Impact of Chitosan as a disintegrant on the bioavailability of furosemide tablets: *In vitro* evaluation and *in vivo* simulation of novel formulations

Bazigha Kadhim Abdul Rasool[1*], Sahar Abdelsattar Fahmy[2] and Omar Waleed Abdul Galeel[3]
[1]Department of Pharmaceutics and Pharmacy Practice, Dubai Pharmacy College, Dubai, UAE
[2]Department of Pharmaceutics and Industrial Pharmacy, College of Pharmacy, Helwan University, Cairo, Egypt
[3]National Center of Drug Control and Research, Baghdad, Iraq

Abstract: To[D1] determine the effect of chitosan, starch powder, polyvinylpyrrolidone (PVP), Avicel PH 101 powder, Avicel PH 102 granules as a function of different concentrations on the solubility, disintegration and hence dissolution of furosemide from immediate release tablet dosage forms. The tablets were prepared by the wet granulation method and evaluated for hardness, friability, disintegration and *in vitro* dissolution. Chitosan 7% w/w showed the fastest disintegration of furosemide tablets among the other disintegrants studied. This was attributed to its highest swelling properties and velocity constant of water uptake. The step of adding chitosan during tablet preparation had a great effect on the physical properties and dissolution profiles of the prepared tablets with external addition of chitosan showed best results compared to best results comparing to internal-external or internal addition. The most appropriate force of compression was 4ton /cm^2. The selected formula F15 containing 7% w/w chitosan was successful and showed a high significant (p<0.001) enhancement in disintegration and dissolution behaviors of furosemide tablets in comparison with the commercially available Furosemide® tablets. These results were supported by the simulated data where F15 formula showed the highest plasma concentration C-max 1.89mcg/mL after 0.5 hr compared to C-max 1.05mcg/mL after 1hr for the reference. The present study demonstrated that chitosan is a very good candidate to be used as a tablet disintegrant and was able to enhance the dissolution of poorly absorbable drugs.

Keywords: Furosemide, Oral tablets, disintegrants, chitosan, dissolution rate, *in vivo* simulation.

INTRODUCTION

Enhancing the bioavailability of sparingly soluble drugs or poorly absorbable drugs has always been a difficult task when formulated in a tablet dosage form (Lachman *et al*., 1987). Bioavailability problems can arise if a fine, well dispersed suspension of drug particles is not generated in the gastrointestinal fluids following tablet administration. Increasing the effective surface area of a poorly soluble drug is an important factor that influences its dissolution and subsequently its onset of therapeutic activity. For this reason, disintegration of a tablet into smaller particles is thus very important to ensure the generation of a large effective surface area of the drug (Aulton, 2002). Disintegrant is an important excipient used in tablet formulation and is usually added to induce tablet breakup when it comes into contact with the aqueous fluids. Over the years, there are many materials have been proposed to be used as tablet disintegrants and have become commercially available. Starches are the most widely used tablet disintegrants (Guyot, 1992). In addition to starches, a large variety of materials have been used and reported to be effective as tablet disintegrants such as Veegum HV, agar, bentonite, cellulose product, natural sponge, cation-exchange resin, guar gum and more modern disintegrants such as cyclodextrin polymer, soya polysaccharides, cross-linked casein, and chitosan (Aulton, 2002).

Chitosan, β (1, 4)2-amino-2-d-glucose, is a cationic biopolymer produced by alkaline N-deacetylation of chitin, which is the main component of the shells of crab, shrimp, and krill. chitosan is currently available in different grades which have difference in their physicochemical properties. This makes it very valuable in developing chitosan based dosage forms which may differ according to the grade of chitosan used (Singh *et al*., 2011).

Its use in various applications has received considerable attention and has found many biomedical applications owing to its biocompatibility, low toxicity and biodegradability (Struszczyk *et al*., 1991). It had been used in the development of conventional pharmaceutical forms as a potential formulation excipient, some of which include tablet matrices (Amrutkar and Gattani, 2009), binder (Kokil *et al*., 2005), and disintegrant (Ritthidej *et al*., 1994).

Furosemide is a loop diuretic that is used orally in the treatment of edematous states associated with cardiac, renal, and hepatic failure and the treatment of

**Corresponding author:* e-mail: bazigha_rasool@hotmail.com

hypertension. Furosemide is practically insoluble in water and its aqueous solubility at room temperature has been reported to be 0.01825 mg/mL. Furosemide is fairly rapidly absorbed from the gastrointestinal (GI) tract. Its bioavailability was reported to be about 50% and the absorption is variable and erratic (Ponto and Schoenwald, 1990). Furosemide was chosen as a model drug in the present study as it has low solubility and low bioavailability, hence classified as class IV drug as per biopharmaceutical system classifications and further research is needed to enhance its dissolution and hence its bioavailability.[D2] Several researchers reported that the use of different excipient and changing processing factors affect the dissolution profile of furosemide. Very little works have been published on the different factors affecting furosemide tablets dissolution (Rubenstein and Rughani, 1989).

The aim of the present study was to investigate the effect of chitosan as a disintegrant along with other types of disintegrants including starch, PVP and microcrystalline cellulose (Avicel®) on the dissolution of furosemide from the prepared tablet formulations compared to commercially available furosemide tablets. Convolution of *in vitro* dissolution profiles for certain developed furosemide and the commercially available furosemide formulations were conducted to predict plasma concentration versus time profiles, assuming these formulations are administered *in vivo.*

MATERIALS AND METHODS

Materials

Medium molecula weight chitosan with a 75-85% degree of acetylation[D3], furosemide, magnesium stearate, polyvinylpyrrolidone (PVP), potassium dihydrogen orthophosphate and disodium hydrogen orthophosphate were all purchased from Sigma–Aldrich (Poole, UK). Maize starch and lactose were bought from Evans Medical, Ltd, (Liverpool, England). Microcrystalline cellulose, avicel, PH 101 and PH 102 were from FMC Corporation, (Pennsylvania, USA) Hydrochloric acid and sodium hydroxide were obtained from Fluka Chemi AG, (Switzerland). Furosemide® tablets BP 40 mg was purchased from Holden Medical, (Netherlands).

Disintegrants Swelling Capacity

This was determined according to the method described by Okhamafe (Okhamafe *et al*., 1991), [D4]where one gram of each disintegrant was placed in a dry cylinder and fixed in calibrated water bath (Memmert, Germany). A certain volume of either deionized water or 0.1N HCl, was added gradually with continuous stirring until the volume inside the cylinder reached up to 100 ml. The samples were incubated at 37°C for 3 hours. The swelling capacity of each disintegrant was computed according to the following equation:

$$S = \frac{(V2 - V1)}{V1} \times 100$$

Where S is the % swelling capacity, V2 is the volume of the hydrated or swollen material and V1 is the tapped volume of the material prior to hydration.

Preparation of furosemide tablets

Furosemide tablets were prepared by the wet granulation method (Riffat *et al*., 2005). The tablets were prepared by mixing 40 mg of furosemide with sufficient quantity of lactose as a diluent. A sufficient volume of starch paste 10%, used as a binder, was gradually added to the mixture. Then the mixture was subjected to coarse sieving to obtain large granules with an average particle size of 3.2 mm. The granules were dried in an oven at 40°C for 3 hour. The granules were sieved to obtain finer particles of a size equal to 1.2 mm. A certain weight of the selected disintegrant was added to the prepared fine granules, mixed with magnesium stearate, as a lubricant and pressed into a tablet form by direct compression using a calibrated[D5] double punch machine with punch and dye of 6 mm in diameter (Korsch, type EKO, Erweka, Germany) and a compression forces of 4 ton/cm^2.

The effect of adding different disintegrants with various concentrations on the physical properties of the prepared tablet formulations were examined. Seventeen tablet formulae (F1-F17) were prepared using different types and concentrations of disintegrants including starch 7%, 10% and 15% w/w, PVP 7%, 10% and 15% w/w, Avicel PH101 7%, 10% and 15% w/w, Avicel PH 102 7%, 10% and 15% w/w and chitosan 3%, 5%,7%,10%,15%w/w. Tablet compositions are shown in table 1.

Moreover, the effect of the addition step of chitosan during tablet preparation on the physical properties of the prepared tablets were investigated. Chitosan was added during tablet preparation in three different ways; a- externally, after granulation b-internally, prior to granulation and c- externally/ internally; half of the calculated amount of chitosan were added before granulation and the other half was added after the granulation process. The effect of the force of compression on the tablet physical properties and drug dissolution profiles were also studied using (F15) tablet formula compressed at 4, 5 and 7 ton/cm^2 compared to that of the reference.

Evaluation of furosemide tablets

The prepared furosemide tablets were subjected to various physical tests including tablet hardness using calibrated Monsanto hardness tester (Monsanto chemical Co., Japan), Friability (Erweka friabilator, Germany), disintegration time (USP XXII apparatus, Hanson Research, USA) using deionized water at 37±1ºC as an immersion medium and tablet dissolution.

The dissolution profiles for all the prepared formulae as well as the reference were tested using calibrated USP dissolution apparatus; paddle type (Copley, UK) maintained at 37±0.5°C and a rotation speed of 50 rpm. The dissolution media used was 900 ml 0.1N HCl. Samples (5 ml) were withdrawn through syringe filter at predetermined time intervals for one hour. The withdrawn volume was replaced by the same volume of phosphate buffer pH 6.8. Drug content was determined by calibrated CECIL, CE-7200 spectrophotometer, France) at 274 nm (Moffate, 1986).

Sorption ability

The sorption ability of the studied disintegrants was calculated according to the following equation (Ruiz and Ghaly, 1997):

$M2(t) = Kt$

Where, M is the absorbed mass of water at a certain time t, K is the velocity constant of the water uptake.

The sorption ability of the studied disintegrants was done for 180 minutes.

Convolution analysis

Convolution of *in vitro* dissolution profiles for selected prepared formulae and the commercially available furosemide® formulation were conducted to predict plasma concentration versus time profiles, assuming these formulations are administered *in vivo*. The dissolution-time profile from the prepared tablet formulations with F1 (starch 7%), F4 (PVP 7%), F7 (Avicel PH101 7%), F10 (Avicel PH102 7%), F15 (chitosan 7%) and the reference furosemide® tablet were convolved to produce simulated plasma concentration-time profiles using a spread sheet (Gabrielsson and Weiner, 2007). The prepared formulations were selected based on the highest dissolution profiles obtained from each disintegrant studied. Simulated plasma concentration time profiles were compared with published data of plasma

Table 1: Composition of the prepared furosemide tablet formulations

Materials	Formulas Code																
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15	F16	F17
Furosemide (mg/tab)	40	40	40	40	40	40	40	40	40	40	40	40	40	40	40	40	40
Lactose (mg/tab)	124	118	108	124	118	108	124	118	108	124	118	108	132	128	124	118	108
Starch paste (10% w/w)	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20
Magnesium stearate (1% w/w)	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Starch (% w/w)	7	10	15														
PVP (%w/w)				7	10	15											
Avicel PH 101(%w/w)							7	10	15								
Avicel PH 102 (%w/w)										7	10	15					
Chitosan (%w/w)													3	5	7	10	15
Total weight (g)	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2

Table 2: Hardness, friability and disintegration time of furosemide tablet formulations (results are mean ± SD)

Formula Code	Disintegrants (% w/w)		Hardness (Kg) (N=20)	Friability (%) (N=20)	Disintegration (min) (N[0]=10)
F1	Starch	7%	6.0 ± 0.10	0.38 ± 0.09	0.48 ± 0.45
F2	Starch	10%	3.0 ± 0.10	2.30 ± 0.1	0.39 ± 0.12
F3	Starch	15%	2.5 ± 0.10	3.00 ± 0.14	0.29 ± 0.16
F4	PVP	7%	5.5 ± 0.31	0.34 ± 0.13	5.0 ± 0.81
F5	PVP	10%	3.0 ± 0.11	2.00 ± 0.23	4.24 ± 0.66
F6	PVP	15%	2.5 ± 0.27	2.50 ± 0.14	3.39 ± 0.62
F7	Avicel101	7%	5.0 ± 0.10	0.39 ± 0.12	0.47 ± 0.12
F8	Avicel101	10%	2.5 ± 0.20	2.50 ± 0.71	0.43 ± 0.12
F9	Avicel101	15%	2.5 ± 0.19	3.09 ± 0.67	0.26 ± 0.10
F10	Avicel102	7%	5.5 ± 0.12	0.32 ± 0.81	0.46 ± 0.30
F11	Avicel102	10%	3.0 ± 0.13	1.51 ± 0.34	0.36 ± 0.50
F12	Avicel102	15%	2.5 ± 0.20	2.73 ± 0.71	0.28 ± 0.11
F13	Chitosan	3%	5.0 ± 0.11	0.46 ± 0.43	0.49 ± 0.09
F14	Chitosan	5%	5.5 ± 0.10	0.43 ± 0.45	0.42 ± 0.19
F15	Chitosan	7%	7.0 ± 0.15	0.24 ± 0.07	0.39 ± 0.15
F16	Chitosan	10%	7.1 ± 0.10	2.10 ± 0.32	0.30 ± 0.32
F17	Chitosan	15%	8.3 ± 0.09	3.90 ± 0.48	0.22 ± 0.11

concentration time profiles for commercially available furosemide® tablets. The Pharmacokinetic parameters (PK) of furosemide were used as reported in literature to simulate the concentration of furosemide. The following reported PK were used in the simulation; furosemide bioavailability is reported to be about 60-70%, clearance is within the range of 0.09-0.18 L/h/kg and elimination half-life is in the range of 30-120 min (Granero *et al*., 2010).

STATISTICAL ANALYSIS

Results are expressed as mean ±S.D. for triplicate samples. The statistically significant difference among the groups were determined by one-way analysis of variance (ANOVA) using SPSS© statistical software (Version 16; SPSS, Inc., Chicago, IL, USA). Statistical significance was considered at a level of $p<0.05$.

RESULTS

Swelling capacity of disintegrants

Fig. 1 represents the swelling capacity of the various disintegrants studied in both deionized water and 0.1N HCl. The swelling capacity of disintegrant powders was in the following order: chitosan > Avicel PH102 > Avicel PH101> starch> PVP (dissolved) in both studied media. The swelling capacity of chitosan in diluted hydrochloric acid was significantly different ($p<0.05$) than that in water. It was observed that chitosan dissolved in diluted hydrochloric acid solution and formed viscous translucent gelatinous solution.

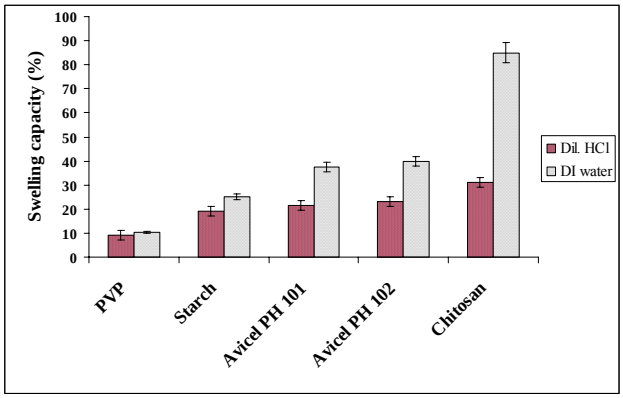

Fig. 1: Swelling capacity of disintegrants powders in deionized water (DI water) and diluted hydrochloric acid (Dil. HCl[D6]) (N[D7]=3).

Furosemide tablet evaluation

The tablet formulations were prepared by the wet granulation method using different disintegrants with different concentrations. The tablets were tested for its hardness, friability and disintegration. The results are shown in table 2. The tablets gave satisfactory physical properties regarding hardness and friability which was in consistence to that of standard USP specifications. Results showed that, increasing disintegrants concentration (starch, Avicel PH 101, Avicel PH 102, PVP and chitosan) concentration from 7% to 15% w/w resulted in a significant ($p<0.05$) decline in tablet hardness and disintegration time and increase in tablet friability. However, increasing chitosan concentration from 3% to 15% w/w resulted in significant ($p<0.05$) increase in tablet hardness.

In vitro release studies

In vitro dissolution data of the prepared furosemide tablets using different types and concentrations of disintegrants along with the reference are presented in figs. 2-4. It was found that, for all disintegrants used (except for chitosan), the increase in the disintegrants' concentration from 7% to 15% w/w resulted in a significant increase in the amount of furosemide dissolved with time. It was noted that for all the prepared tablet formulations, except for (F17), all the prepared tablet formulations gave faster dissolution profiles than the reference with almost 80% of furosemide was dissolved in 60 minutes compared to 60% released from the reference product.

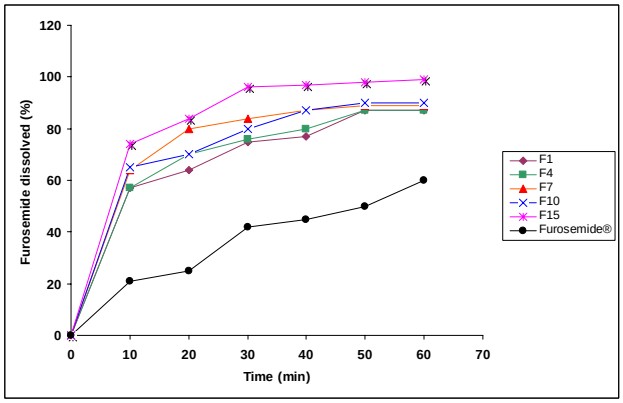

Fig. 2: Percentage of furosemide dissolved in 0.1N HCl from tablets with disintegrants concentration of 7% w/w (N=3).

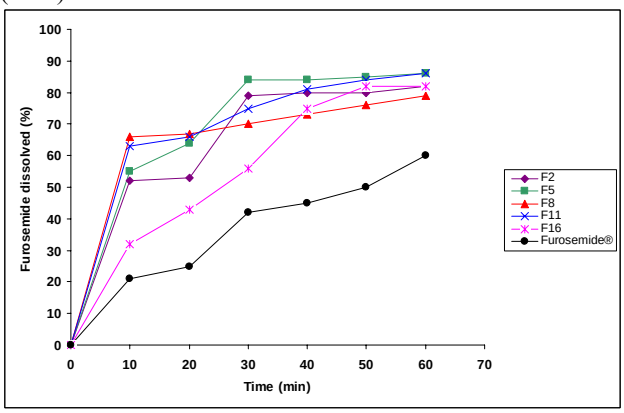

Fig. 3: Percentage of furosemide dissolved in 0.1N HCl from tablets with disintegrants concentration of 10% w/w (N=3).

Velocity of water intake

The velocity constants of water uptake for the different types of disintegrants used according to their absorbed mass (M) was calculated. The calculated velocity constants for the disintegrants were in the following order; chitosan > Avicel PH 102 > Avicel PH 101> starch > PVP, (table 3). The highest amount of furosemide dissolved was obtained from (F15) formula with chitosan was used as a disintegrant in a concentration of 7%. On the other hand, increasing chitosan concentration to 15% w/w resulted in a decline in the amount of furosemide dissolved and increase in the tablet hardness, as shown in table 2.

Table 3: Velocity Constants of Water Uptake ± SD of Furosemide Tablets with Different Disintegrants (N=10[D8])

Disintegrants (7% w/w)	K value (mg^2/min)
Starch	0.88 ± 0.03
PVP	Dissolved
Avicel PH 101	2.0 ± 0.09
Avicel PH 102	5.5 ± 0.07
Chitosan	14 ± 0.12*

*Indicates significant effect ($p<0.05$)

Effect of compression force on furosemide tablet

The effect of force of compression and the addition step of chitosan during tablet preparation on tablet hardness, friability, disintegration time and drug release profile for the selected formula F15 are studied. Data are presented in table 4 and fig. 5. It was observed that increasing the compression force resulted in an increase in tablet hardness and disintegration time while there was a significant decrease ($p<0.05$) in tablet friability and consequently decrease the amount of drug dissolved with time. The best compression force was 4 (ton/cm^2) which resulted in almost 100% drug release within one hour while increasing the compression force to 7(ton/cm^2), resulted in a decline in the percent of drug dissolved to be 82%.

Effect of Chitosan Addition Step on Furosemide Tablet

Studying the effect of adding chitosan on tablet physical properties showed that tablet disintegration time and dissolution profile were faster for F15 formula when adding chitosan externally but this difference was not significant ($p>0.05$) when added internally or internally-externally (table 4, fig. 6).

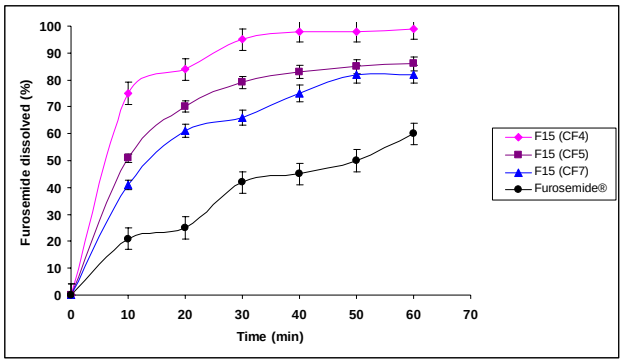

Fig. 5: Effect of the compression force on the dissolution profile of furosemide from (F15) formula in 0.1N HCl (C is the compression force in ton/cm^2) (N=3).

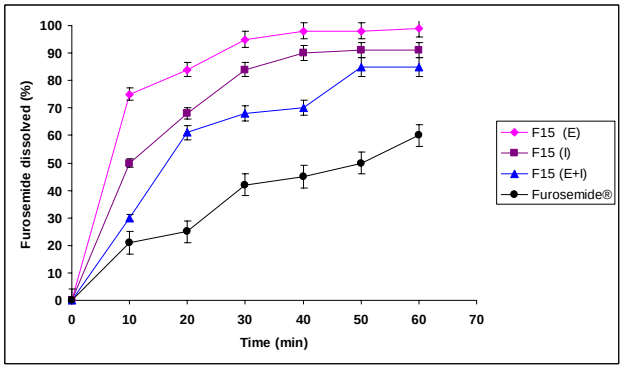

Fig. 6: Effect of the addition step of chitosan during tablet preparation on the dissolution profile of furosemide from the prepared tablet formulations compared to the reference (N=3).

Convolution analysis

Simulation of the expected furosemide plasma concentration versus time profiles was calculated from the dissolution data for the commercially available furosemide® tablet and selected new prepared tablet

Table 4: Tablet hardness, friability and disintegration of f15 compressed at different forces and different steps of chitosan addition

Force of compression (ton/cm^2)	Step of addition	Hardness (Kg) (N=20)	Friability (%) (N=20[0])	Disintegration (min) (N=10)
4	E [a]	7.0 ± 0.15	0.24 ± 0.07	0.39 ± 0.15
5	E	7.5 ± 0.34	0.19 ± 0.09	0.50 ± 0.11
7	E	7.5 ± 0.13	0.19± 0.10	0.54± 0.22
4	I [b]	6.0 ± 0.09	0.27 ± 0.12	0.48 ± 0.09
4	E+I [c]	6.5 ± 0.14	0.23 ± 0.05	0.45 ±0.08

[a]E is the external addition of disintegrant, [b]I is the internal addition of disintegrant, [c]E+I is the external-internal addition of disintegrant

formulations reported herein.

Simulated data showed that F15 (chitosan 7%) produced the highest conc. (C-max) in blood stream with a conc. of 1.89 mcg/ml and T-max reached after 30 min. compared to that of the reference with C-max of 1.05 mcg/ml reached after 1 hr. The simulated drug plasma profiles for the other selected formulations gave good results and were also much higher C-max than that of the reference as follow: for F1 (Starch 7%), C-max was 1.5 mcg/ml reached after 50 min; F4 (PVP 7%), C-max was 1.49 mcg/ml reached after 30 min; F7 (Avicel PH101) C-max was 1.70 mcg/ml reached after 20 min and F10 (Avicel PH 102), with C-max was 1.59 mcg/ml reached after 40 min following oral dose of a 40mg furosemide tablet. Data is shown in fig. 7.

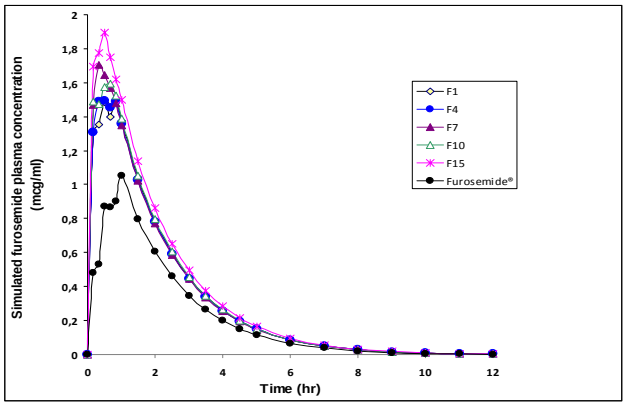

Fig. 7: Simulated furosemide plasma conc. time profiles after the administration of 40 mg oral dose of selected tablet formulations F1, F4, F7, F10, F15 and the reference (N=3).

DISCUSSION

Recent research studies were done to enhance the solubility of furosemide using different techniques such as the use of superdisintegrants as solubilizing agent (Bhise *et al*., 2009), formulation of solid dispersions of Furosemide using sodium starch glycolate (Chaulang *et al*., 2009) and others. The present study demonstrated increased furosemide solubility by simple technique using chitosan as a tablet disintegrant.

Disintegrants swelling capacity

Swelling capacity is generally accepted as an indicator for tablet disintegration ability. Primarily, this is because of the fact that almost all disintegrants swell to some extent (Zhao and Augsburger, 2005). The results showed that the swelling capacity of chitosan was superior to other disintegrants examined particularly in water. This may be attributed to the absence of the hydrogen bonding between the sheets of sugar rings of chitosan which ease polymer swelling in water to produce hydration (Bi *et al*., 1999). This tremendous swelling capacity of chitosan especially in water clearly indicates its great efficiency as tablet disintegrant.

Furosemide tablets evaluation

Different formulae of furosemide tablets were prepared with various types and concentrations of disintegrants. Wet granulation method was utilized for the preparation of furosemide tablets. It is reported that the fastest drug dissolution could be achieved for tablet prepared by wet granulation method rather than other methods of tablet preparation especially for poorly wettable drugs used in high concentrations (Hoshang *et al*., 1988). Magnesium stearate was used in tablet preparation as a lubricant in small concentration (1%) as it is hydrophobic material and if used in high concentration will result in slowing drug dissolution rate since it coats the drug granules and acts as a water repellent (Desai *et al*., 1993). The prepared tablets were within USP specification with regard to hardness, friability and disintegration. The fastest disintegration time and the highest tablet friability were obtained with chitosan 15% w/w (F17). In fact, this may be attributed to the high ability of chitosan to absorb moisture and its high swelling capacity, which may result in tablet softening (Ganderton, 1969). However, increasing chitosan concentration from 3% to15% w/w resulted in increasing tablet hardness. This may be due to the formation of intermolecular attractive forces between polymer molecules inside the tablet (Keith, 1986).

In vitro release study

Drug release profiles from the prepared tablet formulations were faster than that of the reference where almost all tablet formulations released not less than 80% of the drug compared to 60% from the reference within 1 hr. Disintegration of tablet strongly affects its dissolution rate where the time taken for tablet disintegration had shown to be dependent upon type and percentage of the disintegrant used in tablet preparation (Caramella *et al*., 1990).

However, research studies reported that drug dissolution from tablet dosage form depends mainly upon the sorption ability of the granules rather than disintegration time. Chitosan showed the highest velocity constant which may explain the fact that the maximum amount of furosemide dissolved was obtained with (F15) formula compared to other studied disintegrants. These results are in agreement with what was reported by Ritthidej (Ritthidej *et al*. (1994).who proved that, chitosan in a concentration higher than 5% was superior to corn starch and cellulose as tablet disintegrants. On the other hand, increasing chitosan concentration up to 15% resulted in a decrease in the amount of drug dissolved which was attributed to the increase in tablet hardness. In addition, high conc. of the disintegrant inside the granules may form a viscous barrier that slow down tablet erosion and consequently decrease drug released from the tablet

(Rubinstein, 1980). Studies also reported that drug dissolution from chitosan tablet dosage forms was controlled mainly by chitosan concentration rather than tablet hardness (Benita *et al*., 1984).

Medium[D9] molecular weight chitosan was used in the present study to provide disintegration properties when used in small concentrations. It is documented that the viscosity of chitosan solution increases by increasing the molecular weight of chitosan. High molecular weight chitosan was not used as it forms gel in acidic media and this may hinder the release of the drug (Singh *et al*., 2011).

Effect of compression force

The use of high compression force resulted in the prolongation of the disintegration time which could be attributed to the reduction in fluid penetration into the tablet structure and therefore, increasing tablet strength and density and reducing tablet porosity which consequently resulting in decreasing tablet dissolution (Khan and Rhodes, 1976). The same findings were reported by Andries[D10] (Andries *et al*., 2003) who examined the effect of the compression force and the disintegrant concentration on the disintegration and dissolution of directly compressed furosemide tablets using croscarmellose sodium as disintegrant.

Effect of chitosan addition step during tablet preparation

Tablet hardness was increased when adding chitosan externally. This may be due to the fact that more particle-particle contact points were obtained with the external addition of chitosan. It is reported that chitosan particles could create more solid bonds. Therefore, higher crushing strength values were obtained (Ferrari *et al*., 1996).

Tablet disintegration time and dissolution profile were faster for F15 formula when adding chitosan externally. These obtained results may be attributed to the fact that, external addition of disintegrants makes them initially exposed to the disintegration medium, which leads to the absorption of large quantities of water and subsequent generation of higher swelling force. This force activated the mechanism of disintegration and as a result drug dissolution at a faster rate to be obtained than that for internal-external and internal mode of disintegrant addition (Allen *et al*., 2011).

Convolution analysis

Simulation of the expected furosemide plasma concentration versus time profiles was done for the commercially available furosemide® tablet and selected new prepared tablet formulations. This helps guide formulation modification and examines the new formulation behavior assuming its administration *in vivo.* Simulation results obtained from the dissolution data of furosemide tablet formulations as well as the reference were consistent with reported data where it was reported that the maximal plasma levels of furosemide were seen at 1.75 ± 1.22 hr and mounted to1.84 mcg/ml (Beermann, 1978). The maximum plasma conc. was comparable to that obtained from F15 formulations but was faster (T-max after 30 min). This fast tablet drug release may be attributed to the use of chitosan as a disintegrant. The simulated data showed the superiority of all prepared tablet formulations over the reference.

CONCLUSION

In the present study, different[D11] oral furosemide tablet formulations were developed successfully using different disintegrants with different concentrations (starch, Avicel PH101, Avicel PH102 and chitosan). Tablet formulation F15, containing 40mg furosemide, chitosan (7% w/w) with chitosan external addition during tablet preparation and compressed at 4 Ton/cm^2, demonstrated superior physical properties (tablet hardness, friability and disintegration) and dissolution behavior compared to the reference product, Furosemide® tablets. It was also proven that simulated plasma profile for F15 formula was superior to that of the reference with higher C-max and shorter T-max than that of the reference. The present study demonstrated that chitosan is a very good candidate to be used as a tablet disintegrant and was able to enhance the dissolution of poorly absorbable drugs.

REFERENCES

Allen LV, Popvich NG and Ansel HC (2011). Solid dosage forms and solid modified-release drug delivery systems. *In*: Troy DB (editor). Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems, 9th ed., Lippincott Williams & Wilkins, Philadelphia, PA, pp.225-256.

Amrutkar JR and Gattani SG (2009). Chitosan-chondroitin sulfate based matrix tablets for colon specific delivery of indomethacin. *AAPS Pharm. Sci. Tech.*, **10**: 670-677.

Andries FM, Mingna S and Melgardt M (2003). Effect of compression force, humidity and disintegrant concentration on the disintegration and dissolution of directly compressed furosemide tablets using croscarmellose sodium as disintegrant. *Trop. J. Pharm. Res.*, **2**(1): 125-135.

Aulton ME (2002). Pharmaceutics the Science of Dosage Form Design. 2nd ed., Churchill Livingstone, Edinburgh, pp.404-410.

Beermann B, Dalen E and Lindstrom B (1978). Bioavailability of two furosemide preparations. *Br. J. Clin. Pharmac.*, **6**: 537-538.

Benita BS, Shani J, Abdulrazik M and Samuni A (1984). Controlled release of radioprotective agents from

matrix tablets-effect of preparative conditions on release rates. *J. Pharm. Pharmacol.*, **36**: 222-228.

Bhise S[D12], Chaulang G, Patel P, Patel B, Bhosale A and Hardikar S (2009). Superdisintegrants as Solubilizing agent. *Res. J. Pharm. Tech.,* **2**(2): 387-391.

Bi Y, Yonezawa Y and Sunada H (1999). Rapidly disintegrating tablets prepared by the wet compression method: mechanism and optimization. *J. Pharm. Sci.*, 88: 1004-1010.

Caramella C, Ferrari F, Bonferoni MC and Ronchi M (1990). Disintegrants in solid dosage forms. *Drug Dev. Ind. Pharm*., **16**: 2561-2577.

Chaulang G, Patel P, Hardikar S, Kelkar M, Bhosale A and Bhise S (2009). Formulation and evaluation of solid dispersions of furosemide in sodium starch glycolate. *Trop. J. Pharm. Res.,* **8**(1): 43-51.

Desai DS, Rubitski BA, Varia SA and Newman AW (1993). Physical interactions of magnesium stearate with starch-derived disintegrants and their effects on capsule and tablet dissolution. *Int. J. Pharm.*, **91**: 217-226.

Ferrari F, Bertoni M, Bonferoni MC, Rossi S, Caramella C and Nyström C (1996). Investigation on bonding and disintegration properties of pharmaceutical materials. *Int. J. Pharm.*, **136**: 71-79.

Gabrielsson J and Weiner D (2007). Modeling Strategy: Pharmacokinetic and Pharmacodynamic Data Analysis, Concepts and Application, 4th ed., Swedish Pharmaceutical Press, Stockholm, 960-1012.

Garnpimol CR, Parichat C, Sunibhond P and Piamsak M (1994). Chitin and chitosan as disintegrants in paracetamol tablets. *Drug Dev. Ind. Pharm.*, **20**(13): 2109-2134.

Ganderton D (1969). The effect of distribution of magnesium stearate on the penetration of a tablet by water. *J. Pharm. Pharmacol.*, **21**: 9S-18S.

Granero GE, Longhi MR, Mora MJ, Junginger HE, Midha, KK, Shah VP, Stychansky S, Dressman JB and Barends DM (2010). Biowaiver monographs for immediate release solid oral dosage forms: Furosemide. *J. Pharm. Sci.*, **99**(6): 2544-2556.

Guyot H (1992). The disintegration and disintegrating agent. *S.T.P. Pharma. Sci.*, **2**(6): 445-462.

Hoshang MU, Joseph BS and Roger LS (1988). The effect of the wet granulation process on drug dissolution. *Drug Dev. Ind. Pharm.*, **14**(10): 1327-1349.

Lachman L, Herbert A and Kanig J (1987). The Theory and Practice of Industrial Pharmacy. 3rd ed., Varghese Publishing House, Philadelphia, pp.430-456.

Keith M (1986). Compression and Consolidation of Powdered Solids. *In*: Lachman L, Liberman HA and Kang JL, The Theory and Practice of Industrial Pharmacy, 3rd ed., Lea and Febiger, Philadelphia, p.73.

Khan KA and Rhodes CT (1976). Effect of variation in compaction force on properties of six direct compression tablet formulations. *J. Pharm. Sci.*, **65**: 1835-1837.

Kokil S, Patil P, Mahadik K and Paradkar A (2005). Studies on spray-dried mixtures of chitosan and hydrolyzed gelatin as tablet binder: A technical note. *AAPS Pharm. Sci. Tech.*, **6**(3): E437-E443.

Moffate AC (1986). Clark's Isolation and Identification of Drugs. 2nd ed., Pharmaceutical Society of Great Britain, London, pp.428- 429, 740-741, 936-937.

Okhamafe AO, Igboechi A and Obaseki TO (1991). Celluloses extracted from groundnut shell and rice husk 1: Preliminary physicochemical characterization. *Pharm. World J.*, **8**(4): 120-130.

Ponto LL and Schoenwald RD (1990). Furosemide (frusemide) a pharmacokinetic/pharmacodynamic review (Part I). *Clin. Pharmacokinet.*, **18**: 381-408.

Riffat Y, Shoaib MH and Khalid H (2005). Comparative study of different formulations of atenolol. *Pak. J. Pharm Sci.*, **18**(1): 47-51.

Ritthidej GC, Chomto P, Pummangura S and Menasveta P (1994). Chitin and chitosan as disintegrants in paracetamol tablets. *Drug Dev. Ind. Pharm*., **20**(13): 2109-2134.

Rubinstein MH (1980). The effect of disintegrants and processing on the bioavailability of frusemide from compressed tablets. *Drug Dev. Ind. Pharm.*, **6**: 105-19.

Rubenstein MH and Rughani JM (1989). The effect of four particle characteristics on the dissolution rate, tablet binders on bioavailability of frusemide. *Drug Dev. Ind. Pharm.,* **15**: 621-627.

Ruiz NR and Ghaly ES (1997). Mechanism of drug release from matrices with aqueous dispersion of ethyl cellulose. *Drug Dev. Ind. Pharm.*, **23**: 113-17.

Singh MK, Prajapati SK, Mahor A, Rajput N and Singh R (2011). Chitosan: A novel excipient in pharmaceutical formulation: a review. *Int. J. Pharm. Sci. Res.,* **2**(9): 2266-2277.

Struszczyk H, Wawro D and Niekraszewicz A (1991). Biodegradability of chitosan fibres, *In*: Brine CJ, Sandford PA, Zikakis JP, Advances in Chitin and Chitosan, 1st ed., Elsevier Applied Science, London, pp.580-585.

Zhao N and Augsburger LL (2005). The Influence of swelling capacity of super-disintegrants in different pH media on the dissolution of hydrochlorothiazide from directly compressed tablets. *AAPS Pharm. Sci. Tech.*, **6**(1): E120-E126.

Zhang[D13] Y, Law Y and Chakrabarti S (2003). Physical properties and compact analysis of commonly used direct compression binders. *AAPS Pharm. Sci. Tech.*, **4**(4): E62.