American Scientific Research Journal for Engineering, Technology, and Sciences (ASRJETS)
ISSN (Print) 2313-4410, ISSN (Online) 2313-4402

http://asrjetsjournal.org/

Formulation and Comparative *in-vitro* Evaluation of Mucoadhesive Buccal Tablets of Furosemide

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Abstract

This study was conducted to develop mucoadhesive buccal tablet of Frusemide. A Mucoadhesive buccal tablet of Frusemide were prepared by using wet granulation method using dfferent polymer such as HPMC k 100, Carbopol-940 in different ratio. Tablets were analysed by measuring different parameters thickness, hardness weight uniformity, drug content uniformity, LOD, sweeling index, invitro dissolution study and solubility. The tablets were evaluated for in vitro release in pH 6.8-phosphate buffer for 12 hr in standard dissolution apparatus. Mucoadhesion strength was increased with increase in the concentration of carbopol. In order to determine the mode of release, the data was subjected to Zero order, first order, Higuchi and Peppas diffusion model.

Keywords: Mucoadhesive buccal tablet; Furosemide; Swelling index; Mucoadhesive strength; Carbopol 940P.

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1. Introduction

Bioadhesion may be defining as the state in which two materials, at least one of which is biological in nature, are held together for extended period by interfacial forces. In the pharmaceutical sciences, when the adhesive attachment is to mucous membrane the phenomenon is referred to as mucoadhesion (1). Furosemide is a potent loop diuretics chemically designated as 4-chloro-2-(2-furosemideylmethylamino)-5-sulfamoyl-benzoic acid. Sparingly soluble in alcohol, freely soluble in dilute alkali solution and insoluble in dilute acid [3]. Furosemide is rapidly but incompletely absorbed following oral administration and undergoes first pass metabolism resulting in a narrow absorption window, leads to its low bioavailability (43-50 %). The biological half life of Furosemide is (1-2 hrs).The physicochemical properties of Furosemide, its low half-life and molecular weight (330.7g/mol) make it suitable candidate for administration by buccal route. Hence the present study is aimed to prepare and evaluate buccal tablets of Furosemide using various bioadhesive polymers, in order to overcome bioavailability related problems, to reduce dose dependent side effects and frequency of administration [4]. Drug can be administered by many different routes to produce a systemic pharmacological effect. The most convenient and common route of administration is oral probably 90% of the drugs are given by this route [5]. The main problem of furosemide for delivery as potential therapeutic agent is their extensive pre-systemic metabolism resulting in a narrow absorption window, leads to its low bioavailiability (43-50) [4].

2. Materials and methods

Furosemide (AR No.69170 FRSO,ASI_30), and Micro Crystalline Cellulose,Cabopol,HPMCK 100Lactose were obtained from Time Pharma Pvt. Ltd. as gift sample.Talc (B. No.584048 of Nike), Magnesium Stearate (Loba Chemie Pvt. Ltd, Mumbai), Sodium Hydroxide pellets (Qualigens fine chemicals, B.No. K11X/2611/1411/08), Potassium Dihydrogen Orthophosphate (Qualigens fine chemicals, B.No.- 26735), Disodium hydrogen phosphate,PVPK 30 were provided by our college Shree Medical and Technical College by purchasing from local market. Marketed product was purchased from local retail pharmacy.

2.1 Equipment and instruments

2.2 Method of Preparation of buccoadhesive tablets

Wet granulation method was employed to prepare buccal tablets of furosemide using different polymers such as HPMC k 100, Carbopol-940 in different ratio.

2.3 Preparation

Mucoadhesive matrix tablet each containing 40mg of furosemide were prepared by non- aqueous granulation method (using isopropyl alcohol). All the ingredients except lubricants were mixed in the order of ascending weights and blended for 10 min in an inflated polyethylene pouch and then furosemide was added in this mixture then mixed for 2 min for uniform mixing. Granulation was done with binder solution of PVP which was previously dissolved in isopropyl alcohol, this damp mass passed through 10 no. Sieve. This was dried in air and passed through 16 no. Sieve and lubricants such as magnesium stearate, talc & sweetening agent Manitol were

mixed and then compressed it with 10- station rotary compression machine into 150mg tablet, to a hardness of 6- 10 kg/cm2 using 6.5 mm punch.

Table No. 2: Equipment and instruments

S. No.	Instruments and devices	Specifications
1	UV-Visible spectrophotometer	Electrolab, Model No: Double beamLT-2900
2	Rotary tablet press	SHIV (10 station), India
3	Dissolution test apparatus	USP 24 (Type II), Model No : DA-6S
4	Disintegration test apparatus	SHIV, India
5	Analytical balance (d= 0.01)	Shinko Denshi Co. Ltd., China Model No.: AJ220E
6	Tablet Hardness Tester	Monsanto Hardness Tester, India
7	Vernier caliper	-
8	Hot air oven	SHIV, India
9	Friability test apparatus	SHIV, India
10	pH meter	HANNA instrument
11	Magnetic stirrer	MLH
12	Sintered glass of grade 2	Borosilicate, India
13	Glassware	Borosilicate, India
14	Refrigerator	LG, Model No.- GC-151SA

2.4 Calibration Curve

The stock solution of concentration 500 µg/ml was prepared. Various solution of concentration (2, 4, 6 and 8) was prepared from that solution. The data obtained from UV was plotted to obtained plot of absorbance vs. concentration (linearity curve). Finally the correlation coefficient of the solution was calculated to validate the analytical process [8].

3. Evaluation of active Furosemide

Loss on Drying

The sample of Furosemide was taken and heated at 105˚C for 3 hours in hot air oven. The initial weight and the final weight of the sample of furosemide were determined. The difference in initial weight and final weight was obtained which was further processed to calculate loss on drying value of active Furosemide [9].

Assay

Dissolve about 600 mg of furosemide, will be accurately weighed, in 50 ml of dimethylformanide to which has been added 3 drops of bromothymol blue TS, and which previously has been neutralized with 0.1 N Sodium hydroxide. Titrate with 0.1 N sodium hydroxide VS to a blue endpoint [10].

Solubility

Solubility determinations were performed by taking an excess amount of Furosemide in a beaker, in 10 ml of an aqueous and 0.1N HCl solution containing various concentrations of PEG 6000. The samples were shaken at 37 ± 0.5 °C for 24 hrs.in a magnetic stirrer. After 24hrs, the samples were filtered. The filtrate was suitably diluted and analyzed in spectrophotometer at274 nm using a UV spectrophotometer [11].

Evaluation of granules of Furosemide

All the prepared mucoadhesive tablets will be evaluated for following parameters.

Bulk density and Tap densities

Exactly 50 gm of powder blend will be weighed on chemical balance and transferred into a 100 ml measuring cylinder. The cylinder will be dropped on a wooden plat form from a height of 2.5 cm three times at 2 seconds interval. The volume occupied by the granules will be recorded as the bulk volume. The cylinder will be then tapped on the wooden platform until the volume occupied by the powder blend remained constant. This will be repeated three times for blend. The data generated will be used in calculating the Carr's compressibility index and Haunser's ratio [5].

$$\text{Bulk density} = \frac{\text{Mass}}{\text{Untapped volume}}$$

$$\text{Tapped density} = \frac{\text{Mass}}{\text{Tapped volume}}$$

Angle of repose

50 gm of powder blend will be placed in a plugged glass funnel which had a distance of 10 cm from the flat surface. The blend will be then allowed to flow through the 8mm funnel orifice by removing the cotton plug from the funnel orifice. The height of the heap (h) formed as well as the radius of the heap (r) will be noted [5].

$$\text{Tan}\,\theta = \frac{h}{r}$$

Where,

'θ' is the angle of repose

'h' is height of pile

'r' is radius of the base of pile

Carr's Index

The compressibility index of the granules was determined by Carr's index.Carr's index can be calculated by using the following formula [8].

$$\text{Carr's Index} = \left(1 - \frac{\text{Tapped volume}}{\text{Fluppy/Bulk volume}}\right) * 100$$

Hausners Ratio

Hausners ratio is the indication of the compressibility of a power. Hausners ratio of the mixed powder was calculated by following formula [8].

$$\text{Hausners Ratio} = \frac{100}{100 - \text{Carr's index}}$$

Evaluation of furosemide tablets

Friability

Friability is the measure of tablet strength. Roche type friabilator will be used for testing the friability using the following procedure. Twenty tablets will weighed accurately and placed in the tumbling apparatus that revolves at 25 rpm dropping the tablets through a distance of six inches with each revolution. After 4 min, the tablets will be weighed and the percentage loss will be determined [12].

$$\% \text{ loss} = \frac{(\text{initial weight} - \text{Final weight})}{\text{initial weight}} * 1oo$$

In-Vitro dissolution studies

Release of drug, from the Furosemide tablet will be determined using USP dissolution apparatus and the dissolution rate will be studied using 900 ml of phosphate buffer PH 6.8 [13].

Hardness

Hardness will be measured using Monsanto hardness tester. For each batch three tablets will be tested [7].

Swelling index

The swelling index of the buccal tablet will be evaluated by using pH 6.8-phosphate buffer. The initial weight of the tablet will be determined (w1). The tablets will be placed in pH 6.8 phosphate buffer (25 ml) in a Petri-dish will be placed in an incubator at 37 ± 1˚C and tablet will be removed at different time intervals (0.5, 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0 and 8.0 h), excess water will be removed using filter paper without pressing and reweighed (w2). The swelling index will be calculated using the formula:

Swelling index = 100 (w2-w1) / w1 [7].

Thickness

Three tablets was selected randomly from each batch and thickness was measured by using vernical calliper [7].

Weight Variation

Twenty tablets was randomly selected from each batch and individually weighed. The average weight and standard deviation of 20 tablets was calculated. The batch was passed the test for weight variation test if not more than two of the individual tablet weight deviate from the average weight by more than the percentage shown in Table No.3 and none deviate by more than twice the percentage shown [7].

Table No. 3: Percentage deviation allowed under weight variation test

S.N	Average wt. of Tablets (mg)	Percentage
1.	130 or less	10
2.	130-324	7.5
3.	More than 324	5

Assay

Weigh and powder 20 tablets. Weigh accurately a quantity of the powder containing about 0.1 g of Frusemide and shake with 150 ml of *0.1 M sodium hydroxide* for 10 minutes. Add sufficient *0.1 M sodium hydroxide* to produce 250.0 ml and filter. Dilute 5.0 ml to 200.0 ml with *0.1 M sodium hydroxide* and measure the absorbance of the resulting solution at the maximum at about 271 nm (2.4.7). Calculate the content of C12H11ClN2O5S taking 580 as the specific absorbance at 271 nm [9]

4. Results

4.1 Calibration Curve

$$r = \frac{\Sigma xy}{\sqrt{x2 * \Sigma y2}}$$

Correlation Coefficient was found to be 0.997

Table No .4: Table of absorbance at various concentration of furosemide

CONC.(µg/ml)	ABSORBANCE
1	0.027
2	0.044
4	0.072
6	0.1
8	0.123

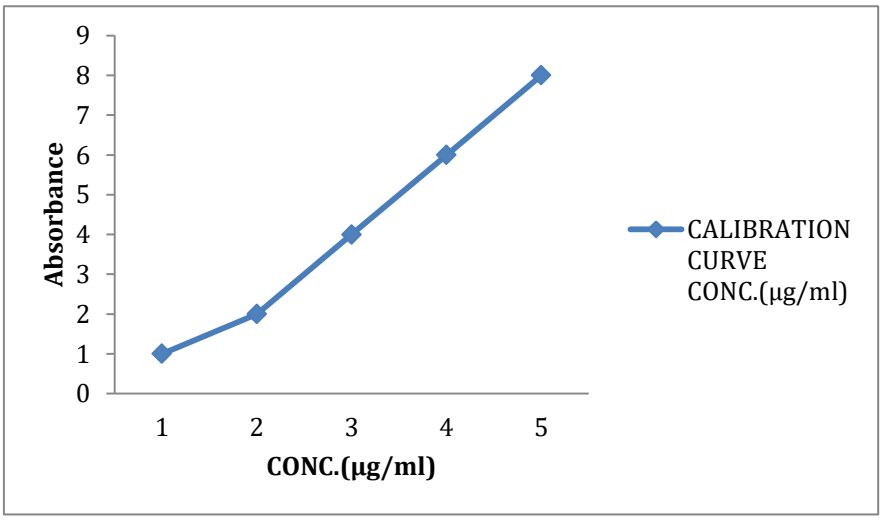

Fig No.2: Standard calibration curve of furosemide in 0.1 M NaOH

4.2 Evaluation of active Furosemide

Loss on Drying

Loss on drying was found to be 0.375%.

Assay

Assay of T_1, T_2 and T_3 and found as 96.001%, 97.41% and 104.234% respectively, average assay = 99.2152%, on dried basis it was 98.62%. Where Limit is 98% - 101% on dried basis according to IP.

4.3 Evaluation of developed formulation

The powder blend of the formulated product was checked for bulk density,tapped density, angle of repose, Carr's index, Hausner's ratio. The results are shown in fig: 4,5,6.

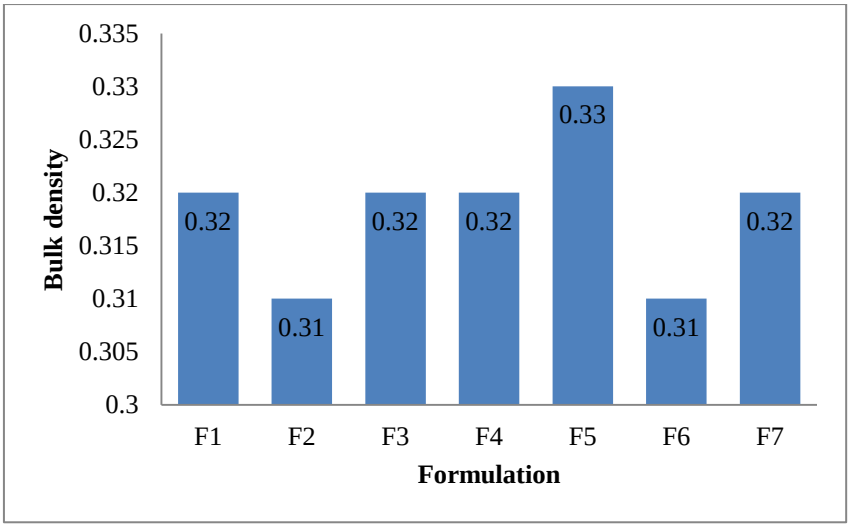

Fig No.3: Bulk density of Formulated Products

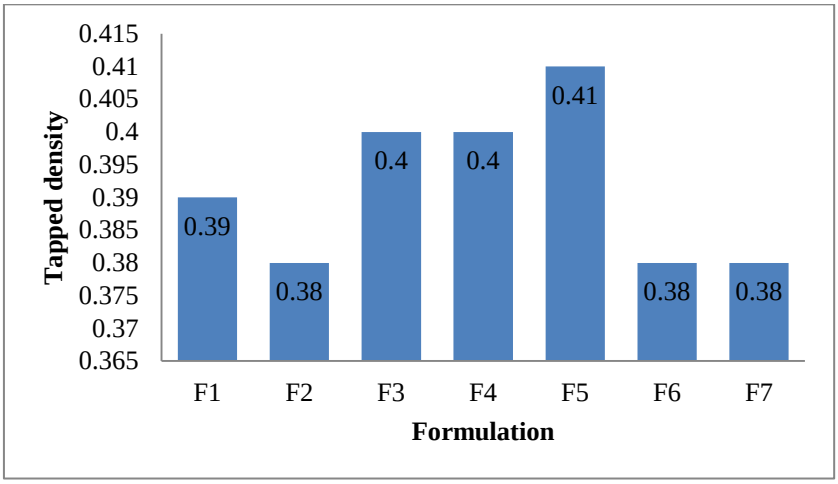

Fig No.4: Tapped density of Formulated Products

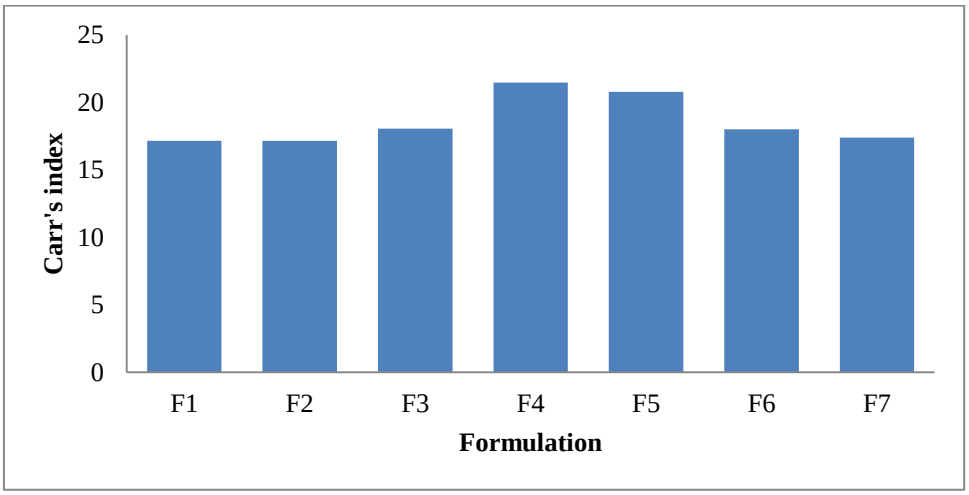

Fig No.5: Carr's index of Formulated Products

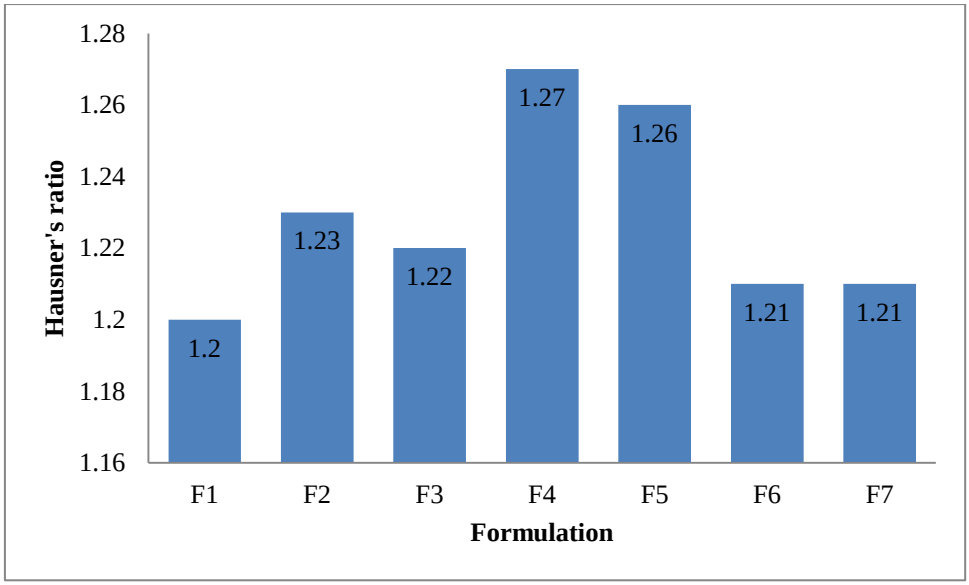

Fig No.6: Hausner's ratio of Formulated Products

4.4 Evaluation of furosemide tablets

Physiochemical Properties

The weight, thickness, hardness, friability of the tablets of furosemide were determined. The hardness was in the range of 5 to 10 kg/cm^2 hardness increases with increasing carbopol porportion in the formulation. Friability was in the range of 0.32 to 0.67% less than 1% indicates good mechanical strength to withstand the rigors of handling and transportations and thickness was in the range of 4.0 mm to 5.1 mm. Weight of buccal tablets were found to be in the range of 138 to 163mg.

The results of all the above parameters are listed in table below.

Table 5

EVALUATION OF BOTH GRANULES OF FUROSEMIDEBUCCAL TABLETS AND FORMULATED FUROSEMIDE TABLETS

Formulation code	Bulk density (gm/cc)	Tap density (gm/cc)	Carr's index%	Hausner's Ratio	Angle of Repose	Hardness (Kg/cm3)*	Friability (%)	Thickness (mm)*	Assay (% purity)	Weight (mg)*
F1	0.32	0.39	17.15	1.2	26	6.5±0	0.033	4±0	102.2	149.4
F2	0.31	0.38	17.15	1.23	28	6.9±0.2	0.033	4.14±0.2	92.9	148.7
	0.32									
F3		0.4	18.05	1.22	30	6.8±0.2	0.035	5.1±0.5	93.25	146.6
F4	0.32	0.4	21.46	1.27	25	9.4±0.8	0.033	4.1±0.5	94.9	147.65
F5	0.33	0.41	20.78	1.26	32	10.1±0.2	0.032	4.36±0.1	92.5	153.6
F6	0.31	0.38	17.99	1.21	30	9.6±0.8	0.032	4.3±0.1	99.28	155
F7	0.32	0.38	17.37	1.21	28	9.8±0.4	0.067	4.1±0.1	93.085	148.7
~										
Mp										
	…	…	…	…	…	5.02±0.3	0.35	2.5±0.3	91.41	219.95

In-Vitro Dissolution Study

The cumulative percentage drug releases from the different formulations were given in Annex No. 10. The dissolution profile of different batch of formulated tablets was shown in Fig No.7.

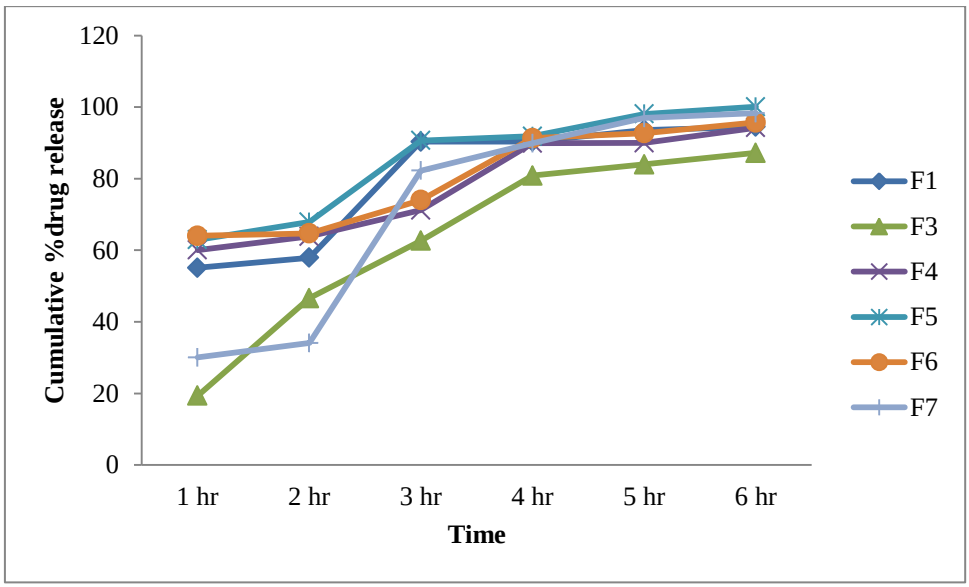

Fig No.7: Dissolution Profile of Formulated Furosemide Tablets

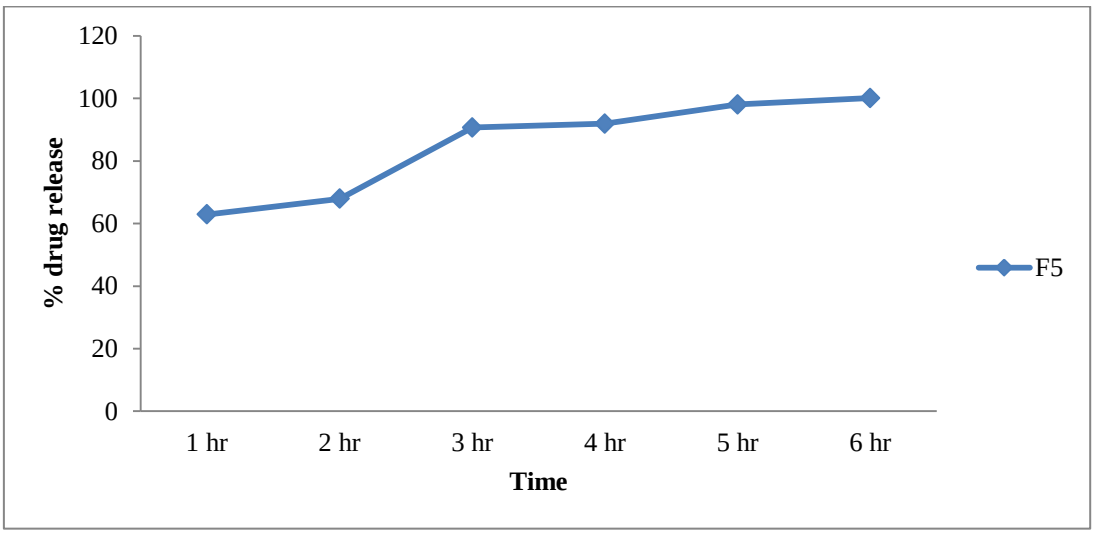

Fig No.8: Dissolution Profile of Formulation 5

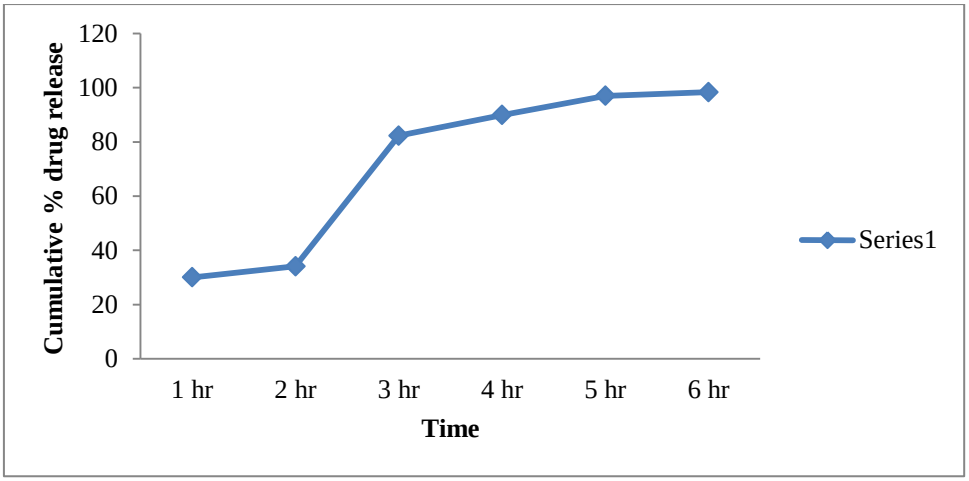

Fig No.9: Dissolution Profile of Formulation 7

4.5 Evaluation of marketed product

Physiochemical Properties

The weight ,hardness, friability of the tablets of market product averages were found to be as 219.95 mg, 5.02kg/cm^2 and 0.350% respectively.

The assay was found to be 91.41. The results of all the above parameters are listed in Annex No. 6 and 7

***In-Vitro* Dissolution Study of Marketed Furosemide Tablets**

The cumulative percentage drug release from the marketed furosemide tablet is given in Annex No. 11. The dissolution profile of furosemide tablet was shown in Figure No.10

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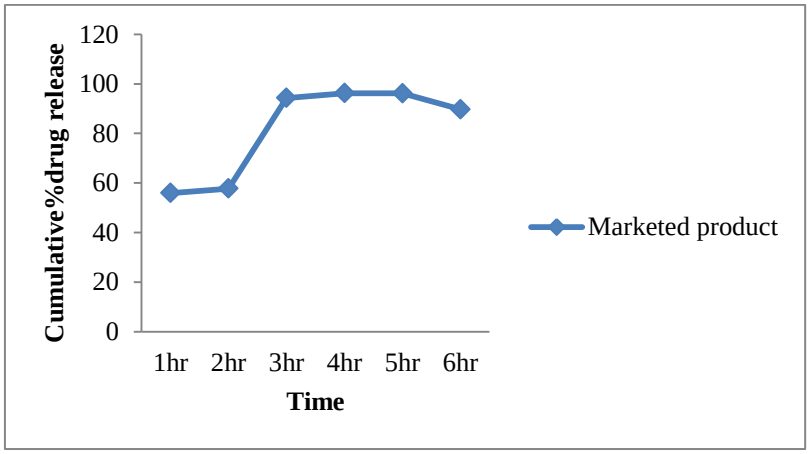

Fig No.10: Dissolution Profile of Marketed Furosemide Tablets

4.6 Comparision between the formulated products with marketed products

The cumulative percentage drug release from the marketed product and formulated product is given in Annex No. 11. The dissolution profile of tablets was shown in Figure No.11.

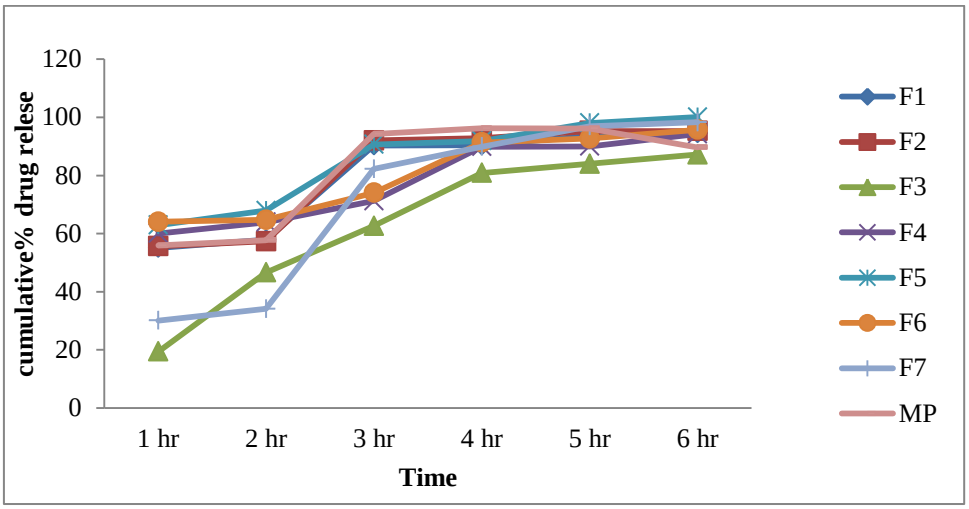

Fig No.11: Dissolution profile of formulated products and marketed products

The % drug release of the Market product F1, F2, F3, F4, F5, F6, F7 was found to be

89.67%, 94.5%, 95.29%, 87.22%, 94.25%, 100.1%, 95.71%, 98.39% at 6 hr respectively.

Table 6

Formulation code	Regression Coefficient values of			
	Zero order	First order	Higuchi	korsemeyer's
F1	-0.43	0.9	0.82	0.9
F2	-0.34	0.87	0.81	0.88
F3	0.84	0.81	0.89	0.95
F4	-1.8	0.92	0.55	0.92
F5	-1.58	0.95	0.63	0.95
F6	-2.26	0.9	0.41	0.88
F7	0.88	0.9	0.84	0.91
MP	-0.62	0.8	0.69	0.83

4.7 Analysis and Intrepretation

Model dependent method

The results of linear regression analysis including regression coefficients were summarized in table below From

the above data it was evident that all the formulations displayed mixed order release kinetics (“r values ranging from -2.26 to 0.952’’)

Model independent method

The similarity factor *f2* was calculated by comparing its dissolution profile with marketed product and was found to be 17.78, which show quite distinct differences in dissolution profile between them.

5. Discussion

Tablets of Furosemide were prepared by wet granulation method using mucoadhesive polymers like carbopol 940, HPMC K100 in different ratios. According to work plan,the Tablets were evaluated for their apperance, thickness, hardness, friability, weight variation, swelling index, in vitro release. The results of granules evaluation suggest that all the granules exhibits good flow properties, as angle of repose values were less than 30. A good packing ability of the granules was indicated by Carr’s index and Hausner ratio. Weight of tablets were found to be uniform. The hardness was in the range of 5 to 10 kg/cm3 hardnes increases with increasing carbopol porportion in the formulation. Similar result was reported by Bhaskar and his colleagues 2012, which showed that the formulated tablet hardness was found to be in the range 5-8 kg/cm3 it was increases by increasing the proportion of Carbopol, And the friability was in the range of 0.32 to 0.67% less than 1% similar result was represented by Bhaskar and his colleagues 2012, Friability of 0.322 to 0.98 %, indicates good mechanical strength to withstand the rigors of handling and transportations and thickness was in the range of 4.0 mm to 5.1 mm. Weight of buccal tablets were found to be in the range of 138 to 163mg. The swelling index carried out for 70 min. These profile indicates the uptake of water into the tablet matrix, producing an increase an weight. The swelling state of the polymer (in the formulation) was reported to be crucial for its bioadhesive behavior. Adhesion occurs shortly after the begining of swelling but the bond formed between mucosal layer and polymer was not very strong. In formulations maximum swelling was seen with the formulation containing Carbopol 940. Result indicates that the concentration of Carbopol 940 increases the swelling index increases. Similar result was indicated by Bhaskar and his colleagues 2012. In vitro release studies were carried out in USP XXIII tablets dissolution test appratus-II employing paddle stirrer at 50 rpm and 900ml of ph 6.8 phosphate buffer as dissolution mmedium. The in vitro dissolution data of all the designated formulations were shown in above tables and dissolution profiles deplicated in figures 7-11, from dissolution data it was evident that designed formulations have displayed in the range of 19.38% to 100.10% drug release in 6 hour. In vitro drug release data of all the buccal tablet formulations of furosemide was subjected to goodness of fit test by linear regression analysis according to zero order kinetics, First order kinetics, Higuchi’s and peppas equations to ascertain mechanism of drug release. The results of linear regression analysis including regression coefficients were summarized in above table; from the above data it was evident that all the formulations displayed mixed order release kinetics (“r values ranging from -2.26 to 0.952’’)

6. Conclusion

From the present study, the following conclusions can be drawn: Mucoadhesive buccal tablets of furosemide

can be prepared by wet granulation method using Carbopol 940, HPMC K 100 as mucoadhesive polymers in different ratios. In all the tablet formulation, PVP-K30 solution in IPA was used as binder, which showed acceptable hardness of prepared tablets. All the prepared tablet formulations were found to be good without capping and chipping. As the amount of Carbopol polymer in the tablets increases, the drug release rate decreases, whereas HPMC K 100 containing formulation show increase in release rate with increase in concentration. Among the 7 formulations, the formulations F5 and F7 released 100.1% and 98.31% respectively in 6 hr. All the designed formulations of furosemide buccal tablets displayed mixed-order release kinetics.

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