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FORMULATION AND EVALUATION OF EXTENDED RELEASE OF BUMETANIDE TABLETS

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ABSTRACT

Oral route is the most oldest and convenient route for the administration of therapeutic agents because of low cost of therapy and ease of administration leads to higher level of patient compliance. The aim of this investigation was to develop and evaluate extended release drug delivery system for **B**umetanide and comparing with marketed product. Hydrophilic matrix based tablets using different concentrations of different grades of HPMC i.e. K4M, K15M , K100M, Metalose 60 SH-50 and Xanthum gum were used to develop twelve formulations (F1 – F12) using direct compression technique and were subjected to physicochemical and *in vitro* dissolution studies by comparing with marketed product. The net content of **B**umetanide was 80mg and the total tablet weight was 265mg. he F12 formulation was compared with the marketed product for drug release pattern and was matched using similarity factor (f2) which showed that formulation F12 performed similar to the marketed product therapeutically.

Key words: **B**umetanide, Metalose 60 SH-50 and Xanthum gum

INTRODUCTION

Oral route is the most oldest and convenient route for the administration of therapeutic agents because of low cost of therapy and ease of administration leads to higher level of patient compliance.[1] Approximately 50% of the drug delivery systems available in the market are oral drug delivery systems and historically too, oral drug administration has been the predominant route for drug delivery.[2,3] It does not pose the sterility problem and minimal risk of damage at the site of administration.[4]

During the past three decades, numerous oral delivery systems have been developed to act as drug reservoirs from which the active substance can be released over a defined period of time at a predetermined and controlled rate.[5] The oral controlled release formulation have been developed for those drug that are easily absorbed from the gastrointestinal tract (GIT) and have a short half-life are eliminated quickly from the blood circulation.[6] As these will release the drug slowly into the GIT and maintain a constant drug concentration in the plasma for a longer period of time.[7] In oral controlled drug delivery the amount of drug

release is constantly predetermined and these constant releases of drug provide a constant blood plasma level of the drug for optimal therapeutic response. The oral controlled drug delivery has many advantages to conventional drug delivery.[8]

The ideal and most important objectives of drug delivery are spatial placement and temporal delivery of the drug. Spatial placement relates to targeting a drug to a specific organ or tissue, while temporal delivery refers to controlling the rate of drug delivery to the target tissue. An appropriately designed sustained release drug delivery system can be a major advance towards solving issues related to spatial placement and temporal delivery. The bulk of research has been directed at oral dosage forms that satisfy the temporal aspect of drug delivery, but many of the newer approaches under investigation may allow allow special placement as well.

The aim of the present study is to develop a robust formulation of anti-diuretic drug as an extended release matrix tablets. The polymers like HPMC K4M, HPMC K15M and HPMC K100M, Metalose 60 SH-50 and Xanthum gum were used as extended release polymer to retard the release. *The in vitro* release pattern of final formulation was compared with the innovator.

MATERIALS AND METHODS

Pre formulation studies [9, 10]

Pre formulation study was an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. It was the first step in the rational development of dosage forms.

DRUG EXCIPIENT COMPATIBILITY STUDIES

The compatibility of drug and formulation components is important prerequisite before formulation. It is therefore necessary to confirm that the drug does not react with the polymers and excipients under experimental conditions and affect the shelf life of product or any other unwanted effects on the formulation. Excipients are mixed with the Bumetanide (API) in following ratios

Table 1: Ratios of drug and excipient

S. no	Composition	Ratio
1	API+ Bumetanide	1:10
2	API+ Methocel K 4 M	1:5
3	API+ Methoel K 15 M	1:5
4	API+ Methoel K 100 M	1:5
5	API+ Metalose 60 SH -50	1:5
6	API+ Xanthum gum	1:5
7	API+ Magnesium stearate	1:0.5

These mixtures were exposed to Room Temperature, 40°C / 75 %RH, and 60°C, in a 5-ml glass vial in exposed condition for 1 month. Observations for physical appearance are made at initial, 2 week, and 4week and the samples were withdrawn for analysis

FTIR study

The compatibility between the drug and excipients is important; and was detected using infra-red spectra.

Infrared spectrum of formulated granules and drug alone were recorded and observed from 400 nm - 4000 nm. Infra -red spectrum of pure drug was also run individually.

Preparation of standard calibration curve

Determination of absorption maxima

A solution of Bumetanide containing the concentration 10 µg/ ml was prepared in 0.01M HCl IN UV spectrum was taken using Double beam UV/VIS spectrophotometer. The solution was scanned in the range of 200 – 400.

Preparation calibration curve For Bumetanide:

10mg of Bumetanide drug was accurately weighed and dissolved in 10ml of 0.01M Hcl and in 10 ml volumetric flask , to make (1000 µg/ml) standard stock solution (1). Then 1 ml stock solution (1) was taken in another 10 ml volumetric flask to make (100 µg/ml) standard stock solution(2), then again 1 ml of stock solution (2) was taken in another 10 ml volumetric flask and then final concentrations were prepared 2, 4 ,6, 8, 10, 12, 14, 16, 18 ,and 20µg/ml with 0.01M HCL.

The absorbance of standard solution was determined using UV/ VIS spectrophotometer at 215nm. Linearity of standard curve was assessed from the square of correlation coefficient (r2) which determined by least-square linear regression analysis.

Formulation of Extended release Bumetanide matrix tablet:

Based on pre formulation data following strategy it is used for developing matrix type drug release i.e Direct Compression.

STEP 1.WEIGHING:

Weighed the required quantities of Bumetanide, Dibasic Calcium Phosphate (A-Tab), Hypromellose, and Magnesium stearate and other dry mix materials as per table given separately.

STEP2. SIFTING:

Sifted the drug, Dibasic Calcium Phosphate (A-Tab), Hypromellose through #30 mesh and mixed the blend in a poly bag for uniform distribution of API.

STEP 3. LUBRICATION:

Required amount of Magnesium stearate was weighed, passed through #80 mesh and blended with above blend

STEP 5.COMPRESSION:

The Blend was compressed using 8.0mm Round shaped standard concave punches using 17 station compression machine.

Table 2: Batch Composition for Formulations F1 – F6

INGRIDIENTS	F1	F2	F3	F4	F5	F6
API						
Bumetanide	2	2	2	2	2	2
EXCIPIENTS						
Di-Basic Calcium Phosphate	127	127	127	147	127	137
Methocel K 4 M	60.000	0.000	0.000	0.000	0.000	0.000
Methocel K 15 M	0.000	60.000	0.000	0.000	0.000	0.000
Methocel K 100 M	0.000	0.000	60.000	20.000	0.000	0.000
Metalose 60 SH 50	0.000	0.000	0.000	0.000	60.000	0.000
Xanthan Gum	0.000	0.000	0.000	0.000	0.000	50.000
Magnesium Stearate	3.000	3.000	3.000	3.000	3.000	3.000
TOTAL	205.00	205.00	205.00	205.00	205.00	205.00

Table 3: Batch Composition for Formulations F7 – F12

	F7	F8	F9	F10	F11	F12
API						
Bumetanide	2	2	2	2	2	2
EXCIPIENTS						
Di-Basic Calcium Phosphate (A-Tab)	157	147	127	127	127	127
Methocel K 4 M	0.000	0.000	30.000	20.000	0.000	0.000
Methocel K 15 M	0.000	0.000	30.000	40.000	30.000	20.000
Methocel K 100 M	0.000	0.000	0.000	0.000	30.000	40.000
Metalose 60 SH 50	0.000	0.000	0.000	0.000	0.000	0.000
Xanthan Gum	30.000	40.000	0.000	0.000	0.000	0.000
Magnesium Stearate	3.000	3.000	3.000	3.000	3.000	3.000
TOTAL	205.000	205.000	205.00	205.00	205.00	205.00

Tablet characterization[11]

Physical characterization was performed by Angle of repose, Determination of bulk density and tapped density, Compressibility index or Carr's index and Hausner's Ratio

Evaluation of Tablet [12, 13, 14, 15]

Post compression parameters

Post compression parameters was performed like Hardness , Thickness and diameter, Friability and Weight Variation

Assay:

Assay is an indicative of the amount of the drug present in the dosage form. Here it gives the insight information about the substances of the process and about effect of changes. Decrease in assay % was insignificant and within limits for the formulations.

Chromatographic conditions

Instrument : Agilent 1200 HPLC

Column : Kromasil 100- C8 (250 X 4.6 mm ID), 5µ.

Wave Length : 215 nm.

Flow rate : About 1.0 mL / min.

Injection Volume : 10µl.

Column Temperature: 30ºC

Run time : 25 min.

Diluent : Water and Acetonitrile 70:30 (v/v).

Mobile phase: Prepared a mixture of 400ml Water, 500 mL of methanol, and 100 mL of tetrahydrofuran, (50:40:10) were mixed well. Filter through 0.45µm nylon membrane filter and degassed.

Diluent: Mobile phase was used as diluent.

Standard Stock solution preparation (2mg/mL): Transferred an accurately weighed amount of about 20mg of working standard into a 100ml volumetric flask 10ml of Acetonitrile added and sonicated for 5 minutes. Diluted to volume with diluent and mixed well.

Preparation of diluted standard solution: Pipette 5ml of above standard stock solution into a 100ml volumetric flask and dilute to volume with dilute and filtered through 0.45µm nylon membrane filter.

Test preparation: Transferred 5 tablets into 200mL of volumetric flask , 20 mL of acetonitrile added sonicated about 15 minutes. Diluted to volume with diluent and mixed well filtered through 0.45 µm nylon membrane filter.

Retention time : About 6.0 minutes.

Procedure: Inject 25 µl portion of the dissolution medium as blank, standard preparation, test preparation into the chromatogram, record the chromatogram and measure the response for the analyte peak.

Calculations:-

$$\textbf{Assay (\%)} = \frac{\text{test area}}{\text{std area}} \times \frac{\text{std wt}}{\text{test wt}} \times \frac{\text{test dil}}{\text{std dil}} \times \frac{\text{potency}}{\text{lc}} \times \frac{\text{avg wt}}{100} \times 100$$

In Vitro Dissolution Studies[16]

Dissolution conditions

Medium : 0.01M HCl

Type of apparatus : USP – Type 1 (Basket)

RPM : 100 rpm

Volume : 900ml

Temperature : 37ºC± 0.5

Time : 24 hrs

Time intervals : 1, 4, 8, 12, 16, 20 and 24 hours

Preparation of Dissolution media (0.01M HCl buffer): Add 16.6ml of HCl in a 2l volumetric flask and with some distilled water.swirl to mix and add distilled water up to the mark of the volumetric flask.

Mobile Phase Preparation: Mix the buffer and Acetonitrile in the ratio 40:60 (v/v).

Buffer Preparation: Dissolve accurately about 3.3 gms of Di-ammonium hydrogen orthophosphate $(NH4)_2HPO4$) in 1000 ml of purified water, sonicate to dissolve. Filter through 0.45µm nylon filter and degas.

Preparation of standard solution : (50µg/ml): Weigh and transfer accurately about 50 mg of Bumetanide working standard in 100 ml of volumetric flask and dissolve and dilute upto the mark with diluents. Pipette out 5 ml of the above solution in 50 ml volumetric flask and dilute upto mark with diluent.

Preparation of test solution : (50µg/ml): Weigh and transfer accurately about 50 mg of test sample in 100 ml volmetric flask and dissolve and dilute upto the mark with diluent. Pipette out 5 ml of the above solution in 50 ml volumetric flask and dilute upto volume with diluent.

Procedure of injection sequence: Injected 25 µl portion of the dissolution medium as blank, standard preparation, test preparation into the chromatogram, record the chromatogram and measure the response for the analyte peak.

RESULTS AND DISCUSSION

DRUG EXCIPIENTS COMPATIBILITY STUDY

FT-IT SPECTROSCOPY STUDY

In the present study FT-IR data of drug and excipient was compared with standard spectrum of pure Bumetanide drug. The characteristic peaks associated with specific functional groups and bonds of the molecule and their presence/absence in the polymer carrier formulation were noted. The IR spectra showed that there is no significant evidence for interaction between the drug and the excipients. The figure 10 shows the IR spectrum of pure Bumetanide while figures 7, 8, 9, 10 and 11 show the compatibility between the drug and, HPMC K15M, HPMCK100M, XANTHUM GUM and MAGNESIUM STEARATE respectively

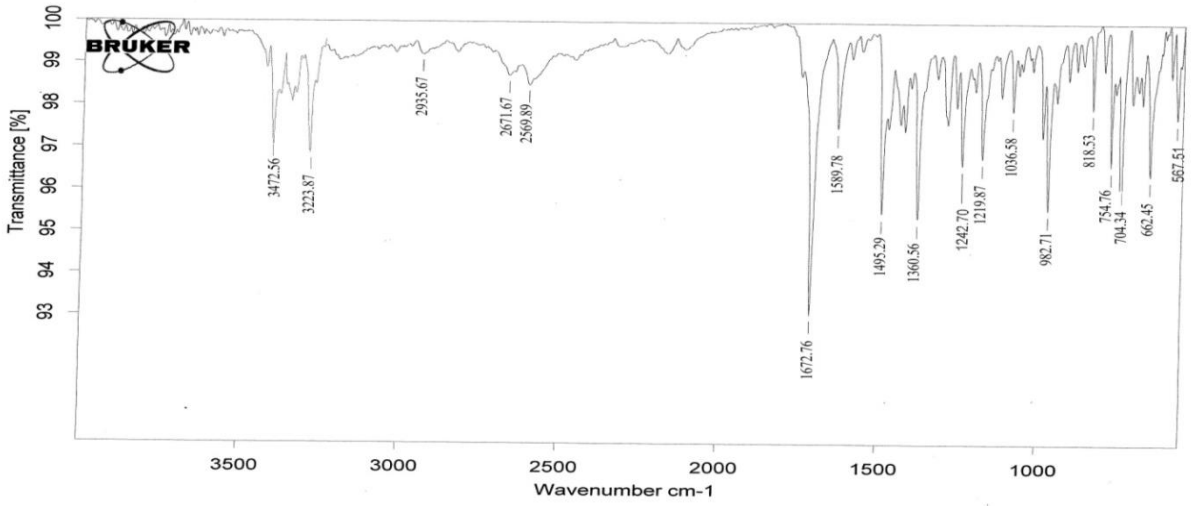

Figure 1: FTIR spectra of Bumetanide

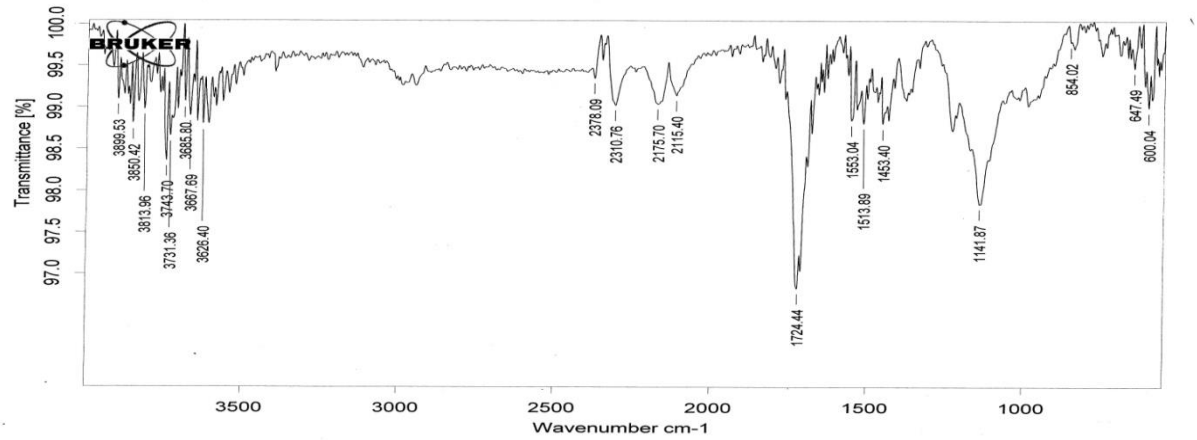

Figure 2: FTIR spectra of Bumetanide and HPMC K 15 M

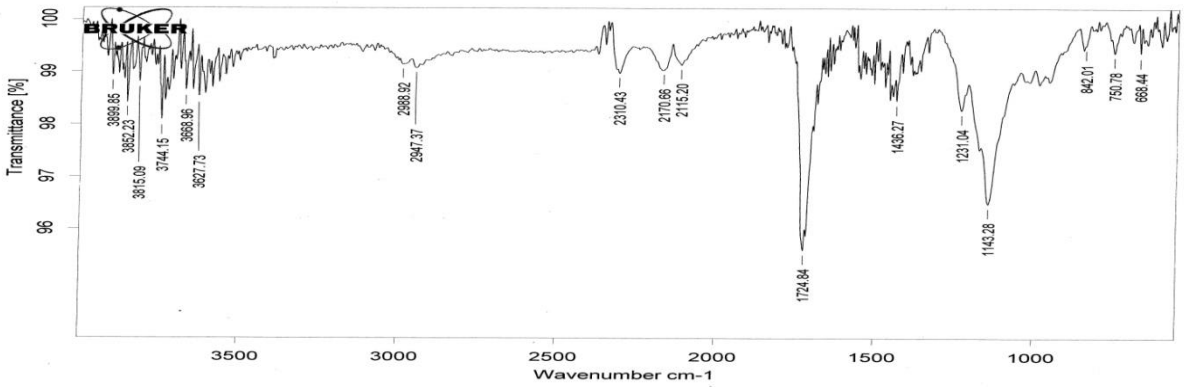

Figure 3: FTIR spectra of Bumetanide and HPMC K 100 M

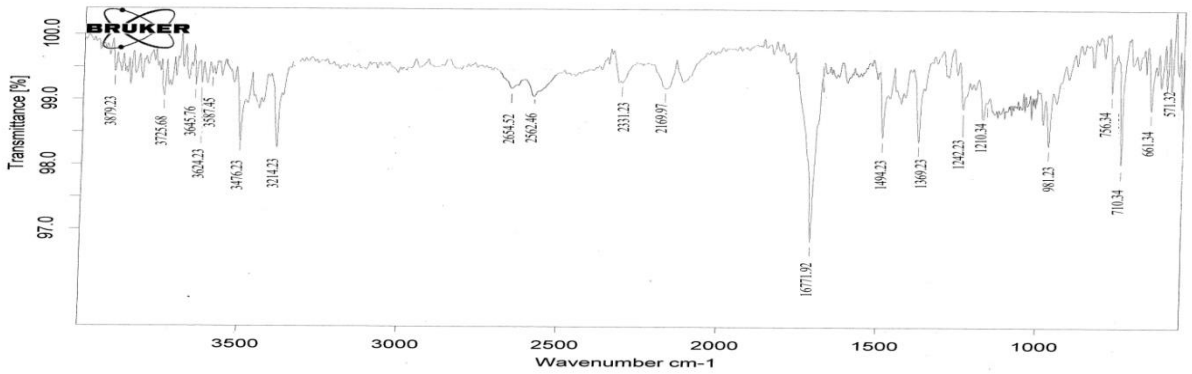

Figure 4: FTIR spectra of Bumetanide and magnesium stearate

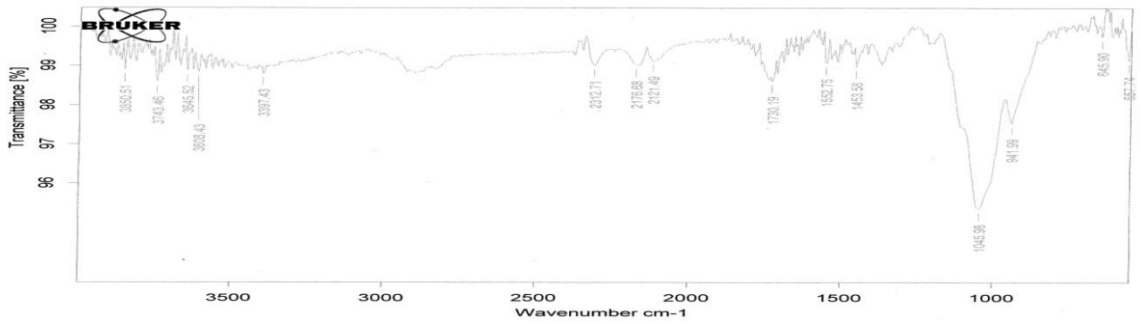

Figure 5: FTIR spectra of Bumetanide and xanthum gum

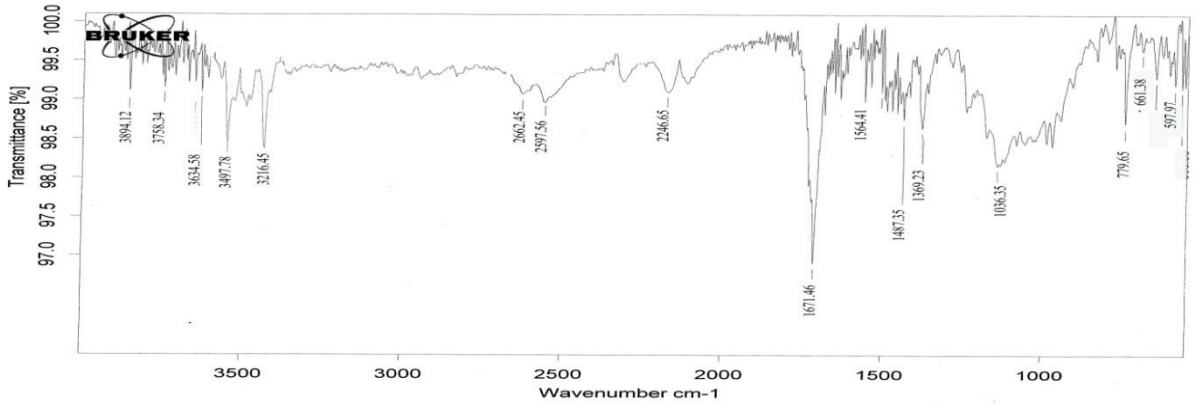

Figure 6: FTIR spectra of the physical mixture of Bumetanide, HPMC K15 and HPMC K100 and magnesium stearate.

Analytical method development of Bumetanide:

The present analytical method obeyed Beer's law in the concentration range of 1 to 18ppm and is suitable for **Bumetanide**. The correlation coefficient (r) value for the linear regression equation was found to be 0.999in 0.01M Hcl in **figure 7**.

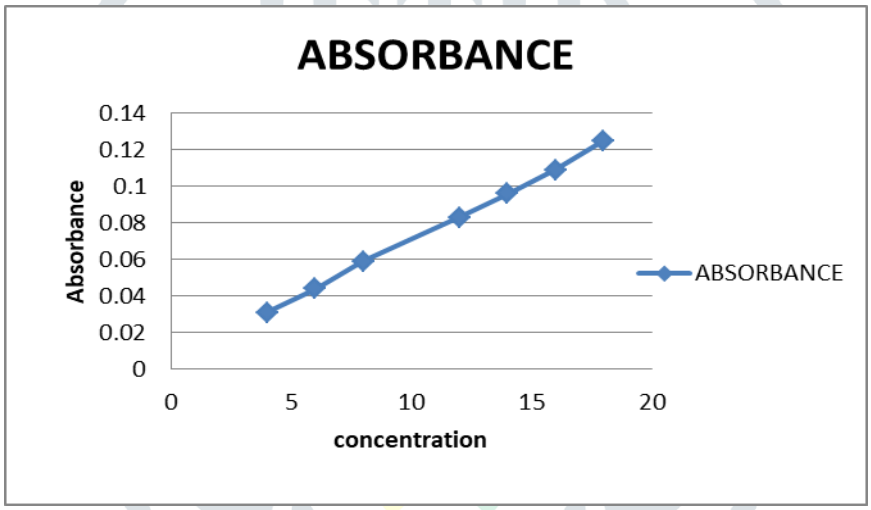

Figure 7: Standard plot of Bumetanide in 0.01M HCL

Pre compression parameters

The results obtained for the pre formulation studies i. e bulk density, tapped density, angle of repose, compressibility index and hausners ratio is given in the **Table 4**.

Table 4: Characterization of Bumetanide matrix blend

Formulation code	Bulk Density	Tapped Density	Angle of Repose	Carr's Index	Hausner's Ratio
F1	0.426	0.485	27.23	12.1	1.14
F2	0.412	0.467	26.45	11.7	1.13
F3	0.436	0.502	23.56	13.1	1.15
F4	0.443	0.509	28.97	12.9	1.15
F5	0.472	0.539	21.74	12.4	1.14
F6	0.423	0.478	25.43	11.5	1.13
F7	0.423	0.478	23.26	11.5	1.13

F8	0.418	0.473	24.12	12.0	1.13
F9	0.453	0.517	28.20	12.3	1.14
F10	0.457	0.512	29.04	11.5	1.12
F11	0.482	0.553	26.86	12.8	1.14
F12	0.424	0.475	27.61	10.9	1.12

The angle of repose of different formulations was ≤ 29.04 which indicates that material had excellent flow property. So it was confirmed that the flow property of blends were free flowing.

The bulk density of blend was found between 0.412g/cm^3 to 0.582 g/cm^3.Tapped density was found between 0.467g/cm^3 to 0.553 g/cm^3.These values indicate that the blends had good flow property.

Carr's index for all the formulations was found to be between 10.9-13.1 and Hausner's ratio from 1.12-1.15 which reveals that the blends have fair flow character.

Post Compression parameters

Evaluation of tablets

All the batches of tablet formulations were characterized for official evaluation parameters like Weight variation, Hardness, Friability, Tablet thickness and drug content and results are shown in the **Table 5**.

Table 5: Characterization of Bumetanide matrix tablets

Formulation	**Hardness (kg/cm^2)**	**Thickness (mm)**	**Weight variation**	**Friability**	**Content uniformity%**
F1	9.5	3.56	0.20	0.18	99.17
F2	8.2	3.49	0.22	0.22	99.44
F3	8.5	3.53	0.25	0.43	98.64
F4	9.1	3.61	0.21	0.20	100.2
F5	9.2	3.57	0.22	0.38	99.89
F6	9.5	3.63	025	0.12	99.97
F7	9.6	3.62	0.24	0.24	99.24
F8	8.3	3.57	0.22	0.16	99.62
F9	8.5	3.63	0.21	0.53	99.19
F10	9.5	3.55	0.23	0.29	99.73
F11	9.4	3.71	0.21	0.17	99.69
F12	9.8	3.59	0.22	0.19	99.82

Hardness of the tablet was acceptable and uniform from batch to batch variation, which was found to be 8 - 10 kg/cm_2.

All the formulations passed the weight variation test as the % weight variation was within the pharmacopoeial limits of ±5% of the tablet weight. Friability values were found to be less than 1% in all the formulations F1 – F12 and considered to be satisfactory ensuring that all the formulations are mechanically stable. The % drug content for all the formulations were close to 100 and varied between 98.64 to 100.2%.

***In vitro* dissolution studies:**

The *in vitro* drug release study of final formulations and reference drug was performed using HPLC in 0.01M Hcl.

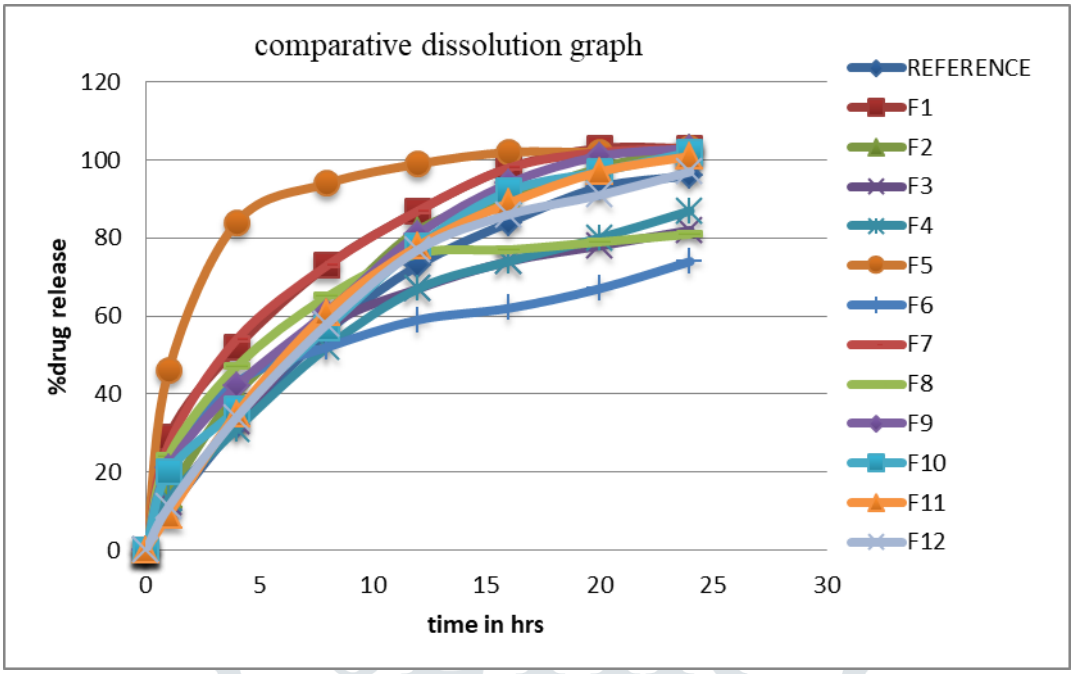

Figure 8: Comparative *in vitro* release graph for formulation F1-F12 with reference

The *in vitro* release profile of formulations F1 was found to be on higher side. 95% of drug dissolved in 8hrs. Dissolution rate was fast when compared to Reference. (73% at 8hrs) and for formulations F2 release was found to be (20% faster). 98% of drug is dissolved after 20 hrs of dissolution study. Dissolution rate was fast when compared to Reference where 96% of drug was dissolved at 24hrs and for formulations F3 release was found to be on lower side. Only 82% of drug is dissolved at 24hrs of dissolution study. Dissolution rate was decreased when compared to F2 and Reference where 96% of drug was dissolved at 24hrs and for formulations .The release rate of HPMC was higher, probably due to faster dissolution of the highly water soluble drug from the core and its diffusion out of the matrix forming the pores for the entry of solvent molecule.

The in vitro release profile of formulations F3 using HPMC H100M (60mg) the release was found to be on lower side. Only 82% of drug is dissolved at 24hrs of dissolution study. Dissolution rate was decreased when compared to F2. And Reference where 100% of drug was dissolved at 24hrs and for formulations F4 using HPMC K100M (20mg), release was found to be on lower side. Only 87% of drug is dissolved at 24hrs of dissolution study. Dissolution rate was increased when compared to F3. And Reference where 100% of drug was dissolved at 24hrs and for formulations F5 by using Metolose 60 SH 50, release was found to be on higher side. 99% of drug dissolved at 12hrs. Dissolution rate was very high when compared to Reference where 84% of drug was dissolved at 4hrs. The prolonged release is probably due to use of higher viscosity grade of HPMC in matrix. Increasing the molecular weight or viscosity of the polymer in the matrix formulation increases the gel layer viscosity and thus retards drug dissolution. Greater the viscosity of the gel more will be the resistant to the gel to dilute and erode, thus controls the drug dissolution.

The in vitro release profile of formulations F6 using xanthum gum (60mg) found to be too low due to low binding properties showing 74% of drug dissolved at 24hrs and for formulations F7 using xanthum gum (30mg), release rate was found to be too high. Complete release of drug was achieved within 16 hrs of dissolution. By increasing the concentration from 30mg to 40mg per unit in formulation F8, the release rate was found to be on lower side. Complete release of drug was not achieved. Only 79% of drug was dissolved even after 20 hrs of dissolution.

The in vitro release profile of formulations F9 with 1:1 ratio of HPMC K4M (30mg) + K15M (30mg) per unit, the release rate were found to be too high. Complete release of drug was achieved too fast as 94% of drug was dissolved even after 16hrs of dissolution and for formulation F10 with 1:2 ratio of HPMC K4M (20mg) +K15M (40mg) per unit, release rate were found to be slightly on the higher side as 97% of drug was dissolved even after 20hrs of dissolution. Dissolution rate was fast when compared to Reference, where 96% of drug was dissolved at 24hrs

The in vitro release profile of formulations F11 1:1 ratio of HPMC K15M (30mg) +K100M (30mg) per unit, the release rate were found to be slightly on the higher side. 97% of drug was dissolved even after 20 hrs of dissolution. Dissolution rate was fast when compared to Reference, where 96% of drug was dissolved at 24hrs. The drug release was not matched with the innovator

The in vitro release profile of formulations with 1:2 ratio of HPMC K15M (20mg) +K100M (40mg) per unit, the release rate were found to be similar when compared to Reference. Complete release of drug was observed in a Sustained way.

CONCLUSION

The study involves pre formulation studies, formulation, and evaluation and stability studies of prepared matrix tablets. The physical evaluation of API along with excipients has shown compatibility supporting the choice of excipients. FTIR studies reveal no incompatibility between drug, polymer and various excipients used in the formulations.

The analytical method used in the present study was found to be suitable for the estimation of Flovastatin sodium in different Medias which is indicated by the high regression values obtained in the standard plots.

An optimized formulation was not obtained for F1 to F11 may be due to loose matrix formation, high level of standard deviation in drug release. Formulation F1 to F11 were failed due to various reasons like increased impurities profiles during the course of stability or less *in vitro* drug release compared to innovator. Even though all the formulations are releasing the drug but those are not comparable to innovator product.

Among all formulations, HPMC K15 M an K100M IN (1:2) showed better release as a polymer to extend the release. The F12 formulation was compared with the marketed product for drug release pattern and was matched using similarity factor (f2) which showed that formulation F12 performed similar to the marketed product therapeutically.

REFERENCES

1. Aher K B, Bhavar G B, Joshi H P, Chaudhari S R, Recent advances in compression-coated tablets as a controlled drug delivery system, Saudi Pharmaceutical Journal, 2011, 01.
2. Shivakumar H G, Gowda D V, Kumar T M P, Floating controlled drug delivery systems for prolonged gastric residence: a review, Ind. J. Pharm., 2004, 38(45), 172-78.
3. Sharma A, Sharma S, Jha K K, The study of salbutamol matrix tablets using different polymers as release retarding agent, The Pharma Research, 2009, 01, 15-22.
4. Sharma P P, Sharma S, Khokra S L, Sahu R K, Jangde R, Singh J, Formulation, development and evaluation of sustained release matrix tablets containing salbutamol sulphate, Pharmacologyonline. 2, 2011, 1197-1203
5. Chein Y W, Oral Drug Delivery and Delivery Systems, Marcel Dekker, inc., New York, 1992, 01, 139-196.
6. Ahsan M Q, Rahman M M, Jha M K, Ahmed I, Moghal M M R, Rahman M H, Development and *in-vitro* evaluation of sustained release matrix tablets of salbutamol sulphate using methocel K100M CR polymer, International Journal of Pharmaceutical Sciences and Research, 2011, 02(03), 567-76.
7. Modi S A, Gaikwad P D, Bankar V H, Pawar S P, Sustained release drug delivery system: A review, International Journal of Pharma. Research and Development, 2011, 02(12), 147-59.
8. Chien Y W, "Novel Drug Delivery System", Marcel Dekker, New York, 2_{nd} edition, Revised and Expanded, Vol II, 1992, 139-140.
9. Verma R K, Krishna D M, Garg S, Formulation aspects in the development of osmotically controlled oral drug delivery systems, Journal of Controlled Release, 2002, 79, 7-27.
10. Vyas S P and Khar R K. "Controlled Drug Delivery Concepts and Advances", Delhi, India; 1_{st} edition, Vallabh Prakashan, 2002, 175-186.
11. Remington. "The Science and Practice of pharmacy", Lippincott Williams and Wikins, New York, 20_{th} edition, Vol.I, 905-915.
12. D M Brahmankar and Sunil B Jaiswal. "Biopharmaceutics and Pharmacokinetics", Vallabh Prakashan, 1stedition, 1995, 292-293.
13. Banker G S and Rhodes C T. "Modern pharmaceutics", 4 edition, Vol.I, Marcel Dekker, New York, 2002, 503-519
14. Vyas S P and Khar R K. "Controlled Drug Delivery Concepts and Advances", Delhi, India; 1_{st} edition, Vallabh Prakashan, 2002, 155-195.
15. Anirbandeep Bose, Tin Wui Wong and Navjot Singh. "Formulation development and optimization of sustained release matrix tablet of Itopride HCl by response surface methodology and its evaluation of release kinetics." *Saudi Pharmaceutical Journal*, 2012: In Press.
16. Ibrahim El-Bagory *et al*. "Formulation and in vitro evaluation of theophylline matrix tablets prepared by direct compression: Effect of polymer blends." *Saudi Pharmaceutical Journal* , (2012) 20 : 229-238.