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Formulation and evaluation of oral disintegrating tablets of furosemide

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Abstract

Orally disintegrating tablets of Furosemide were prepared, evaluated and the comparison of the action of different concentrations of disintegrants on disintegration and dissolution of the tablets were studied. Direct compression method was used to prepare the orally disintegrating tablets containing 20 mg of Furosemide. The formulation was conducted using different concentrations of crospovidone, croscarmellose and sodium starch glycolate as superdisintegrants and their interactions with Furosemide were also evaluated using FTIR. FTIR studies using the drug and its mixtures with the excipients showed that the peaks correlate with one another which signify that there is no interaction between the drug molecule and the excipients used. The obtained results revealed that the disintegration time of ODTs were between 9 to 59 seconds. The percentage drug content of tablets in all the formulations was found between 91.51% to 106.69%, which complies with the limits established in pharmacopoeia. The in-vitro dissolution studies show maximum release of 89.47% in formulation F3 and minimum of 77.64% in formulation F12. Higher concentration of crospovidone and croscarmellose in formulations F3 and F6 showed better dissolution properties than SSG. So by varying the concentrations of super disintegrants, oral disintegrating tablets can be formulated.

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Introduction

Orally disintegrating tablets are the dosage forms that get disintegrated when they come in contact with the saliva present in the oral cavity. The saliva penetrates the tablets and disrupts its structural integrity which results in the release of the drug from the dosage form [1]. The rapid disintegration of the tablets in the oral cavity may be rendered by the use of super disintegrants, such as crospovidone, croscarmellose and sodium starch glycolate, thus making the dosage form favorable for the pediatric population, geriatric population, bed-ridden patients and patients with dysphagia [2]. According to the United States Food and Drug Administration, an Oral Disintegrating Tablet is defined as "A solid dosage form which contains a medicinal substance or an active ingredient which rapidly disintegrates when placed upon the tongue, usually within matter of seconds [3]. The names such as rapid dissolving, mouth dissolving and fast melt tablets has also been given to the orally disintegrating tablets. The orally disintegrating tablets disperse and disintegrate when they come in contact with the saliva present in the oral cavity that omits the use of liquid to take the tablet, to swallow the whole dosage form or to chew the tablet. This dosage form is thus beneficial to the pediatric and geriatric patients and also to those who have swallowing difficulties including dysphagia and patients with psychiatric disorders [4]. Furosemide is a loop diuretic or often called as a high ceiling diuretic used in the treatment of edematous states which prevents and treats the fluid retention in the body. The usual dosage forms of furosemide available are 20 and 40 mg tablets. Chemically Furosemide is 5-(aminosulphonyl)-4-chloro-2-[(2-fuanyl-methyl) amino] benzoic acid [5]. The Biopharmaceutics Classification System (BCS) classifies furosemide as a Class IV compound, which means that furosemide has a low solubility and a low permeability. The bioavailability of furosemide is found to be 37-70% with its peak plasma concentration (Cmax) found to be achieved within 60 to 90 min. The plasma half-life (t1/2) of furosemide is 1.3±0.8 h in healthy subjects [6]. The purpose of this study is to formulate the ODTs of Furosemide and to perform the evaluation of those formulations for different parameters. The use of the superdisintegrants i.e. Crosspovidone, Croscarmellose sodium and Sodium starch glycolate and their effects on the tablets' disintegration and dissolution has been studied.

Materials and Methods

Raw materials were obtained with coordination with the Department of Pharmacy MMIHS and Lomus and Qmed Pharmaceuticals. Furosemide, MCC, sucralose and mannitol

Were obtained from Lomus Pharmaceuticals Pvt. Ltd., Gothatar, Kathmandu. Similarly, crospovidone, croscarmelose, SSG, talc and magnesium stearate were obtained from Qmed Pharmaceuticals Pvt. Ltd., Chhaling, Bhaktpur. All the other components used for the formulation were of Pharmaceutical grade.

Preparation of Furosemide ODT

Table 1: Direct compression method was used to prepare oral disintegrating tablet of Furosemide. At first all the ingredients excluding lubricant, glidant, sweetner and diluent (Mannitol) were passed through sieve of mesh size 30 and the remaining ingredients were passed through sieve of mesh size 50. Then all the ingredients except glidant and lubricant were weighed correctly and mixed thoroughly in a plastic pouch. Finally lubricant and glidant were added to the powder and mixed thoroughly to obtain uniform particle size. The prepared powder blend was then compressed with tablet compression machine using die of 7 mm diameter.

Table no. 1: Formulation of Furosemide ODTs.

Formulation	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)	F8 (mg)	F9 (mg)	F10 (mg)	F11 (mg)	F12 (mg)
Furosemide	20	20	20	20	20	20	20	20	20	20	20	20
MCC	120	120	120	120	120	120	120	120	120	120	120	120
Crospovidone	8	12	16	-	-	-	-	-	-	-	-	-
Croscarmelose	-	-	-	8	12	16	-	-	-	8	12	16
Sodium starch Glycolate	-	-	-	-	-	-	8	12	16	8	12	16
Talc	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Magnesium stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Sucralose	2	2	2	2	2	2	2	2	2	2	2	2
Mannitol	45	41	37	45	41	37	37	29	21	45	41	37
Total	200											

Evaluation of pre-compression flow properties of powder blend

Organoleptic properties

Organoleptic properties of API like color, odor and stability were observed and recorded. Solubility was observed in methanol and sodium hydroxide.

Bulk Density

Bulk density was measured using bulk density apparatus. Fixed weight of powder was poured in the measuring cylinder and volume was recorded.

Bulk density = Bulk weight/Bulk volume

Tapped Density

Fixed weight of powder was poured in the measuring cylinder and tapped 50 cycles multiple times. Volume was recorded after each 50 tapping cycles until fixed (concurrent) reading was obtained. The tapped density was obtained by using following equation:

Tapped Density = Bulk weight/Tapped volume

Carr's Index

Carr's index was obtained by using following equation:

$$\text{Carr's index (\%)} = \frac{\text{tapped density-bulk density}}{\text{Tapped density}} \times 100$$

Value less than 1.25 indicate good flow (=20% Carr), where greater than 1.25 indicates poor flow (=33% Carr) [7].

Angle of Repose

Fixed weight of powder was poured through funnel. The height and diameter of the power pile was noted.

Angle of repose was obtained by using following equation:

$$\text{Angle of repose } \theta = \tan^{-1}(2h/d)$$

Where, h = maximum cone height

D = Average diameter

Hausner's ratio

Flow properties of the powder can also be examined using hausner's ratio. Hausner's ratio was obtained by using following equation:

$$\text{Hausner's ratio} = \frac{\text{Tapped Density}}{\text{Bulk Density}}$$

The value of ratio below 1.25 indicates good flow while above 1.35 indicates the poor flow [7].

Post Compression Studies

Weight variation

For each batch, 20 tablets were taken and weighed for weight of each tablet using a digital balance. The average weight of tablet for was determined and minimum and maximum deviation was calculated for each batch.

Dimensions

Dimension of 10 tablets for each batch was determined using vernier caliper and the average diameter and thickness was determined.

Hardness

Using Monsanto Hardness tester, the hardness of 10 tablets was measured and average hardness of tablets was determined.

Friability

The weight of tablets equal to 6.5 grams were taken and rotated for 100 cycles in a friabilator. After 100 revolutions, the tablets were weighed and percentage loss was calculated.

Assay

The assay of the tablets was determined using UV spectrophotometer, which was calibrated prior to its use.

Preparation of sample for assay

20 tablets were taken; they were weighed and then powdered. The quantity of powder containing 0.1g of Furosemide was taken and shaken with 150 ml of 0.1 M sodium hydroxide for 10 minutes. Sufficient quantity of NaOH was added to it to produce 250 ml volume and was filtered. 5 ml of this solution was diluted to 200 ml with 0.1 M NaOH and the absorbance of resulting solution was measured at maximum wavelength 274 nm [8].

Preparation of standard for assay

0.1g of standard Furosemide was weighed and shaken with 150 ml of 0.1 M sodium hydroxide for 10 minutes. Sufficient quantity of NaOH was added to it to produce 250 ml volume and was filtered. 5 ml of this solution was diluted to 200 ml with 0.1 M NaOH and the absorbance of resulting solution was measured at maximum wavelength 274 nm [8].

Amount of drug = (Abs. of Sample/Abs. of standard) x (wt. of standard/250) x (5/200) x (250/wt. of sample) x (200/5) x Avg. wt.

Calibration

The calibration of UV spectrophotometer was done with the help of standard Furosemide. At first 25 PPM solution was prepared by dissolving 6.25 mg of standard Furosemide in 250ml 0.1 M NaOH. Similarly, 20 PPM, 15 PPM, 10PPM, and 5PPM solutions were prepared by taking 40 ml, 30ml, 20 ml and 10 ml respectively of the prepared solution and making volume up to 50 ml. the absorbance of the solutions were measured at 274 nm.

Disintegration Time

The disintegration time of each batch of tablets was determined using USP disintegration test apparatus. To test the disintegration time, one tablet was placed in each small basket sinkers and the basket rack was positioned in a 1 liter beaker containing phosphate buffer of PH 6.8 at 37$\pm$1^{o}C such that the tablet can remain 2.5 cm below the surface of liquid. The time taken for the completion of disintegration of tablet was noted.

In-Vitro Dissolution test

Dissolution of the Furosemide oral disintegrating tablets were performed using USP Type II Apparatus (Paddle Type) at 50 rpm. The dissolution flask was filled with 900ml of Phosphate buffer (pH 6.8) and was maintained at a temperature of 37±0.5^{0}C. The dissolution apparatus was allowed to run for 30 minutes at a speed of 50 rpm after placing a tablet in the flask of the dissolution apparatus. At time interval of 5 minutes, 5 ml of dissolution medium was withdrawn, filtered and again replaced with 5 ml of fresh medium. The withdrawn dissolution medium was diluted to 50 ml and was analyzed spectrophotometrically at λ max is 274 nm using a UV-spectrophotometer. Finally the cumulative percentage release of drug was calculated.

Working formula:

$$\text{Sample\%} = \frac{\text{Absorbance of spl}}{\text{Absorbance of ref}} \times \text{wt of ref} \times \frac{5}{100} \times \frac{900}{50} \times \frac{\text{wt. of spl}}{50} \times \frac{\text{Purity \%}}{5}$$

Results

Calibration Curve

When absorbance v/s concentration was plotted, a straight line was obtained which suggests that the process used to measure the absorbance of sample is validated.

Table 2: Precompression Evaluation results

Formulation	Bulk Density	Tapped Density	Angle of Repose	Carr's Index	Hausner's ratio	Remarks
F1	0.5681	0.68172	32.98°	16.67	1.2	Good
F2	0.55	0.74	35.4°	25.7	1.3	Passable
F3	0.58	0.77	30.8°	23.9	1.32	Passable
F4	0.56	0.75	34.5°	27.2	1.33	Passable
F5	0.59	0.77	33.6°	23.3	1.3	Passable
F6	0.54	0.6981	31.3°	22.4	1.29	Passable
F7	0.574	0.73	30.23°	21.36	1.27	Passable
F8	0.52	0.717	31.2°	27.47	1.37	Passable
F9	0.561	0.71	33.9°	20.98	1.26	Passable
F10	0.54	0.694	34.2°	22.19	1.28	Passable
F11	0.55	0.76	31.8°	27.63	1.37	Passable
F12	0.549	0.691	33.1	20.54	1.25	Passable

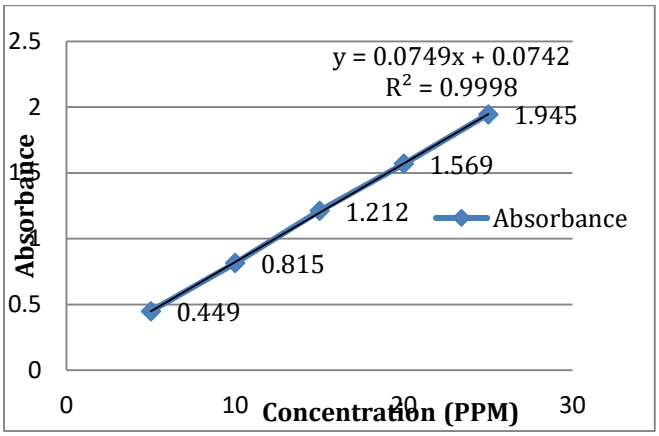

Fig 1: Standard calibration curve of Furosemide

General appearance

Visual observation revealed that all the tablets of twelve formulations were round and flat.

Precompression Studies

Table 2: The Precompression studies' result were within the limit and passable as per USP. The flow properties of powder blend was suitable for compression. Thus the study was further continued by compression of the powder blend into tablets.

Post compression Studies

Table 3: Post compression Evaluation results

Batch	Weight Variation (mg±SD)	Average Diameter(mm±SD)	Average Thickness (mm±SD)	Average Hardness (kg/cm²±SD)	Friability (%) (<1%)
F1	0.1993±0.003422	7.21±0.02087	3.88±0.06809	3.5±0.357	0.61
F2	0.1989±0.002573	7.25±0.02458	3.86±0.06323	3.3±0.205	0.165
F3	0.1987±0.001997	7.22±0.03441	3.88±0.07542	3.2±0.401	0.317
F4	0.1991±0.002231	7.26±0.02012	3.91±0.05253	3.5±0.266	0.531
F5	0.1983±0.002231	7.23±0.05742	3.89±0.08002	3.7±0.281	0.622
F6	0.2005±0.004224	7.26±0.02365	3.84±0.06537	3.3±0.152	0.472
F7	0.1947±0.00452	7.23±0.06511	3.93±0.08184	4.0±0.159	0.594
F8	0.1941±0.003243	7.24±0.03987	3.85±0.06357	3.8±0.254	0.633
F9	0.1946±0.004332	7.22±0.03514	3.88±0.07530	3.6±0.253	0.335
F10	0.1986±0.00278	7.24±0.03427	3.81±0.06782	4.3±0.256	0.608
F11	0.1971±0.003567	7.29±0.06621	3.83±0.08244	4.1±0.301	0.284
F12	0.1907±0.009002	7.27±0.03987	3.90±0.05311	3.5±0.357	0.736

Table 4: The disintegration time of the formulated batches was between 9 seconds to 59 seconds. The drug content of tablets was in between 93.22% to 106.69%. The content uniformity was in range of 79.68% to 114.38%.

Table 4: Post compression Evaluation results

Batch	Disintegration time (Sec) (NMT 1min)	Assay (%) (90% to110%)	Drug Content Uniformity (Q±15%)
F1	33	96.32	88.23% to 97.36%
F2	16	96.78	89.32% to 101.2%
F3	9	98.55	91.78% to100.18%
F4	26	100.42	82.54% to 103.1%
F5	22	97.78	88.52% to 96.69%
F6	15	102.63	89.19% to 101.7%
F7	55	93.22	79.68% to 99.70%
F8	47	106.69	84.82% to 105.72%
F9	35	98.91	81.41% to 109.37%
F10	59	94.51	77.4% to 96.83%
F11	34	105.011	79.71% to 109.25%
F12	29	96.14	83.62% to 114.38%

In-Vitro Dissolution Studies

Table 5-8: The dissolution of the formulation varied with variation in the concentration of the superdisintegrants. The in-vitro dissolution studies show maximum release of 89.47% in formulation F3 and minimum of 77.64% in formulation F12.

Dissolution Profile of formulations F1 to F3

Table 5: Dissolution Profile of formulations F1 to F3

Time	F1	F2	F3
0	0.00	0.00	0.00
5	36.58	39.98	42.56
10	45.27	49.57	54.15
15	53.90	58.63	61.25
20	65.85	69.33	76.32
30	81.69	83.21	89.47

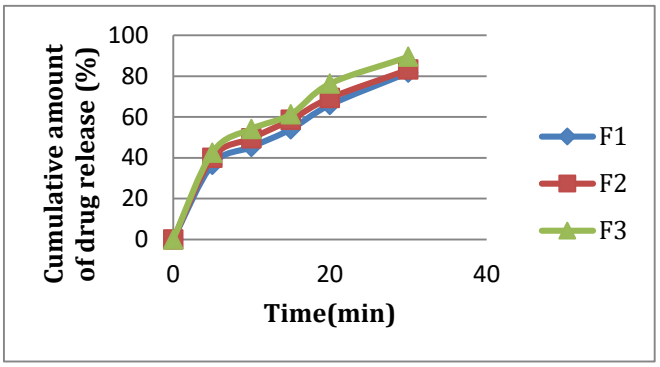

Fig 2: Comparison of cumulative amount of drug release vs time of formulations F1, F2 and F3

Dissolution Profile of formulations F4 to F6

Table 6: Dissolution Profile of formulations F4 to F6

Time	F4	F5	F6
0	0.00	0.00	0.00
5	38.52	36.32	40.56
10	51.21	47.71	51.27
15	59.74	51.68	63.57
20	67.13	66.27	71.21
30	83.35	82.84	87.17

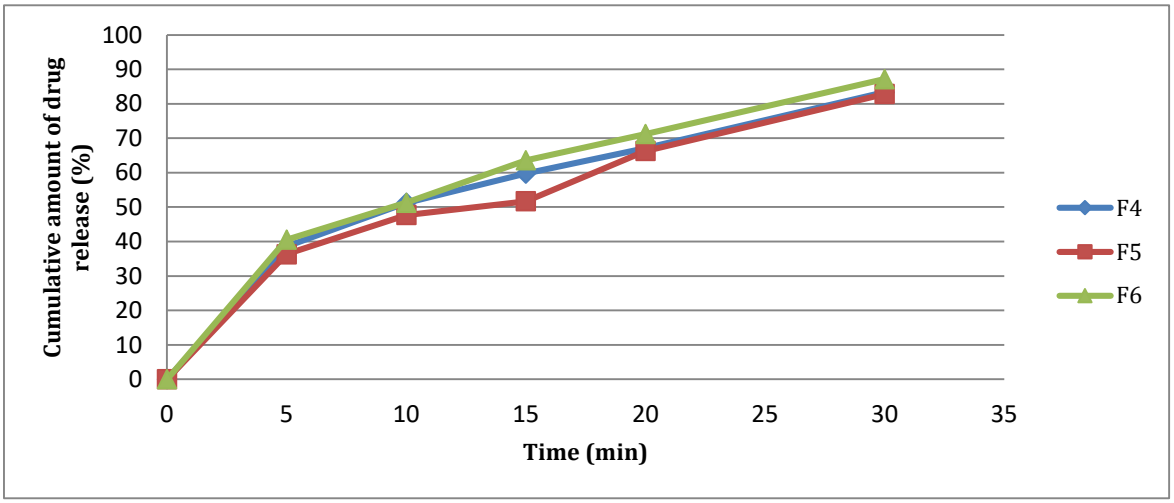

Fig 3: Comparison of cumulative amount of drug release vs time of formulations F4, F5 and F6

Dissolution Profile of formulations F7 to F9

Table 7: Dissolution Profile of formulations F7 to F9

Time	F7	F8	F9
0	0.00	0.00	0.00
5	32.56	34.21	38.47
10	41.25	48.86	44.61
15	53.14	57.93	57.32
20	65.35	70.31	68.54
30	78.91	79.53	81.26

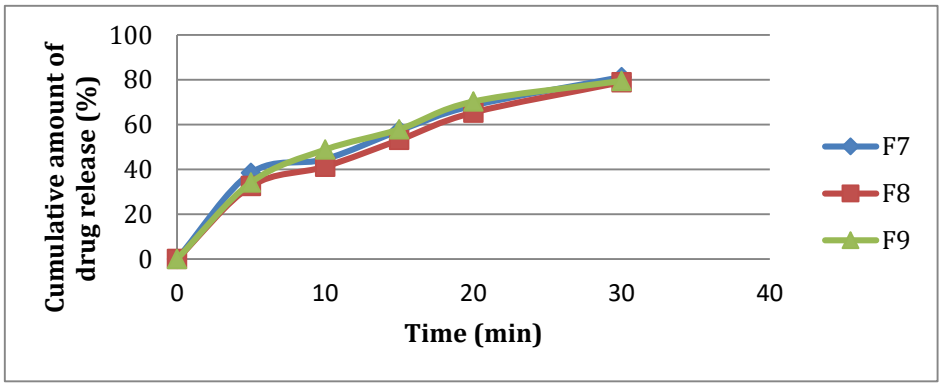

Fig 4: Comparison of cumulative amount of drug release vs time of formulations F7, F8 and F9

Dissolution Profile of formulations F10 to F12

Table 8: Dissolution Profile of formulations F10 to F12

Time	F10	F11	F12
0	0.00	0.00	0.00
5	31.89	33.56	29.43
10	43.53	45.36	41.54
15	51.24	53.75	50.39
20	65.44	64.23	61.27
30	79.36	81.66	77.64

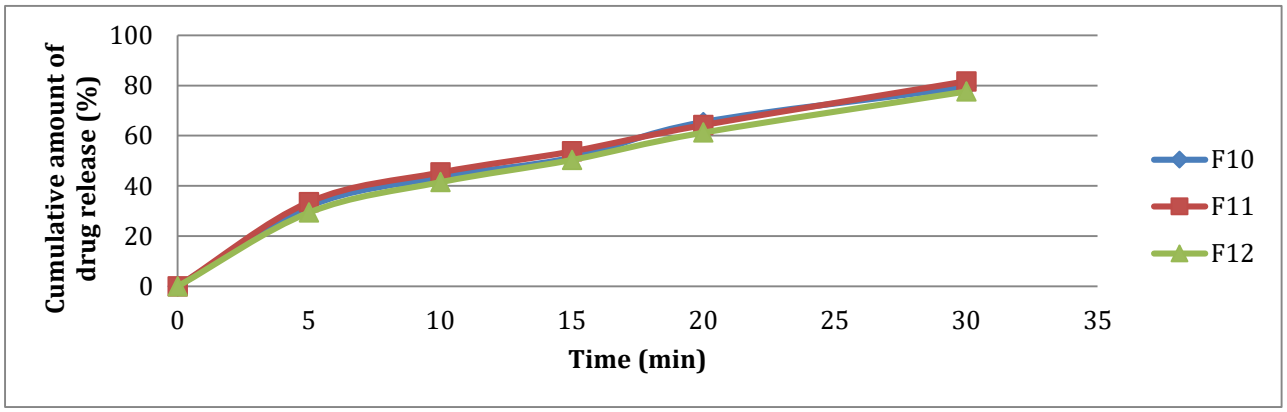

Fig 5: Comparison of cumulative amount of drug release vs time of formulations F10, F11 and F12

FTIR Results

FTIR studies were done to evaluate whether there is any interaction between the active ingredient Furosemide and the excipients used in the formulations. The peaks of the active ingredient Furosemide and the mixture of excipients correlate with one another, the peaks positions are at the same wave number, however there is a broadband of amine group at 3340 cm^{-1} which may probably be due to the interactions caused by intramolecular hydrogen bonding, other than that there are no other interactions between the active ingredient and the excipients used.

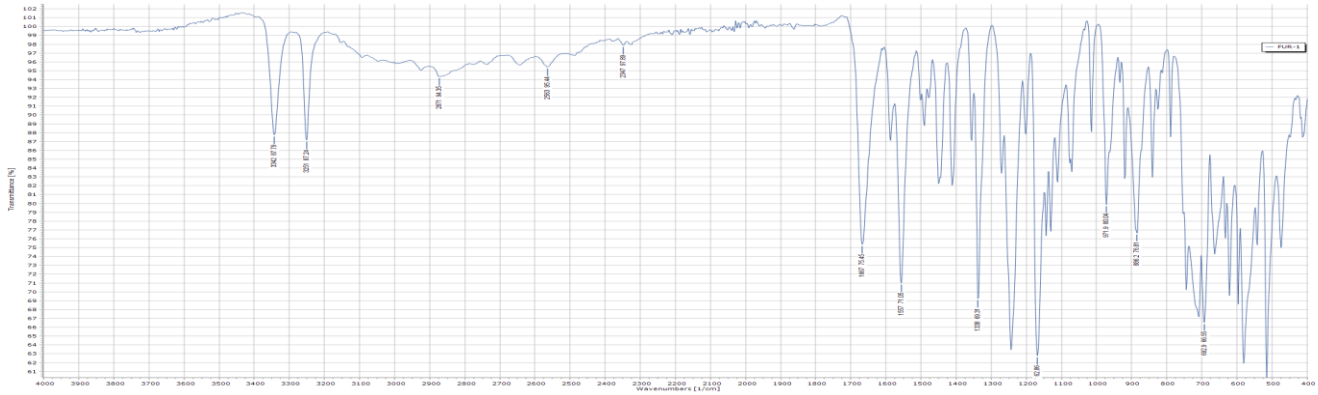

Fig 6: FTIR Spectra of Furosemide pure drug

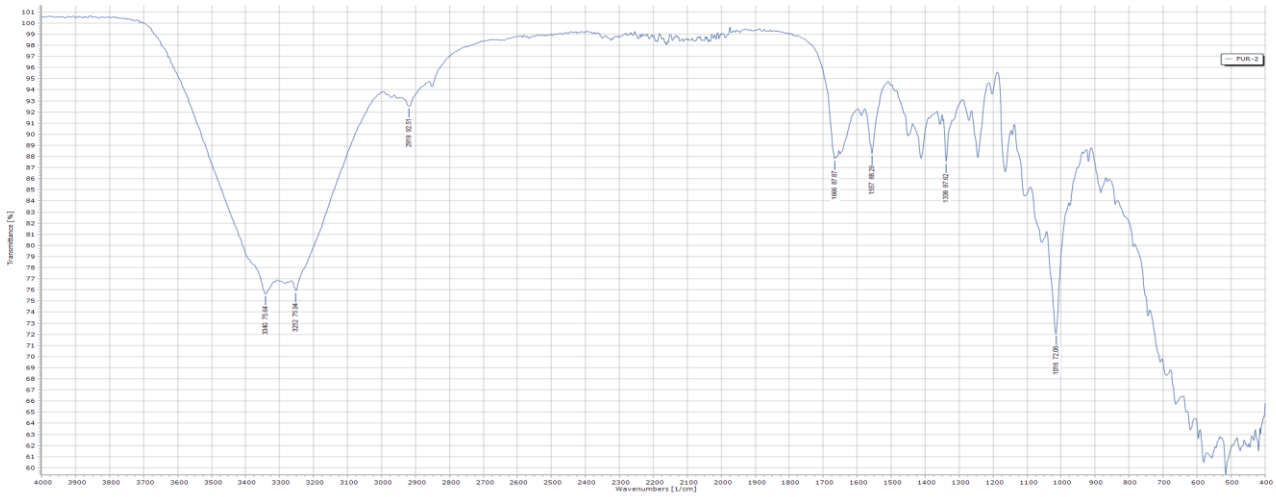

Fig 7: FTIR Spectra of Furosemide Optimized formulation

Discussion

The oral disintegrating tablets of Furosemide were formulated and evaluated. The use of superdisintegrants for the formulation of the ODTs was satisfactory and commercially feasible. The use of superdisintegrants caused quick disintegration and prompt dissolution of the tablet.

The FTIR studies of the drug molecule and its mixture with the excipients were performed to confirm the compatibility of the drug molecule and the excipients. The FTIR peak of the drug molecule correlates with that of the mixture which confirms that the mixture is compatible and there is no interaction between the components [9].

The use of the superdisintegrants alone showed better results with better hardness, disintegration and dissolution, rather than combining them. This may be due to the fact that the concentration of superdisintegrants we used in combination was higher than the critical concentration which results in the retardation of water swellability of the superdisintegrants, which is reflected by our results [10].

The use of crospovidone and croscarmelose as superdisintegrants showed better results than sodium starch glycolate. These findings are also supported by other studies performed by Nagoba Shivappa, Warkari Rajan, Shimge Krishna, Gaikwad in Channabasweshwar Pharmacy College, Latur, India [11] and also by T.Gulsun, N.Ozturk, M.S. Kaynak, I.Vural, S.Sahin in İnönü University, Malatya, Turkey [12]. However the study conducted by Dr. Shahid Mohammed in Deccan School of Pharmacy, Hyderabad on Formulation and evaluation of Furosemide oral dispersible tablets showed better results in use of sodium starch glycolate as superdisintegrant [13].

This could be due to the reason that the ingredients used for trial formulations by Dr. Shahid Mohammed are different from ours. Dr. Shahid Mohammed primarily used mannitol as the fillers in tablets whereas MCC was used on our tablets as diluents. MCC is often used as a diluent and this excipient also possess the ability to improve the disintegration of the tablets [14].

The use of MCC and its property to act as a disintegrating agent and the different concentrations of the ingredients could be the reason for variation of our results from the results of research conducted by Dr. Shahid Mohammed.

All the tablets passed the weight variation test as the percentage weight variation was within USP limits. The average weight of formulation varies from 190.75 mg to 200.5 mg. The hardness of the tablets was in between 3.2 to 4.3 kg/cm^2. The friability of the tablets was in between 0.165% to 0.736%. The disintegration time of the formulated batches was between 9 seconds to 59 seconds. The drug content of tablets was in between 93.22% to 106.69%

Disintegration time is one of the important parameters that govern the evaluation of the different formulations. For most formulations, it was observed that when the concentration of superdisintegrants was increased, the disintegration time was decreased. The batch F3 has the lowest DT as compared to other formulations with acceptable hardness and friability. Also, the data obtained from in-vitro dissolution studies suggests that the formulation F3 has the highest cumulative drug release of 89.47%. Thus, the formulation as per batch F3 is found to be the most promising batch**.**

Conclusion

The oral disintegrating tablets of Furosemide were prepared successfully by the use of direct compression method. Different formulations were designed to evaluate the influence of different concentrations of superdisintegrants on ODTs of Furosemide. Twelve formulations with different concentrations of superdisintegrants were prepared. FTIR studies using the drug and its mixtures with the excipients showed that the peaks correlate with one another which signify that there is no interaction between the drug molecule and the excipients used. The results justify that the increase in the concentration of superdisintegrants leads to the decrease in the disintegration time. The formulation prepared by using crospovidone as superdisintegrant has shown good in-vitro dispersion time. Among the formulations, the formulation as per batch F3 is found to be the most promising batch where 8% of crospovidone is used in each tablet as superdisintegrant, with the drug release of 89.47% within 30 minutes.

This suggests that the composition of Furosemide ODTs could be optimized so as to obtain rapid disintegration and drug dissolution along with acceptable tablets hardness and friability. This could be beneficial to improve the drug's

absorption and bioavailability, which ensues better patient compliance and convenience.

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Conflict Of Interest

The authors declare that there is no conflict of interest.

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