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Formulation and evaluation of Furosemide oral dispersible tablets

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ABSTRACT

The oral disintegrating tablets of furosemide with sufficient mechanical strength, acceptable taste and smaller disintegration time were achieved employing suitable superdisintegrants and other excipients at optimum concentration. FTIR studies revealed that there was no shift in peaks, indicating there is no interaction between furosemide and other ingredients used. Among three superdisintegrants used sodium starch glycolate showed better performance in disintegration time when compared to crospovidone and cross caramellose sodium used alone. In the *invitro* dissolution study comparison among all formulations, OF5 showed best results. So the formulation of OF5 was found to be best among all other formulations, because it has exhibited good taste and faster disintegration time when compared to all other formulations.

Keywords: FTIR studies, Crospovidone and cross Caramellose sodium.

INTRODUCTION

An Oral route of drug administration have wide acceptance up 50-60% of total dosage form. Solid dosage forms are popular because of ease of administration, accurate dosage, self-medication, pain avoidance and most importance patience compliance [1].

The U.S food and drug administration center for drug evaluation and research (CDER) defines, an ODT as "a solid dosage form containing medicinal substances, which disintegrates rapidly usually within a matter of seconds, when placed upon the tongue. The most desirable formulation for use by the elderly is one that is easy to swallow and easy to handle [2]. Taking these requirements into consideration, attempts have been made to develop a rapid dissolving tablet. Since such a tablet can disintegrate in only a small amount of water in the oral cavity, it is easy to take for any age patient, regardless of time or place. For example, it can be taken anywhere at any time by anyone who do not have easy access to water. It is also easy to dose the aged, bed-ridden patients, or infants who have problems swallowing tablets and capsules[3]. Recently, many companies have researched and developed various types of fast-disintegrating dosage form technologies with the potential to accommodate various physicochemical, pharmacokinetic and pharmacodynamic characteristics of drugs.

AIM AND OBJECTIVE

The aim of the study is to formulate and evaluate furosemide oral disintegrated tablet

Objectives

1. Preparation of mouth dissolving tablets of furosemide by direct compression using different concentration of superdisintegrants like CCS, sodium starch glycolate (Explotab) and cross povidone (polyphasdone XL).
2. Drug-excipients interaction using FTIR studies.
3. Mouth dissolving tablets of furosemide were evaluated for hardness, friability, weight variation, disintegration time, drug content, water absorption ratio, water absorption time.
4. Study in vitro dissolution of furosemide from the formulated mouth dissolving tablets

5. Stability study of formulation as per the ICH guidelines.

METHODOLOGY

Formulation of furosemide orodispersible tablets

Direct compression

Micro crystalline cellulose, Mannitol, cross Carmellose sodium/sodium starch glycolate/cross povidone were weighed and sifted through 40 mesh. To the above blend Furosemide was added and sifted through 18 mesh.

The sifted material was placed in poly bag and mixed for 5 min. To the above blend add magnesium Stearate, aerosil and aspartame and placed in poly bag and mixed for 2-3 min. The lubricated blend was compressed using 8mm round punches.

Table 1: Composition of formulations

Ingredients	OF1	OF2	OF3	OF4	OF5	OF6
Furosemide	25mg	25mg	25mg	25mg	25mg	25mg
CP	10mg	15mg	-	-	-	-
CCS	-	-	10mg	15mg	-	-
SSG	-	-	-	-	10mg	15mg
Aerosil	2mg	2mg	2mg	2mg	2mg	2mg
Mg.stearate	2mg	2mg	2mg	2mg	2mg	2mg
Aspartame	4mg	4mg	4mg	4mg	4mg	4mg
Mannitol	20mg	20mg	20mg	20mg	20mg	20mg
MCC	152mg	147mg	152mg	147mg	152mg	147mg
Total weight	200mg	200mg	200mg	200mg	200mg	200mg

Post compression evaluation of tablets

To design tablets and later monitor tablet production quality, quantitative evaluation and assessment of tablet chemical, physical and bioavailability properties must be made. The important parameters in the evaluation of tablets can be divided into physical and chemical parameters [3].

Physical appearance

The general appearance of tablets, its visual identity and overall elegance is essential for consumer acceptance. The control of general appearance of tablet involves measurement of number of attributes such as tablet size, shape, colour, presence or absence of odour, taste, surface texture and consistency of any identification marks.

Hardness test

This is the force required to break a tablet in a diametric compression. Hardness of the tablet is determined by Stock's Monsanto hardness tester which consists of a barrel with a compressible spring. The pointer moves along the gauze in the barrel fracture.

Tablet size and Thickness

Control of physical dimensions of the tablets such as size and thickness is essential for consumer acceptance and tablet-tablet uniformity. The diameter size and punch size of tablets depends on the die and punches selected for making the tablets. The thickness of tablet is measured by Vernier Callipers scale [4]. The thickness of the tablet related to the tablet hardness and can be used an initial control parameter. Tablet thickness should be controlled within a ±5%. In addition thickness must be controlled to facilitate packaging.

Friability

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 friabilator, rotating at 25rpm for 4min [5]. The difference in the weight is noted and expressed as percentage. It should be preferably between 0.5 to 1.0%.

% Friability = $(W_1-W_2)/W_1$ X 100

Where, W_1= weight o f tablets before test

W_2 = weight of tablets after test

Weight variation of Tablets

It is desirable that all the tablets of a particular batch should be uniform in weight. If any weight variation is there, that should fall within the prescribed limits

Table 2: Acceptance criteria for tablet weight variation

Average weight of tablet(mg)	Maximum % difference allowed
130 or Less than	± 10
130-324	± 7.5
More than 324	± 5

Twenty tablets were taken randomly and weighed accurately. The average weight was calculated by,

$$\text{Average weight} = \frac{\text{weight of 20 tablets}}{20}$$

Disintegration test

Disintegration time is considered to be one of the important criteria in selecting the best formulation. To achieve correlation between disintegration time in-vitro and in-vivo, several methods were proposed, developed and followed at their convenience [6]. One tablet was placed into each tube and the assembly was suspended into the 1000ml beaker containing water maintained at 37±2^{o}c and operated the apparatus for 15 minutes. The assembly was removed from the liquid and the tablets were observed. If one or two tablets fail to disintegrate completely, repeat the test on 12 additional tablets [7]. The requirement is met if not less than 16 of the total of 18 tablets tested are disintegrated.

Dissolution test

Dissolution

It is the amount of the solid substance that goes into the solution per unit time under standard conditions of the temperature and pressure

Types of dissolution apparatus

Different types of dissolution apparatus are used. They are

1. Apparatus 1 or rotating basket type
2. Apparatus 2 or paddle assembly type
3. Apparatus 3 or reciprocating cylinder type
4. Apparatus 4 or flow through cell type
5. Apparatus 5 or paddle over disk type

Method

Dissolution media was taken as 6.8pH phosphate buffer, 500ml was placed in the vessel and the USP apparatus –2 (paddle) was assembled. The medium was allowed to equilibrate to temp of 37 $\pm$ 0.5°C. Tablet was placed in the vessel; the apparatus was operated at 50 rpm [8]. At definite time intervals, 5 ml of the fluid was withdrawn; filtered and again 5ml of the fluid was replaced. The samples were analyzed using U.V.

Dissolution parameters

Medium: 6.8pH phosphate buffer, 500ml.
Apparatus: USP Type 2 (paddle).
Rotation speed: 50 RPM
Temperature: 37±5^{o}C.
Time: 5, 10, 15, 20, 30 min.

RESULTS AND DISCUSSION

Pre-formulation studies

Description

These tests were performed and the results were illustrated in the following table:

Table 3: Description of Furosemide (API)

Colour	Dull to white colour
Taste	Slightly bitter

Solubility

These tests were performed and the results are illustrated in the table

Table 4: Table showing the Solubility of furosemide (API) in various solvents

Freely Soluble	Water
Soluble	methanol
Slightly soluble	Ethanol
Slightly soluble	Ethyl acetate

Sparingly soluble	Isopropyl alcohol

Melting Point

This test is performed and the result was illustrated in the following table.

Table 5: Melting point of API's

Material	Melting Point
Furosemide	184^0c

Result: The Result was found to be within limit.

Preparation of standard curve

Calibration curve of Furosemide potassium in pH 6.8 Phosphate buffer

The calibration curve data of Furosemide in pH 6.8 Phosphate buffer at 234nm. Fig. 1 shows the standard calibration curve with a regression value of 0.9998, slope of 0.0592 and intercept of 0.0027 in pH 6.8Phosphate buffer. The curve was found to be linear in the concentration range of 2-12µg/ml.

Table 6: Calibration curve data for Furosemide potassium in pH 6.8 Phosphate buffer

Concentration (µg /ml)	Absorbance
0	0
2	0.112
4	0.239
6	0.353
8	0.466
10	0.588
12	0.713

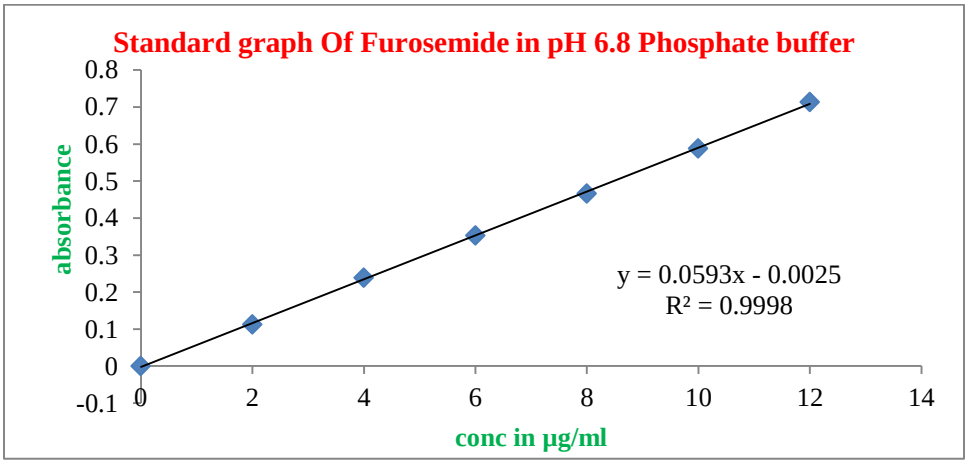

Figure 1: Standard graph Of Furosemide in pH 6.8 Phosphate buffer

Drug-excipient compatibility studies

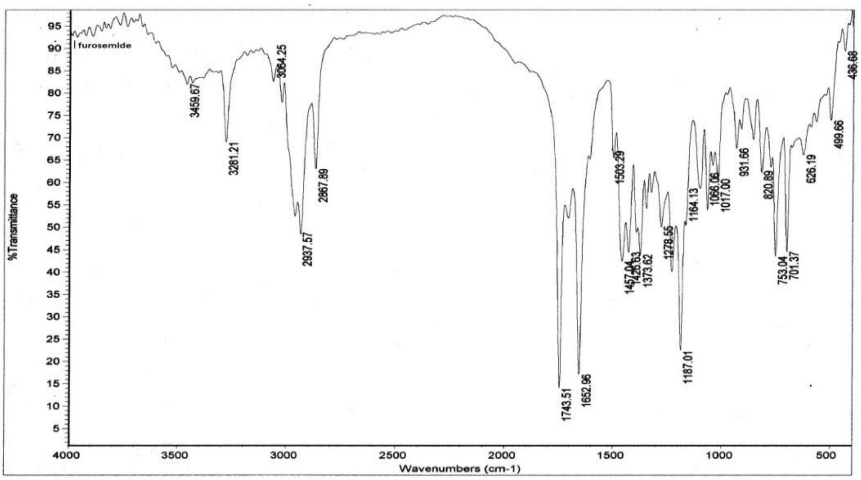

Figure 2: IR Spectra of Furosemide pure drug

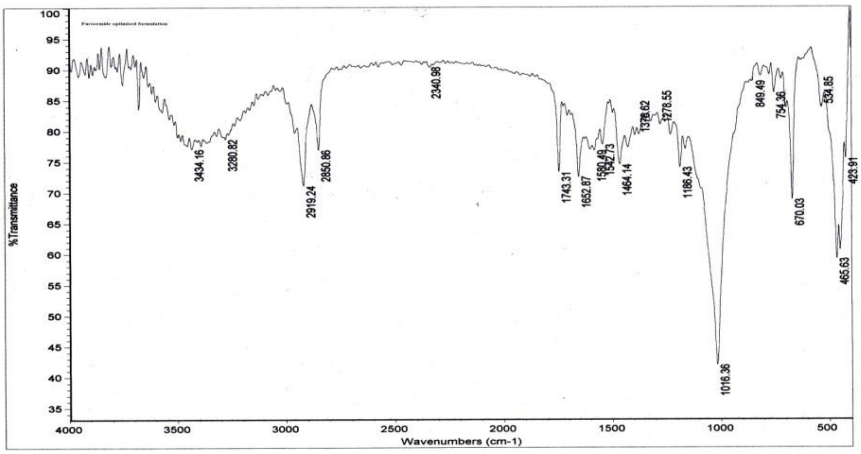

Figure 3: IR Spectra of Furosemide Optimised formulation

Preformulation studies

All the formulations were evaluated for bulk density, tapped density, % compressibility, hausner's ratio and angle of repose. The results of % compressibility, hausner's ratio and angle of repose were found to be <16, <1.25 and <30 respectively. These results show that the formulations have very good flow properties.

Table 7: Preformulation studies

Formulation code	Bulk density (g/cc)	Tapped density (g/cc)	Carr's Index	Hausner Ratio	Angle of repose(θ)	Flow property
F1	0.45	0.52	15.60	1.15	28.4	Good
F2	0.45	0.50	12.23	1.11	27.5	Good
F3	0.44	0.50	12.58	1.13	28.4	Good
F4	0.45	0.52	15.19	1.15	28. 3	Good
F5	0.44	0.52	15.48	1.18	28.1	Good
F6	0.45	0.51	13.48	1.13	29. 1	Good

Table 8: Post compression evaluation parameters for oro dispersible formulations

Formulation Code	Hardness (kg/cm^2)	Thickness (mm)	Weight (mg)	Friability (%)	Drug content	Disintegration time (min)
F1	4.3	2.84	202	0.32	96.25	1min 45 sec
F2	4.8	2.9	201	0.30	96.58	1min 20 sec
F3	4.8	2.80	200	0.36	99.32	2min
F4	4.5	2.82	202	0.31	101.23	1min 45 sec
F5	4.3	2.68	197	0.34	99.54	1 min
F6	4.3	2.63	200	0.35	97.33	1min 20 sec

Table 9: In-Vitro Release Profile of Furosemide from formulations OF1— OF6

Time (min)	OF1	OF2	OF3	OF4	OF5	OF6
0	0	0	0	0	0	0
5	24	22	22	16	20	20
10	38	39	42	35	38	36
15	59	61	59	49	55	54
20	71	76	69	68	75	73
30	84	89	82	86	95	82

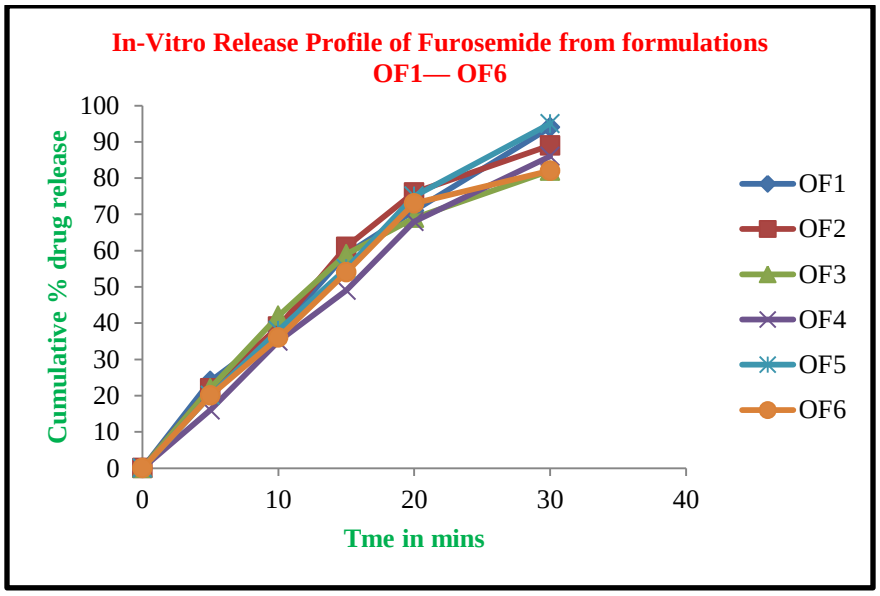

Fig 4: Graph showing dissolution profile of OF1— OF6

DISCUSSION

Orodispersible tablets of Furosemide were formulated by direct compression method using, Microcrystalline cellulose as diluent, SSG as super disintegrant, Magnesium stearate as lubricant. Compatibility studies were performed using IR spectrophotometer. The IR spectrum of pure drug and physical mixture of drug and excipients were studied as shown in Figures The peaks obtained in the spectra's of each formulation correlates with the peaks of drug spectrum. This indicates that the drug is compatible with the formulation components.

The blends were analyzed for parameters such as Bulk density, Tapped density, Compressibility index and Hausner's ratio and the results were found to be within limits. Bulk density and tapped density values were found to be within limits. Compressibility index has been proposed as an indirect measure of bulk density, size and shape, surface area and

cohesiveness of material. The powdered blend has required flow property.

After compression, all the tablets were dried at 60^{o}C for 12hrs and were evaluated for various parameters like weight variation, hardness, thickness, friability, disintegration and in-vitro drug release. All formulations were found to have good hardness so they were taken for further studies. The measured hardness of tablets of each batch are in the range of 4.3 to 4.8 kg/cm^{2}.

Tablets mean thickness were almost uniform in all formulations and were found to be in the range of 2.63mm to 2.9mm. Friability values are found to be less than 1% in all the cases and considered to be satisfactory.

The total weight of each formulation was maintained constant and the weight variation of the tablets was within limits.

All the tablets passed the pharmacopoeial specifications for disintegration of tablets within 3 minutes. The optimized formulation OF5 containing Sodium starch glycolate as super disintegrant showed in-vitro drug release of almost 95% of furosemide in 30mins and the disintegration time was found to be 1min.

Stability studies

Furosemide tablets of F4 formulation were packed in HDPE (High density polyethylene) container with child resistant caps (CRC) and induction sealed. These bottles were charged for stability study at 40^{0}C &75% RH.

After one month

Table 10: Physical evaluation of tablets for stability studies of Optimized formulation

Parameter	Initial	40^{0}C / 75%RH
Color	White	White
Surface	Smooth	Smooth
Disintegration(min)	1min 4sec	1min 4sec
Thickness(mm)	3.50mm	3.50mm
Hardness(Kp)	3.50±0.04	3.4± 1.0
Weight(mg)	201.9mg	201.8mg
Assay	98.64±0.58	98.53± 0.28

Observation

The Furosemide porous tablets were subjected to stability studies at 40^{o}C and 75% RH for 1 month and from the above results, it was found that there is no significant effect on the tablets.

After Three months

Table 11: Physical evaluation of tablets for stability studies of optimized formulation

Parameter	Initial	40^{0}C / 75%RH
Colour	White	White
Surface	Smooth	Smooth
Disintegration (min)	1min 4sec	1min10sec
Thickness(mm)	3.50mm	3.50mm
Hardness(Kp)	3.50±0.04	3.4± 1.0
Weight(mg)	201.9mg	200.3 mg
Assay	98.60 ± 0.68	97.70 ± 0.28

Observation

The Furosemide porous tablets were subjected to stability studies at 40^{o}C and 75% RH for 3 months and from the above results, it was found that there is no effect on the tablets and was found to be within the limits according to ICH guidelines.

CONCLUSION

The oral disintegrating tablets of furosemide with sufficient mechanical strength, acceptable taste and smaller disintegration time were achieved employing suitable superdisintegrants and other excipients at optimum concentration. FTIR studies revealed that there was no shift in peaks, indicating there is no interaction between furosemide and other ingredients used. Among three superdisintegrants used sodium starch glycolate showed better performance in disintegration time when compared to crospovidone and cross caramellose sodium used alone. In the *invitro* dissolution study comparison among all formulations, OF5 showed best results. So the formulation of OF5 was found to be best among all other formulations, because it has exhibited good taste and faster disintegration time when compared to all other formulations.

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