RESEARCH ARTICLE

Effect of some physical parameters and crospovidone on directly compressed frusemide tablets

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The aim of this study was to evaluate the effect of increasing crospovidone (superdisintegrant) load on the characteristics of fast-disintegrating tablets for the potential use of the drug for its therapeutic effect. Five tablet formulations, F_0, F_1, F_3, F_7, and F_{10} containing 0%, 1%, 3%, 7%, and 10% (w/w) of crospovidone, respectively, frusemide and microcrystalline cellulose (PH102), were prepared by direct compression, at a different compression forces. Tablet weight variation, content uniformity, crushing strength, disintegration time, wetting time, and *in vitro* release were measured for each formulation at each compression force. A linear increase in compression force resulted in an exponential increase in hardness for all formulations, a linear increase in disintegration and wetting times was observed for the formulations F_0, F_1, F_3 with the increase in compression force. The tablet formulation F_7 indicated, there was no effect of compression force on disintegration and wetting time. The *in vitro* release of the drug was increased with increase in concentration of crospovidone irrespective the compression force. However, storage under high humidity conditions caused the softening of the tablets containing the high amount of crospovidone, leading to softening of tablets. Fast disintegration of the tablets within 1-2 min is prerequisite for improving the dissolution of frusemide, attributed to increase in speed at which maximum surface area of sparingly soluble drug is exposed to the dissolution medium. However, tablet containing high amount of crospovidone must be protected from the atmospheric moisture because storage of these tablets at high humidity led to softening and losing the tablet characteristics.

Key words: *Compression force, crosspovidone, disintegration, relative humidity, dissolution*

INTRODUCTION

A rapid onset of action of any drug is required in so many diseased conditions to get desired pharmacological response. For a rapid onset of action, fast dissolution and absorption are primary objectives for any dosage form. The tablet dosage forms are very popular among the other dosage forms, showing the need of fast dispersion of drug for rapid dissolution and absorption.[1] The development of fast dispersible tablet using superdisintegrant has become popular for various reasons. Theoretically, for improvement of dissolution can be achieved by increasing the surface area of the drug by micronization. This phenomenon was attributed to the agglomeration tendency of micronized, poorly soluble, hydrophobic drugs, which effect results in a decreased effective surface for dissolution.[2-4] For tablet containing sparingly water soluble drugs, the start of dissolution is often delayed by poor wettability of tablet or slow liquid penetration into tablet matrix.[5,6] This causes increase in disintegration time and retards the drug release. This can be overcome by addition of superdisintegrant. The shorter disintegration time requirement stimulated continuous efforts in the search for new, more efficient disintegrating agents.[7-9] Wicking and swelling were found to be the primary mechanisms of action for tablet disintegrants, while other mechanisms, such as deformation recovery, particle repulsion theory, heat of wetting and evolution of a gas etc; may play a role in particular cases of tablets disintegration.[10] Potential disadvantages of use of disintegrant in tablet formulation, using direct compression as the method of manufacture are - (1) high concentration needed for optimum disintegrating efficiency, (2) poor disintegration, (3) susceptibility to high compression forces which decrease the efficiency, (4) poor compression properties, and (5) decreased

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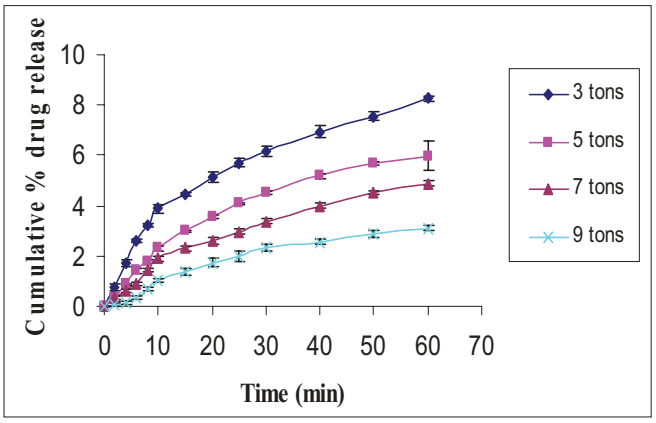

Figure 1: *In vitro* release profile of frusemide tablets at variable compression force containing 0% crospovidone (F_0)

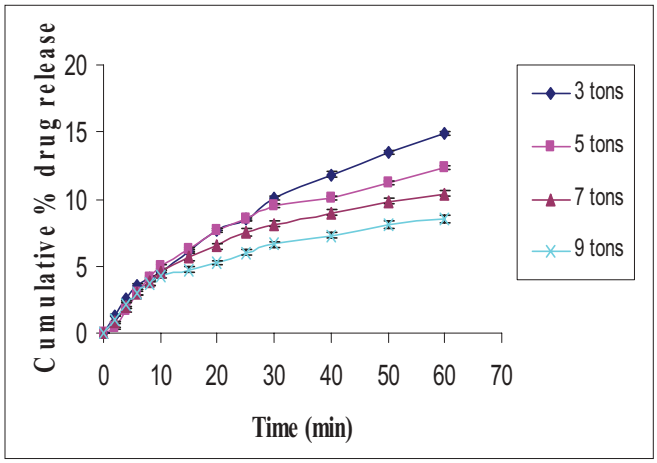

Figure 2: *In vitro* release profile of frusemide tablets at variable compression force containing 1% crospovidone (F_1)

disintegrating efficiency in hydrophobic formulations.[11] A group of superdisintegrants including crosscamellose sodium (*Ac-Di-Sol*) sodium starch glycolate (*Primojel* and *Explotab*) and crosspovidone (*Polyplasdone XL*) alleviate most of these problems.[12] Use of the superdisintegrants in fast dispersible tablet is possible as tablet shows optimum physical properties. Factors affecting disintegrant efficiency include tablet solubility,[11] tablet hygroscopicity,[13-15] compression force,[5,6,17] and storage under high relative humidity.[11] All the factors are related to accessibility of liquid molecules to disintegrant particles inside the tablet.[18,19]

Furosemide is a loop diuretic and effectively used in problems like hypertension, the drug having low solubility and low bioavailability, hence classified as class IV drug as per biopharmaceutical system. The purpose of this study was to determine the effect of concentration of crosspovidone, compression pressure, and relative humidity on directly compressed furosemide tablet properties like hardness, wetting time, disintegration time, and dissolution profile. The furosemide was chosen for this work because it was proved by several researchers that excipient and processing factors affect the dissolution profile of furosemide.[20-22]

MATERIALS AND METHODS

Material

Furosemide was supplied as gift sample from Samruddha Pharmaceuticals, Thane, Mumbai, Avicel (PH 102) was supplied as gift sample from F.M.C. Biopolymer, Ireland and Crosspovidone from ISP Technologies, INC. Wayane, NJ. All other excipient were of analytical grade.

Standard calibration curve of furosemide

Solutions ranging from 2 to 20 μg/ml were prepared in simulated gastric fluid (pH 1.2 without enzyme). Absorbance was measured at λ_{max} 274 nm using, double beam UV visible spectrophotometer Model No. UV 2401 PC Shimadzu Corporation, Koyto, Japan.

Formulation of tablets of furosemide

All ingredients were passed through sieve No.100, and blended in glass mortar uniformly. After sufficient mixing of all components, magnesium stearate was added and again mixed for additional 2-3 min. The tablets were compressed using 8 mm flat punch on 16-station rotary tablet compression machine (Type - CMD3 - 16, Cadmach Machinery Pvt. Ltd., Ahamadabad). Each blend was compressed at different compression pressures i.e., 3, 5, 7, and 9 tons at 18 rpm speed. The composition of each formulation using crospovidone as superdisintegrant and Avicel (PH102) as a diluent is given in Table 1.

Stability study of tablets

The tablets of F_7 batch (containing 7% w/w crospovidone concentration) were stored under different humidity conditions at 25°C for 3 months. The humidity chambers were developed in desiccators by using saturated salt solutions. The tablets were stored in glass petri-dishes similar to condition described as 'open dish' method for stability testing. The following humidity conditions were used for storage of tablets according to climatic zones of the world, specified by ICH guidelines. Zone-I (21°C, 45% relative humidity [RH]), zone-II (25°C, 60% RH), zone-III (25°C, 35% RH) and zone-IV (30°C, 70% RH).[23-25]

Evaluation of tablet

The tablets were evaluated before keeping at different

Table 1: Formulations of frusemide tablet containing different concentration of crospovidone

Ingredients	Formulations				
	F0	F1	F3	F7	F10
Frusemide	30	30	30	30	30
Crospovidone	0	1	3	7	10
Mg. stearate	1	1	1	1	1
Avicel PH102	69	68	66	62	59
Total weight (mg)	100	100	100	100	100

All figures in table indicate weight in mg

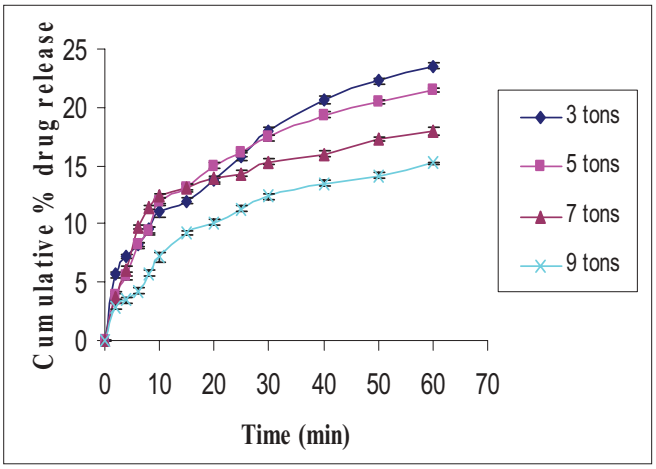

Figure 3: *In vitro* release profile of frusemide tablets at variable compression force containing 3% crospovidone (F_3)

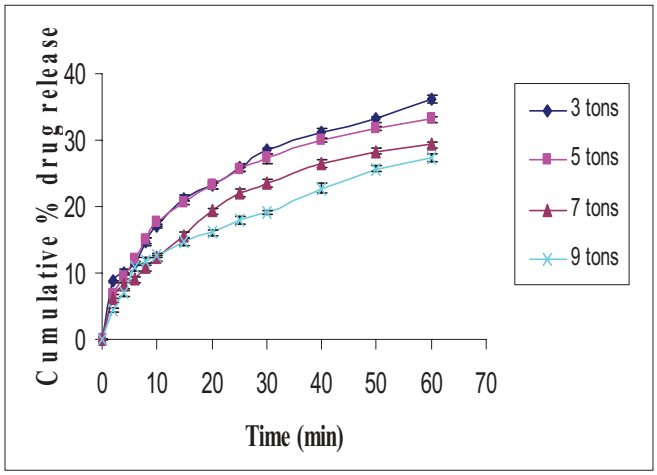

Figure 4: *In vitro* release profile of frusemide tablets at variable compression force containing 7% crospovidone (F_7)

humidity conditions as well as after three months storing at different humidity conditions. The tablets were evaluated for different parameters viz. weight variation, drug content, disintegration time, crushing strength, wetting time and *in vitro* release of the drug. The results are reported in Table 2.

Weight variation

The weight variation study was performed as per the method specified in IP 1996.[26]

Drug content

The drug content of all formulated batches was determined as per the procedure specified in IP.[26] Twenty tablets were weighed accurately and powdered. Powder equivalent to 0.1 g of furosemide was taken to 150 mL of 0.1 M NaOH and shaken for 10 min. To the mixture, 0.1 M NaOH was added again to produce 250 mL. The resultant solution was filtered through Whatman filter paper no. 42. The 5 mL of this solution was taken and diluted up to 200 mL with 0.1 NaOH and the absorbance of resulting solution was measured at 271 nm. $A^{1\%}$ cm value was 580 at 271 nm.

Crushing strength

Crushing strength was measured diametrically, using Campbell Electronic Tablet tester. The tablets from each batch were taken and kept on horizontal surface of the

Table 2: Effect of disintegrant concentration, at variable compression force on disintegration time, crushing strength, wetting time and drug content (%w/w)

Formulation no.	Compression force (tone)	Parameters			
		DT (s)*	CS (N)*	WT (s)*	% drug release after 1 h
F0	3	213.67 ± 3.86	77.14 ± 0.88	125.33 ± 1.70	8.264 ± 0.11
	5	400.33 ± 1.25	130.54 ± 0.94	143.67 ± 1.70	5.983 ± 0.58
	7	607 ± 1.63	172.65 ± 0.80	164.33 ± 3.30	4.895 ± 0.11
	9	805.67± 1.25	203.19 ± 1.13	200.33 ± 2.05	3.111 ± 0.11
F1	3	211± 2.16	91.80 ± 1.27	95 ± 1.63	14.890 ± 0.19
	5	329.67± 1.25	133.73 ± 0.71	104.33 ± 1.25	12.307 ± 0.17
	7	467.33 ± 3.40	199.41 ± 0.63	122 ± 1.63	10.419 ± 0.22
	9	582.33 ± 4.03	213.07 ± 1.32	135.67 ± 1.25	8.535 ± 0.25
F3	3	122.33 ± 1.70	121.89 ± 1.30	33.67 ± 1.70	23.523 ± 0.26
	5	151.33 ± 1.25	168.57 ± 0.75	41.67 ± 1.70	21.472 ± 0.24
	7	170 ± 1.63	201.60 ± 0.60	54.67 ± 1.25	17.940 ± 0.28
	9	181 ± 2.16	232.50 ± 0.76	67.33 ± 1.70	15.216 ± 0.13
F7	3	79 ± 1.63	137.21 ± 1.30	21.33 ± 1.25	36.136 ± 0.48
	5	94.33 ± 1.70	177.04 ± 0.43	32.67 ± 1.70	33.092 ± 0.50
	7	113.67 ± 1.70	212.35 ± 1.29	42.67 ± 2.05	29.307 ± 0.40
	9	133.67 ± 2.05	243.50 ± 0.83	46.33 ± 1.25	27.388 ± 0.59
F10	3	82.67 ± 2.05	152.62 ± 0.58	31.33 ± 1.25	36.336 ± 0.41
	5	79.33 ± 1.25	182.43 ± 1.75	31 ± 2.16	37.460 ± 0.27
	7	83.33 ± 1.25	223.17 ± 1.79	29.33 ± 1.25	37.330 ± 0.70
	9	79.67 ± 1.25	254.13 ± 2.71	30 ± 1.63	36.511 ± 0.58

*Represents mean ± SD (n = 3), DT: disintegration time, CS: crushing strength, WT: wetting time

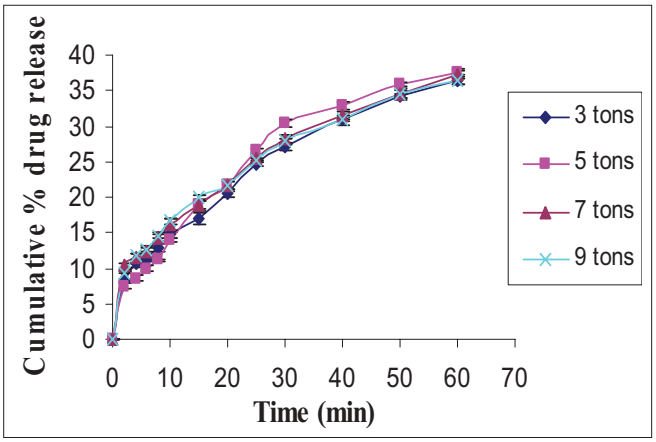

Figure 5: *In vitro* release profile of frusemide tablets at variable compression force containing 10% crospovidone (F_{10})

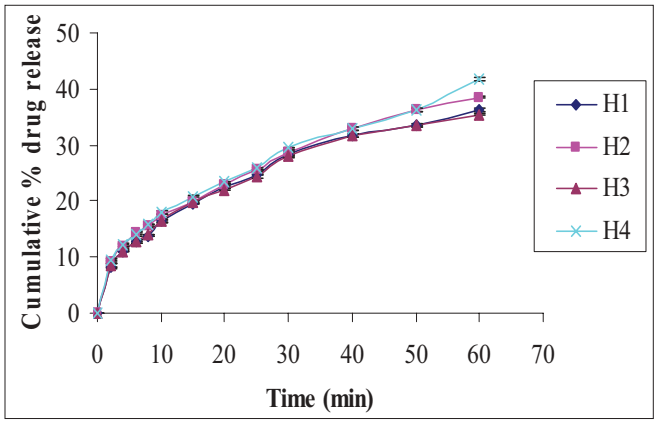

Figure 6: *In vitro* release profile of frusemide tablets containing 7% w/w crospovidone (F_7), compressed at 3 tons and stored under different humidity conditions

jaw of machine, and tablets were crushed mechanically with automatic working and direct reading for the crushing strength was obtained digitally. For each batch three tablets were tested.[27]

Disintegration time

Disintegration test was carried out as described under procedure for uncoated tablets in IP. One tablet each was placed in each of six tubes of the basket of the assembly. Apparatus was operated using water, maintained at 37 ± 2°C as the immersion fluid.[28]

Wetting time

Wetting time was determined by procedure similar to the one used by Aly AM, *et al*. A two-fold piece of tissue paper was kept in small culture dish (i.d. - 6.5 cm) containing 6 mL water. A tablet for testing was kept on tissue paper and time required to wet the whole tablet was measured and recorded as the wetting time.[29]

In vitro **dissolution study**

The dissolution was studied using USP apparatus II taking 900 ml of dissolution medium, simulated gastric fluid without pepsin (pH 1.2) for one hour. The rotational speed of the paddle was set at 50 rpm at 37 ± 0.5°C. The 5 mL of aliquots was withdrawn at predetermined time interval for every 2, 4, 6, 8, 10, 15, 20, 25, 30, 40, 50, and 60 min and maintaining sink condition. The samples were analyzed for drug content using double beam UV spectrophotometer (Model No. UV 2401 PC Shimadzu Corporation, Koyto, Japan) at 274 nm. The *in vitro* dissolution study was carried out in triplicate for each formulated batch.[30]

RESULT AND DISCUSSION

Primarily the tablets were evaluated for weight variation and content variation and found to be satisfactory as per official standards. The crushing strength of the tablets formulation increased with increasing compression force as shown in Table 2. Crushing strength of tablets clearly describes a certain mechanical property of a whole tablet. Crushing strength is obviously a parameter which can be related quite directly to the compression force used as shown in Table 2. The disintegration time of the tablet was also increased with increase in compression pressure, and the effect was observed up to the 7% (w/w) concentration of crospovidone. The increase in disintegration time with an increase in compression force may be because of decreased porosity hence reduced penetration of dissolution medium in tablet bulk.[31] At higher concentration of superdisintegrant 10% (w/w) the disintegration time of the tablet was constant irrespective of compression pressure, though crushing strength was increased with increase in compression force. The results are shown in Table 2.

The wetting time of tablet was increased with increase in compression pressure as there was decrease in porosity of the tablet, but the effect was leveled off after 7% (w/w) concentration of crospovidone. The results are shown in Table 2.

In vitro dissolution studies of tablets from each batch were carried out. The percent cumulative drug release at compression force 3 tons, containing 0, 1, 3, 7, and 10% w/w concentration of disintegrant are shown in Table 2 [Figures 1-5]. It was observed that with increase in concentration of superdisintegrant, the release rate of drug was increased. This may be, because of the increase in concentration of superdisintegrant, the particles were exposed to dissolution medium at comparatively faster rate. The presence of the superdisintegrant in dissolution medium kept the drug particles in dispersed condition i.e., agglomeration of drug particles was avoided and also promoted the wetting of dispersed particles due to fixation of hydrophobic drug particles upon hydrophilic crosspovidone during the tabletting process.[32]

The cumulative percent drug release of batch F_3 (containing

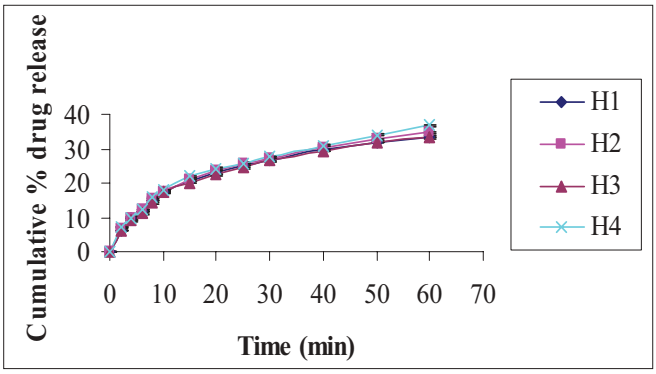

Figure 7: *In vitro* release profile of frusemide tablets containing 7% w/w crospovidone (F_7), compressed at 5 tons and stored under different humidity conditions

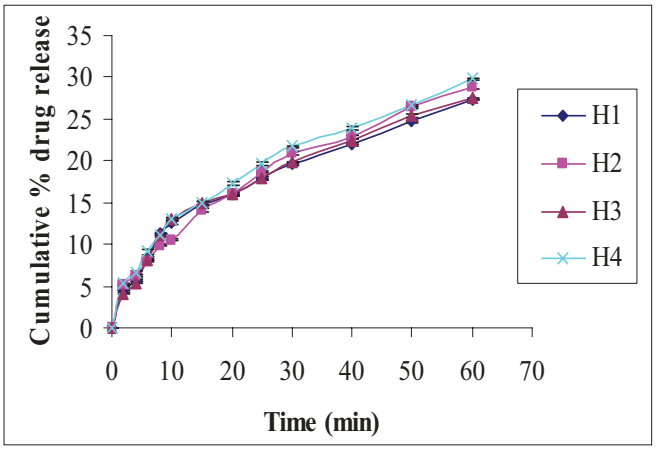

Figure 9: *In vitro* release profile of frusemide tablets containing 7% w/w crospovidone (F_7), compressed at 9 tons and stored under different humidity conditions

3% of disintegrant) and F_7 (containing 7% of disintegrant) at compression forces 3, 5, 7, and 9 tons are shown in Table

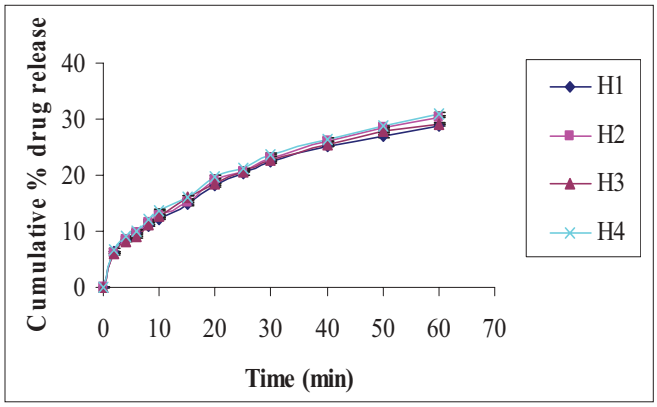

Figure 8: *In vitro* release profile of frusemide tablets containing 7% w/w crospovidone (F_7), compressed at 7 tons and stored under different humidity conditions

2 [Figures 3 and 4]. It was observed that, the drug release was decreased with increase in compression force at fixed concentration of disintegrant, because the increase in compression force decreases the porosity of the tablet.

The *in vitro* dissolution study showed that there was no significant difference in dissolution profile of batch F_7. The results are shown in Table 3 [Figures 6-9].

From all the above data, as the tablet of F_7 batch (containing 7% w/w crospovidone concentration) showed the critical results, at this concentration the disintegration rate was maximum at different compression pressures viz. 3, 5, 7, and 9 tons. These tablets were selected for the stability studies.

After 3 months, the tablets were evaluated for its physical properties like crushing strength, disintegration time, and wetting time. Also the dissolution study was carried out.

Table 3: Effect of compression force and humidity on disintegration time, crushing strength, wetting time and drug content (%w/w) of tablets of F_7 batch (tablet containing 7% w/w crospovidone)

Compression force (tons)	Climatic zone	Parameters			
		DT (s)*	CS (N)*	WT (s)*	Drug content (% w/w)*
3	H-I	63 ± 0.82	128.66 ± 0.66	22.67 ± 1.25	97.13 ± 1.70
	H-II	47.67 ± 1.25	98.44 ± 0.51	16.67 ± 1.25	98.69 ± 1.25
	H-III	67.33 ± 1.25	126.58 ± 0.53	22.67 ± 1.25	98.78 ± 1.63
	H-IV	35.67 ± 2.05	87.45 ± 0.86	16 ± 0.82	101.34 ± 2.16
5	H-I	74.33 ± 1.25	164.51 ± 0.63	34.33 ± 1.70	101.46 ± 1.63
	H-II	55.33 ± 2.05	120.53 ± 0.65	24.33 ± 1.25	98.87 ± 1.70
	H-III	81.33 ± 1.25	168.63 ± 0.89	30.33 ± 1.70	100.5 ± 1.70
	H-IV	43.67 ± 1.25	100.71 ± 0.69	20 ± 0.82	101.72 ± 2.05
7	H-I	102.33±1.25	197.79 ± 0.75	36 ± 1.63	97.55 ± 0.88
	H-II	76.33 ± 1.25	161.81 ± 1.37	26 ± 0.82	96.93 ± 0.94
	H-III	91.33 ± 1.25	201.50 ± 1.08	36.33 ± 1.70	99.28 ± 0.80
	H-IV	59.33 ± 1.25	148.23 ± 0.86	20.33 ± 1.25	98.80 ± 1.13
9	H-I	114 ± 1.63	232.51 ± 0.68	43.33 ± 1.25	100.22 ± 1.27
	H-II	96.67 ± 1.25	178.03 ± 1.27	35.33± 1.25	103.64 ± 0.71
	H-III	121 ± 1.63	225.53 ± 0.66	46.33 ± 1.25	96.44 ± 0.63
	H-IV	77.67 ± 1.25	158.37 ± 1.02	31 ± 0.82	97.12 ± 1.32

*Represents mean ± SD (n = 3), DT: disintegration time, CS: crushing strength, WT: wetting time

The crushing strength, disintegration time, and wetting time of tablet was observed to be decreased for the tablets stored under the conditions of zone II (60% RH) and zone IV (70% RH), while there was not significant difference for the tablets stored under the conditions of zone I (45% RH) and zone III (35% RH). This was observed as the tablets get soften by absorbing the moisture in humidity zones II and IV. The results are shown in Table 3.

CONCLUSION

From the study for physical properties and dissolution profile of tablets it was concluded that there was increase in dissolution of drug with increase in the concentration of superdisintegrant (crosspovidone) in tablet formulation. The significant difference was observed in dissolution profile between tablets containing 0% and 10% crospovidone.

It was also observed that at fixed concentration of crosspovidone the release of drug decreased as compression pressure was increased.

The above findings showed the need of superdisintegrant for better dissolution of poorly soluble drugs like furosemide. Also tablets stored under different humidity conditions showed softening and indicated the need of proper packaging for the tablets to be marketed in higher humidity zone (II and IV).

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