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DISSOLUTION ENHANCEMENT OF A POOR WATER SOLUBLE DRUG FUROSEMIDE BY SOLID DISPERSION TECHNIQUE

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ABSTRACT

The aim of the present study was to enhance the dissolution rate of a poor water-soluble drug furosemide by solid dispersion technique using different hydrophilic carriers, superdisintegrants and surfactants by kneading method. Plackett Burman Design as an Experimental Design was used for screening of the carriers such as β-cyclodextrin, Mannitol, Crospovidone, Croscarmellose Sodium, Sodium Starch Glycolate, Tween 80 and Milk powder. Among the carriers, β-cyclodextrin and Crospovidone showed best effect on dissolution. For the optimization of the concentration of β-cyclodextrin and Crospovidone in solid dispersion, Central Composite Design was employed. Response surface plot, contour plot, overlaid contour plot and response optimizer plot were drawn and an optimum formulation was selected as CCD F8 which contains 40 mg (20 %) of β-cyclodextrin and 11.24 mg (5.62 %) of Crospovidone. The in-vitro dissolution study was carried in USP Type II apparatus at different time interval in different medium. The comparative dissolution profile of the optimized solid dispersion formulation, conventional drug formulation and market product of furosemide indicated that the solid dispersion product showed significantly greater dissolution. Thus solid dispersion technique is a promising technique that can be successfully employed for the enhancement of the dissolution profile of poor water soluble drug furosemide.

KEYWORDS: Solid Dispersion, Furosemide, Dissolution enhancement, Poor water soluble drug, β-cyclodextrin, Crospovidone.

INTRODUCTION

Oral route of drug delivery is becoming the most desirable and preferred method of administration of therapeutic agents for their systemic as well as local effects.[1] The biggest problem in oral drug delivery is poor aqueous solubility and low intestinal permeability which leads to low and erratic bioavailability of drug. The poor solubility of drug substances in water and their low dissolution rate in aqueous gastro intestinal tract (G.I.T) fluid often leads to insufficient bioavailability.[2] Among various approaches, the solid dispersion technique is a promising and most successful method because of its simplicity, economical and advantages. A solid dispersion can be defined as the dispersion of one or more active ingredients in an inert carrier matrix. Furosemide a potent loop diuretic is practically insoluble in water which leads to its poor bioavailability.[3] Mechanism responsible for solubility enhancement from solid dispersion includes high porosity of drug particle, reduced particle size, improved wettability[4] and drug in amorphous state.[5] Methods for solid dispersion preparation includes Solvent method, Melting solvent method (melt evaporation), Fusion / Melting method , Melt extrusion methods, Lyophilization techniques, Melt agglomeration process, The use of surfactant, Electro spinning,[6] Super Critical Fluid (SCF) technology, Inclusion complex,[5] capsule filling[7] and Kneading method.[8] Kneading method is simplest technique to prepare drug solid dispersion which is economic, environment friendly, avoids thermal degradation of drug and usage of organic solvents.[9]

Carrier selection in solid dispersion is a difficult process. Highly water-soluble carriers are preferred for solubility, bioavailability and dissolution rate enhancement. On contrary, water insoluble or slowly soluble or swellable or enteric polymers are used to prepare controlled or delayed-release formulations. The carriers should be heat stable, freely water soluble or soluble in organic solvents, nontoxic and pharmacologically inert.[10] Interesting method to improve the dissolution of solid dispersion tablet with high drug load might be incorporation of superdisintegrants in solid dispersion; because tablet will rapidly disintegrate, prevent crystallization of the drug, don't irritate gastrointestinal tract and can be used at low amounts in formulation.[11]

The objective of this study was to prepare solid dispersion of furosemide using different carriers and disintegrant to increase dissolution, study of effect of different excipients used in the formulation on the dissolution profile, formulation of furosemide tablet using chosen

carriers and finally comparison of dissolution profile with conventional drug formulation and market product.

MATERIAL AND METHOD

Materials

Furosemide and its reference standard (Potency: 99.19 %) along with excipients such as Mannitol, Croscarmellose sodium, Crospovidone, Sodium Starch Glycolate were received from Lomus Pharmaceutical Pvt ltd, Gothatar, Bhaktapur, Nepal as a gift sample. Other excipients such as β-cyclodextrin, Tween 80, Aerosil, Magnesium stearate and Talc were bought from market. Market products of furosemide were purchased from local pharmacy and Milk powder was bought from the local market.

METHODS

Analytical method development

Scanning for the determination of λ max of Furosemide

A 100 mg of furosemide RS with potency 99.19 % was weighed accurately and shaked with 150 ml of 0.1 M Sodium Hydroxide (NaOH) for 10 minutes. Then sufficient 0.1 M NaOH was added to produce 250 ml. The solution was filtered and from filtrate 5 ml was taken and diluted to 200 ml with 0.1M NaOH solution and labeled as stock solution. The spectrum of this solution was run from 200-400 nm range in UV-visible spectrophotometer.

Analytical method validation

UV visible-spectrophotometric method for assay was developed and validated. Assay method validation was done in terms of Linearity, Specificity, Accuracy and Precision, Limit of Detection (LOD) and Limit of Quantification (LOQ) and Range.[12]

Design of Experiment (DOE)

For DOE Minitab 16 software was used. Initially, ten excipients such as β-cyclodextrin, Mannitol, Crospovidone, Croscarmellose Sodium, Sodium Starch Glycolate, Polysorbate 80, Milk powder, talc, magnesium stearate and aerosil were used for Plackett-Burman Design (PBD) to determine their role in dissolution of tablet and then screen the excipients that has major effects on dissolution rate.

After that, central composite design (CCD) was used for the optimization of the concentration of carriers. Two level full factorial central composite design with 4 cube points (α=1.414), 5 center points and 4 axial points with 1 replication resulting in a total of 13 experiments.

Preparation of solid dispersion granules

The drug and carriers as per respective design were passed through sieve no 60. Then furosemide and carrier of each formulation were weighed according to respective design and mixed in poly bag for 10 minutes. The blend was kneaded thoroughly for 15 minutes in mortar by the use of ethanol and water (1:1) ratio as solvent. The paste so formed was dried at 40-60 ^{0}C in hot air oven. Dried granules were pulverized through 14 mm mesh. The granules were stored in desiccator until further use.

Preparation of solid dispersion tablets

Solid dispersion granules were subjected for dry granule mixing with aerosil and MCC for 5 minutes. After that powder blend was lubricated with Magnesium stearate and Talcum (Only in Plackett Burman Design) for 2 minutes. Micromeritic properties of furosemide powder blend were evaluated and finally subjected for compression in 10 station rotatory compression machine to get solid dispersion tablet.

Evaluation of solid dispersion tablet

The solid dispersion tablets were evaluated in terms of weight variation, thickness and diameter, hardness, friability, disintegration time, wetting time, assay and in vitro dissolution. Weight variation of solid dispersion tablet (n=20) was evaluated using electronic balance,[13] thickness and diameter of tablets were measured using vernier caliper, hardness of tablets (n=6) were determined using tablet hardness tester (Thermonik), friability test of tablets (n=20) were done by Roche friabilator rotated at 25 rpm for 4 minutes,[14] wetting time of tablets was determined by placing tablets on wet surface of tissue paper kept on petri dish of 10 cm diameter.[15] Disintegration time of tablets (n=6) were evaluated using 900 ml de mineralized water at 37±0.5 ^{0}C in disintegration test apparatus, Assay of tablets was carried out by measuring absorbance of sample at 271 nm using UV-Visible spectrophotometer (Shimadzu).[13]

In-vitro Dissolution test[16]

The dissolution test was carried out using USP Apparatus II. The medium used was 900 ml of phosphate buffer pH 5.8 kept at 37 $\pm$ 0.5 ^{0}C. The paddle was rotated at 50 revolutions per

minute for 60 minutes. A sample of 10 ml was withdrawn and filtered through Whatsmann filter paper no 1 at different interval of time. Then 5 ml of filtrate was sufficiently diluted with dissolution medium. Furosemide reference standard solution was prepared and absorbance was taken at 277 nm. The percentage of drug release in the sample was determined by taking absorbance of sample solution at 277 nm against dissolution medium as blank.

$$\% \text{ Drug Release} = \frac{\text{Absorbance of sample} \times \text{Dilution factor} \times \text{Potency of standard} \times 100}{\text{Absorbance of standard}} \quad \text{.....1}$$

$$\text{Dilution factor} = \frac{\text{Standard weight taken} \times \text{Sample dilution}}{\text{Average assay of sample} \times \text{Standard dilution}} \quad \text{.....2}$$

Optimization of the formulation

Different formulations of the solid dispersion tablet containing variable concentration of carriers were optimized using distance based optimality, surface plot, contour plot, composite counter plot and response optimizer plot.

Comparison of Dissolution profile of optimized batch with conventional drug formulation and Market product

The dissolution profile of optimized batch was compared with the conventional drug formulation and conventional market product of furosemide.

RESULT AND DISCUSSION

Analytical method development and validation

Suitable analytical method based on UV- visible spectrophotometer was developed for furosemide at λ max 271 nm in 0.1 M NaOH.

Analytical method validation was performed in terms of linearity, specificity, accuracy, precision, detection limit, quantification limit and range. The regression analysis for linearity showed very good correlation (R^2=0.999) as shown in figure 1.

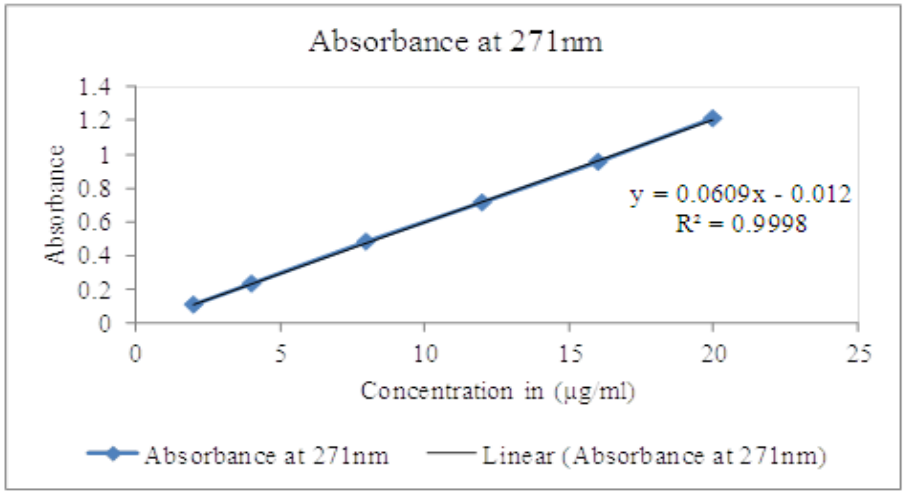

Figure 1: Standard calibration curve of furosemide in 0.1 M sodium hydroxide

The method was found to be specific to furosemide with negligible interference. The method also holds good accuracy with % recovery of 99.06 % -101.50 % and good precision with % RSD of 1.06 % which is NMT 2 %. The detection limit was 0.034µg/ml and quantification limit was 0.103µg/ml. The range was found to be 0.103µg/ml to16.44µg/ml.

Experimental Designs

Plackett Burman Design

Plackett Burman Experimental Design with Ten variables viz. Mannitol, Milk Powder, β-Cyclodextrin, Croscarmellose sodium, Sodium starch Glycolate, Crospovidone, Tween 80, Aerosil, Talc and Magnesium stearate was performed using Minitab 16 to screen excipients that were significantly the drug release.

Table 1: Formulation of tablet as per factors considered during Plackett Burman Design (PBD)

Formulation Code	FRU	Mannitol	BCD	MP	CCS	SSG	CP	T80	ASL	Talc	Mg S	MCC	Total
PBD F1	40	20	0	20	0	0	0	6	2	4	2	151	250
PBD F2	40	20	20	0	7.5	0	0	2	2	4	4	145.5	250
PBD F3	40	0	20	20	0	9	0	2	1	4	4	150	250
PBD F4	40	20	0	20	7.5	0	7.5	2	1	2	4	141	250
PBD F5	40	20	20	0	7.5	9	0	6	1	2	2	137.5	250
PBD F6	40	20	20	20	0	9	7.5	2	2	2	2	120.5	250
PBD F7	40	0	20	20	7.5	0	7.5	6	1	4	2	142	250
PBD F8	40	0	0	20	7.5	9	0	6	2	2	4	159.5	250
PBD F9	40	0	0	0	7.5	9	7.5	2	2	4	2	176	250
PBD F10	40	20	0	0	0	9	7.5	6	1	4	4	153.5	250
PBD F11	40	0	20	0	0	0	7.5	6	2	2	4	168.5	250
PBD F12	40	0	0	0	0	0	0	2	1	2	2	203	250

Table 2: Assay and dissolution of formulations prepared according to Plackett Burman Design (PBD)

Formulation Code	Average assay (%)	Absorbance of Sample at 277nm	Cumulative % release at 15 min
PBD F1	98.1	0.315	71.08
PBD F2	98.0	0.432	97.38
PBD F3	99.66	0.424	95.58
PBD F4	97.12	0.488	109.99
PBD F5	100.42	0.464	104.59
PBD F6	99.13	0.517	116.51
PBD F7	98.56	0.376	89.28
PBD F8	102.52	0.380	85.68
PBD F9	99.67	0.327	73.76
PBD F10	100.33	0.413	93.11
PBD F11	99.93	0.444	100.09
PBD F12	98.33	0.170	38.43

During the statistical evaluation, the excipients required for better drug release were determined using Main effect plot of Plackett Burman Design.

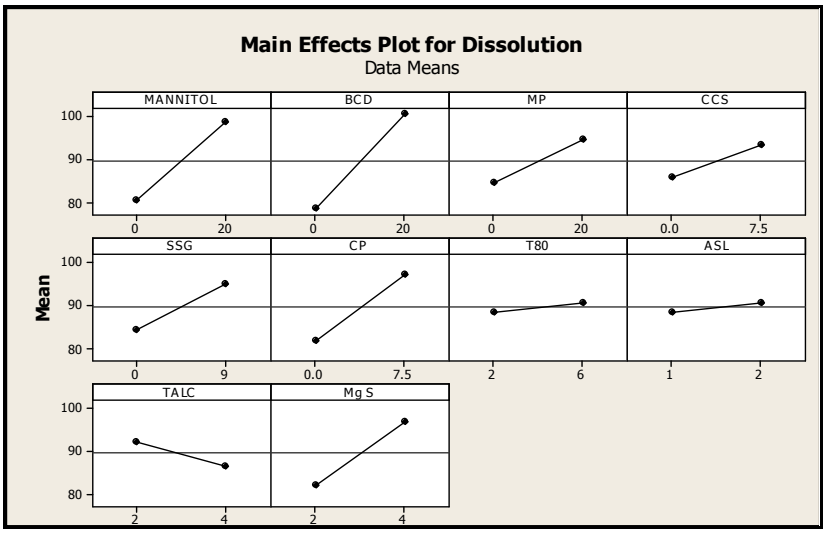

Figure 2: Main effect plot showing effect of different factors on dissolution of Furosemide tablets at 5 minutes

The result of main effect plot showed that Mannitol, β-cyclodextrin, Milk powder Croscarmellose sodium, Sodium starch Glycolate, Crospovidone are significant factors with positive coefficient for drug release and Talc is found insignificant with negative coefficient for drug release. Tween 80, Aerosil and Magnesium stearate affected dissolution with minimal coefficient for drug release. Among the three carrier viz. Mannitol, β-cyclodextrin and Milk powder, β- cyclodextrin has maximum effects on drug release. Among the three super disintegrant viz. Sodium Starch Glycolate, Crospovidone and Croscarmellose sodium

the maximum effect for dissolution was shown by the crospovidone. Hence β- cyclodextrin and crospovidone were chosen for preparation of solid dispersion.

Central composite Design

Significant factors β-cyclodextrin and Crospovidone as per Plackett-Burman Design that contribute in drug release were further optimized by response surface methodology using Minitab 16 software.

Table 3: Formulation of tablet according to Central Composite Design (CCD)

Formulation Code	Furosemide (mg)	β-cyclodextrin (mg)	Crospovidone (mg)	Aerosil (mg)	Magnesium Stearate (mg)	MCC (mg)	Total (mg)
CCD F1	40	20	4	2	2	132	200
CCD F2	40	60	4	2	2	92	200
CCD F3	40	20	10	2	2	126	200
CCD F4	40	60	10	2	2	86	200
CCD F5	40	11.71	7	2	2	137.29	200
CCD F6	40	68.28	7	2	2	80.72	200
CCD F7	40	40	2.75	2	2	113.25	200
CCD F8	40	40	11.24	2	2	104.76	200
CCD F9	40	40	7	2	2	109	200
CCD F10	40	40	7	2	2	109	200
CCD F11	40	40	7	2	2	109	200
CCD F12	40	40	7	2	2	109	200
CCD F13	40	40	7	2	2	109	200

Optimization of the formulation

For the optimization of the concentration of β-cyclodextrin and Crospovidone distance based optimality in minitab 16 was used.

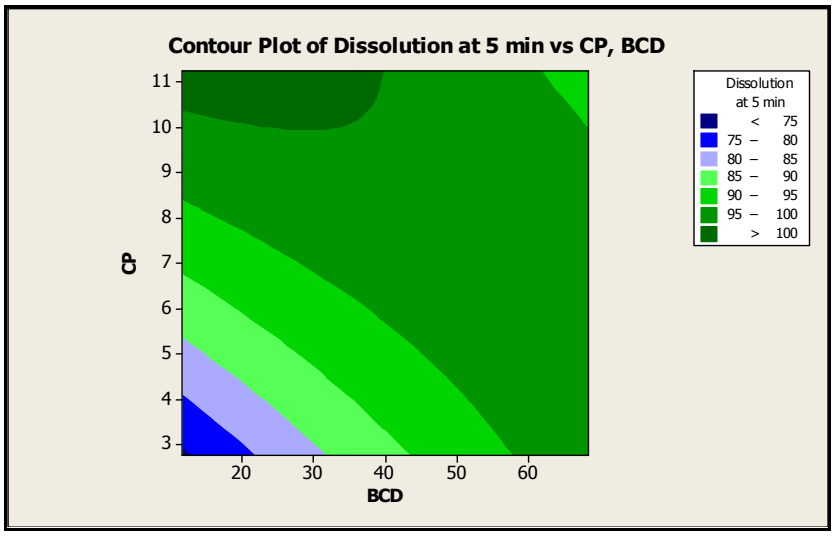

Figure 3: Contour plot of dissolution at 5 minute vs crospovidone, β-cyclodextrin

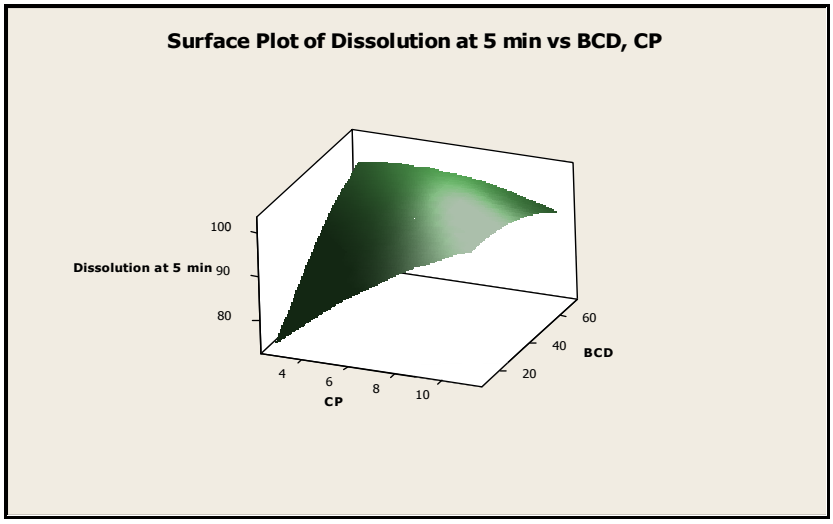

Figure 4: Surface plot of dissolution at 5 minute vs β-cyclodextrin, crospovidone

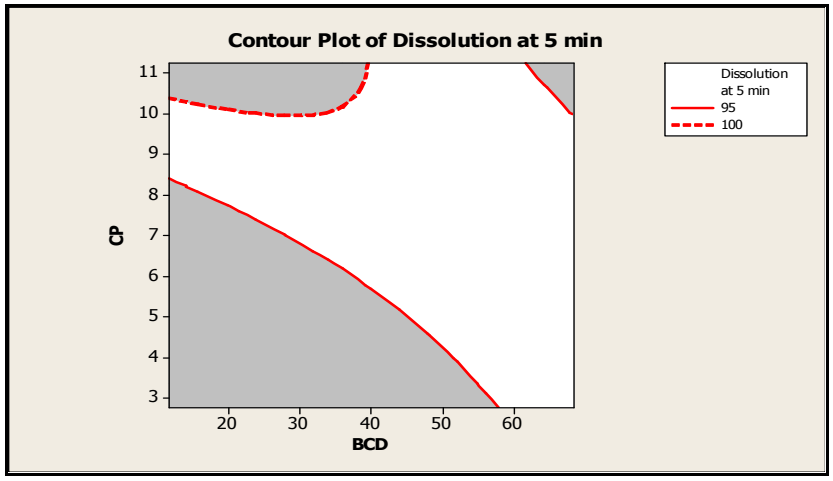

Figure 5: Overlaid contour plot of dissolution at 5 minute vs crospovidone, β-cyclodextrin

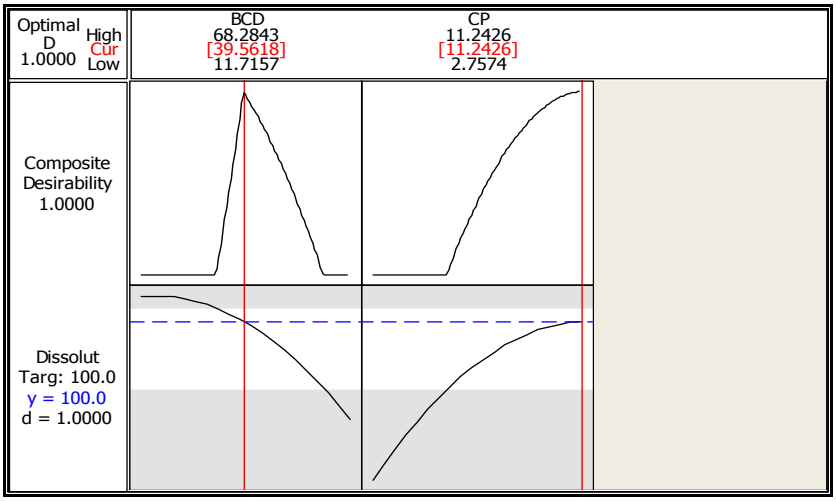

Figure 6: Response optimizer plot for two variables with desired target of 100% drug release at 5 minutes

After evaluation of the Contour plot, Surface plot, Overlaid contour plot and Response optimizer plot the optimum batch was obtained to be CCD F8.

Evaluation of Pre- compressional parameters

Micromeritic properties of lubricated granules of furosemide solid dispersion tablet were determined.

Table 4: Result of pre-compression parameter of formulated batches by CCD

Formulation Code	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Hausner's ratio	Angle of repose(θ)	Carr's index (%)	Flow property
CCD F1	0.392	0.487	1.24	39.22	19.67	Fair
CCD F2	0.384	0.570	1.48	42.92	33.33	Passable
CCD F3	0.408	0.526	1.28	39.80	22.43	Fair
CCD F4	0.476	0.710	1.50	38.65	33.80	Fair
CCD F5	0.384	0.465	1.21	37.04	17.43	Fair
CCD F6	0.465	0.760	1.65	44.29	39.47	Passable
CCD F7	0.408	0.555	1.36	42.92	26.48	Passable
CCD F8	0.400	0.550	1.38	37.56	27.87	Fair
CCD F9	0.321	0.442	1.37	44.29	27.47	Passable
CCD F10	0.324	0.445	1.37	42.92	27.47	Passable
CCD F11	0.317	0.440	1.38	43.60	27.47	Passable
CCD F12	0.327	0.449	1.37	44.29	27.47	Passable
CCD F13	0.318	0.438	1.37	43.60	27.47	Passable

The overall flow properties of the granules were found fair and passable.

Evaluation of Post- compressional parameters

Table 5: Result of post-compression parameter of formulated batches according to CCD

Experiments	Weight variation (mg) (n=20)	±SD	Average Thickness (mm) (n=10)	±SD	Average Diameter (mm) (n=10)	±SD	Average Hardness (Kg/cm^2) (n=10)	±SD	Friability (%)	Assay (n=3)	±SD	DT (sec)	Wetting Time (sec)
CCD F1	202.97	3.29	3.08	0.04	8.00	0.00	6.15	0.24	0.049	99.99	0.47	10	28
CCD F2	203.47	3.29	3.58	0.27	7.99	2.51	5.10	0.31	0.127	101.04	0.81	8	20
CCD F3	204.57	3.02	4.00	0.06	8.03	2.39	5.30	0.34	0.048	101.56	0.44	6	13
CCD F4	204.86	3.52	4.00	0.06	8.00	0.00	4.30	0.34	0.385	99.18	1.31	18	22
CCD F5	203.5	2.20	4.04	0.65	8.03	2.39	4.80	0.42	0.147	99.99	0.27	8	14
CCD F6	203.57	2.12	4.02	0.06	8.02	0.04	5.05	0.28	0.088	99.70	0.62	14	18
CCD F7	203.57	2.24	3.99	0.07	8.00	0.04	4.80	0.25	0.157	98.08	0.08	6	13
CCD F8	204.27	2.95	3.95	0.05	8.02	0.04	4.70	0.34	0.029	100.46	0.19	4	12
CCD F9	202.22	1.74	4.00	0.86	8.02	0.04	4.20	0.25	0.044	99.01	0.94	12	18
CCD F10	201.77	1.83	3.90	0.87	8.00	0.00	4.20	0.25	0.049	99.98	0.84	13	18.5
CCD F11	202.11	2.31	3.95	0.76	8.02	0.04	4.15	0.24	0.014	100.01	0.93	12	18
CCD F12	203.22	2.22	3.99	0.86	8.00	0.00	4.20	0.25	0.088	100.11	0.94	11	18.5
CCD F13	201.90	2.31	3.95	0.88	8.00	0.00	4.20	0.25	0.014	99.89	0.93	12	18

The weight variation of all the prepared tablets were found to be within range of 201.77 mg to 204.86 mg which was within acceptable limit (±7.5% of average weight ranging from

185mg-215mg) as per IP specifications. The hardness of the tablet was between 4.15 ± 0.24 Kg/cm^2 of formulation CCD F11 to 6.15±0.24 Kg/cm^2 of formulation CCD F1. The thickness of tablet was found between 3.08 ± 0.04 mm of formulation CCD F1 to 4.04±0.65 mm of formulation CCD F5. The diameter of tablet was found between 7.99±2.51 mm of formulation CCD F2 to 8.03±2.39 mm of formulations CCD F3 and CCD F5. The friability was between 0.014 % of formulation CCD F11 and CCD F13 to 0.385 % of formulation CCD F4 which was below 1 %. The average wetting times and disintegration times of all the formulation prepared according to CCD were determined.

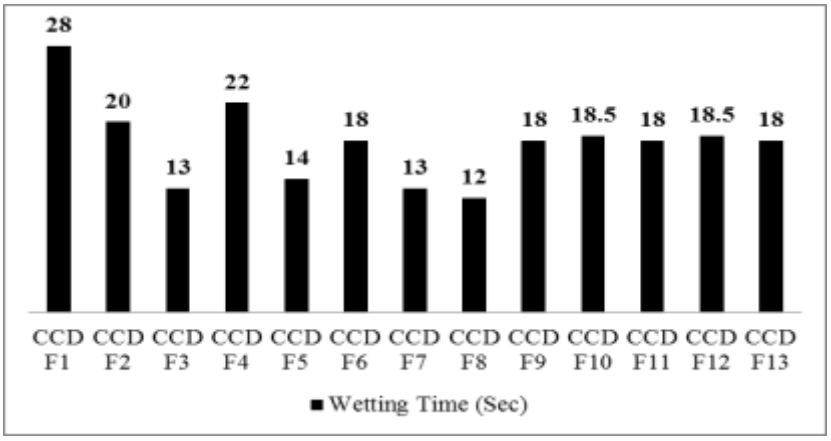

Figure 7: Wetting time of all CCD batches in water

Among formulation prepared according to the CCD, the formulation which shows least wetting time (12 sec) was CCD F8 and formulation which shows highest wetting time (28 sec) was CCD F1. The least wetting time of CCD F8 might be due to the highest concentration of crospovidone. Faster wetting of tablets containing crospovidone might be due to its rapid water absorbing nature involving both capillary and swelling mechanisms.[17]

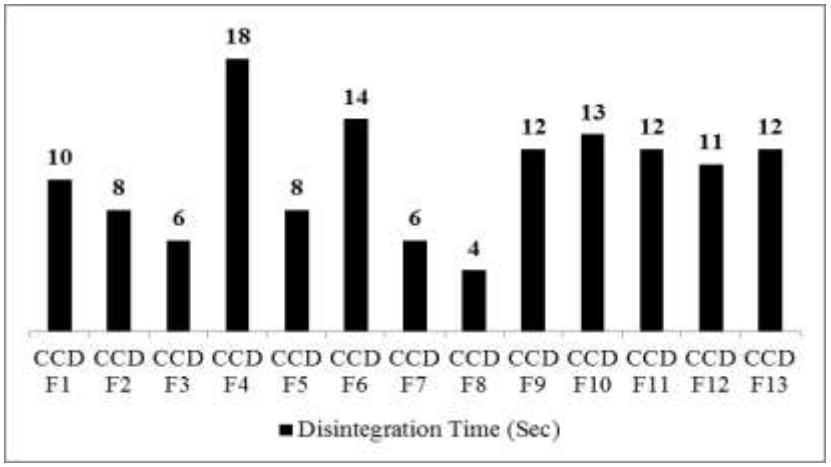

Figure 8: Disintegration time of all the CCD batches in water

Among various batches of CCD formulation, the batch which shows least disintegrating time was CCD F8 (4 sec) which might be due to presence of highest amount of crospovidone and the batch which shows highest disintegration was shown by CCD F4 (18 sec). Crospovidone polymers, with their porous particle morphology rapidly absorb water (wicking) via capillary action. As the deformed crospovidone particles come in contact with water that is wicked into the tablet, the crospovidone particles recover their normal structure and then swell, resulting in rapid volume expansion and high hydrostatic pressures that cause tablet disintegration.[18]

Assay

The assay of all the tablets was found in the range of 97.12% to 102.52% which was within the limit as shown in the table 2 and table 5. Furosemide tablets contain not less than 90.0 percent and not more than 110.0 percent of stated amount of furosemide.

In-vitro dissolution studies

Table 6: Dissolution study of CCD formulation at different time

Formulation Code	5 min	15 min	30min	45 min	60 min
CCD F1	88.62	94.70	97.85	100.77	101.22
CCD F2	100.62	100.62	100.84	101.06	101.06
CCD F3	100.84	101.28	101.50	101.95	102.39
CCD F4	96.56	99.83	99.94	100.05	101.29
CCD F5	87.50	105.28	105.51	106.18	106.18
CCD F6	96.69	99.23	99.93	100.16	100.39
CCD F7	83.46	90.77	95.44	99.57	101.41
CCD F8	100.40	100.62	100.85	101.07	101.07
CCD F9	97.00	100.40	100.86	101.31	101.54
CCD F10	97.00	100.21	100.66	100.68	100.68
CCD F11	97.00	100.00	100.11	100.11	100.11
CCD F12	97.00	100.01	100.11	100.19	100.20
CCD F13	97.00	100.40	100.80	100.98	101.00

All the formulation showed similar kind of drug release pattern i.e. immediate release at earlier and constant after that. Among the formulation, at 5 min, CCD F2, CCD F3 and CCD F8 showed highest drug release i.e above 100% and CCD F7 showed least percent of drug release i.e 83.46%. At 15 min and 30 min, almost all the CCD batches nearly showed 100% drug release except CCD F1 and CCD F7. After 45 min almost all the batches showed 100% drug release.

Comparison of dissolution profile of solid dispersion batches and market product in phosphate buffer pH 5.8

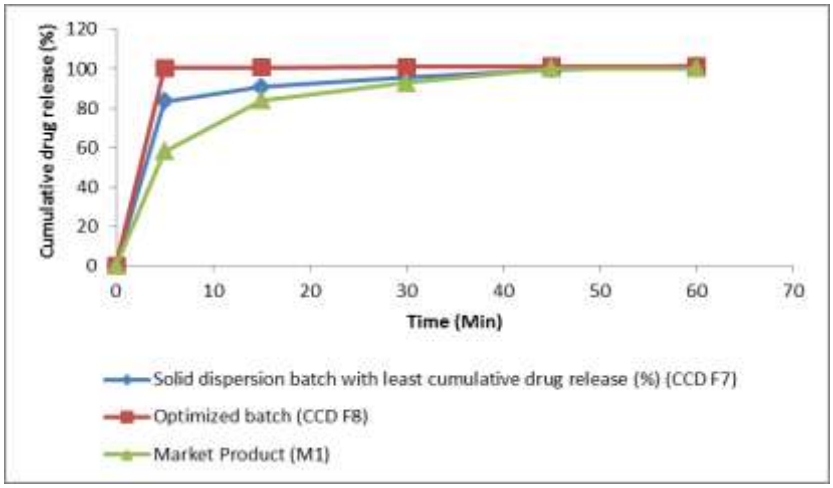

Figure 9: Dissolution profile of solid dispersion batch with least cumulative drug release (%) (CCD F7), optimized batch (CCD F8) and market product (M1) in phosphate buffer pH 5.8

The solid dispersion batches showed better drug release than market product. This might be due to the presence of the solid dispersed particle of drug inside hydrophilic carrier and superdisintegrants which makes faster wetting and disintegration of tablet.

Comparison of dissolution profile of conventional drug formulation (CDF), optimized batch (CCD F8) and market product (M1) in different mediums

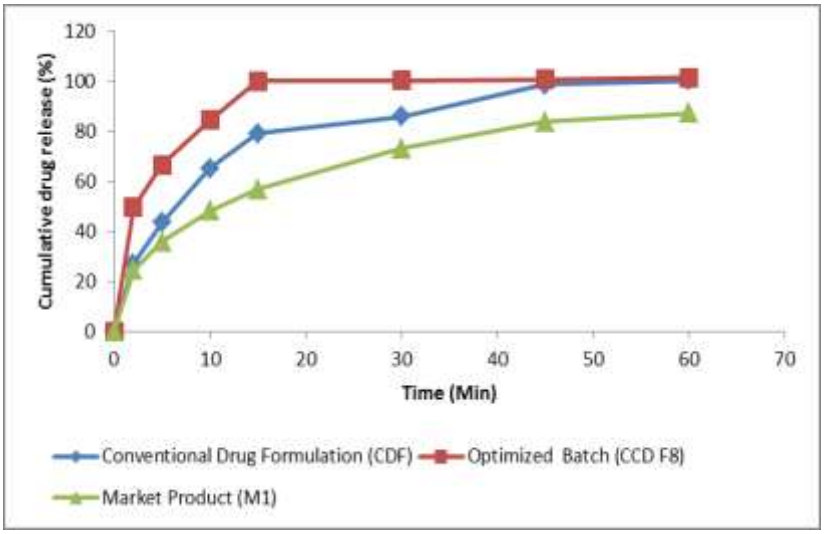

Figure 10: Dissolution profile of conventional drug formulation (CDF), optimized batch (CCD F8) and market product (M1) in 0.1 N HCL

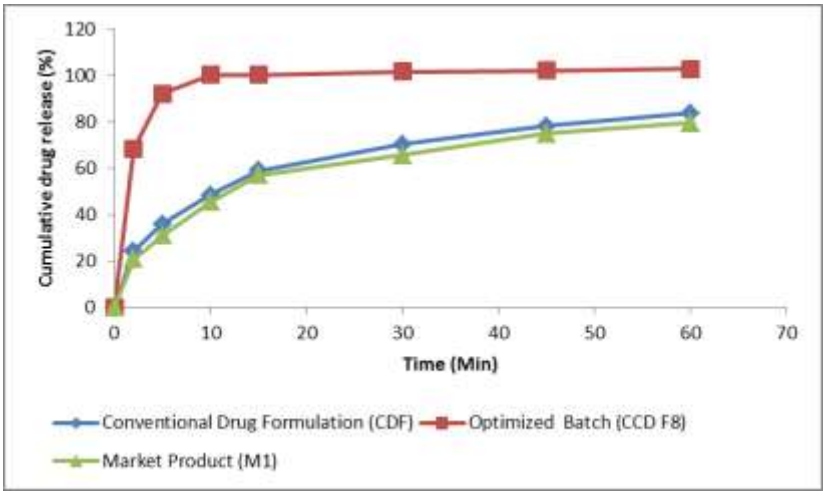

Figure 11: Dissolution profile of conventional drug formulation (CDF), optimized batch (CCD F8) and market product (M1) in water

The comparative dissolution profile in both mediums showed that optimized batch have significantly better dissolution profile than conventional drug formulation and market product. This might be due to the presence of finely dispersed furosemide in hydrophilic carrier (β-cyclodextrin) and superdisintegrant (Crospovidone) in the optimized batch. The β-cyclodextrin and crospovidone showed combined effect to increase the wetting rate, disintegration rate and finally dissolution rate.

CONCLUSION

Solid dispersion tablet with a view of obtaining faster action of the drug can be formulated by kneading method using carriers and superdisintegrants. Among all the formulations, the formulation CCD F8 prepared by solid dispersion of drug (40 mg), β-cyclodextrin (40 mg) and crospovidone (11.24 mg) was the optimized batch which meets the study objective. Thus it can be concluded that solid dispersion technique using combination of carrier and super disintegrant is the promising approach to enhance the dissolution rate of furosemide and other poor water soluble active pharmaceutical ingredients.

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