

Development and Evaluation of Fast Dissolving Furosemide Tablet

Sandeep A. Wathore*, V.M.Kale Yuvraj L. Pandhare, Sandesh R. Sul.
MUPS College of Pharmacy (B.Pharm), Degaon-444506, Tq-Risod, Dist- Washim (MS), India
Corresponding Author: Sandeepa.Wathore

Abstract: Problems of swallowing and provides a quicker onset of action overcomes by fast dissolving tablets constitute an innovative excipients. The bioavailability of some drugs may be increased due to absorption of drugs in oral cavity. Fast dissolving tablets of Furosemide, prepared by sublimation method using camphor as subliming agent and croscarmellose sodium, sodium starch glycolate and cross povidone as a super disintegrates by direct compression method. FTIR Spectroscopy was carried out to determine the suitability of superdisintegrates with the drug. The prepared fast dissolving tablets of Furosemide, were evaluated for post compression parameters. Optimum formulation of Croscarmellose sodium S3 showed disintegration time of 9 seconds and 97.07% of drug release.

Key words: Mouth dissolving tablet, Sublimation technique, Furosemide, Subliming agent, Superdisintegrates.

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I. Introduction

Solid dosage forms like tablet and capsule are most popular and preferred drug delivery system because they have high patient compliance, relatively easy to produce, easy to market, accurate dosing, and good physical and chemical stability [1]. Many patients find difficulty to swallow tablet and hard gelatin capsule, consequently they do not take medication as prescribed. It is estimated that 50% of the population is affected by this problem which results in a high incidence of non-compliance and ineffective therapy [2-3].

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.

II. Materials And Methods

Materials

Furosemide was received as a gift sample from the Rajesh Chemicals Co. Mumbai. India. Sodium Starch Glycolate gift sample from Glenmark Pvt Ltd, Nashik. Croscarmellose Sodium Vishal Chem, Mumbai. Crosspovidone from Molychem, Mumbai and Camphor from Vishal Chem, Mumbai and other are used as AR grade.

Experimental

FT-IR Spectroscopic Study

The dry sample of Furosemide was prepared by triturating with dry potassium bromide (A.R. Grade) and placed in sample cell [5-6]. The IR spectrum of the drug sample was recorded and the spectral analysis was done and the spectrum was shown in Fig. No.1-2. and interpretation in Table No.2.

Preparation of Formulation

Fast dissolving tablets of Furosemide were prepared using the subliming agents, camphor, Sodium starch glycolate, Crosspovidon and Croscarmellose Sodium used as superdisintegrants, spray dried mannitol as diluents, sodium saccharine as sweetening agent, the drug and other ingredients were mixed together by using a glass mortar and pestle, and then passed through sieve no. 60. Tablets were directly compressed by using 7 mm punch of using rotary table for 24 hrs to facilitate sublimation of camphor. A porous structure was obtained. The end point of drying was indicated by constant weight of tablet. Table No. 1 outlines the composition of various Fast dissolving formulations.

Sodium Saccharine -1%, Magnesium Stearate -1 %, Talc- 1 %.

Pre Compression Parameters

Immediate release powder blend was evaluated for various precompression parameters such as Angle of repose, Bulk density (BD), Tapped density (TD), Hausner's ratio, Compressibility index was calculated by following equations [8-10].

$$\theta = \tan^{-1} (h/r) \text{ ----- (1)}$$

Where, θ = Angle of repose

h = Height of granule above flat surface

r = Radius of circle formed by the granule pile.

$$C.I. = \left\{ \frac{\rho_t - \rho_0}{\rho_t} \right\} \times 100 \text{ ----- (2)}$$

Where, ρ_t - tapped density, ρ_0 - bulk density.

$$C = \left(\frac{H_0 - H_p}{H_0} \right) \times 100 \text{ ----- (3)}$$

Where, C - Degree of compression

H_0 - height of granule bed in the die before compression.

H_p - height of granule bed in the die at a pressure p.

$$\text{Hausner's ratio} = \frac{TBD}{LBD} \text{ ----- (4)}$$

Where, TBD - Tapped Bulk Densities

LBD - Loose Bulk Density

Post Compression Parameters

All the batches of tablets were evaluated for various parameters like weight variation, friability, hardness, drug content, disintegration and dissolution [11- 14], and results shown in Table No.2.

Weight Variation Test

The test was carried as per IP procedure.

Hardness Test

The hardness of the tablet was determined using Monsanto Hardness Tester.

Friability Test

Six tablets from each batch were examined for friability using Roche Friabilator (Tropical Equipment Pvt. Ltd. Mumbai, India) and the equipment was run for 4min at 25 revolutions per minute. The tablets were taken out, dedusted and reweighed and % friability was calculated.

$$\% \text{ Friability} = \left(\frac{\text{Loss in weight}}{\text{Initial weight}} \right) \times 100$$

Water Absorption Ratio

A piece of tissue paper folded twice was kept in a Petri dish (internal diameter 5.5cm) containing 6ml of purified water. The tablet was placed on the tissue paper and allowed to wet completely. The wetted tablet was removed and reweighed. Water absorption ratio, R was determined according to the following equation.

$$R = 100 (W_a - W_b) / W_b$$

Where W_b and W_a are the weight before and after water absorption, respectively.

Wetting Time

A piece of tissue paper folded twice was kept in a Petri dish (inter diameter 5.5cm) containing 6ml of purified water. The tablet was placed on the tissue paper and allowed to wet completely. The time required for complete wetting of the tablet was recorded.

Content uniformity test

Five tablets were weighed and powdered, 10 mg of equivalent of was weighed and dissolved in suitable quantity of 0.1N HCL(pH 1.2) the solution was filtered suitably diluted and the drug content was analyzed using UV spectrometer at 274 nm.

In vitro Disintegration Time

The disintegration test was performed using an USP disintegration apparatus, with distilled water at $24 \pm 0.50^\circ\text{C}$. The time reported to obtain complete disintegration of six tablets were recorded and average was reported.

In vitro Dissolution Testing

Dissolution study was conducted for all the formulation using USP type-II apparatus (Electrolab, Mumbai, In-dia.). The dissolution test was performed using 900 ml of 0.1 N HCL (pH1.2) was taken as the dissolution medium at 50 rpm and $37C \pm 0.5C$. Aliquots 10 milliliters were periodically withdrawn and the volume was replaced with an equal volume of fresh dissolution medium. The samples were analyzed spectro photometrically at 274 nm.

Differential Scanning Colorimetry:-

Thermal behavior of drug and polymers were studied by differential scanning calorimetry (DSC) using DSC 7 (Perkin-Elmer, Norwalk, CT). The instrument comprises of calorimeter, flow controller, thermal analyzer and operating software. The instruments were calibrated using indium standards. Accurately weighed samples (5- 10 mg) were hermetically sealed in flat bottom Aluminum Standard 40 μ l pans and heated from 50 to 300C at a rate of 100C/min. under an atmosphere of nitrogen. Melting endotherms of drug, placebo and optimized formulation were determined in the same way. Thermo grams were normalized and rescaled as needed before overlapping. An empty Aluminum pan was used as reference [15-16].

Accelerated Stability Studies

Stability of medicinal products may be defined as the capability of a particular formulation in a specific container to remain within its physical, chemical, microbial, therapeutic and toxicological specification, i.e. stability of drug is its ability to resists deterioration. 90% of labeled potency is generally recognized as the minimum acceptable potency level. Deterioration of drug may take several forms arising from changes in physical, chemical and microbiological properties. The changes may affect the therapeutic value of preparation or increase its toxicity. The formulated Furosemide tablets were studied for its stability as per ICH guidelines where, the tablets are to be tested for its efficiency of release for long term period [17-18].

As per ICH guidelines samples were stored at stability testing of formulation batch was carried out to determine the stability of drug and carrier and also to determine the physical stability of formulation under accelerated storage condition. The prepared tablet were stored in an aluminum foil and placed environmental chamber .The samples were kept at condition of $40 \pm 2^{\circ}C / 75 \pm 5\%$ RH and were analyzed at initial 30, 60 and 90 days for hardness, drug content %, percent drug release.

III. Results And Discussion

Physical Evaluation of Tablets

All the tablet preparations were evaluated for various physical parameters and content uniformity before proceeding further. Table 2,4 includes the values (mean + SD) of weight variation, hardness, diameter and thickness of 10 tablet batches prepared using different combinations of functional excipients.

Infrared Spectroscopy

The IR Spectrum of Furosemide shown in following Figure No. 1. The interpretations of IR frequencies are shown in Table No. 1

Compatibility for Drug and Excipients:-

The FT-IR spectra of the pure Furosemide and physical mixture of drug and polymers were recorded to check interaction between drug and polymers. The characteristic peaks of Furosemide were appeared in all the spectra and values were shifted slightly due to the formation of complex. This indicated that there was no chemical interaction between Furosemide and polymers. The Figure No. 2 -09 showed the spectral values obtained after the drug and polymer was kept for 21 days.

PrecompressedParameterThe results predict that, the Carr's index is in the range of 10-20% which is considered as excellent compression property. Angle of repose less than 30° gives the excellent flow property to the powder blend. Similarly, the bulk density and tapped density value was found to be less than one. Hence have good flow property.

All these results indicate that, the powder blend possess satisfactory flow and compressibility properties. The results are shown in Table No.3.

Post Compression Parameters

Tablet weights in all batches varied between 120.98 to 121.46, thickness between 2.86 mm to 2.95 mm and tablet hardness between 3.18 to 3.59 kg/cm². Thus all the physical parameters of the manually compressed tablets were quite within control. The percentage friability, as depicted in Table No. 4 was in the range of 0.550 – 1.03. The tablets of S3 & S6 formulation with high friability of more than 1% as compared to tablets of S1 to S10 having a comparatively low to medium concentration of superdisintegrant [19].The reason behind that the

usage of higher percentage subliming ingredient, porosity of tablets increased thus giving tablets which were friable. However, for orodispersible tablets the percentage friability up to or slightly above 1% is permissible. Some other important parameters tested viz Disintegration time, Wetting time, Water absorption ratio and content uniformity are enlisted in following Table No. 5.

Wetting Time

The wetting time of all six formulations was in the range of 8 to 15 seconds. The wetting time is closely related to the disintegration time. There is a direct relationship between the wetting time and disintegration time, which is faster the wetting time, faster is the disintegration time. Wetting Time was showed in figure No.10.

Uniformity of Content

The drug content for tablets of all formulations was found to be in the range of 98.23 – 99.90. Thus all formulation batches of Furosemide found to be contain the drug within the acceptable range.

Dissolution Studies in 0.1N HCL(pH 1.2):

The dissolution studies were carried out on optimum formulations are shown in Figure No.11. The release of drug was largely depended on the disintegration time. That is faster the disintegration of tablets, better and faster is the release. S3 of Crosscarmalose sodium releases 97.07% of drug after 10 min [19].while S6 of Crosspovidone showed only 85.24% and Sodium starch glycolate gives 81.24% release after 10 minutes. Hence, Crosscarmalose sodium showed most efficient drugrelease than Crosspovidone and S9 Sodium starch glycolate formulation in 0.1N HCL (pH 1.2).

Differential Scanning Calorimetry

Furosemide showed a sharp melting endotherm at 1390 C. From the DSC scans of crushed tablet, no shift of melting endotherms was observed with respect to the melting endotherm of Furosemide. The DSC thermogram of Furosemide was shown in Fig No. 12. And for optimum batch was shown in Fig No. 13.

Accelerated Stability Study

Accelerated stability studies (AST) was carried for optimized batch S3 exposing it to 40±20C%75±5%RH for 0, 60, 120 and 180 days. The sample was analyzed forHardness, Drug Content, In-vitro disintegration time and In-vitro dissolution studies.

The FT-IR spectra of the pure Furosemide characteristic peaks of Furosemide were appeared in the pre and post accelerated stability testing and no such significant changes occurred in the peaks. This indicated that there was no chemical interaction between Furosemide and polymers with formulation. No significant reduction in the content of the active drug was observed over a period of 90 days; hence shelf life of the formulation could extrapolate to a minimum of two years. The optimum formulation did not show any significant change in disintegration time, friability and drug content when kept at different condition and period.

Table 1.Preparation of Final Formulation

Ingredient	S1	S2	S3	S4	S5	S6	S7	S8	S9
Drug(mg)	40	40	40	40	40	40	40	40	40
Camphor(mg)	15	20	25	15	20	25	15	20	25
Crosscarmelose Sodium(mg)	4	6	8	-----	-----	-----	-----	-----	-----
Crosspovidon(mg)	-----	-----	-----	4	6	8	-----	-----	-----
Sodium starch Glycolate(mg)	-----	-----	-----	-----	-----	-----	2	4	6
Microcrystalline Cellulose(mg)	10	10	10	10	10	10	10	10	10
Lactose(mg)	38	31	24	38	31	24	40	33	26
Total (mg)	110	110	110	110	110	110	110	110	110

Table 2. Interpretation of FT-IR for Furosemide

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 3. Pre compressed Blend Properties of Formulation of Furosemide

Parameters Formulations	Angle of Repose (°) ±SD	Bulk Density (g/ml) ±SD	Tapped Density (g/ml) ±SD	Carr's Index (%)±SD	Hausner's Ratio ±SD
S 1	25.43±0.50	0.57±0.031	0.63±0.040	11.67±0.73	1.10±0.41
S 2	27.97±0.34	0.59±0.022	0.69±0.022	14.87±0.60	1.17±0.31
S 3	26.69±0.55	0.58±0.018	0.64±0.020	13.72±0.27	1.09±0.52
S 4	27.65±0.39	0.55±0.024	0.62±0.024	15.71±0.71	1.13±0.49
S 5	24.32±0.78	0.57±0.037	0.67±0.051	15.31±0.99	1.18±0.46
S 6	25.71±0.59	0.54±0.025	0.65±0.036	16.81±0.77	1.20±0.57
S 7	26.93±0.46	0.59±0.024	0.66±0.032	12.96±0.49	1.13±0.43
S 8	25.53±0.32	0.53±0.012	0.59±0.012	12.20±0.34	1.11±0.36
S 9	27.40±0.43	0.55±0.029	0.61±0.036	10.43±0.23	1.11±0.52

(N=3)

Table 4. Physical Evaluation of Tablets Prepared by Sublimation Method

Parameters Formulations	Thickness (mm) ± SD	Hardness (kg/cm ²)± SD	Weight Variation (mg) ± SD	% Friability ± SD
S1	2.91±0.045	3.59±0.31	115.45±0.45	0.703±0.21
S2	2.96±0.035	3.51±0.29	114.30±0.62	0.687±0.33
S3	2.95±0.090	3.45±0.11	113.35±0.35	0.549±0.56
S4	2.92±0.036	3.15±0.51	116.60±0.54	0.527±0.32
S5	2.89±0.080	3.35±0.37	117.58±0.45	0.674±0.64
S6	2.92±0.032	3.49±0.40	116.25±0.38	1.01 ±0.51
S7	2.90±0.075	3.35±0.49	118.47±0.68	0.550±0.36
S8	2.86±0.050	3.33±0.52	117.54±0.72	0.575±0.35
S9	2.93±0.040	3.50±0.56	116.69±0.43	1.03±0.30

(n=3)

Table 5. Post Compression Parameters (S1-S9)

Parameter Formulations	Disintegration Time (Sec) Mean ± SD	Wetting Time (Sec) Mean ± SD	Water Absorption Ratio Mean ± SD	Uniformity of Content Mean ± SD
S1	14 ± 1.33	13±1.14	96.03 ± 0.044	98.72± 0.60
S2	13± 0.5	12±1.673	94.02± 0.046	98.23± 0.48
S3	9± 0.05	8±1.673	98.98± 0.086	98.93± 0.30
S4	15± 0.2	14±1.483	97.95± 0.029	98.99±0.60
S5	14± 0.60	13± 1.580	97.94±0.031	98.72± 0.83
S6	13± 0.60	12± 1.571	91.95±0.023	98.59± 0.52
S7	11± 0.07	10±2.236	94.14±0.019	98.21± 0.52
S8	10± 0.05	9±3.050	95.60±0.047	98.20±0.70
S9	10± 0.5	11 ± 2.00	91.91± 0.058	98.34± 0.62

Table 6. Accelerated Stability Testing for Batch S3

Parameters ↓ Days →	0	60	120	180
Hardness (Kg/cm ²)	3.50±0.11	3.50 ± 0.14	3.50 ± 0.20	3.50 ± 0.40
Drug Content (%)	99.93± 0.87	99.90 ± 0.59	99.67 ± 0.35	99.41 ± 0.74
In-vitro disintegration time(Sec)	9± 0.05	8.8± 0.39	8.2 ± 0.67	8 ± 0.44
In-vitro dissolution studies%	97.07±0.32	97.06 ± 0.75	97.04± 0.39	96.92± 0.47

(n=3)

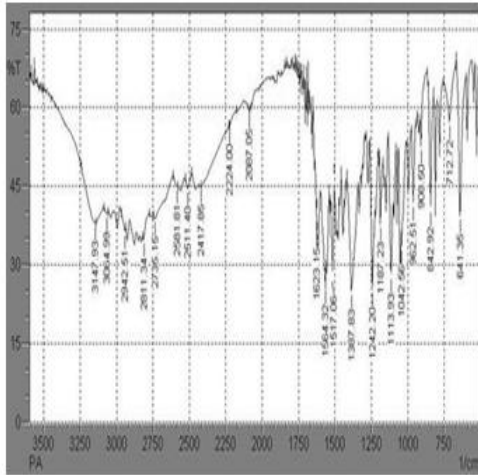


Figure 1: FTIR Spectra of Furosemide

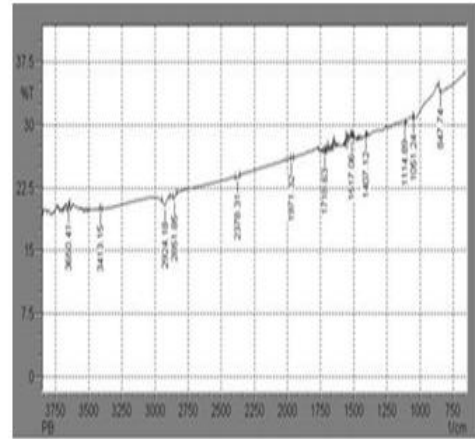


Figure 2: FTIR Spectra of Camphor

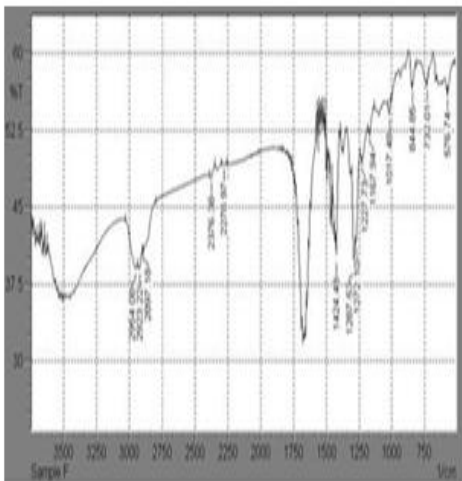


Figure 3: FTIR Spectra of Crospovidone

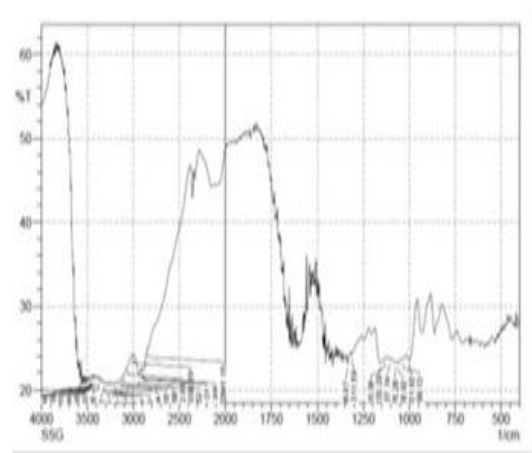


Figure 4: FTIR Spectra of Sodium Starch Glycolate

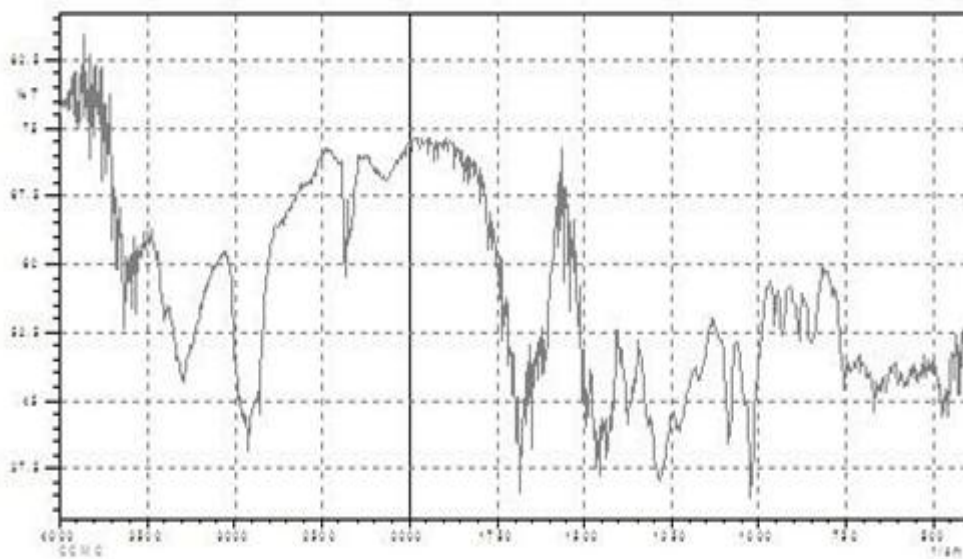


Figure 5: FTIR Spectra of Crosscarmalose Sodium

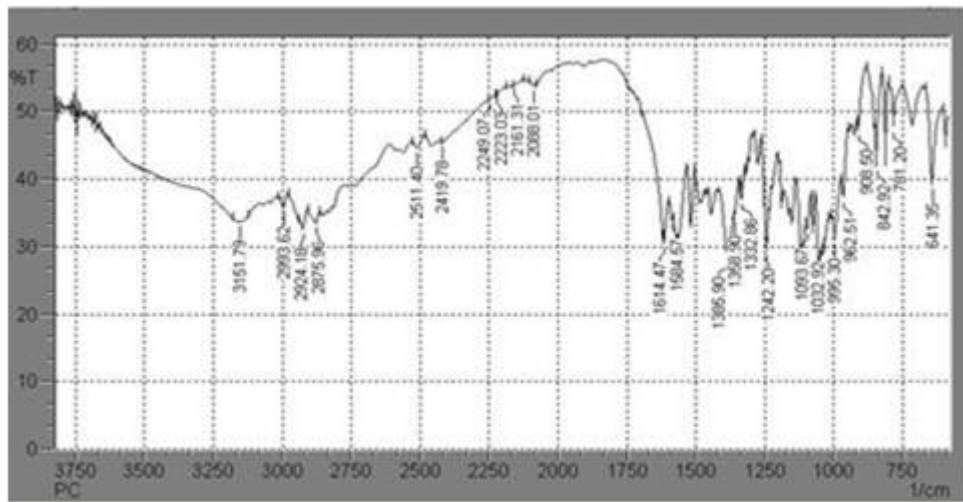


Figure 6. FTIR Spectra of Furosemide + Camphor + Crosscarmalose Sodium.

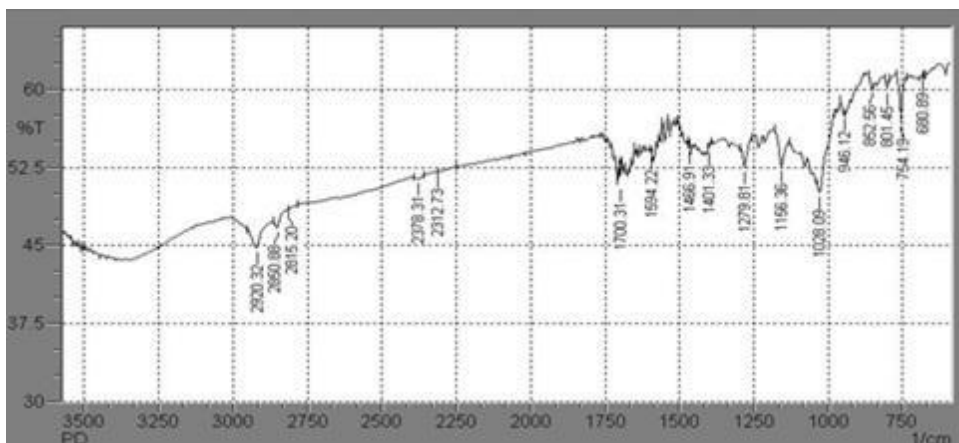


Figure 7. FTIR Spectra of Furosemide + Camphor + Sodium Starch Glycolate

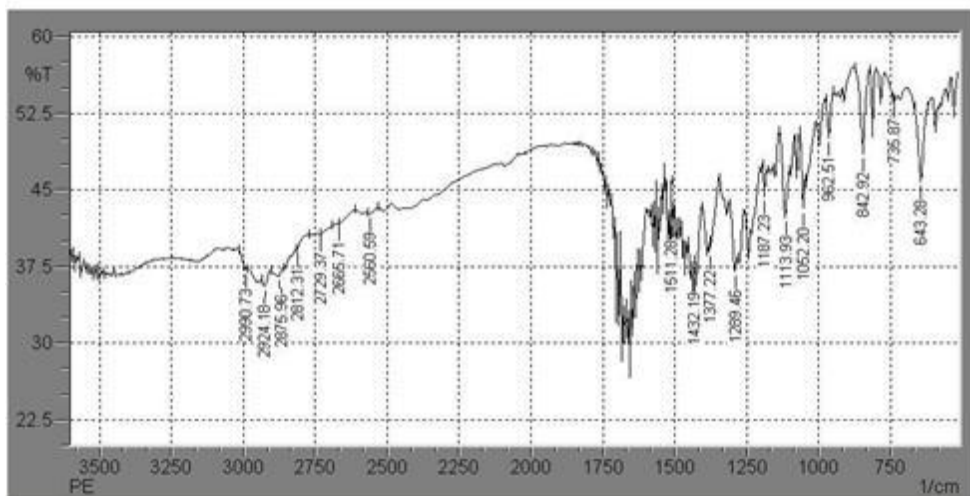


Figure 8. FTIR Spectra of Furosemide + Camphor + Crossprovidone

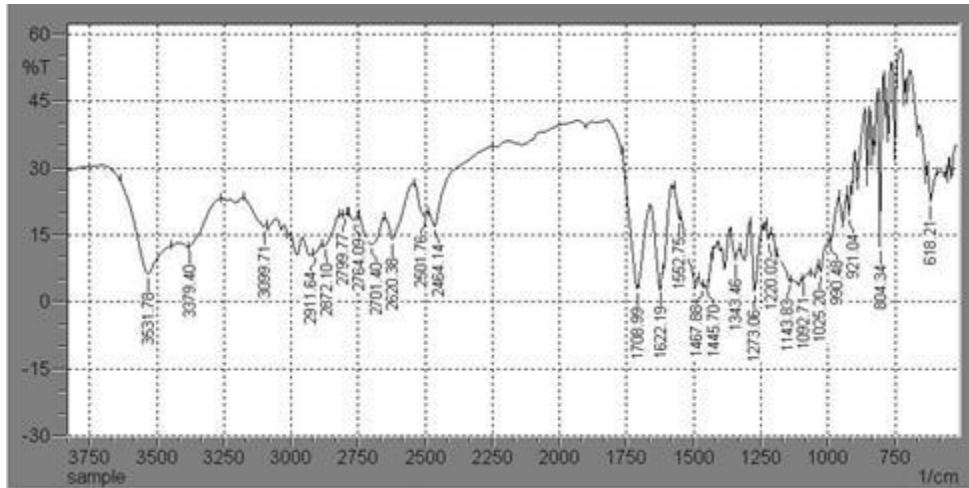
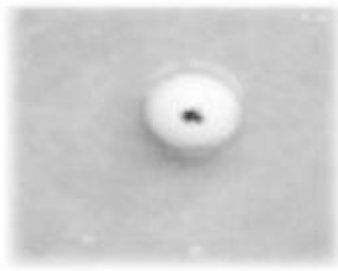
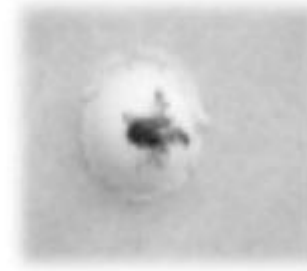


Figure 9. FTIR Spectrum of Physical Mixture



AFTER 5SEC



AFTER 10 SEC.

Figure 10. Wetting Time

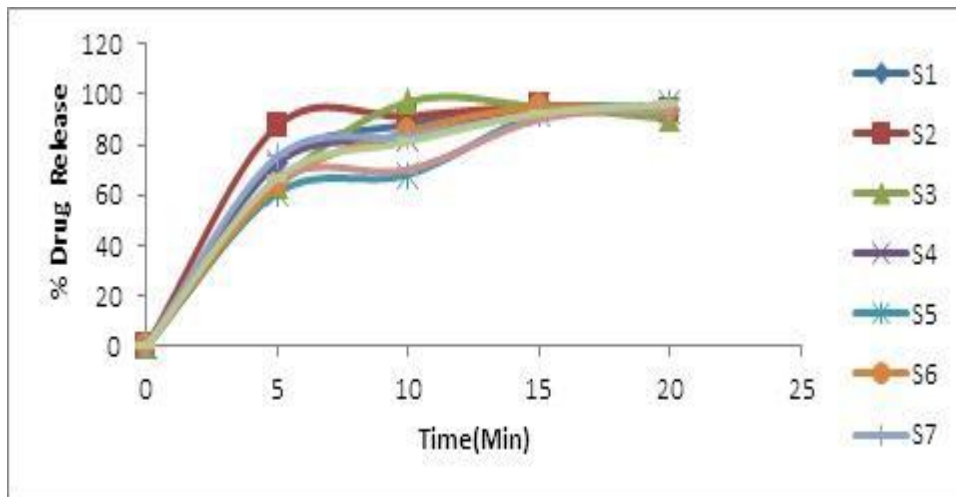


Figure 11. Dissolution Profile of S1-S9 Formulation

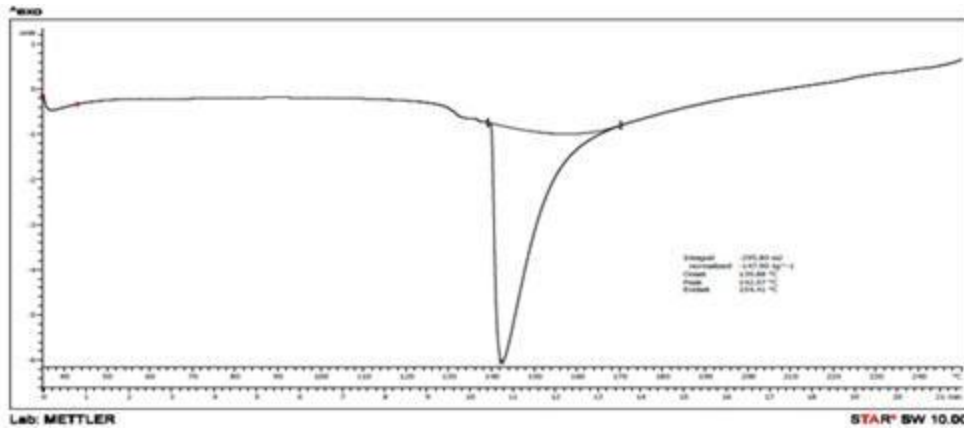


Figure 12. DSC Furosemide

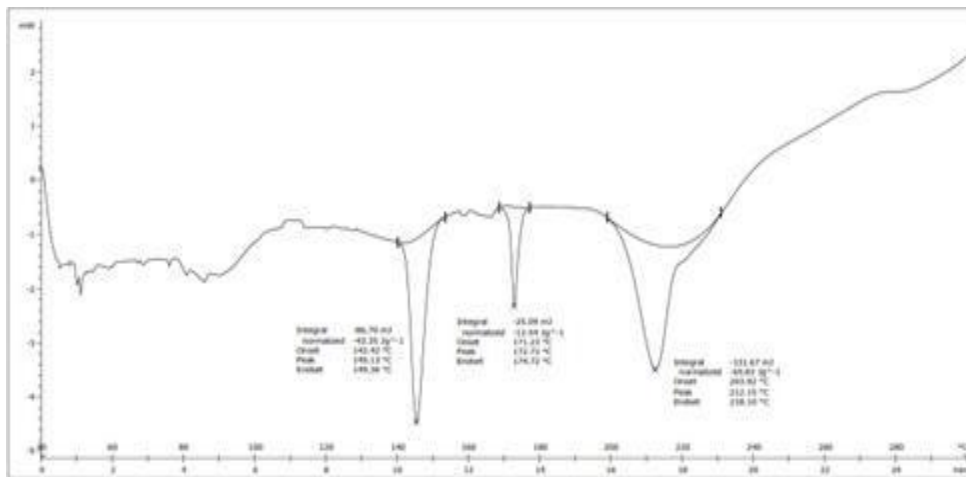


Figure 13. DSC of Optimum Batch S3

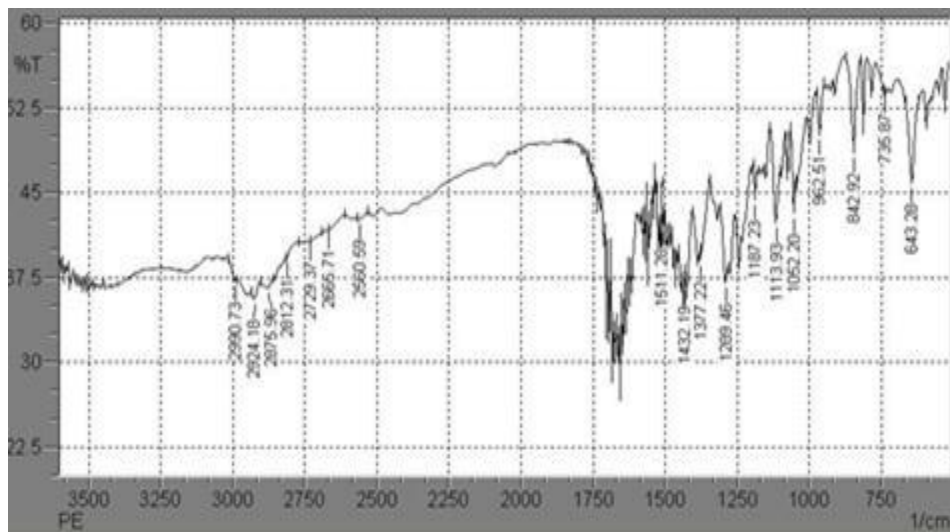


Figure 14. FTIR Spectra of Batch No.S3

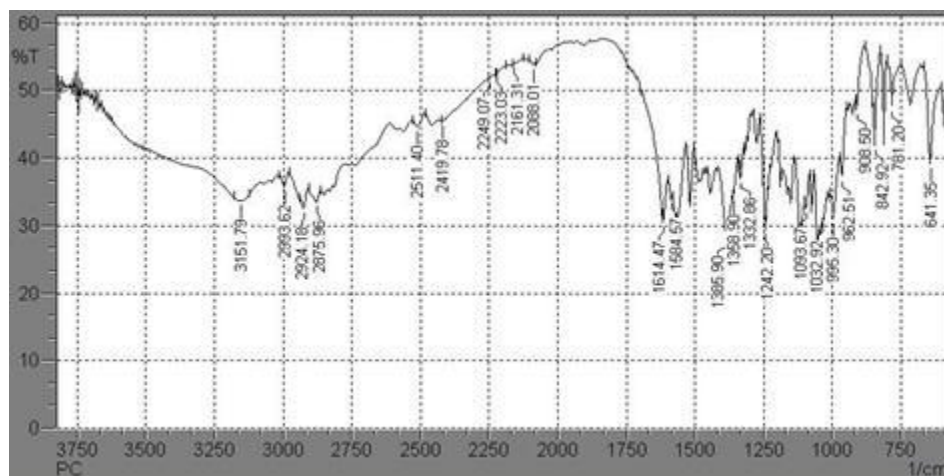


Figure 15. FTIR Spectra of Batch No.S3 After Accelerated Stability Testing.

IV. Conclusion

The study conclusively demonstrated significant results of Furosemide and rapid disintegration and dissolution of FDT's. The fast dissolving tablets of are more Furosemide palatable, also helpful to the patients with cardiac failure, hypertension which can lead to patient discomfort with or unwillingness to swallow the available oral tablet and associated water. Thus, the patient – friendly dosage form of drug, Hence, at the end of this investigation it can be concluded that FDT of Furosemide was successfully prepared by conventional sublimation method using different superdisintegrants and the objectives of this study are achieved. Fast Dissolving Tablets can offer several biopharmaceutical advantages such as improved efficiency over conventional dosage forms. For example, they require smaller amount of active ingredient to be effective, improve absorption profiles and offer better drug bioavailability than regular tablets and capsules. In addition FDT's may be suitable for oral delivery of drugs such as protein and peptide based therapeutics that has limited bioavailability when administered by conventional tablets. These products usually degrade rapidly in stomach. Because drugs delivered in FDT's may be absorbed in the pregastric sites of highly permeable buccal and mucosal tissues of oral cavity, they may be suitable for delivering relatively low-molecular weight and highly permeable drugs[19-20].

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Sandeep A. Wathore*¹ Development and Evaluation of Fast Dissolving Furosemide Tablet"
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