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Development and Characterization of Fast Dissolving Tablets of Bumetanide Solid Dispersion

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ABSTRACT: Background: The enhancement of the solubility and dissolution profile by solid dispersion is expected to significantly improve the bioavailability of drug. **Aim:** The primary objective of the study to formulate the solid dispersion of Bumetanide and secondary objective of the research to formulate and evaluate the fast dissolving tablet of Bumetanide solid dispersion. **Methods:** The Bumetanide solid dispersion was prepared by solvent evaporation method by using urea as carrier in the ratios of 1:1, 1:3, 1:6 and 1:9. The prepared Bumetanide solid dispersions were formulated as fast dissolving tablet (FDTs) by direct compression method. The blended Bumetanide FDTs granules were evaluated for flow properties with respect to angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio. The FDTs were evaluated for thickness, hardness, weight variation, content uniformity, friability, disintegration test and *in vitro* drug release studies. The drug excipient interaction was evaluated by FTIR. **Results:** The tablets were passed all the tests as per the Pharmacopoeia specification. Among all the formulations, F4 formulation containing, Drug and Crospovidone showed good result that is the tablet released the 98.21 % of drug in 60 min. As the concentration of polymer increases the drug release was increased. While the formulations containing Croscarmellose sodium showed less release. **Conclusion:** Hence from the dissolution data it was evident that F4 formulation is the better formulation.

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Keywords: Bumetanide, Solid dispersions, Fast Dissolving, Disintegration test, Crospovidone.

INTRODUCTION:

The enhancements of oral bioavailability of such poorly water-soluble drugs often show poor bioavailability because of low and erratic levels of absorption. Drugs that undergo dissolution rate limited gastrointestinal absorption generally show improved dissolution and bio availability as a result of reduction in particle size [1]. Methods available to improve dissolution include salt formation, micronization and addition of solvent or surface active agents. Solid dispersion (SD) is one of such methods and it involves a dispersion of one or more active ingredients in an inner carrier or matrix in solid

state prepared by melting, dissolution in solvent or melting-solvent method [2,3].

Bumetanide is sulfamoylbenzoic acid deriviative (Fig 1) loop diuretic and works by decreasing the reabsorption of sodium by the kidneys. The side effects include dizziness, low blood pressure, low blood potassium, muscle cramps, hearing LOSS, low platelet count and kidney problems. Bumetanide is, characterized by low solubility and high permeability therefore, the enhancement of its solubility and dissolution profile is expected to significantly improve its bioavailability and reduce its side effects [4,5].

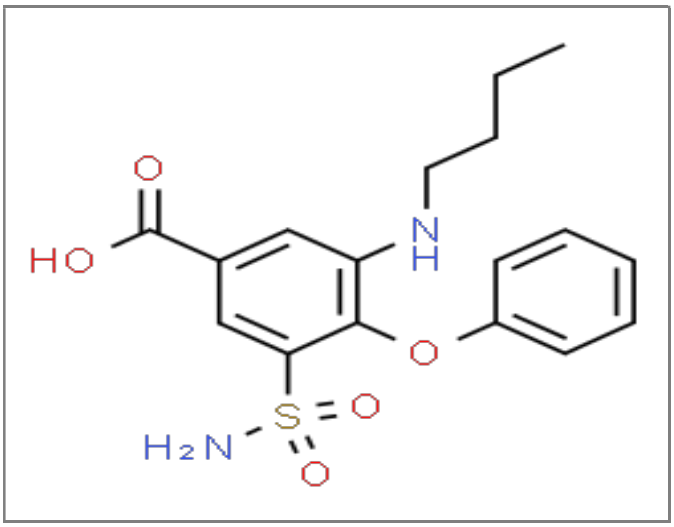

Fig 1. The chemical structure of Bumetanide.

The main objective of this work is to design, prepare and evaluate the fast dissolving tablet of Bumetanide solid dispersion.

MATERIALS AND METHODS:

The pure drug Bumetanide was procured from Avet Pharmaceuticals INC., Mumbai. The urea, crossprovidone sodium, sodium starch glycolate and crosscarmellose sodium were purchased from HiMedia Laboratories, Mumbai. The Microcrystalline cellulose (MCC), Talc and Magnesium stearate were purchased from Merck, India. All chemicals and reagents used in this research were of analytical grade.

Scanning of pure drug Bumetanide:

About 10 mg of pure drug was weighed (Shimadzu Analytical Balance AUW2200, Shimadzu, Japan) and dissolved in 10 ml methanol and treated as primary stock solution strength was 1000 µg/m. From this primary stock solution, 1 ml was pipette out into 10 ml volumetric flask and made it up to 10 ml with the methanol and treated as secondary stock solution of strength 100 µg/ml. From secondary stock solution again 1 ml was taken it in to another volumetric flask and made it up to 10 ml with media (working solution strength is 10 µg/ml. The working solution was analyzed in wavelength region of 200 to 400 nm by using UV-Visible spectrophotometer (UV 1700, Shimdzu, Japan) for determination of λ_{max}.

Determination of Calibration Curve:

About 10 mg of pure drug was dissolved in 10 ml methanol (Primary stock solution - 1000 µg/ml). From this primary stock solution, 1 ml was pipette out into 10 ml volumetric flask and made it up to 10 ml with the media (Secondary stock solution – 100 µg/ml). From secondary stock solution required concentrations were prepared and those concentrations absorbance were found out at observed λ_{max} of 228 nm.

Formulation development for solid dispersion:

Solid dispersions were prepared by solvent evaporation method. Methanol was used as solvent. Bumetanide and water soluble carrier urea were used in preparation of solid dispersion in the drug carrier ratios of 1:1, 1:3, 1:6 and 1:9 (SD1, SD2, SD3 and SD4) [6-8].

Formulation design and preparation of Bumetanide solid dispersion Tablet:

The Bumetanide solid dispersion (SD1, Drug carrier ratio 1:1) was formulated as 12 tablet formulations by direct compression method by using superdisintegrates such as Crospovidone, Croscarmellose sodium and sodium starch glycollate in various proportions [8,9]. The prepared solid dispersions were passed through the sieve no 20 to get uniform size particles. The solid dispersions were mixed with required quantities of super disintegrates, MCC as diluents, magnesium stearate as lubricant and Talc as glidant (Table 2). The blend was passed through sieve no 20. The granules was mixed with talc and magnesium stearate. The prepared blend was compressed into tablet by using 16 station automatic Tablet punching machine with 8 mm punch (Cadmak, WB, India). Same procedure was adopted for other solid dispersion formulations SD2, SD3 and SD4. The twelve (F1 to F12) tablet formulations were prepared.

Evaluation of Bumetanide solid dispersion granules:

The micrometric properties of blend of Bumetanide solid dispersion were characterized with respect to angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio [10-12].

Table 2. Formulation design of Bumetanide solid dispersion fast dissolving tablets.

Ingredients (mg)	Formulation code											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Drug (SD – 1 mg)	2	4	7	10	2	4	7	10	2	4	7	10
Crospovidone	2	2	2	2	-	-	-	-	-	-	-	-
Croscarmellose sodium	-	-	-	-	2	2	2	2	-	-	-	-
sodium starch glycolate	-	-	-	-	-	-	-	-	2	2	2	2
Talc	3	3	3	3	3	3	3	3	3	3	3	3
Magnesium Stearate	5	5	5	5	5	5	5	5	5	5	5	5
MCC	108	106	103	100	108	106	103	100	108	106	103	100
TW	120	120	120	120	120	120	120	120	120	120	120	120

Solid dispersions (SD1 in F1, F5 and F9; SD2 in F2, F6 and F10; SD3 in F3, F7 and F11; SD4 in F4, F8 and F12 Tablet formulation) equivalent to 1 mg was used. MCC – Microcrystalline cellulose, TW – Total weight.

Characterization of Bumetanide Tablets:

The prepared Bumetanide fast dissolving Tablet formulations (F1 to F12) were evaluated for thickness, hardness, friability, weight variation, disintegration, drug content uniformity and dissolution test [13-16].

***Thickness*:**

The crown thickness of individual tablet may be measured with a Vernier caliper (IP54 Digital Caliper, MGW Precision, Mumbai) which permits accurate measurements and provides information on the variation between tablets. It is expressed in mm.

***Hardness Test*:**

Tablets require a certain amount of strength, or hardness and resistance to friability, to withstand mechanical shocks of handling in manufacture, packaging and shipping. The hardness of the tablets was determined using Pfizer Hardness tester (Kingston Lab Solution, India). It is expressed in Kg/cm^2.

Friability Test:

It is the phenomenon where by tablet surfaces are damaged and/or show evidence of lamination or breakage when subjected to mechanical shock or attrition. The friability of tablets was determined by using Roche Friabilator (Model FTV-2, Pharmatron, India). It is expressed in percentage (%). Ten tablets were initially weighed (W_1) and transferred into friabilator. The friabilator was operated at 25 rpm for 4 min or run up to 100 revolutions. The tablets were reweighed again (W_2). The percentage friability was then calculated by,

Friability (%) = $(W_2\text{-}W_1/W_1) \times 100$ ……. (1)

Weight Variation Test:

The tablets were selected randomly from each formulation and weighed individually (Shimadzu Analytical Balance AUW2200, Shimadzu, Japan) to check for weight variation. About twenty tablets were weighed together, their average weight and difference of individual weight from average weight were calculated. The U.S Pharmacopoeia allows a little variation in the weight of a tablet. The percentage deviation in weight variation is shown in Table 2 [17].

Table 2. I.P. specification in weight variation deviation.

Average weight of a tablet	Percentage deviation
130 mg or less	10
More than 130 mg and less than 324 mg	7.5
324 mg or more	5

Drug content uniformity:

About 10 tablets were powdered, and 10 mg equivalent weight of Bumetanide tablet powder was accurately weighed and transferred into a 100 ml volumetric flask. Initially, 10 ml of 0.1 phosphate buffer pH 6.8 was added and shaken for 10 min. Then, the volume was made up to 100 ml with phosphate buffer pH 6.8. The solution in the volumetric flask was filtered, diluted suitably and analysed spectrophotometric ally at 228 nm and the drug content in the tablets was estimated from the standard graph.

***In vitro* disintegration time:**

The process of breakdown of a tablet into smaller particles is called as disintegration. The *in-vitro* disintegration time of a tablet was determined using disintegration apparatus (Disintegration Test Apparatus Model 2901, Electronics India, Mumbai) as per I.P. specifications.

One tablet in each of the 6 tubes of the basket was placed and run the apparatus using phosphate buffer pH 6.8 maintained at (37±1)°C as the immersion liquid. The assembly should be raised and lowered between 100 cycles per min. The time in min was taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was recorded [18].

***In vitro drug release study*:**

The prepared solid dispersion Tablets of Bumetanide were evaluated for drug release study by using USP Grade XXI type II dissolution apparatus [19,20]. The dissolution study was carried out in phosphate buffer pH 6.8 maintained as dissolution fluid at temperature of 37±1 °C, at paddle stirring speed of 50 RPM. At specific interval of time (5, 10, 15, 30, 45 and 60 min) an aliquot of 5 ml drug sample solution was pipetted out and it was immediately replaced with 5ml of fresh 0.1N HCl to maintain sink condition. The total study period was 1 h. The absorbance of drug solution samples was determined by UV-Visible spectroscopy. The concentration of drug in solution from absorbance was determined by using regression equation as obtained from calibration of curve of Bumetanide. From the drug concentration, the cumulative percentage drug release was determined.

Fourier Transform Infrared (FTIR) spectroscopy study:

The formulations were subjected to FTIR studies to find out the possible interaction between the drug Bumetanide and the excipients during the time of preparation. FTIR analysis of the pure drug and optimized formulation were carried out using an FTIR spectrophotometer (Bruker FT-IR, Germany) at frequency ranges of 1000 to 3500 cm^{-1}. The addition new peak or deletion of existing peak in comparison to the major peaks of pure drug will ascertain whether interaction has taken place or not.

RESULTS AND DISCUSSIONS:

The λ_{max} of Bumetanide phosphate buffer in pH 6.8 was found to be at 228 nm. Standard graphs data of Bumetanide in phosphate buffer pH 6.8 is shown in Table 3 and Fig 2. Good linearity was observed with concentration verses absorbance. Its regression co-efficient (R^2) value in phosphate buffer pH 6.8 was 0.999 which were very nearer to 1 and so obeys Beer -Lambert law.

Table 3. Calibration curve of Bumetanide.

Sl. No.	Concentration (µg/ml)	Absorbance
1	10	0.154
2	20	0.301
3	30	0.422
4	40	0.561
5	50	0.692

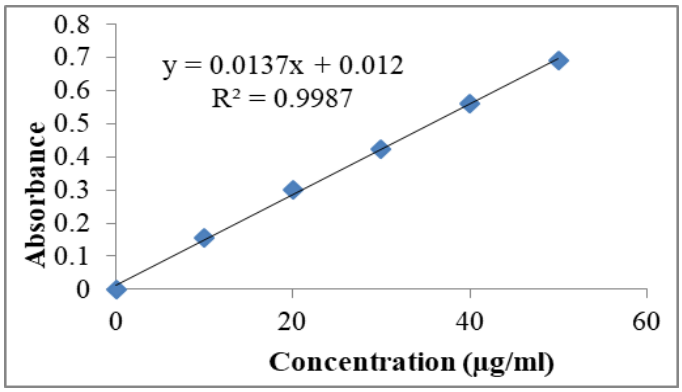

Fig 2. Calibration curve of Bumetanide in phosphate buffer pH 6.8.

The micrometric study data of various Bumetanide fast dissolving tablet blend is given in Table 4. The angle of repose was less than 29.54°, Carr's index values was 11.604 to 13.934 for the pre compression blend of all the batches indicating good flow ability and compressibility. Hausner's ratio was less than 1.388 for all the batches indicating good flow properties. The fast dissolving formulations F2, F3, F4 and F6 possess excellent flow property, whereas formulations F1, F5 and F7 to F12 exhibited good flow property.

The results of the weight variation, hardness, thickness, friability, and drug content of the solid dispersion tablets were given in Table 5. All the tablets of different batches complied with the official requirement of weight variation as their weight variation passes the limits. The hardness of the tablets ranged from 3.1 to 3.9 kg/cm^2 and the friability values was less than 1 % indicating that the tablets were compact and hard. The thickness of the tablets ranged between 2.10 to 2.86 mm. All the formulations satisfied the content of the drug as they contained 96.35 to 99.65 % of Bumetanide and good uniformity in drug content was observed.

Table 4. Evaluation of pre compression parameters of solid dispersion blend.

Formulation Code	Angle of repose (θ)	Bulk density (g/cc)	Tapped density (g/cc)	Carr's index (%)	Hausner ratio
F1	25.23	0.515	0.598	13.88	1.161
F2	23.25	0.525	0.61	13.934	1.162
F3	24.62	0.535	0.609	12.151	1.138
F4	24.56	0.512	0.587	12.777	1.146
F5	25.72	0.499	0.574	13.066	1.15
F6	24.3	0.512	0.582	12.027	1.137
F7	27.8	0.502	0.572	12.238	1.139
F8	25.54	0.518	0.586	11.604	1.131
F9	26.32	0.486	0.564	13.83	1.16
F10	29.54	0.476	0.546	12.821	1.147
F11	29.41	0.453	0.515	12.039	1.137
F12	29.36	0.462	0.534	13.483	1.388

Table 5. Evaluation of post compression parameters of solid dispersion tablet.

Formulation code	Average weight (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Disintegration time (s)	Content uniformity (%)
F1	118.42	2.14	3.4	0.43	15	96.47
F2	117.85	2.65	3.6	0.65	29	98.72
F3	119.24	2.86	3.8	0.72	41	99.12
F4	117.32	2.10	3.4	0.82	13	96.35
F5	115.92	2.42	3.9	0.28	24	99.25
F6	119.78	2.61	3.1	0.76	58	97.18
F7	118.76	2.58	3.6	0.19	14	99.65
F8	117.49	2.41	3.2	0.47	59	98.25
F9	119.27	2.37	3.7	0.67	12	99.10
F10	118.39	2.64	3.9	0.59	37	97.38
F11	119.72	2.11	3.6	0.47	41	99.42
F12	117.28	2.33	3.2	0.36	28	98.24

Thus all the physical attributes of the prepared tablets were found to be practically within control limits.

From the above pre and post compression of solid dispersion tablets of all the required evaluation tests were found to be within limit as per the IP [21-23]. Almost all tablet formulation exhibited fast dissolving properties as their disintegration time was less than the 1 min (Table 5 and Fig 3). Among all the fast dissolving tablet formulation, the tablet formulation F4 containing crossprovidone exhibited least disintegration time that is 13 s. All the tablet formulations of Bumetanide solid dispersion were subjected to *in vitro* dissolution studies, these studies were carried out using phosphate buffer pH 6.8 by using dissolution apparatus type II. The dissolution profile of Bumetanide tablets were compared between solid dispersion tablets. The Bumetanide solid dispersion tablets showed better release in phosphate buffer pH 6, in that F4 showed good drug release i.e. 98.21 % in 60 min (Table 6 and Fig 4 to 6). Almost all tablet formulation showed satisfactory drug release. From the above graphs it was revealed that F4 tablet formulation was optimized formulation, as because the F4 showed maximum drug release and least disintegration time.

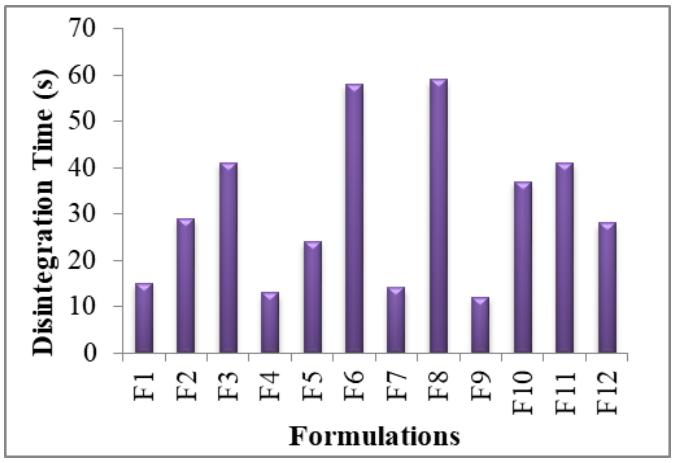

Fig 3. The disintegration time of Bumetanide fast dissolving tablets.

Table 6. *In vitro* dissolution studies of formulated Bumetanide solid dispersion fast dissolving tablets.

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
	Cumulative % drug release											
0	0	0	0	0	0	0	0	0	0	0	0	0
5	12.42	15.21	18.14	21.12	23.92	18.13	16.18	13.14	23.11	21.59	17.33	12.27
10	25.91	28.49	31.10	35.21	38.51	27.67	24.32	22.99	37.62	34.81	31.57	22.95
15	37.19	41.73	43.91	49.66	56.29	45.96	36.25	31.17	48.93	43.75	45.36	34.89
20	49.37	49.91	55.82	58.78	65.35	59.85	52.87	47.59	65.36	51.18	56.75	43.77
30	56.51	56.86	67.19	72.52	74.94	67.93	61.83	51.16	77.15	69.64	62.33	56.83
45	61.29	74.62	75.26	86.97	83.73	79.28	72.45	64.94	89.78	86.52	75.18	62.16
60	72.51	83.41	87.15	98.21	94.14	87.35	81.63	78.28	95.12	90.11	86.15	72.28

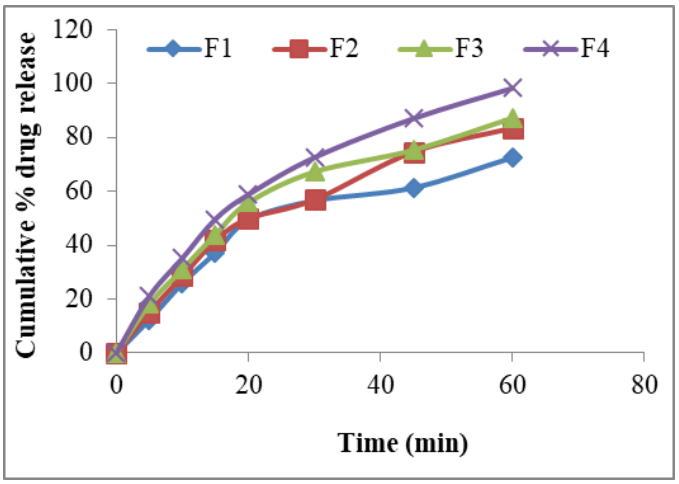

Fig 4. *In vitro* dissolution studies of formulated solid dispersion tablets (F1 to F4) by using Crospovidone.

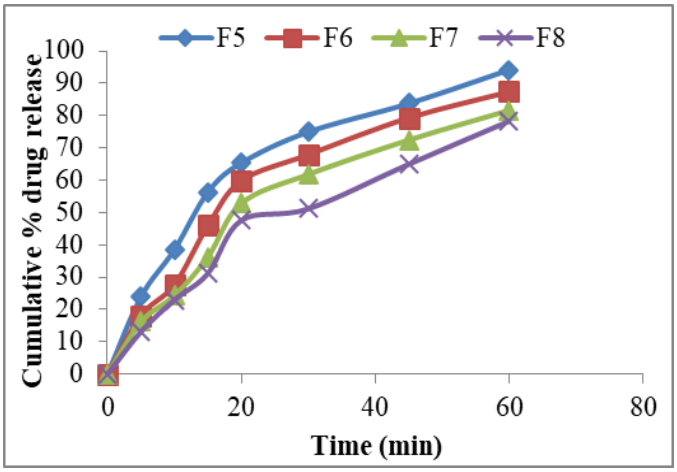

Fig 5. *In vitro* dissolution studies of formulated solid dispersion tablets (F5 to F8) by using Croscarmellose sodium.

The pure drug and the optimized fast dissolving tablet formulation (F4) were subjected to FTIR studies. The results were showed that there is no interaction between the drug and excipients (Fig 7 and 8) has taken place as no such addition new peak or deletion of existing peak in comparison to the major peaks of pure drug has been taken place.

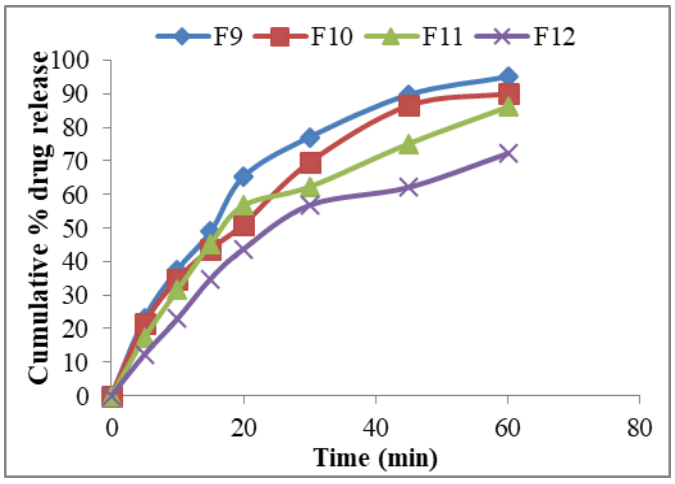

Fig 6. *In vitro* dissolution studies of formulated solid dispersion tablets (F9 to F12) by using sodium starch glycolate.

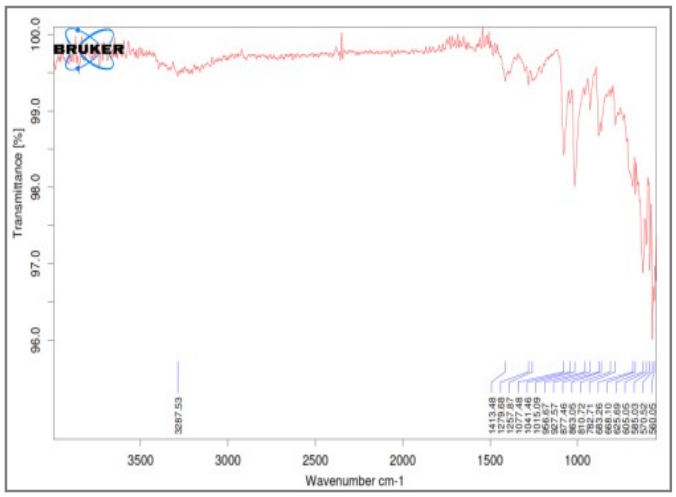

Fig 7. FT-IR Spectrum of Bumetanide pure drug.

CONCLUSION:

Among all the batches of fast dissolving tablet of Bumetanide, formulation F4 containing drug and carrier (SD4 - Bumetanide and urea 1:9) solid dispersion along with Crospovidone as superdisintegrant showed highest drug release profile and lease disintegration time. As the concentration of polymer increases the drug release was

increased. Hence the F4 formulation is the best fast dissolving tablet formulation and it could be successfully use for safe and management of hypertension in Pregnancy state as diuretic.

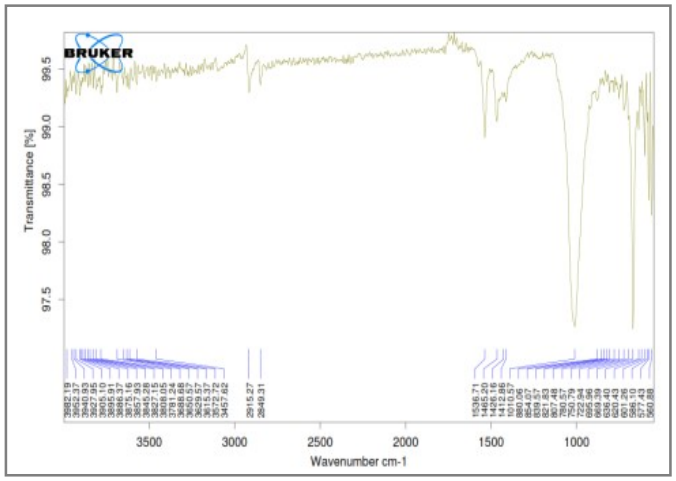

Fig 8. FT-IR Spectrum of Optimized fast dissolving tablet of Bumetanide solid dispersion.

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