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DEVELOPMENT AND *IN VITRO* EVALUATION OF FUROSEMIDE ORODISPERSIBLE TABLETS BY 3^2 FACTORIAL DESIGN APPROACH

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ABSTRACT

The objective of the work was to develop Oro dispersible tablets of Furosemide with a view to enhance patient acceptance and rate of dissolution by direct compression method using 3^2 full factorial design. Croscarmellose sodium; X1 (2-10% w/w) was used as superdisintegrant and Microcrystalline cellulose; X2 (0-30% w/w) was used as diluent, along with Pearlitol SD-200 to enhance mouth feel. The tablets were evaluated for thickness, hardness, friability, drug content uniformity, *in vitro* dispersion time and wetting time. Based on *in vitro* dispersion time (approximately 30s); the formulation containing 10% w/w Croscarmellose sodium and 30%w/w Microcrystalline cellulose was found to be promising and evaluated for *in vitro* drug release pattern (in pH 6.8 phosphate buffer), short-term stability studies (at 40º/75% RH for 3 months) and drug-excipient interaction. Surface response plots are presented to graphically represent the effect of independent variables (concentrations of Croscarmellose sodium and Microcrystalline cellulose) on the *in vitro* dispersion time; Y1. The validity of the generated mathematical model was tested by preparing two extra-design check point formulations. The optimized tablet formulation was compared with conventional commercial tablet formulation for drug release profiles. This formulation showed nearly four-fold faster drug release ($t_{50\%}$ 2.60 min) compared to the conventional commercial tablet formulation ($t_{50\%}$ 7.90 min). Short-term stability studies on the formulation indicated that there are insignificant changes in drug content and *in vitro* dispersion time ($p < 0.05$).

KEYWORDS: Furosemide, Orodispersible tablets, Croscarmellose sodium, microcrystalline cellulose, 3^2 full factorial design.

INTRODUCTION

Difficulty in swallowing (Dysphagia) is a common problem of all age groups in concern to solid unit dosage form, especially geriatrics and pediatrics, because of physiological changes associated with these groups, which results in high incidence of non-compliance and ineffective therapy.[1] Recent advances in novel drug delivery systems (NDDS) aim to enhance safety and efficacy of drug molecule by formulating a convenient dosage form for administration and to achieve better patient compliance i.e., one, which will readily disintegrate in the mouth without need of water. Advantages of this system include administration without water, accuracy of dosage, easy portability, alternative to liquid dosage forms, ideal for pediatric and elderly patients and rapid onset of action.[2-4] Furosemide is a potent loop diuretic used in the treatment of congestive heart failure, cirrhosis of the liver, renal disease and chronic hypertension. The usual oral doses are 20, 40 and 80mg given as a single dose. According to the Biopharmaceutics classification system (BCS) furosemide is a class IV compound with low solubility and low permeability, because of its weak acidic properties (pKa=3.8). Furosemide is mostly absorbed in the stomach and upper intestine and also sublingual administration.[5-6] Aim of the present study was to develop such a novel novel system for furosemide by simple and cost effective direct compression method.[7-10]

MATERIALS AND METHODS

Furosemide was obtained as gift sample from Rajesh chemicals Co, Mumbai. Croscarmellose sodium, directly compressible mannitol (PearlitolSD200), sodium stearyl fumarate and microcrystalline cellulose (Avicel PH-102) were generous gifts from Strides Arco Labs, Bangalore, Glenmark Ltd., Nashik and Alkem Labs Pvt. Ltd, Mumbai, India. All other chemicals used were of analytical reagent grade.

Preparation of Oro Dispersible Tablets of Furosemide

Oro dispersible tablets of Furosemide were prepared by direct compression method.[11-13] According to the formulae given in Tab.1. All the ingredients were passed through #60 mesh separately. The drug and MCC were mixed by taking small portion of both each time and

blending it to get a uniform mixture and kept aside.[14-16] Then the other ingredients were weighed and mixed in geometrical order and tablets were compressed using 6 mm round flat punches to get tablets of 100 mg weight on a 10-station rotary tablet machine (Clit, Ahmadabad).

Table 1: Factorial design formulations of furosemide prepared by direct compression method.

Ingredients (mg/tablet)	Formulation code											
	Ff_0	Ff_1	Ff_2	Ff_3	Ff_4	Ff_5	Ff_6	Ff_7	Ff_8	Ff_9	C_1	C_2
Furosemide	20	20	20	20	20	20	20	20	20	20	20	20
Ccs	---	2	2	2	6	6	6	10	10	10	4	8
Mcc	10	0	15	30	0	15	30	0	15	30	7.5	22.5
Aspartame	3	3	3	3	3	3	3	3	3	3	3	3
Sodium stearyl fumarate	2	2	2	2	2	2	2	2	2	2	2	2
Talc	2	2	2	2	2	2	2	2	2	2	2	2
Banana flavour	1	1	1	1	1	1	1	1	1	1	1	1
Mannitol sd-200	62	70	55	40	66	51	36	62	57	32	60.5	41.5
Total	100	100	100	100	100	100	100	100	100	100	100	100

Formulation FF_9 was selected as the best and used in further studies;
FF_0 control formulation, C_1 and C_2 are extra design check-point formulations.

Evaluation of Oro Dispersible Tablets

Hardness

The crushing strength of tablets was measured by using Monsanto hardness tester.

Thickness

Tablet thickness was measured by using Screw gauge. Three tablets were randomly taken and measured by placing between two arms of Screw gauge.

Weight variation test

Twenty tablets were selected at random and average weight was determined using an electronic balance (Shimadzu BL-220H). Tablets were weighed individually and compared with average weight.

Friability test

The friability of tablets was measured in Roche friabilator. Twenty tablets were dedusted at 25 rpm for 4 min and weighed again. Percentage friability was calculated from loss in weight as given in equation below. The weight loss should not be more than 1% shown in Table 2.

% Friability = [(Initial weight _ Final weight)/Initial weight] ×100.

Table 2: Evaluation of factorial formulations.

Formulation	Hardness* (kg/cm2)± SD	Thickness (mm)	Friability (%)	*In vitro* dispersion time* (sec) ±SD	Drug content* (%)±SD	Wetting time* (seconds) ±SD
FF_0	3.48±0.11	3.12	0.34	160±1.22	99.2±0.57	172.10±1.0
FF_1	3.43±0.10	2.53	0.72	90.35±0.52	98.52±0.22	92.49±0.52
FF_2	3.60±0.102	2.92	0.46	81.73±0.75	95.88±0.7	83.47±0.59
FF_3	3.45±0.057	2.96	0.58	76.21±0.57	97.5±0.10	79.5±0.2
FF_4	3.27±0.155	3.16	0.51	80.64±0.5	104.36±0.25	82.15±0.72
FF_5	3.55±0.057	2.80	0.38	60.15±0.54	105.89±0.2	63.68±0.42
FF_6	3.38±0.052	2.72	0.25	53.09±0.17	100.15±0.3	55.33±1.05
FF_7	3.33±0.15	2.28	0.62	56.47±1.15	99.4±0.15	58.96±1.22
FF_8	3.90±0.20	2.94	0.35	45.10±0.63	100.02±0.33	47.92±0.87
FF_9	3.16±0.053	3.02	0.5	30.03±0.28	98.33±0.76	32.14±0.43
C_1	4.00±0.10	3.19	0.66	70.17±0.46	100.5±0.47	74.47±1.57
C_2	3.96±0.05	3.06	0.48	41.82±0.72	99.73±0.8	43.32±0.79

*Average of three determinations. Weight variation (97-105 mg) within the IP limits of ±10%

Drug content

In this test, ten tablets were weighed and powdered. The drug content was determined by measuring the absorbance at 276 nm. The drug content was determined using the standard calibration curve. The mean percent drug content was calculated as an average of three determinations.

Wetting time

For determination of wetting time and water absorption ratio a piece of tissue paper folded twice was placed in a small Petri dish (internal diameter of 5 cm) containing 6 ml of water. A tablet was placed on the paper and the time required for complete wetting was measured.

***In vitro* dispersion time**

In vitro dispersion time was determined by placing one tablet in a Petri dish containing 10 ml of water and the time required for complete dispersion was determined.

***In vitro* dissolution test**

In vitro dissolution studies of the optimized Oro dispersible tablets of furosemide and commercial conventional tablet was performed according to USP XXIII Type-II dissolution apparatus (Electrolab, model TDT-06N) employing a paddle stirrer at 50 rpm using pH 6.8 phosphate buffer at 37±0.5º as dissolution medium. One tablet was used in each basket. Aliquotes of the dissolution medium (5 ml) were withdrawn at specific time intervals (2, 4, 6, 8, 10 and 12 min) and replaced with the equal volume of fresh medium. The samples were analyzed for drug content by measuring the absorbance at 276 nm. Drug concentration was calculated from the standard calibration curve and states cumulative percent drug dissolved.

Drug-excipient interaction study

IR spectra of Furosemide and its formulations were obtained by KBr pellet method using Perkin-Elmer FTIR series (Model 1615) spectrophotometer in order to ruled out drug-excipients interactions.

Stability testing

Accelerated stability studies on formulation FF_9 were carried out by storing 15 tablets in an amber coloured rubber stoppered vials at 40^o/75% RH over a period of 3months. At intervals of one month, the tablets were visually examined for any physical changes, changes in drug Content and *in vitro* dispersion time.

Experimental design

The 3^2 factorial design was used for the optimization of Oro dispersible tablets of Furosemide (Design Expert 8.0.7.1). The two independent factors, concentration of Croscarmellose sodium (X_1) and concentration of Microcrystalline cellulose (X_2), were set to three different levels and experimental trials were performed for all nine possible combinations. The dependent response, *in-vitro* dispersion time (Y_1) was evaluated.

Validation of the experimental design

To validate the experimental design using a polynomial equation, the dependent response, in-*vitro* dispersion time was selected. The following second order polynomial equation was applied as a tool of mathematical modeling.

$$\mathbf{Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_1^2 + b_{22}X_2^2}$$

Where, Y is the dependent variable, b_0 is the arithmetic mean response of the nine runs and b_1 (b_1,b_2,b_{12},b_{11} and b_{22}) is the estimated coefficient for corresponding factor X_1(X_1,X_2,X_{12},X_{11}, and X_{22}), which represents the average results of changing one factor at a time from its low to high value. The interaction term (X_1X_2) describes the changes in the response when two factors are simultaneously changed. The polynomial terms (X_1^2 and X_2^2) are included to investigate on linearity.

RESULTS AND DISCUSSION

Oro dispersible tablets of Furosemide were prepared by direct compression method using Croscarmellose sodium (CCS) as a superdisintigrant and Microcrystalline cellulose (MCC) as diluent along with directly compressible mannitol (Pearlitol SD 200), which was used to enhance the mouth feel. A total of nine formulations, a control formulation (FF_0, without superdisintegrant) and two extra design check point formulations (C_1 and C_2 to check validity of the developed polynomial equation), were designed. Powder blends were evaluated for the flow parameters such as angle of repose, tapped density, bulk density and Carr's index. As the material was free flowing (angle of repose values were found to be $<30^o$ and Carr's index <15%). The tablets were evaluated for weight variation, uniformity of drug content, hardness, friability, *invitro* dispersion time, *in vitro* dissolution studies, tablets obtained were of uniform weight (due to uniform die fill), with acceptable variation as per IP specifications (±10%). Drug content was found to be in the range of 95-105%, which is within acceptable limits. Hardness of the tablets was found to be 3.1 to 4.0 kg/cm². Friability below 1% was an indication of good mechanical resistance of the tablets. Formulation FF_9 was found to be promising and shown an *invitro* dispersion time of 30 s, which facilitates faster dispersion in the mouth. In order to investigate the factors systematically, a factorial design was employed in the present investigation. Formulation has been done by using 3^2 full factorial design, preparing nine batches of formulations (FF_1 to FF_9). A polynomial equation was derived for *in vitro* dispersion time, by Design Expert 8.0.7.1 software. Formulation FF_9 containing 10% w/w Croscarmellose sodium, 30% w/w MCC was found to be promising with an *in vitro* dispersion time of 30s against the 160s displayed by control formulation (FF_0),which does not contain the superdisintegrant CCS. *In vitro* dissolution studies on the promising formulation (FF_9), the control (FF_0) and conventional commercial tablet formulation (CCF) were carried out in pH 6.8 phosphate buffer and the various dissolution parameter values, viz., percent drug dissolved in 5min (D_5), 10 min (D_{10}), dissolution efficiency at 10min (DE_{10}min), $t_{25\%}$, $t_{50\%}$ and $t_{90\%}$ are shown in Tab.3 and the dissolution profile shown in Fig.1. This data reveals that overall, the formulation FF_9 has shown nearly two-fold faster drug release ($t_{50\%}$ 3.80 min) when compared to CCF ($t_{50\%}$ 4.60 min).

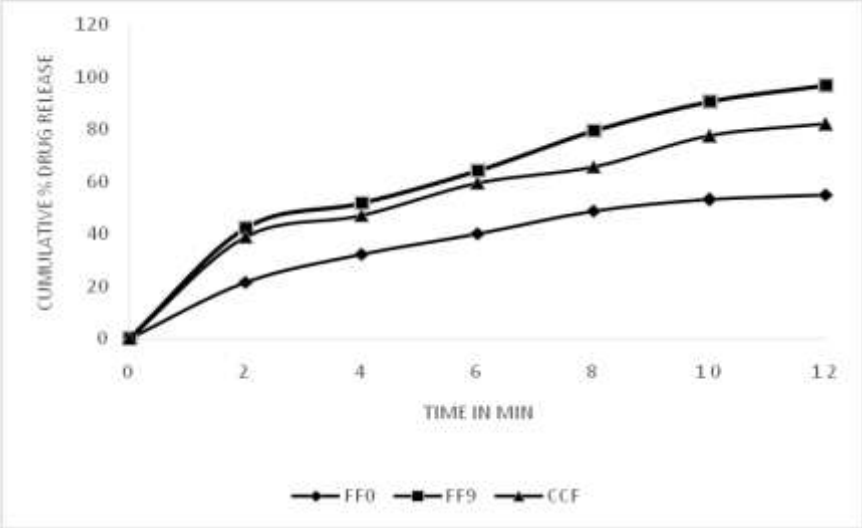

Fig. 1: *In vitro* cumulative percent drug release versus time profile of promising Furosemide formulations.
Plot showing cumulative percent drug release in pH 6.8 phosphate buffer from control formulations (-♦-); promising FF_9 formulation (-▪-); conventional commercial tablet formulation CCF (-▲-).

Table 3: *In Vitro* Dissolution Parameters in PH 6.8 Phosphate Buffer.

Formulation code	D_5 (%)	D_{10} (%)	DE_{10min} (%)	$t_{25\%}$ (min)	$t_{50\%}$ (min)	$t_{90\%}$ (min)
FF_0	36.0	53.00	33.34	2.7	8.7	>12
FF_9	57.5	91.00	55.92	1.2	3.8	9.9
CCF	52.5	77.60	49.44	1.3	4.6	>12

FF_0 is control formulation, $FF_9$is promising Oro dispersible tablet formulation, CCF is conventional commercial tablet formulation, D_5 is percent drug released in 5 min, D_{10} is percent drug release in 10 min, DE_{10min} is dissolution efficiency at 10 min, $t_{25\%}$ is time for 25% drug dissolution, $t_{50\%}$ is time for 50% drug dissolution, $t_{90\%}$ is time for 90% drug dissolution.

IR studies indicated that the drug is compatible with all the excipients. The IR spectrum of FF_9 shown all the characteristic peaks of Furosemide, thus confirming that no interaction of drug with the components of the formulation. Short-term stability studies of the above formulation indicated that there are no significant changes in drug content and *in vitro* dispersion time at the end of 3months period (P<0.05).

The equation derived for *in vitro* dispersion time of the factorial formulations is, Y_1= 63.67- 11.38 X_1-19.48X_2. The negative sign for coefficients of X_1 and X_2 indicate that as the concentration of disintegrants increases, *invitro* dispersion time decreases. Validity of this equation was verified by designing two extra design check point formulations (C_1 and C_2) and determining the *in vitro* dispersion time. The *in vitro* dispersion time values predicted from the equation for these formulations are 79.1 and 48.24 sec, whereas those observed from experimental results are 70.17 and 41.82 sec, respectively. The closeness of the predicted and observed values forC_1 and C_2 in the method indicates validity of derived equation for the dependent variable (*in vitro* dispersion time). The computer generated response surface and contour plots for the dependent variable are shown in Fig. 2 and 3 respectively.

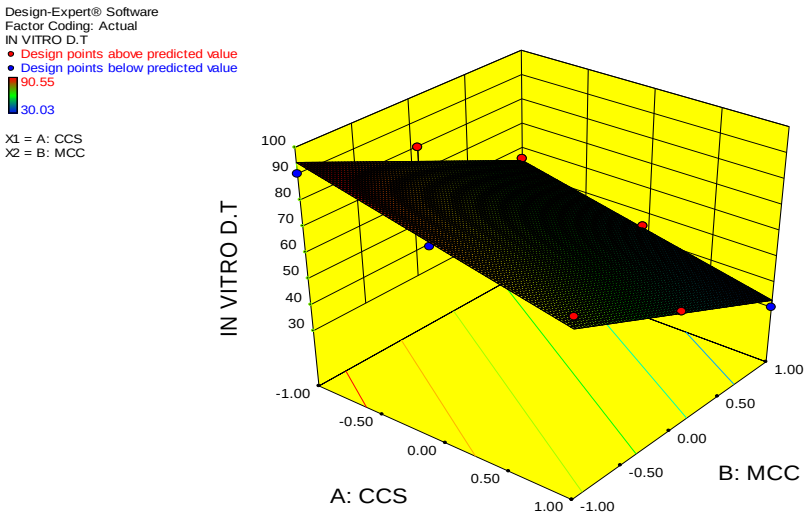

Fig. 2: Response surface plot of factorial variables on *in vitro* dispersion time.

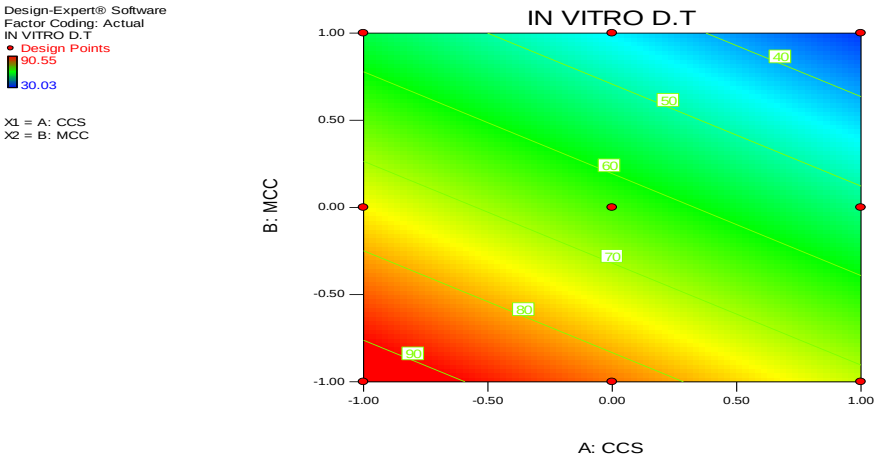

Fig. 3: Contour plot of factorial variables on *in vitro* dispersion time.

CONCLUSION

A 3^2 factorial design revealed that the amounts of Croscarmellose sodium (X_1) and Microcrystalline cellulose (X_2) significantly affect the dependent variable (Y_1), the *in vitro* dispersion time. By adopting a systematic formulation approach, an optimum point can be reached in the shortest time with minimum efforts. Direct compression method by using superdisintegrant would be an effective approach compared with the use of more expensive excipients in the formulation of Orodispersible tablets with smaller disintegration time, improved drug dissolution, patient compliance, convenience and acceptability.

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REFERENCES

1. Prakash.G, Doddayya H. Development and Evaluation of Fast Disintegrating Tablets of Granisetron HCl with Natural and Synthetic Polymers. Asian J Pharm Res, 2011; 1(3): 72-77.
2. Sawarikar P.P, Sridhar B K., Formulation and Evaluation of Fast Dissolving/ Disintegrating Tablets of Isoxsuprine Hydrochloride. Journal of Current Pharmaceutical Research, 2010; 3(1): 41-46.
3. Mahajan.H.S, Patil S.B., Rapidly disintegrating tablets for elderly patients, The Pharma Review, 2005; 3: 49-51.
4. Sreenivas S.A. Dandagi P.M. Orodispersible tablets: New-fangled drug delivery system, A review. Indian J. Pharm. Educ Res, 2005; 3(9): 177-180.
5. Haegeli L, Wenk M and Drewe J. Sublingual administration of furosemide: new application of an old drug. Br J Clin Pharmacol, 2007; 64: 804-09.
6. Sweetman SC, Ed. Martindale: The complete drug reference, pharmaceutical press: 2009.

7. Shirsand S.B, Sarasija Suresh. Plantago ovata mucilage in the design of Fast disintegrating tablets. Indian J Pharm Sci, 2009; 71(1): 41-45.
8. Devendre RR, Vikas VP. Formulation and evaluation of fast dissolving tablet of albendazole. Int. Current Pharm J, 2012; 1(10): 311-16.
9. Banker GS, Anderson GR. Tablets. In: Lachman L, Liberman HA, Kanig JL, editors, The theory and practice of industrial pharmacy. 3rd ed. Mumbai: Varghese Publishing House, 1987; 293-9.
10. Lachman L, Lieberman A and Kinig JL. The Theory and Practice of Industrial Pharmacy. Varghese Publishing House, 1991; 67-68.
11. Indian Pharmacopoeia, 4th Ed., Vol.2, New Delhi: Controller of Publication, Govt. of India, 1996.
12. Sahin S, Gulsun T and Vural I. Preparation and evaluation of furosemide containing orally disintegrating tablets by direct compression. Pharmazie, 2017; 72: 389-94.
13. Nilesh.J, Suman M. Effect of superdisintegrans on formulation of taste masked fast disintegrating ciprofloxacin tablets. Int. Current Pharm J, 2012; 1(4): 62-67.
14. Shivappa.N, Rajan W D and Krishna S. Formulation and evaluation of furosemide oral disintegrating tablets. Int. J Pharm Sci Invention, 2018; 7(6): 1-10.
15. Bolton S. Pharmaceutical Statistics. 2nd Ed., New York: Marcel Decker Inc, 1990; 234-6.
16. Singh J, Philip AK and Pathak K. (2008), Optimization studies on design and evaluation of orodispersible pediatric formulation of indomethacin. AAPS Pharm Sci Tech., 9: 60-66.