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FORMULATION AND DEVELOPMENT OF ORAL DISSOLVING FILMS OF BUMETANIDE

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Abstract:

Objective: *Formulation and Development of oral dissolving Films of Bumetanide.*

Materials and methods: *BUMETANIDE, HPMC E-50, HPMC E-5, HPMC E-3, PE, 4000 (Flakes) and Aspartame. Citric Acid could be formulated with low viscosity film formers viz. HPMC E50 in combination with HPMC E5, E15. Bumetanide could be successfully incorporated in FDFs with of the above polymers and polyethylene glycol 4000 is used as a plasticizer. PEG 4000 itself has a solubulizing affect and result in faster dissolution. Hence, there is no need of superdisintegrants. Use of low viscosity grade HPMC polymers resulted in giving films with transparent and smooth texture.*

Conclusion: *Among all the developed formulations, F9 formulation formulated with HPMC E15 and HPMC E50 in the ratio of 1:1 showed good in vitro disintegration time and dissolution profile.*

Key words: *Bumetanide, PEG, HPMC*

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INTRODUCTION:

Fast dissolving oral films are most advanced forms of solid dosage form due to more flexibility and comfort. It improves the efficacy of API dissolving within minute in oral cavity after the contact with less saliva as compared to fast dissolving tablet without chewing and no need of water for administration. It gives quick absorption and instant bioavailability of drug due to high load flow and permeability of oral mucosa which is 4-1000 times greater than that of skin. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablet dosage form. Fast dissolving oral films are useful in patients such as pediatric, geriatric, bedridden, emetic patients, diarrhea, sudden episode of allergic attacks, or coughing for those who have an active life style. It is also useful whether local action desired such as local anesthetic for toothaches, oral ulcers, cold sores or teething.

The aim of the study is to design and develop a novel fast dissolving oral films of Bumetanide with the disintegration time less than 20 seconds, so as to disintegrate the film rapidly and to achieve rapid drug release [1-3].

MATERIALS AND METHODS:

Table 1: List of Materials and sources

S. No.	Materials	Sources
1.	BUMETANIDE	Killicks Pharma, Mumbai, India.
2.	HPMC E-50	SD Fine Chem. Ltd., Mumbai, India.
3.	HPMC E-5	SD Fine Chem. Ltd., Mumbai, India.
4.	HPMC E-3	SD Fine Chem. Ltd., Mumbai, India.
6.	PEG 4000 (Flakes)	Central Drug House (P) Ltd., New Delhi, India.
7.	Aspartame	SD Fine Chem. Ltd., Mumbai, India.
8.	Citric Acid	SD Fine Chem. Ltd., Mumbai, India.

Preparation of calibration curve of Bumetanide:

Standard plot of Bumetanide was prepared using pH phosphate buffer. 100 mg of Bumetanide was weighed and transferred into volumetric flask. To this add small quantity of p^H 6.8 phosphate buffer to dissolve the drug and then the solution was made upto 100 ml using p^H phosphate buffer. This is stock solution (A).

From stock solution (A), 1 ml was transferred into 100 ml volumetric flask and made up to the mark. This is stock solution (B).

From stock solution (B), appropriate dilutions 2, 4, 6, 8, 10 were made and absorbance was measured by using UV-Spectrophotometer at 254 nm.

FTIR interaction studies:

Fourier Transform Infrared (FTIR) Spectroscopy

Drug-excipients compatibility study was performed by Fourier transform infrared (FTIR) Spectroscopy. A small quantity of sample is grind with specially purified salt bromide and the mixture is heated to 100 °C for 1 hr to remove moisture and is pressed in a mechanical press to form a pellet through which beam of spectrophotometer light was passed.

The peaks of samples were obtained using spectrophotometer (FTIR 8400S Shimadzu, Japan). Pure Drug (BUMETANIDE), individual polymers (HPMC E50, E5 and E15) and physical mixtures of optimized formulation were subjected to FTIR studies [3-6].

Formulation Development:

Method of Preparation of Fast Dissolving Oral Films of Bumetanide

Fast dissolving oral films of Bumetanide were prepared by solvent casting method. Initially solution (A) was prepared by dissolving polymer and plasticizer, polyethylene glycol 4000 in 9 ml of water and kept for stirring for 1 hr and solution (B) was prepared by dissolving drug, citric acid, Aspartame in 1 ml of water as per formulation in appropriate quantities, add solution (B) to solution (A) and kept for stirring for 2 hrs. Care was taken as air bubble entrapment occurs during stirring. After uniform mixing of two solutions, degassing is done to remove air bubbles and finally the solution was casted into pre-fabricated glass mould of size 4X4 cm^2 size and dried overnight and the dried film was cut into appropriate sizes for further evaluation [7-9]. Compositions of fast dissolving oral films of Bumetanide were shown in Table 2.

Table 2: Formulation Chart

Ingredients	FORMULATION CODES								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
BUMETANIDE	10	10	10	10	10	10	10	10	10
HPMC E50	200	450	700	150	100	50	150	100	50
HPMC E5	-	-	-	50	100	150	-	-	-
HPMC E15	-	-	-	-	-	-	50	100	150
PEG 4000	40	90	140	40	40	40	40	40	40
Citric Acid	4	8	14	4	4	4	4	4	4
Aspartame	2	4.5	7	2	2	2	2	2	2
Water (ml)	9	9	9	9	9	9	9	9	9
Ethanol (ml)	1	1	1	1	1	1	1	1	1

RESULTS AND DISCUSSION:

Spectrophotometric determination of Bumetanide:

The standard graph and whole analysis was performed in pH 6.8 phosphate buffer. The wavelength selected was 273nm.

Table 3: Standard graph of Bumetanide

Concentration (µg/ml)	Absorbance (nm)
0	0
2	0.146
4	0.297
6	0.449
8	0.599
10	0.736

Standard graph for Bumetanide in 6.8 pH phosphate buffer at 273nm was showed in figure 7. The standard graph of BUMETANIDE in pH 6.8 phosphate buffer showed a good linearity with r^2 of 0.9997 in the concentration range of 0-10 µg/ml.

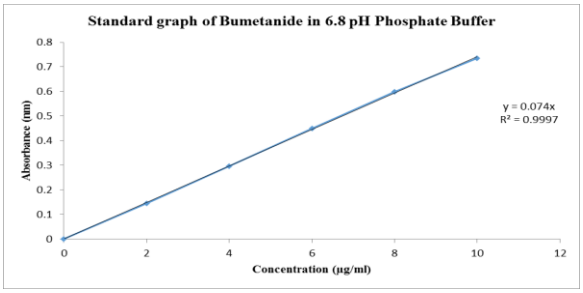

Fig 1: Standard graph of Bumetanide.

Compatibility Studies:

A proper design and formulation of a dosage form requires considerations of the physical, chemical and biological characteristics of both the drug and excipients used in the fabrication of the product. To facilitate the development of novel drug delivery systems, the demand of new excipients has been increased**.** Excipients is selected and used because it contributes one or more functional attributes to the product characteristics. Therefore, before producing the actual formulation, compatibility of BUMETANIDE with polymers and excipients was tested using the Fourier Transform Infrared Spectroscopy (FTIR) technique and Differential Scanning Microscopy (DSC) Technique.

FTIR interaction studies.

As described in the methodology section, drug-polymer compatibility studies were carried out using Fourier Transform Infrared Spectroscopy to establish any possible interaction of Bumetanide with the polymers used in the formulation. It was expected that the intermolecular hydrogen bonding between hydroxyl groups of HPMC and amino (-NH) groups of Bumetanide might be involved. In order to have better understanding of type of interaction between the blended polymers, FTIR spectra of all different combinations of polymers with the drug were studied. The results indicated that the characteristic absorption peaks due to pure Bumetanide have appeared in the formulated FDF's, without any significant change in their position after successful formulation, indicating no chemical interaction between Bumetanide and polymers.

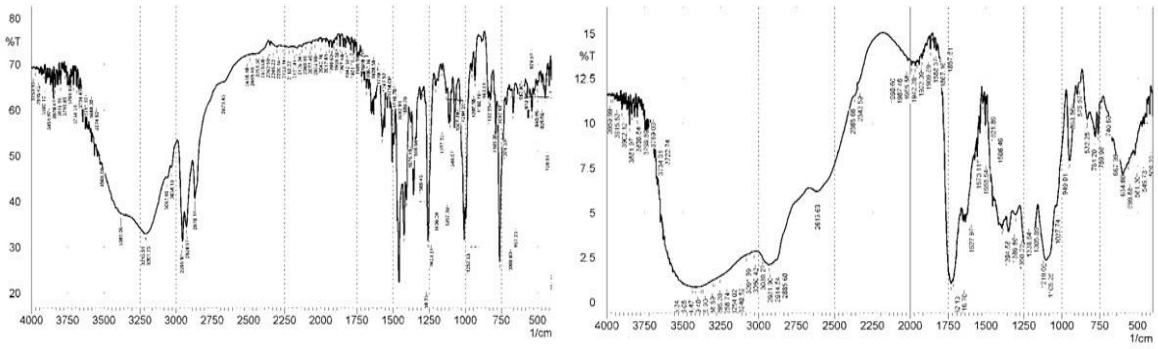

Fig 2: FTIR Spectra of pure drug Bumetanide, FTIR Spectra of formulation F11

Table 4: Melting points of pure drug and excipients

Drug/Excipients	Melting Point (ºC)
Bumetanide	170 - 185
HPMC	170 - 180
PEG 4000	55 – 60
Aspartame	246.5

Evaluation of Physico-mechanical Properties of FDF's of Bumetanide [10-12]

Physical Appearance:

Physical appearance was examined with visual inspection of films and texture by touching it. All the films are of having smooth texture. As lower grades of HPMC E50, E5 and E15 known for having good film forming properties, were used to prepare films which has shown excellent films of transparent, tough, and good flexible films from aqueous solutions.

Thickness:

Thickness of each film was measured using Vernier calipers at different locations. It is essential to determine uniformity in the thickness of the thickness of the film as this is directly related to accuracy of dose in films. The average thickness and standard deviation were reported below in Table 17. All the films prepared showed uniform thickness as it is important factor to consider which ascertains the accuracy and uniform distribution of dose in the strip and as thickness of the films increases disintegration and dissolution time of the film increases and as the thickness of the film decreases disintegration and dissolution time of film decreases. Too much thickness of film takes more to dissolve and films having less thickness are difficult to handle, as the film may tear. As per the formulation F3 made of HPMC E50 7% has highest thickness of 0.8 ± 0.02 and formulation F9 film made of HPMC E50 and HPMC E15 has the lowest thickness of 0.13 ± 0.01. Samples with air bubbles, nicks or tears and having mean thickness variations of >5% were excluded from analysis.

Folding endurance:

Folding endurance was determined by repeated folding of the film at the same place till the film breaks. The number of times the film is folded without breaking is considered as the folding endurance value. Results were reported in Table 17. Three films of each formulation of size 2x4 cm were cut by using sharp blade and film was folded repeatedly until it breaks. The folding endurance gives an impact over the flexibility of films as brittle films gives less value of folding endurance and films with good flexibility gives high value of folding endurance. It is measured manually by folding repeatedly till cracks developed on the film which gives indication of the brittleness of the film. All film Formulations were of having good folding endurance value, which is an indication of having good film properties. Also, it was observed that increase in thickness of polymer concentration decreases folding endurance value.

Weight variation:

Three films each of 1 cm was cut at three different places from the casted film were taken and weighed individually on analytical electronic balance and weight of each film was noted and weight variation was calculated. Average weight results were shown in Table 17. It was found to be in a range of 33.77 ± 0.26 to 153.5 ± 0.53. The weight of all the films was found to be uniform. From all the formulations it has been observed that increase in concentration of polymer increases weight of the film. Weight variation is an important parameter to consider as any variation in the weight of film leads to under medication or over medication.

Table 5:Evaluation Parameters of FDF's of Bumetanide

Formulation	Thickness (µm)*	Folding Endurance*	Mean Weight (1X1 Film) (mg)*
F1	0.3±0.01	380±0.12	53.74 ± 0.43
F2	0.5±0.01	260±0.09	118.89 ± 0.12
F3	0.8±0.02	53±0.21	153.5 ± 0.53
F4	0.3±0.01	352±0.01	53.68 ± 0.33
F5	0.25±0.01	423±0.03	61.22±0.14
F6	0.23±0.01	446±0.11	54.22±0.67
F7	0.25±0.02	298±0.04	54.13±0.11
F8	0.15±0.01	426±0.01	54.36±0.22
F9	0.13±0.01	482±0.01	33.77±0.26

* Mean ± SD; n = 3

Moisture absorption:

Moisture absorption study was performed to check the physical integrity of films. The films were weighed accurately and placed on a pre weighed stainless steel wire mesh. The wire mesh was then submerged in a Petri dish containing 20 ml distilled water. Increase in weight of the film was determined at regular time intervals until a constant weight was obtained.

Moisture absorption study is an important parameter to be performed, as the presence of moisture possesses a critical challenge on drug stability. Moisture accelerates the hydrolysis of drug as well as facilitates reaction with other excipients, thereby affecting stability and shelf life of the final dosage form. All the reported values were shown in the Table. And it has been observed that all the film forming polymers HPMC E50, E5 and E15 were of hydrophilic in nature and the obtained values were in a range of 6.38 to 25.7.

Moisture loss:

Moisture loss study was performed to check physical stability of films at dry environment. Film was weighed accurately and kept in desicator containing anhydrous calcium chloride for 3 days and films were removed and reweighed and moisture loss was calculated. It also gives an idea about hydrophilicity of film formulations. All the obtained values were reported in Table 18. The obtained values were in a range of 0.21to 0.96.

Tensile strength:

The Tensile strength value of the films directly characterizes the flexibility of films. Tensile Strength of films was performed using tensile tester. (Instron 1122). Tensile strength gives an indication of the strength and elasticity of the film, tensile strength of all the formulations were shown in Table 18. Results revealed that all the formulations showed better tensile strength. Tensile strength of all formulations was found to be in a range of 2.96 ± 0.09 to 5.98 ± 0.05. It has been observed that the increase in thickness of the film, there is a decrease in tensile strength of the film.

Table 6: Evaluation Parameters of FDF's of Bumetanide

Formulation	% Moisture Uptake	% Moisture Loss	Tensile Strength*
F1	12.87	0.90	5.26 ± 0.04
F2	25.70	0.33	3.82 ± 0.02
F3	21.58	0.28	2.96 ± 0.09
F4	21.79	0.74	5.34 ± 0.04
F5	19.57	0.75	5.26 ± 0.07
F6	21.29	0.80	5.43 ± 0.02
F7	19.27	0.96	5.34 ± 0.08
F8	13.44	0.80	5.73 ± 0.06
F9	6.38	1.21	5.98 ± 0.05

* Mean ± SD; n = 3

Drug content estimation:
Film was dissolved in p^H 6.8 phosphate buffer and continuously stirred for 1 hr and the solution was filtered and suitable dilutions were made and absorbance was measured using UV Spectrophotometer at 273 nm. The limit for drug content estimation is 85-115%. The drug content estimation was performed to ensure the accurate distribution of drug. The test was performed for all the formulations in triplicate. Each formulation was analyzed spectrophotometrically and the mean value and standard deviation of all the formulations were calculated. The drug content or percentage of drug content is varied in between 95.61 % to 97.19 %.

In vitro disintegration test:
Disintegration test of the film was performed by dissolving the film in a glass beaker containing 25 ml of water with occasional gentle swirling and shaking for every 10 sec. The disintegration time is the time when the film starts to break or disintegrate and time was noted.
Results of disintegration time of all the formulations were tabulated in Table. The disintegration time of all the formulations were in a range of 16 ± 2.6 sec to 615 ± 1.9 sec. Also it has been observed as the concentration of polymer increases thickness of film increases and thereby times taken for the film to disintegrate increases, results were shown in table 7.

In vitro dissolution study:
Dissolution test of the film was performed using USP Type II dissolution apparatus in 300 ml pH 6.8 phosphate buffer at 100 rpm. 5 ml of sample was withdrawn in a time intervals of 5, 10, 15, 30, 45, 60, 90 min and 5 ml buffer was replaced to maintain sink conditions. Withdrawn samples were diluted and absorbance was measured using UV-Spectrophotometer at 273nm report shown in table 8.

Table 7: Evaluation Parameters of FDF's of Bumetanide

Formulation	% Drug content*	*In vitro* disintegration test (sec)*
F1	96.517	184±1.0
F2	95.956	426±1.3
F3	96.517	615±1.9
F4	96.180	140±1.0
F5	95.956	123±2.2
F6	95.619	98±1.8
F7	96.967	126±2.1
F8	96.967	22±3.0
F9	97.192	16±2.6

Table 8: *In vitro* release profile of Bumetanide from formulation F1

Time (min)	Absorbance	Concentration (µg/ml)	Amount (mg)	Pre-concentration x 5/1000	Cumulative amount of drug release	% CDR*
5	0.612	8.252	2.476	0.000	2.476	10.31 ± 0.06
10	0.933	12.581	3.774	0.041	3.816	15.89 ± 0.02
15	0.165	2.225	6.675	0.063	6.738	28.07 ± 0.04
30	0.258	3.479	10.437	0.011	10.448	43.53 ± 0.09
45	0.365	4.922	14.765	0.017	14.783	61.59 ± 0.10
60	0.427	5.758	17.273	0.025	17.298	72.06 ± 0.14
90	0.553	7.457	22.371	0.029	22.399	93.32 ± 0.09

* Mean ± SD; n = 3

Table 9:In vitro release profile of Bumetanide from formulation F2

Time (min)	Absorbance	Concentration (µg/ml)	Amount (mg)	Pre-concentration x 5/1000	Cumulative amount of drug release	% CDR*
5	0.588	7.929	2.379	0.000	2.379	9.91 ± 0.19
10	0.876	11.812	3.544	0.040	3.583	14.93 ± 0.11
15	0.134	1.807	5.421	0.059	5.480	22.83 ± 0.15
30	0.156	2.104	6.311	0.009	6.320	26.33 ± 0.03
45	0.264	3.560	10.680	0.011	10.690	44.54 ± 0.07
60	0.413	5.569	16.707	0.018	16.725	69.68 ± 0.15
90	0.531	7.160	21.481	0.028	21.508	89.61 ± 0.19

* Mean ± SD; n = 3

Table 10: *In vitro* release profile of Bumetanide from formulation F3

Time (min)	Absorbance	Concentration (µg/ml)	Amount (mg)	Pre-concentration x 5/1000	Cumulative amount of drug release	% CDR*
5	0.296	3.997	1.199	0.000	1.199	4.99 ± 0.07
10	0.576	7.767	2.330	0.020	2.350	9.79 ± 0.11
15	0.860	11.597	3.479	0.039	3.518	14.65 ± 0.14
30	0.099	1.338	4.013	0.058	4.071	16.96 ± 0.09
45	0.206	2.778	8.333	0.007	8.340	34.74 ± 0.13
60	0.398	5.367	16.100	0.014	16.114	67.13 ± 0.12
90	0.501	6.756	20.267	0.027	20.294	84.55 ± 0.08

* Mean ± SD; n = 3

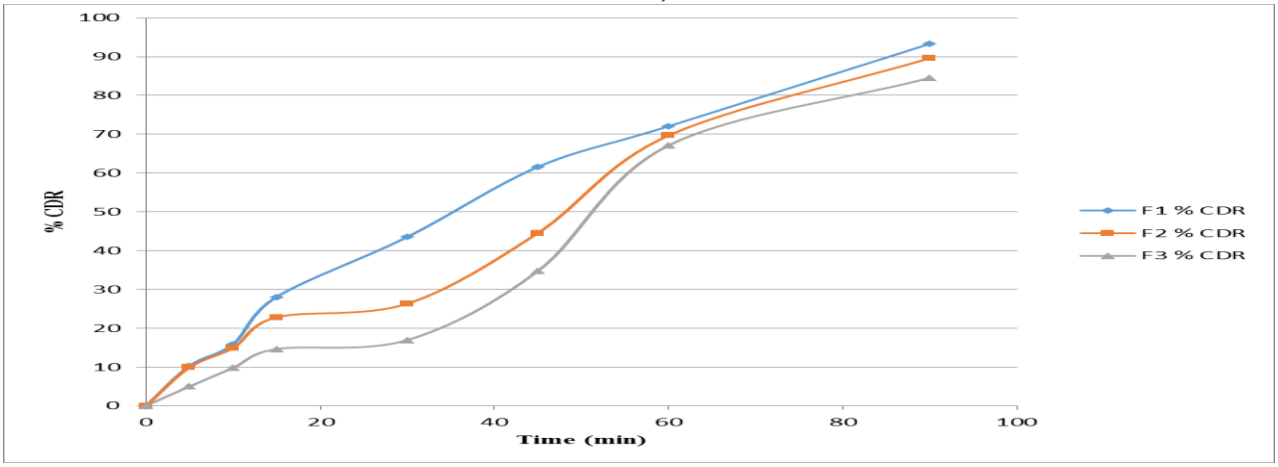

Fig 3: *In vitro* release profile of Bumetanide from formulation F1-F3

In vitro release of Bumetanide from formulation F1, F2, F3. The order of drug release in three formulations F1, F2, F3 is F1>F2>F3. And it is evident that as the concentration of polymer increase the time taken for the drug to be released is increased. F1, F2, F3 formulations has not given satisfactory results; further attempts were made to achieve a better drug release in 90 min.

Table 11: *In vitro* release profile of Bumetanide from formulations F4

Time (min)	Absorbance	Concentration (µg/ml)	Amount (mg)	Pre-concentration x 5/1000	Cumulative amount of drug release	% CDR*
5	0.867	11.692	3.508	0.000	3.507	14.61 ± 0.08
10	0.093	1.259	3.778	0.058	3.837	15.98 ± 0.07
15	0.173	2.338	7.015	0.006	7.021	29.25 ± 0.12
30	0.283	3.820	11.460	0.012	11.472	47.79 ± 0.06
45	0.370	4.987	14.960	0.019	14.979	62.40 ± 0.02
60	0.432	5.827	17.480	0.025	17.505	72.93 ± 0.09
90	0.559	7.543	22.629	0.029	22.659	94.40 ± 0.19

* Mean ± SD; n = 3

Table 12: *In vitro* release profile of Bumetanide from formulations F5

Time (min)	Absorbance	Concentration (µg/ml)	Amount (mg)	Pre-concentration x 5/1000	Cumulative amount of drug release	% CDR*
5	0.868	11.703	3.511	0.000	3.511	14.62 ± 0.16
10	0.099	1.336	4.009	0.059	4.067	16.94 ± 0.19
15	0.179	2.419	7.257	0.007	7.264	30.26 ± 0.17
30	0.287	3.863	11.590	0.012	11.602	48.33 ± 0.12
45	0.370	4.991	14.972	0.019	14.991	62.45 ± 0.20
60	0.439	5.921	17.763	0.025	17.788	74.11 ± 0.19
90	0.568	7.665	22.994	0.030	23.023	95.92 ± 0.23

* Mean ± SD; n = 3

Table 13: *In vitro* release profile of Bumetanide from formulations F6

Time (min)	Absorbance	Concentration (µg/ml)	Amount (mg)	Pre-concentration x 5/1000	Cumulative amount of drug release	% CDR*
5	0.100	1.347	4.041	0.000	4.041	16.83 ± 0.02
10	0.103	1.390	4.171	0.007	4.177	17.40 ± 0.07
15	0.184	2.484	7.451	0.007	7.458	31.07 ± 0.19
30	0.292	3.940	11.820	0.012	11.833	49.29 ± 0.13
45	0.380	5.117	15.352	0.020	15.372	64.04 ± 0.13
60	0.445	5.995	17.985	0.026	18.011	75.04 ± 0.03
90	0.572	7.709	23.127	0.030	23.157	96.47 ± 0.08

* Mean ± SD; n = 3

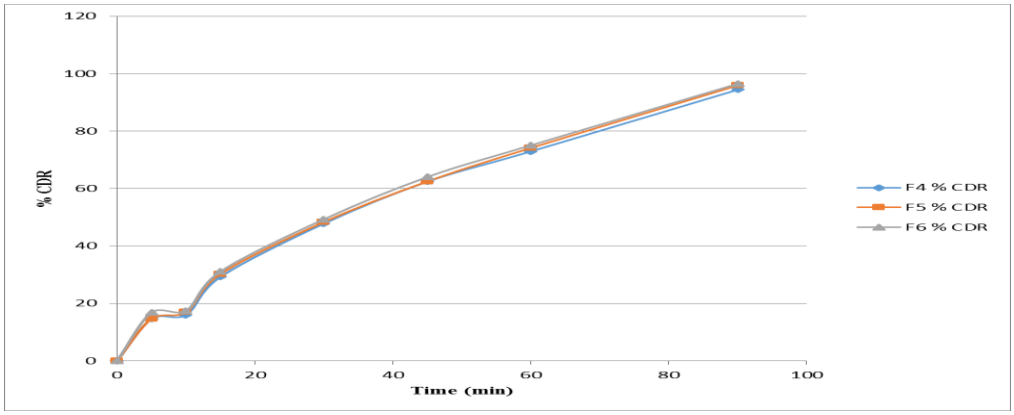

Fig 4: In vitro release profile of Bumetanide from formulation F4-F6

The order of drug release in three formulations F4, F5, F6 is F4<F5< F6. And it is evident that as the concentration of polymer HPMC E50 increase the time taken for the drug to be released is increased. F4, F5, F6 formulations has not given satisfactory results; further attempts were made to achieve a better drug release in 90 min.

Table 14:*In vitro* release profile of Bumetanide from formulations F7

Time (min)	Absorbance	Concentration (µg/ml)	Amount (mg)	Pre-concentration x 5/1000	Cumulative amount of drug release	% CDR*
5	0.088	1.180	3.540	0.000	3.540	14.74 ± 0.03
10	0.100	1.343	4.029	0.006	4.035	16.81 ± 0.09
15	0.179	2.419	7.257	0.007	7.264	30.26 ± 0.05
30	0.287	3.863	11.590	0.012	11.602	48.33 ± 0.05
45	0.370	4.991	14.972	0.019	14.991	62.45 ± 0.09
60	0.439	5.921	17.763	0.025	17.788	74.11 ± 0.04
90	0.568	7.665	22.994	0.030	23.023	95.92 ± 0.04

* Mean ± SD; n = 3

Table 15: *In vitro* release profile of Bumetanide from formulations F8

Time (min)	Absorbance	Concentration (µg/ml)	Amount (mg)	Pre-concentration x 5/1000	Cumulative amount of drug release	% CDR*
5	0.222	2.998	8.993	0.000	6.521	27.16 ± 0.10
10	0.267	3.604	10.813	0.015	10.828	45.11 ± 0.09
15	0.300	4.039	12.116	0.018	12.134	50.55 ± 0.07
30	0.392	5.283	15.850	0.020	15.870	66.11 ± 0.08
45	0.495	6.675	20.024	0.026	20.051	83.53 ± 0.09
60	0.537	7.241	21.723	0.033	21.757	90.64 ± 0.12
90	0.583	7.861	23.584	0.036	23.620	98.41 ± 0.10

* Mean ± SD; n = 3

Table 16: *In vitro* release profile of Bumetanide from formulations F9

Time (min)	Absorbance	Concentration (µg/ml)	Amount (mg)	Pre-concentration x 5/1000	Cumulative amount of drug release	% CDR*
5	0.242	3.267	9.802	0.000	9.802	40.83 ± 0.12
10	0.287	3.874	11.622	0.016	11.639	48.49 ± 0.09
15	0.336	4.524	13.572	0.019	13.591	56.62 ± 0.05
30	0.392	5.283	15.850	0.023	15.872	66.12 ± 0.06
45	0.495	6.675	20.024	0.026	20.051	83.53 ± 0.09
60	0.567	7.646	22.937	0.033	22.970	95.70 ± 0.03
90	0.585	7.894	23.681	0.038	23.719	98.82 ± 0.05

* Mean ± SD; n = 3

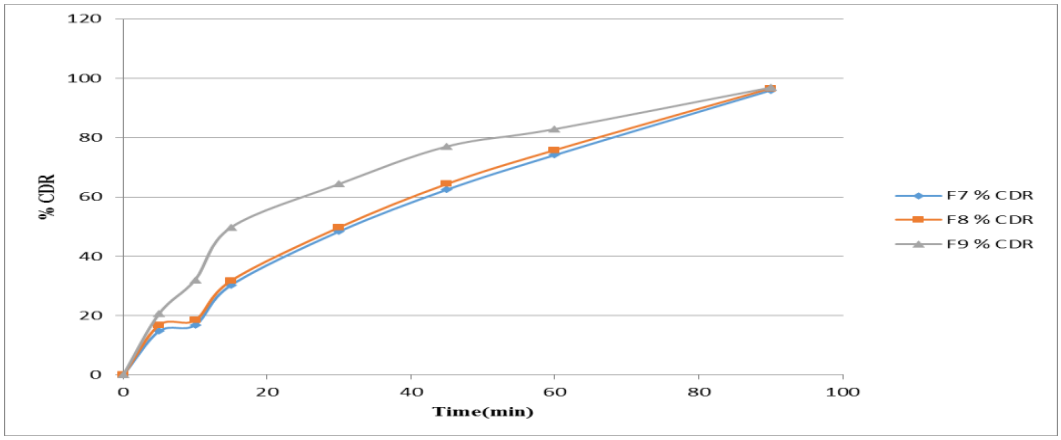

Fig 5: In vitro release profile of Bumetanide from formulation F7-F9

The order of drug release in three formulations F7, F8, F9 is F7<F8<F9. And it is evident that as the concentration of polymer HPMC E50 increase the time taken for the drug to be released is increased. F7, F8, F9 formulations has given satisfactory results; Here F9 formulation has given a good immediate release. so the formulation F9 was concluded as a optimized one.

Comparision of all the formulations F1-F9 containing the HPMC grades in single and in combination:

The overall order of drug release of formulations from F1 to F9 is:

F9 >F8 >F6 > F7 > F5 > F4 > F1 > F2 > F3

Table 17: Percentage in vitro release of Bumetanide from F1 to F9

Formulation Code	% CDR at 90 min
F1	93.32 ± 0.05
F2	89.62 ± 0.11
F3	84.55 ± 0.05
F4	94.40 ± 0.08
F5	95.92 ± 0.06
F6	96.47 ± 0.10
F7	95.92 ± 0.11
F8	98.40 ± 0.05
F9	98.82 ± 0.04

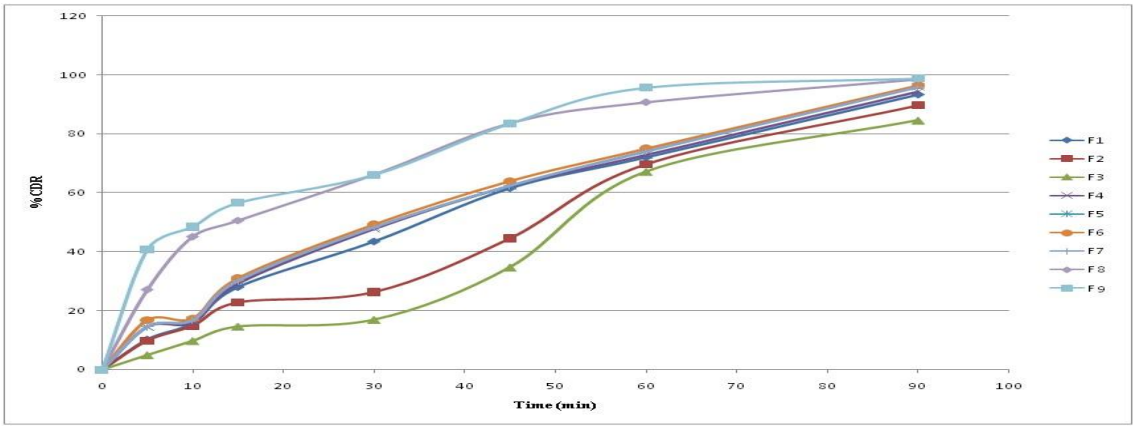

Fig 6: *In vitro* drug release profiles of formulations F1 to F9

Table: 18. Kinetics of Drug Release for Fdf's of Bumetanide

	Zero Order	**First Order**	**Higuchi**	Hixson -Crowell	Korsemeyer - Peppas	"n"
Slope	1.2726	**-0.0191**	**11.4732**	-0.0034	0.3374	0.3374
Correlation	0.9084	**-0.9572**	**0.9848**	-0.8453	0.9834	
R^2	0.8252	**0.9163**	**0.9699**	0.7146	0.9671	

Fig7: Zero order drug release of Bumetanide FDF's

Fig 8: First Order Drug Release of Bumetanide Fdf's

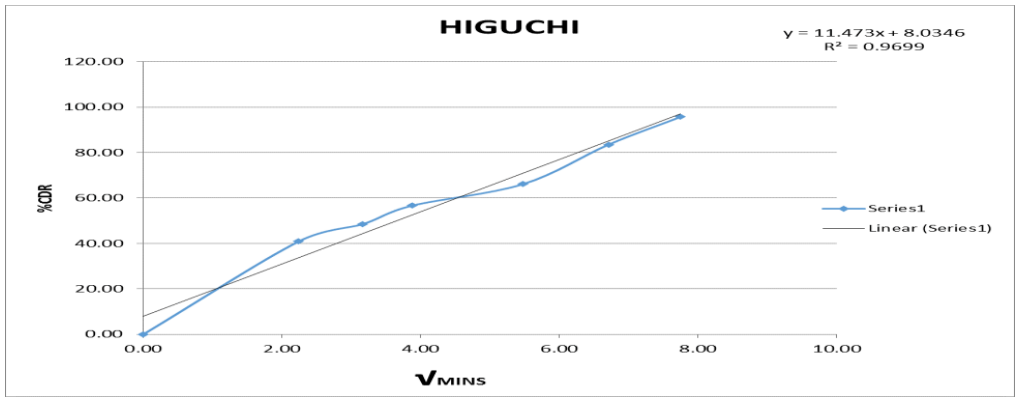

Fig 9: Higuchi Type of Drug release of Bumetanide Fdf's

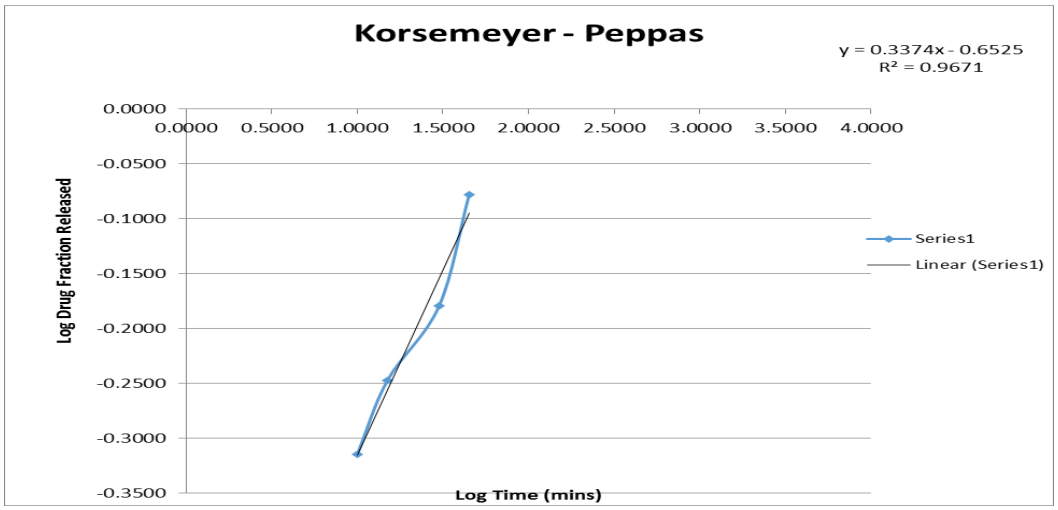

Fig 10: Korse Meyer Type of drug release of Bumetanide Fdf's

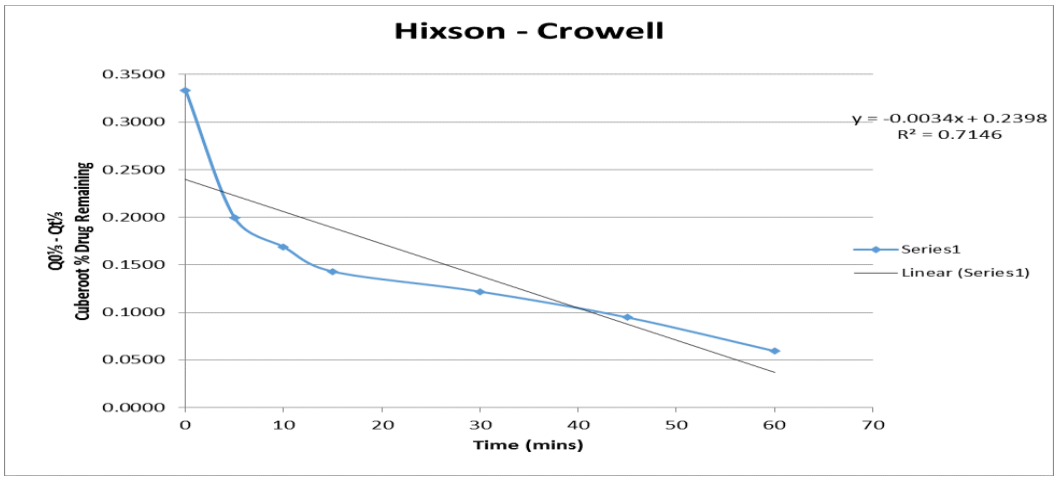

Fig 11: Hixson Crowell Type of Drug release of Bumetanide Fdf's

CONCLUSION:

The summary and conclusions extracted from the present investigation are illustrated below:

HPMC E50 is more viscous than other grades and 2% polymer has given thin films and the drug release was not satisfactory, and on increasing the concentration of polymer, more thick films was formed which has an increased disintegration time. HPMC E5 along with HPMC E15 in 1:3 ratios has given thin films with a better drug release compared to HPMC E15 films that has not achieved the objective. Further formulations with HPMC E50 along with HPMC E15 in 1:3 ratios has given thin films with a better drug release compared to HPMC E50 : HPMC E5 (1:3).

FDF's of BUMETANIDE could be formulated with available low viscosity film formers viz. HPMC E50 in combination with HPMC E5, E15. Bumetanide could be successfully incorporated in FDF's with Bumetanide of the above polymers and polyethylene glycol 4000 is used as a plasticizer. PEG 4000 itself has a solubulizing effect and resulted in faster dissolution. Hence, there is no need of superdisintegrants. Use of low viscosity grade HPMC polymers resulted in giving films with transparent and having smooth texture. Among all the developed formulations, F9 formulation formulated with HPMC E15 and HPMC E50 in the ratio of 1:1 showed good *in vitro* disintegration time and dissolution profile.

The films were evaluated as per Pharmacopoeial tests. Based on the above results formulation F9 (98.82% drug release) was identified as best formulation amongst all the formulations.

In vitro release of optimized formulation of Bumetanide films of formulation F9 was found to be 98.82% in 90 min with 16 sec of disintegration time.

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