) at the wavelength of 271 nm.

Preparation of furosemide tablets consisting of sodium lauryl sulfate

From the first stage of the experiment, the two formulations of furosemide tablets showing the fastest dissolution profiles (F4 and F8) and good physical properties were considered for the next stage of experiment. Hence, additional seven furosemide tablet formulations as listed in Table 3 (F9-F14) were also prepared by wet granulation using PVP and CS as co-binders. A surfactant, sodium lauryl sulfate (SLS) in the amount of 1 % or 2 % was incorporated into the selected tablet formulations as represented by Formulation F9-F11 and F13-F14 (Table 3). Sodium starch glycolate (Explotab)® in the concentration of 4% was used instead of Ac-Di-Sol® in the furosemide tablets of F12-F14 (Table 3). The SLS was added to the mixture of drug and excipients before granulation.

Test for tablet properties

The furosemide tablets prepared in the latter stage of the experiment (F9-F14) were tested for their physical properties, disintegration times and dissolution profiles by the same procedures previously described.

Table 4. Properties of the furosemide tablets prepared according to factorial design**.**

Formulation	Hardness (S.D.) (kg)	Friability (%)	% CV (weight variation)	Disintegration time (S.D.) (minutes)	Q_{60} (S.D.) (%)	Q_{90} (S.D.) (%)
F1	6.6 (0.66)	0.83	1.38	5.5 (1.92)	67.61 (6.29)	78.61 (2.04)
F2	7.2 (0.60)	0.77	1.59	5.2 (1.77)	72.61 (7.58)	80.34 (6.75)
F3	7.7 (0.34)	0.53	1.25	10.2 (1.72)	67.44 (8.81)	76.95 (7.28)
F4	7.6 (0.32)	0.15	1.86	7.0 (2.76)	86.48 (3.83)	92.39 (1.69)
F5	6.5 (0.32)	0.30	1.58	7.8 (1.94)	86.80 (4.25)	93.59 (1.52)
F6	7.9 (0.12)	0.12	2.70	9.5 (1.92)	78.48 (4.78)	88.91 (3.26)
F7	6.6 (0.43)	0.47	1.08	11.0 (3.10)	71.94 (6.45)	88.26 (7.94)
F8	7.8 (0.55)	0.12	0.78	8.3 (3.39)	84.39 (5.25)	90.49 (3.52)

RESULTS AND DISCUSSION

For the furosemide tablets (F1-F8 and F0) prepared by using CS and/or PVP as binder(s), the use of CS alone in the amount of 0.1 mg per tablet as binder (F0) did not provide the granulation regarding the insufficient of binding property. As the result, the granules could not be compressed into tablets of required hardness. The higher amount of CS might be needed in order to provide the sufficient compressibility of the granule. However, the CS solution of the higher concentration was difficult to prepare due to its high viscosity.

Properties of the prepared furosemide tablets are shown in Table 4. The correlation of variation (% CV) values of the tablet weight variation and the percentages of tablet friability of the eight tablet formulations varied from 0.78 % to 2.70 % and 0.12 % to 0.83 %, respectively. The uniformity of weight of each tablet formulations was acceptable (The Department of Health, Great Britain, 2008). The tablet hardness was controlled within the range of 6.0 kg to 8.0 kg. Average disintegration times of the FS tablets were in the range of 5.2-11.0 minutes.

According to the full factorial experimental design (F1-F8), the relationship between tablet friability (F), disintegration time (DT) and percentage of drug dissolved at 60^{th} minute time interval (Q_{60}) as function of the levels (-1 to 1) of PVP K30 (X_1), chitosan (X_2) and Ac-Di-Sol® (X_3) were computed by multiple linear regression and shown as the following.

$F = -0.095X_1-0.123X_2-0.159X_3-0.062X_1X_2+0.137X_1X_3-0.012X_2X_3+0.410$ ($r^2 = 0.993990$)

$DT = 1.038X_1-0.563X_2+1.088X_3-0.888\ X_1X_2-0.538\ X_1X_3+0.313\ X_2X_3+8.063$ ($r^2 = 0.988101$)

$Q_{60} = 0.594X_1+3.521X_2+3.433X_3+4.351X_1X_2-2.832X_1X_3-2.488X_2X_3+76.970$ ($r^2 = 0.993942$)

In the FS tablet formulations where chitosan was absent ($X_2 = -1$), the equations of F, DT and Q_{60} were modified as the following.

$F = -0.033X_1-0.147X_3+0.136X_1X_3+0.533$

$DT = 1.925X_1+0.775X_3-0.538X_1X_3+8.625$

$Q_{60} = -3.757X_1+5.921X_3-2.832X_1X_3+73.449$

However, when chitosan was employed ($X_2 = 1$) in the tablet formulations, the F, DT and Q_{60} equations became to be as the following.

$F = -0.157\ X_1-0.172X_3+0.136\ X_1X_3+0.287$

$DT = 0.150\ X_1+1.400\ X_3-0.538\ X_1X_3+7.500$

$Q_{60} = 4.945X_1+0.945\ X_3-2.832X_1X_3+80.491$

The contour plots of F, DT and Q_{60} as functions of PVP K30 (X_1) and Ac-Di-Sol® (X_3) levels, when CS is present and absent, are demonstrated in Figure 1.

From Figure 1, it is obviously demonstrated that the use of PVP and CS as combined binders ($X_2 = 1$, Figure 1a) can result in the tablets of lower friability as compared to the use of PVP alone as a binder ($X_2 = -1$, figure 1b). However, the comparable of disintegration times are obtained by using PVP (Figure 1 d) and PVP-CS (Figure 1c) as binders. By comparing the percentages of tablet friability of F1 (0.83%), F3 (0.53%), F5 (0.30%) and F7 (0.47%) to those of F2 (0.77%), F4 (0.15%), F6 (0.12%) and F8 (0.12%); it was shown that the lower percentages of tablet friability were obtained when CS was utilized in the co-binding system. Disintegration times of the tablets prepared by using PVP and PVP-CS as binders were in the range of 5.5 to 11.0 minutes. Therefore, the usage of the co-binders improved the tablet friability and slightly affected the tablet disintegration.

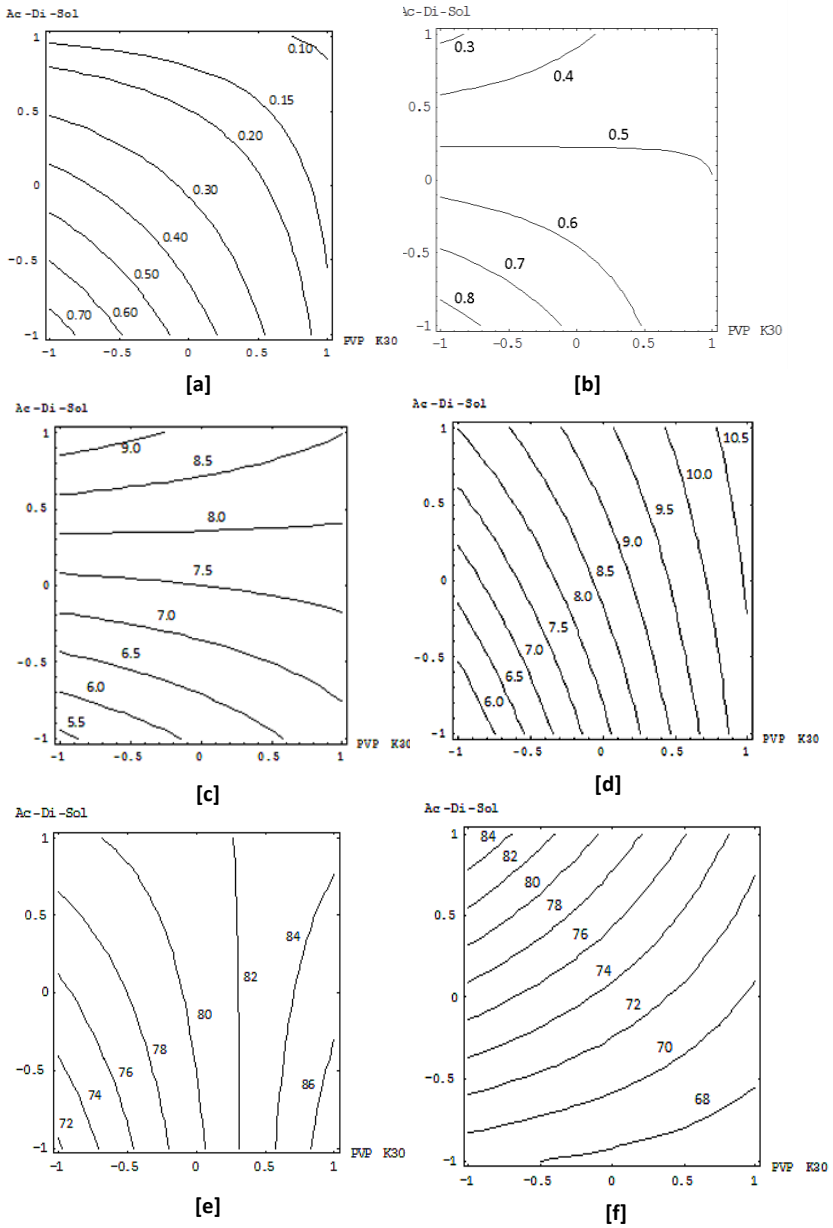

Figure 1. Contour plots of the percentage of friability (F), disintegration time (DT) and percentage of drug dissolved at 60th minute time interval (Q_{60}) equations as functions of PVP K30 and Ac-Di-Sol® levels: (a) F, with CS (X_2 = 1), (b) F, without CS (X_2 = -1), (c) DT, with CS (X_2 = 1), (d) DT, without CS (X_2 = -1), (e) Q_{60}, with CS (X_2 = 1), (f) Q_{60}, without CS (X_2 = -1)

The dissolution profiles of the FS tablets are illustrated in Figure 2. These profiles showed variation in drug dissolution rates. The formulations of interest were F4, F5 and F8 that demonstrated the fastest profiles and good physical tablet properties. F5 was prepared by using PVP as binder while F4 and F8 were prepared by using PVP-CS as co-binders. The values of tablet friability of F4, F5 and F8 were 0.15%, 0.30% and 0.12%, respectively. From Figure 2, the dissolution profile of F5 was the fastest one among the profiles obtained from the tablets prepared by using PVP alone as binding agent (F1, F3, F5 and F7). Hence, the dissolution profiles obtained from the tablets containing proper amounts of the co-binders in F4 and F8 were comparable to that of F5. While the tablets prepared by using co-binders

provided tablets of lower friability (0.15% and 0.12%) than that prepared by using the single binder (0.30%).

The disintegration times of the FS tablets prepared by using PVP alone as binder were 5.5, 10.2, 7.8 and 11.0 minutes for F1, F3, F5 and F7, respectively. Therefore, the disintegration of the tablets through the 10-mesh sieve of the basket rack assembly was not a factor in controlling tablet dissolution rates. For the FS tablets, the disintegrated granules that passed through the 10 mesh sieve containing poorly water-soluble particles of FS that exhibited slow drug dissolution. The presence of PVP and Ac-Di-Sol® within the granules was responsible for further disintegration of the granules, due to its swelling action, into smaller particles. The optimum contents of Ac-Di-Sol® and PVP presented in the granules were responsible for fast disintegration of the granules into particles. The contents of Ac-Di-Sol® and PVP utilized in F5 were the most optimum. The FS granule of F5 consisting of the low content of the binder, PVP, and the high content of the disintegrant, Ac-Di-Sol®, therefore, the granule tended to rapidly disintegrate into drug particles. As the result, the tablet dissolution of F5 was found to be the fastest.

The tolerance of furosemide tablet dissolution states that furosemide is dissolved not less than 80% at the 60th minute time interval (The United States Pharmacopeia, 2009). From the contour plot of Q_{60} equation in Figure 1f (chitosan was absent from the tablet formulations), the Q_{60} of more than 70% cannot be obtained when Ac-Di-Sol® content is used at low level (-1) in the tablet formulations. However, when chitosan is employed in the tablet formulations of low Ac-Di-Sol® content of -1 level (Figure 1e), the Q_{60} of more than 80% can be obtained by using PVP at the levels of 0.1 up to 1. Since the low content of the expensive tablet disintegrant, Ac-Di-Sol®, utilized in the FS tablet formulations provides the beneficial aspect on lowering the production cost. Therefore, the inclusion of low content of CS (0.1 mg per tablet) in the co-binder system of PVP-CS provides the FS tablet of low friability and high percentage of drug dissolution with lower production cost.

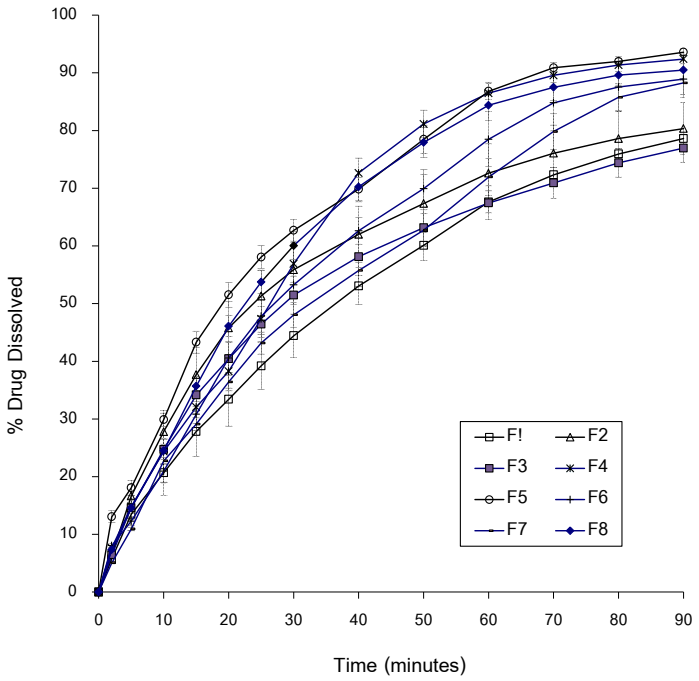

Figure 2. Dissolution profiles of furosemide tablets prepared according to a full factorial design.

Table 5. Properties of the furosemide tablets prepared in the latter stage of the experiment.

Formulation	Hardness (S.D.) (kg)	Friability (%)	% CV (weight variation)	Disintegration time (S.D.) (minutes)	Q_{60} (S.D.) (%)	Q_{90} (S.D.) (%)
F9	7.7 (0.51)	0.26	1.53	10.66 (2.94)	83.45 (5.15)	90.71 (3.11)
F10	7.3 (0.67)	0.30	0.58	9.33 (1.22)	67.03 (7.97)	79.97 (4.40)
F11	7.3 (0.50)	0.23	1.71	9.5 (2.95)	68.23 (7.14)	86.38 (4.61)
F12	6.3 (0.33)	0.27	0.86	8.67 (1.75)	83.44 (3.78)	90.72 (1.54)
F13	7.8 (0.41)	0.23	1.54	10.53 (2.63)	87.37 (3.29)	96.72 (3.35)
F14	6.5 (0.62)	0.35	1.71	9.71 (3.22)	76.37 (6.16)	90.96 (5.30)

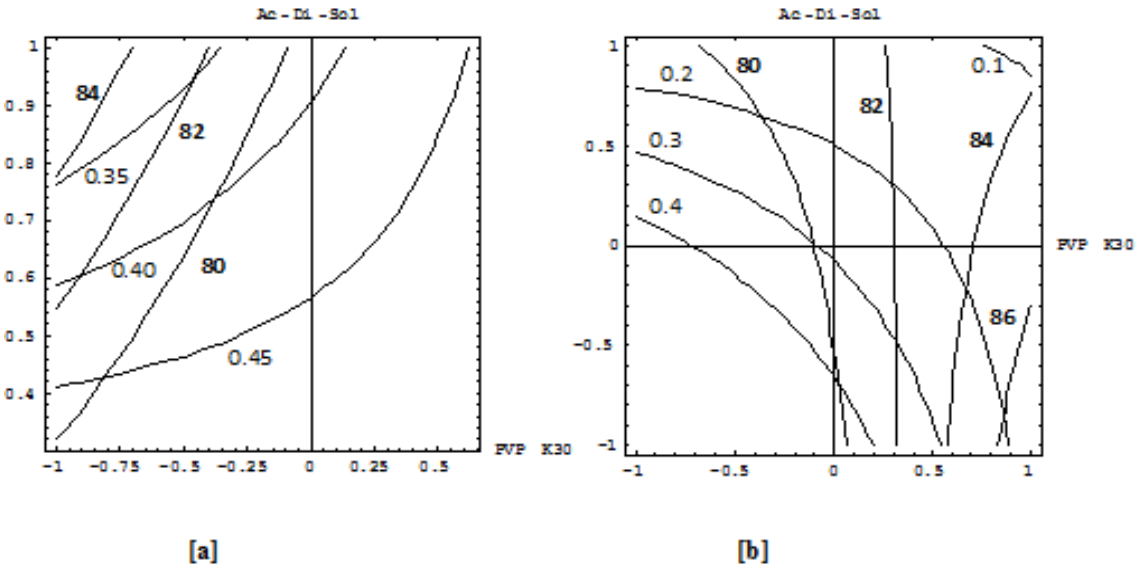

Figure 3. The superimposed contour plots of tablet friability (F) and Q_{60} equations as functions of PVP K30 and Ac-Di-Sol® levels when CS was [a] absent (X_2= -1) and [b] present (X_2 = 1) in the tablet formulations. ($Q_{60} \geq 80\%$)

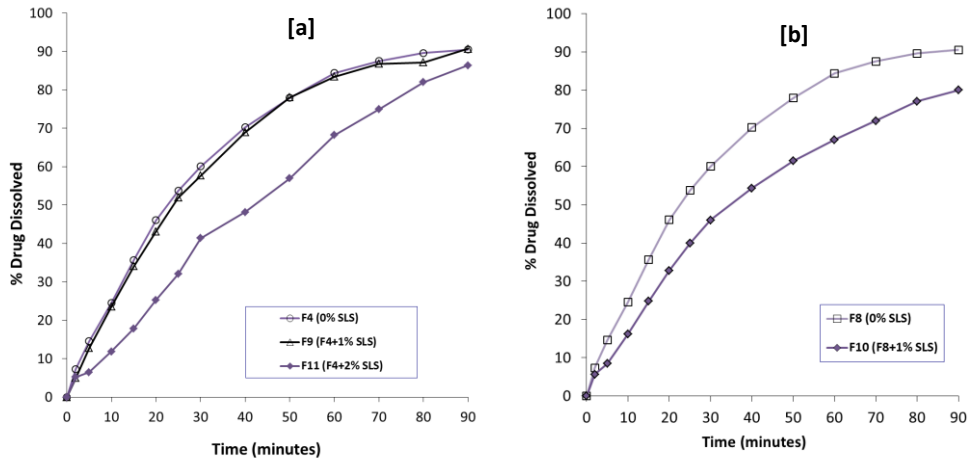

Figure 4. Dissolution profiles of furosemide tablets: [a] F4 and F4 with SLS (F9, F11), [b] F8 and F8 with SLS (F10)

The superimposed contour plots of tablet friability and Q_{60} equations as functions of PVP K30 (X_1) and Ac-Di-Sol® (X_3) levels, when chitosan is absent (X_2 = -1) and present (X_2 = 1) in the furosemide tablet formulations, are displayed in Figure 3. When chitosan was absent in the formulations (Figure 3a), the furosemide tablets having Q_{60} of at least 80% and friability downing to only about 0.3 % can be prepared. However, when chitosan is employed in the formulation (Figure 3b), the furosemide tablets having Q_{60} of at least 80% and low friability downing to 0.1 % can be prepared. Therefore, the incorporation of chitosan to the binding system of PVP K30 reduced tablet friability without causing deterioration in Q_{60} of the prepared furosemide tablets.

Three furosemide tablet formulations (F4, F5 and F8) met the tablet dissolution requirement of $Q_{60} \geq 80\%$. Due to their lower tablet friability values, F4 and F8 were chosen for the next stage of study in order to improve their dissolution. A surfactant, sodium lauryl sulfate (SLS), in the amount of 1% (1.4 mg per tablet) was added to the two formulations, F4 and F8, resulting in F9 and F10, respectively. Physical properties and disintegration times of these formulations are shown in Table 5, while their dissolution profiles are demonstrated in Figure 4. The physical properties of these three tablet formulations were acceptable (Table 5). The values of the tablet friability were 0.26% and 0.30% for F9 and F10, respectively. The inclusion of 1% SLS to F8 (F10) did not improve the drug dissolution rate. In contrast, slower dissolution profiles were obtained in F10 (1% SLS) as compared to F8 (0% SLS), as shown in Figure 4b. The dissolution profile of F9 (1% SLS) was comparable to F4 (0% SLS). The observed results indicated that the inclusion of 1% SLS to F4 and F8 did not provide improvement in tablet dissolution. Since the addition of 1% SLS to F4 showed no effect on tablet dissolution rate, thereby the 2% of SLS was added to F4 resulting in F11. As shown by Figure 4a, the tablet prepared by F11 (2% SLS) provided slower dissolution profile than that provided by F4. Increasing amount of SLS resulted in higher viscosity of the environment around the tablet and disintegrated agglomerates and thereby its dissolution was further retarded due to the slower diffusion of the dissolved drug through the viscous environment (Florence, 1981).

Wet granulation is also considered as a process of tablet production that can improve wettability of a poorly water-soluble drug (Bandelin, 1989). Therefore, the effect of SLS on improving the wettability of furosemide might be quite low since the drug wettability has been already improved by wet granulation process of tablet production. In such manner, the viscosity inducing effect of SLS played more important role than the wettability enhancing effect. As the result, the addition of SLS in the FS tablets consisting of a water insoluble diluent, spray-dried rice starch (Era-Tab®), and a disintegrant, Ac-Di-Sol®, did not provide any beneficial effect on tablet dissolution. Upon disintegration, the tablets disintegrated into small agglomerates. Higher viscosity derived from dissolved SLS might cause slower release of drug from the viscous agglomerates consisting of the poorly soluble drug and the insoluble diluent, Era-Tab®.

At this point of study, it seemed that the best formulation was F4 that consisted of 1.6 mg of Ac-Di-Sol® as disintegrant and using co-binders, PVP and CS in the amounts of 10 mg and 0.1 mg, respectively. Since, its dissolution profile and friability were comparable to those of F8 but less amount of Ac-Di-Sol® was used. In an effort to improve dissolution of the FS tablet prepared by using the co-binders, Ac-Di-Sol® in F4 was replaced by another tablet disintegrant, Explotab®. In general, the optimum content of Explotab® utilizing in the tablet formulation was suggested as about 4% (Rowe, Sheskey, Quinn 2009). Thus, the amount of 6.0 mg per tablet of Explotab® was employed instead of 1.6 mg of Ac-Di-Sol®.

Figure 5 demonstrated the dissolution profiles of the FS tablet prepared by changing the disintegrant employed in F4 from 1.6 mg of Ac-Di-Sol® to 6.0 mg of Explotab® (F12). The effect of SLS on the modified tablet formulations was also investigated in F13 and F14.

Table 5 lists the physical properties of the FS tablets consisting of Explotab® as disintegrant. Their percentages of tablet friability ranged from 0.23% to 0.35% that were low enough, while the uniformity of weight of each tablet formulations was acceptable (The Department of Health, Great Britain, 2008). Dissolution profile of the FS tablet containing Explotab® met the dissolution requirement of FS tablet dissolution (The United States Pharmacopeia, 2009) and was comparable to that of the FS tablet containing Ac-Di-Sol®. The percentages of drug dissolved at the 60th minute time interval of F4 and F12 were 86.5% and 83.4 %, respectively.

The inclusion of 1% SLS (1.4 mg) in the tablet using Explotab® as disintegrant (F13) showed improvement in tablet dissolution. However, when 2% SLS was used (F14) the retardation of drug dissolution was observed. Viscosity increment at high concentration of surfactant was recognized as a reason for decreased dissolution rate of a drug from solid dosage form (Florence, 1981). Viscous environment resulting from dissolution of excessive SLS content thereby was responsible for delaying in the FS tablet dissolution of F14. Sodium starch glycolate (Explotab®) is a starch derivative that swells up to 300 times of its volume upon contacting to water (Allen, Popovich and Ansel, 2011). Too high in Explotab® content resulted in decreasing tablet dissolution due to its viscous nature after swelling in the dissolution medium (Rowe, Sheskey and Quinn, 2009). Therefore, the suitable contents of Explotab® and SLS employed in F13 were responsible for the improved tablet dissolution. In the case of 1% SLS (F13), the dissolution enhancing effect of SLS overcame its viscosity inducing effect. In contrast, the latter effect became dominant in the case where 2% SLS (F14) was used.

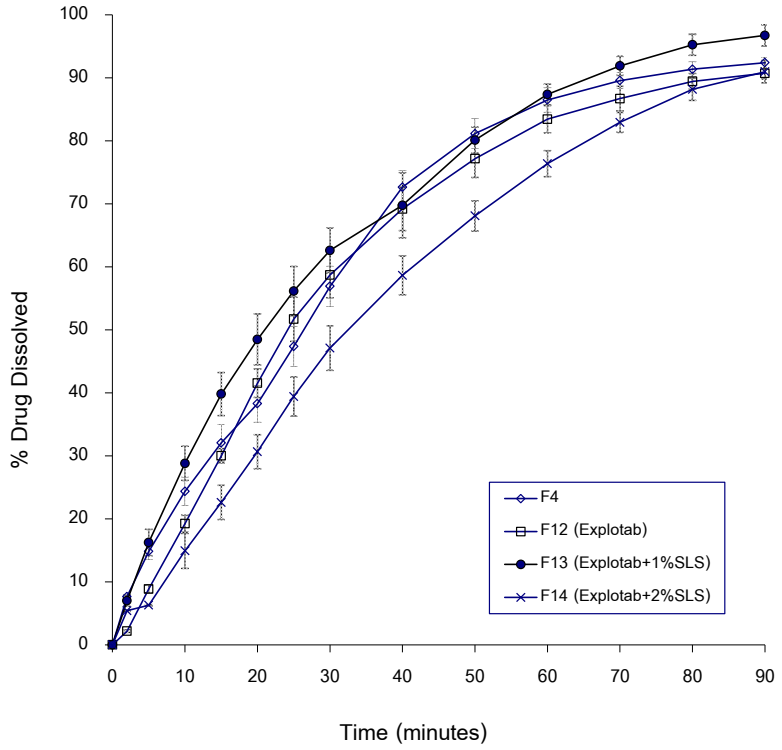

Figure 5. Dissolution profiles of FS tablets prepared by using PVP-CS as co-binders and Explotab® as disintegrant as compared to the FS tablet prepared by using PVP-CS as co-binders and Ac-Di-Sol® as disintegrant.

At the 90th minute time interval, the percentages of drug dissolution (Q_{90}) of F4 and F13 were 92.4% and 96.7%, respectively. The results indicated that more completeness in drug dissolution was achieved from F13 as compared to F4. Therefore, in this study the FS tablet that prepared by using 10 mg PVP and 0.1 mg CS as co-binders and consisted of 6.0 mg Explotab® and 1.4 mg SLS (F13) was found to be the better formulation.

CONCLUSION

The application of chitosan and polyvinylpyrrolidone K30 as co-binders in preparing FS tablets resulted in the FS tablets of improved friability comparing to the tablets prepared by using polyvinylpyrrolidone K30 alone as binder. By choosing the optimum amount of PVP in the co-binder system, the prepared FS tablet also provided the required percentage of drug dissolution even when low content of Ac-Di-Sol® was used. When Ac-Di-Sol® was replaced by Explotab®, in the FS tablet prepared by using proper amounts of the co-binders, the tablet of good physical properties and required fast dissolution was developed. Inclusion of sodium lauryl sufate into the FS tablet containing Explotab® resulted in improved tablet dissolution, if an optimum amount of SLS was employed.

REFERENCES

Allen LV, Popovich NG, Ansel, HC. 2011. *Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems.* 9th ed. Philadelphia: Lippincott Williams & Wilkins.

Bandelin FJ. 1989. Compressed tablets by wet granulation. In: Lieberman HA, Lachman L, Schwartz JB, editors. *Pharmaceutical Dosage Forms. Tablets. Volume 1.* 2nd ed. New York: Marcel Dekker; 149-150.

Brine CJ. 1989. Controlled release pharmaceutical applications of chitosan. In: Gudmund Skjak-Braek G, Anthonsen T, Sandford P, editors. *Chitin and chitosan: sources, chemistry, biochemistry, physical properties, and applications.* London: Elsevier Science; pp. 679-691.

Florence AT. 1981. Drug solubilization in surfactant systems. In: Yalkowsky SH. editor. *Techniques of Solubilization of Drugs.* New York: Marcel Dekker; pp. 60-63.

Kepsutlu AR, Savaser A, Ozkan Y, Dikmen N, Isimer A. 1999. Evaluation of chitosan as an excipient in tablet formulations. *Acta Poloniae Pharmaceutica-Drug Research*. 56(3): 227-235.

Rinaudo M. 2006. Chitin and chitosan: Properties and applications. *Prog Poly. Sci.* 31: 603-632

Rowe RC, Sheskey, PJ, Quinn., ME. 2009. *Handbook of Pharmaceutical Excipients.* 6th Edition. Chicago: Pharmaceutical Press.

Sandford P. 1989. Chitosan, commercial uses and potential applications. In: Gudmund Skjak-Braek G, Anthonsen T, Sandford P, editors. *Chitin and chitosan: sources, chemistry, biochemistry, physical properties, and applications.* London: Elsevier Science; pp. 51.

The Department of Health, Great Britain. The Department of Health, Social, Services and Public Safety, Northern Ireland. 2008. *British Pharmacopoeia. Volume IV.* London: The Stationary Office. Appendix XII C A313.

The United States Pharmacopeia. The National Formulary. 2009. *USP 32 and NF 27. Volume 1.1. Volume 2.2.* Rockville: The United States Pharmacopeial Convention, Rockville.