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FORMULATION AND EVALUATION OF ORAL DISINTEGRATING TABLETS OF FUROSEMIDE

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ABSTRACT

Orally disintegrating tablets (ODTs) are a rapidly growing category of dosage form in the pharmaceutical industry which has received ever-increasing demand during the last decade. They especially find application in target category like geriatrics and pediatrics. There are three main manufacturing methods used for the production of ODTs, namely, freeze drying, molding and compression method. Some methods of manufacturing ODTs are complex, require multiple processes and don't provide all ODTs ideal properties. For example, freeze drying and molding provide very light and porous products which disintegrate very rapidly, but they are expensive and produce fragile products. On the other hand, compression method is the easiest and cost effective method for the production of ODTs. Orally disintegrating tablets containing 20 mg of Furosemide were manufactured using direct compression method. Experiments were evaluated for effects of formulation parameters like type & concentration of diluents, concentration of disintegrating agent and their interactions on Furosemide ODTs properties, and Microcrystalline cellulose, Mannitol were used as diluents of different properties, in addition to croscarmellose sodium (CCS) and Crospovidone which was used as a superdisintegrants. The obtained results revealed that disintegration time of the optimized ODTs formula (35 sec. to 50 sec). ODTs composed of croscarmellose sodium superdisintegrants was optimized formula, as it showed the lowest disintegration time with the highest drug release up to 92.70%. Furthermore, hardness of the manufactured tablets was not significantly affected by the use of Crospovidone and CCS. Finally, it was concluded that Furosemide oral disintegrating tablets were developed using croscarmellose sodium. These tablets provided low disintegration time and high hardness that are acceptable for ODTs.

KEYWORDS: Orally disintegrating tablet, Croscarmellose sodium, Crospovidone, Furosemide.

INTRODUCTION[1,2,3,4,5,6,7]

Recent developments in the technology have prompted scientists to develop orally disintegrating tablets with improved patient compliance and convenience. Orally disintegrating tablets are solid dosage forms that disintegrate rapidly when placed upon the tongue, usually within a matter of seconds. ODTs are intended to disperse, dissolve, or disintegrate quickly in the mouth cavity due to saliva, which results in release of the drug due to rapid absorption of the medium into the tablet core followed by prompt tablet disintegration under the effect of superdisintegrants. Orally disintegrating tablets provide an advantage particularly for pediatric and geriatric populations who have difficulty in swallowing conventional tablets and capsules. Additionally, pediatric patients may suffer from ingestion problems as a result of underdeveloped muscular and nervous Control. Moreover, patients traveling with little or no access to water, limit utility of orally administered conventional tablets or capsules. Rapid disintegration of tablet results in quick dissolution and rapid absorption which provide rapid onset of action. Moreover, drug candidates that undergo pre-gastric absorption when formulated as ODTs may show increased oral bioavailability. It provides good stability, accurate dosing, easy manufacturing, small packaging size, and easy to handle by patients. It is easy to administer for pediatric, geriatric, and institutionalized patients (especially for mentally retarded and psychiatric patients). Many technologies have come up for fast dissolve tablets like Zydis, Ora Solv, Dura Solv, Flash Tab and Wow Tab. Technologies like Zydis, Flash Tab have resulted in tablets with a very low disintegration time, but poor mechanical strength. On the other hand, techniques like Ora Solv, Dura Solv have resulted in products with sufficient mechanical strength but a comparatively longer disintegration time. Formulation of drugs as orally disintegrating tablets (ODTs) is one of the approaches to achieve enhanced patient acceptance toward orally solid dosage forms.

Furosemide (FUR), 5-(aminosulphonyl)-4-chloro-2-[(2-fuanyl-methyl) amino] benzoic acid, is a potent loop (high ceiling) diuretic used mainly in the management of hypertension. According to the biopharmaceutical classification system(BCS), FUR is classified as a class IV drug due to its low solubility(5–20 mg/ml) and low permeability. Therefore, low oral bioavailability of FUR has been reported.

The aim of this study is to optimize, formulate & evaluate ODTs containing Furosemide. The effects of the superdisintegrants i.e. Crosspovidone, Croscarmellose sodium etc. on the tablets disintegration and dissolution will be investigated.

MATERIALS AND METHOD[8,9,10]

Furosemide was received as a gift sample from the Rajesh Chemicals Co. Mumbai. India. Microcrystalline cellulose, Mannitol, Cross carmellose sodium, Crospovidone, Aspartame and Magnesium stearate was received as a gift sample from Ozone International Mumbai, India., All other materials and chemicals used were of either pharmaceutical or analytical grade.

Preparation of ODT Tablets[11,12,13,14,15,16,]

Oral disintegrating tablet of Furosemide were prepared by using direct compression method according to the formulae as shown in the table 1. This method involves a simple procedure of blending of API with other ingredients and the resulted mixture is subjected to direct compaction. The required ingredients were taken in a mortar and the powder blend was mixed for a time period of 15-20 min by using mortar and pestle. Then each mixture was passed through sieve no.60 and finally magnesium stearate was added as lubricant and thoroughly mixed. It was then compressed by using 10 station tablet compression machine (Rimek minipress-II MT, Karnavati Ltd.) to get at 8 mm size of tablets each weighing 200 mg.

Table No. 1: Formulation of Furosemide ODT Tablets.

Formulation	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)
Furosemide	20	20	20	20	20	20
MCC	148	146	143	148	146	143
Mannitol	15	15	15	15	15	15
Crospovidone	10	12	15	-	-	-
Croscarmellose sodium	-	-	-	10	12	15
Aspartame	2	2	2	2	2	2
Magnesium Stearate	2.5	2.5	2.5	2.5	2.5	2.5
Talc	2.5	2.5	2.5	2.5	2.5	2.5
Total	200	200	200	200	200	200

Post Compression Studies

1. Weight Variation

20 tablets were selected and weighed collectively and individually. From the collective weight, average weight was calculated. Each tablet weight was then compared with average weight to assure whether it was within permissible limits or not. Not more than two of the individual weights deviated from the average weight by more than 7.5% for 200 mg tablets and none by more than double that percentage.

2. Hardness test

The hardness of tablet of each formulation was measured by Monsanto hardness tester. The hardness was measured in terms of kg/cm^2. The hardness of tablet was found in between 3.3±0.30 to 4.3±0.30.

3. Thickness

The Thickness of tablet was measured by Vernier caliper & the Furosemide tablet of thickness were found in between the 2.30±0.45 to 2.70±0.05.

4. Friability test

This test is performed to evaluate the ability of tablets to withstand abrasion in packing, handling and transporting. Initial weight of 20 tablets is taken and these are placed in the Roche friabilator, rotating at 100 rpm for 4 min. The tablets are then taken out, dedusted and were weighed. The difference in the weight is noted and expressed as percentage.

5. Content uniformity

Twenty tablets were crushed and powder equivalent to weight of one tablet was dissolved in phosphate buffer 6.8. Then suitable dilutions were made and absorbance at 276 nm wavelength was taken by using a UV visible spectrophotometer. The content uniformity of Furosemide were found to be 95.23±1.09 to 99.36±0.48.

6. Disintegration time

Fast Disintegrating tablets apply the tests observe the tablets within the time limit all of the tablets have disintegrated. If 1 or 2 tablets fail to disintegrate completely repeat the test on 12 additional tablets, not less than 16 of the total of 18 tablets tested disintegrate completely. The Furosemide tablets were found in between the 35 sec. to 50 sec.

In-vitro drug release studies

In-vitro drug release studies were carried out by using USP-type II dissolution apparatus.

900 ml of Phosphate buffer (pH 6.8) was placed in the dissolution flask maintained at a temperature of 37±0.50 C. One tablet was placed in the flask of the dissolution apparatus and was operated to run up to 30 mins at 50 rpm. At definite time intervals, 5 ml of dissolution medium was withdrawn, filtered and again replaced with 5 ml of fresh medium. Suitable dilutions were done with dissolution medium and were analyzed spectrophotometrically at λ max is 276 nm using a UV-spectrophotometer (Lab India; Mumbai). The in-vitro drug release of ODT tablets of Furosemide was shown in fig 3-4.

Table No. 2: Evaluation (Post-compression) parameters of all formulation.

Formulation	Hardness kg/cm^2	Friability (%)	Weight variation	Content uniformity	Disintegration time (sec.)	Thickness
F1	3.5±0.35	0.85±0.13	200.3±0.5	95.23±1.09	43	2.86±0.15
F2	3.3±0.20	0.70±0.06	200.33±1.04	96.32±1.06	40	2.63±0.15
F3	3.2±0.40	0.75±0.01	200.22±0.76	99.18±0.63	37	2.80±0.10
F4	3.5±0.26	0.85±0.02	200±1.32	99.07±0.61	46	2.83±0.15
F5	3.3±0.2	0.77±0.02	200.5±0.5	99.01±0.72	38	2.60±0.2
F6	3.6±0.15	0.85±0.03	200.55±0.76	98.89±0.47	35	2.53±0.20

All values are represented as mean ±standard deviation (n=3).

Thickness, hardness, weight variation, & drug content are mean of n determination values are given in mean ± standard deviation.

FTIR RESULT

FTIR studies were conducted and the spectrum was recorded in the range of 4000-400cm-1.No significant interaction between drug and Excipients was observed. All the spectrum i.e. drug and Excipients were concordant with that of standard IR spectra of pure drug Furosemide.

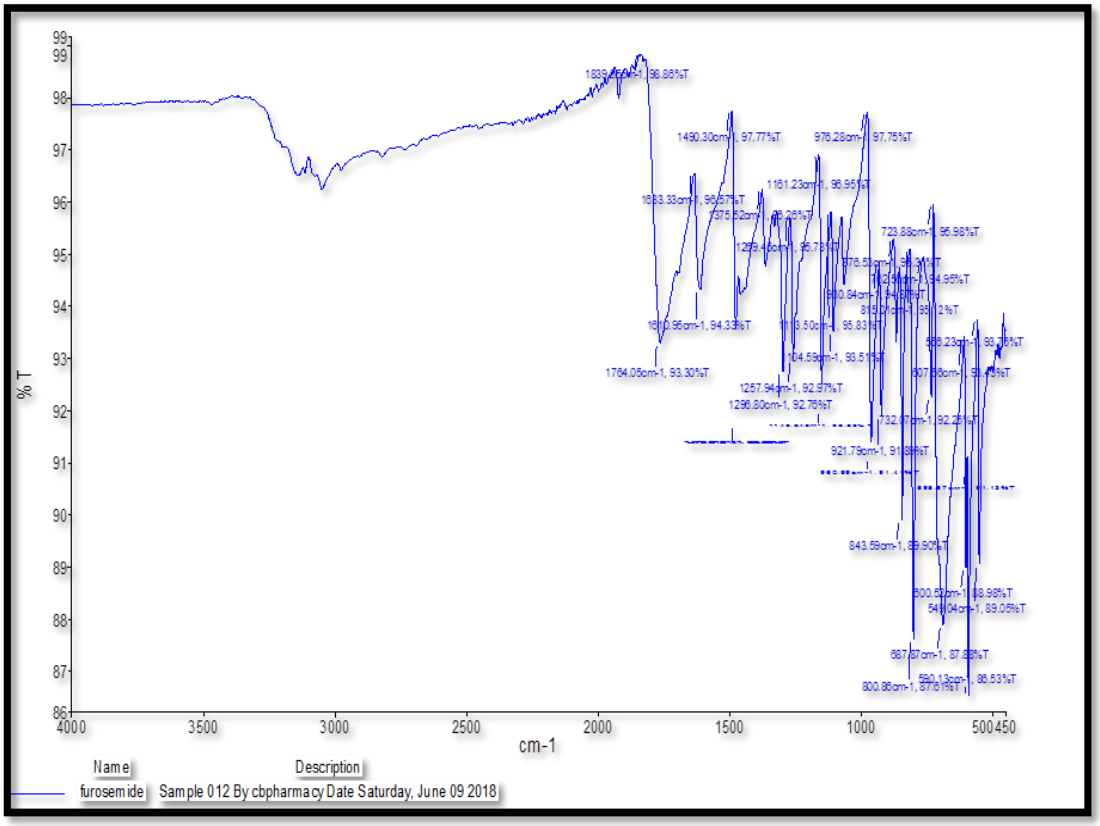

Figure No. 1: FTIR spectra of Furosemide.

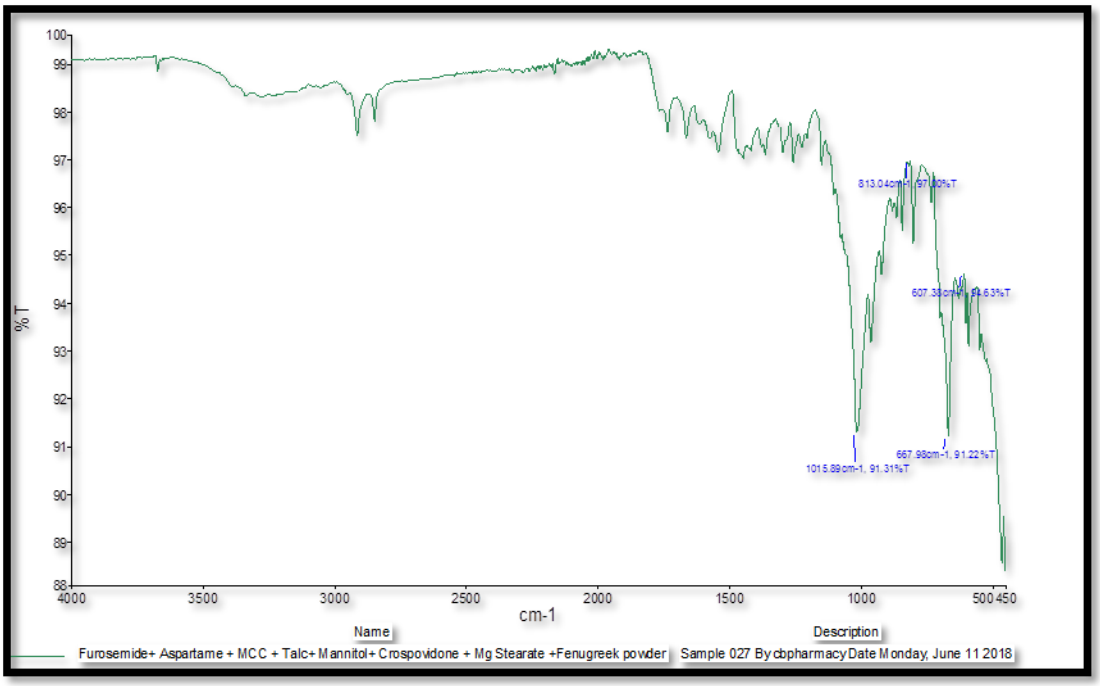

Figure No. 2: FTIR spectra of Furosemide +MCC+ Mannitol + Talc + Crospovidone + Croscarmellose sodium+ Aspartame+ Magnesium stearate.

Table No. 3: List of Functional Group.

Sr.No.	Functional Group	Peaks Observed
1	C=C stretch of the aromatic group; N-H bond scissoring	1621.24
2	C-H stretch of the aromatic group	2976.52
3	C-C stretching mode	1487.79
4	O-H deformation of the hydroxyl groups	1582,1487,1450
5	C-O stretching mode	1194.90
6	In plane bending mode	1192.24-1265.96
7	C-H bond out of plane bending mode; Ring deformation of the aromatic group	685.01

Table No. 4: Dissolution Profiles of Formulations F1-F3.

Time	F1	F2	F3
0	0.00	0.00	0.00
5	32.68	36.27	38.87
10	44.84	46.85	49.46
15	52.27	54.90	57.52
20	68.13	65.58	68.22
25	71.10	76.32	78.97
30	79.27	81.93	82.00

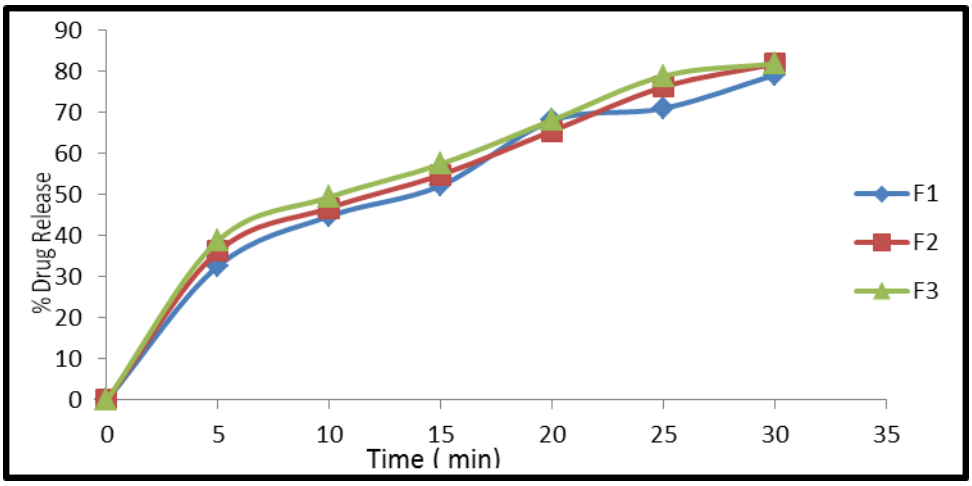

Figure No. 3: % drug release for F1-F3.

Table No. 5: Dissolution Profiles of Formulations F4-F6.

Time	F4	F5	F6
0	0.00	0.00	0.00
5	38.87	46.65	51.81
10	46.87	52.10	57.32
15	57.51	62.77	70.61
20	70.80	78.68	81.38
25	76.38	84.31	89.61
30	81.39	89.96	92.70

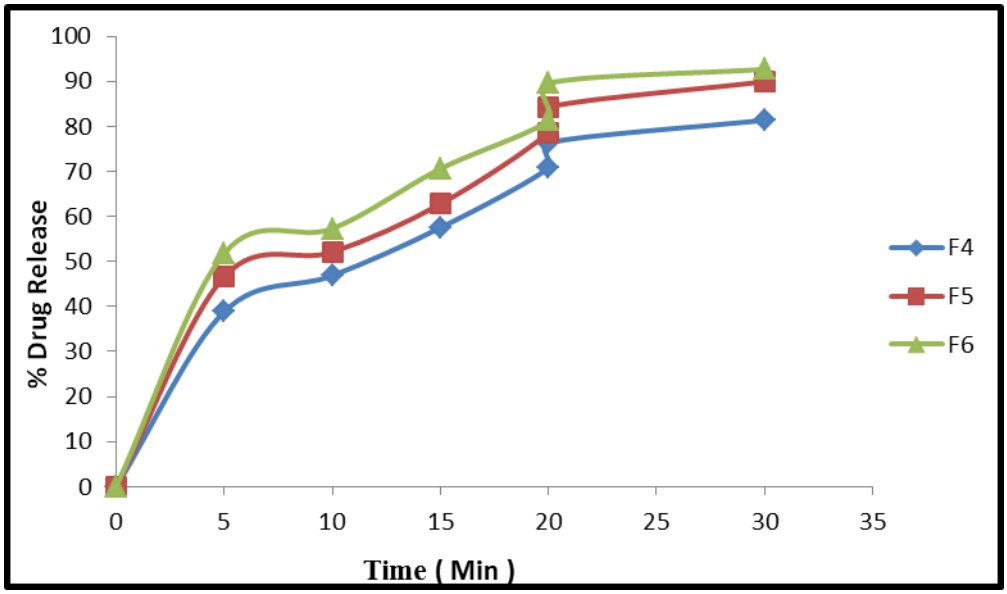

Figure No. 4: % drug release for F4-F6.

CONCLUSION

Furosemide ODTs were successfully prepared using direct compression method. A full factorial design was a useful tool to optimize and evaluate the influence of type and concentration of diluents and concentration of superdisintegrant on optimizing Furosemide ODTs. There were good correlations between the predicted values and experimental data of the optimized formula validated by response surface optimization. The type and concentration of diluents and superdisintegrant concentration had a great influence on Furosemide ODTs properties. The disintegration time was significantly decreased by using Croscarmellose sodium instead of Crospovidone. Finally, Furosemide the composition of ODTs could be optimized so as to obtain rapid disintegration and drug dissolution along with acceptable tablets hardness and friability. This could enhance drug absorption and bioavailability, resulting in improved patient compliance and convenience.

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