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Research

FORMULATION AND EVALUATION OF SUBLINGUAL TABLETS OF BUMETANIDE

Gayathri. R[1*], Madhan Raj. T[2], Ajmal Khan. J[2], Vinothini. M[2], Sneka. M[2], Asika. I[2], Pasupathi. B[2]

[1,2]*Associate Professor, Department of Pharmaceutics, Dr Kalam College of Pharmacy, Thanjavur – 614623, India*

*Corresponding author: Gayathri. R
Email: gayathrisathesh2019@gmail.com

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Abstract

Bumetanide is a loop diuretic drug used to treat edema brought on by kidney, liver, or congestive heart failure. A formulation and evaluation attempt was undertaken for the 0.5 mg, 1 mg, and 2 mg Bumetanide Sublingual tablets. When taken orally, a fast-dissolving sublingual tablet dissolves or disperses quickly and is ingested as a liquid. To create the product, a direct blending and compression procedure using a dose-proportional, scale-up, and scale-down approach was used. Among the excipients are 0.5 percent Sucralose, 2 percent Sodium Stearyl Fumerate, 5 percent Sodium Starch Glycolate, 45.9 percent Mannitol SD 200, and 45.9 percent Pearlitol Flash (a co-processed excipient of 80 percent D-Mannitol and 20 percent Maize Starch) and 0.2 percent Capsil Orange Flavour. According to the SUPAC IR and IIG guidance documents, the composition and procedure were optimized. The finished product was judged to have a smooth mouthfeel, a pleasing flavor, and an organoleptic appearance. A member of BCS Class II (Low Solubility and High Permeability) is bumetanide. Injection and oral tablets that are currently on the market may be replaced by the designed product.

Keywords: Bumetanide, Direct blending, Compression, Co-processed excipients, BCS class.

INTRODUCTION:

SUBLINGUAL TABLETS:

The process of administering a medication by mouth is known as oral administration. Since many medications are meant to have a systemic effect-that is, to travel via the bloodstream to various parts of the body, they are often taken orally. A compacted solid dosage form that contains medications, either with or without excipient, is called a tablet.

Tablets that quickly disintegrate or dissolve in the patient's mouth are ideal for young children, elderly individuals, patients with intellectual disabilities, and those who are bedridden, as they often struggle with dysphagia and hand tremors. A rapidly dissolving sublingual tablet, when placed in the mouth, swiftly disperses or dissolves and is swallowed in liquid form.

When sublingual tablets are situated beneath the tongue, they generate an immediate systemic effect by allowing the drug to be rapidly absorbed directly through the mucosal lining found under the tongue. In contrast, drugs absorbed in the stomach enter the mesenteric circulation via the portal vein. Therefore, absorption through the oral cavity bypasses first-pass metabolism.

Sublingual tablets are typically compact and flat, lightly compressed to maintain their softness. These tablets are intended to dissolve rapidly to ensure quick absorption of the active pharmaceutical ingredient (API). They are designed to dissolve in a small amount of saliva; once the tablet is placed under the tongue, the patient should refrain from eating, drinking, smoking, and possibly talking to keep the tablet in its intended position.

Sublingual products have been developed for various purposes, including migraine treatment (where a quick onset of action is crucial) and mental health conditions (where adherence is essential for managing long-term issues like depression and schizophrenia).

The sublingual method offers (3-10) times higher drug absorption compared to the oral route and
is only outperformed by hypodermic injections. This route is particularly suitable for drugs that act quickly.

The sublingual route typically results in a faster onset of action than oral tablets. Children frequently struggle with swallowing due to immature muscles and neural systems, but this can be readily resolved with the use of quickly dissolving sublingual pills.

By allowing the medication to be absorbed straight via the mucosal lining of the mouth beneath the tongue, they are intended to be positioned beneath the tongue and provide an instant systemic action. The medication that the stomach absorbs travels to the mesenteric circulation, which is connected to the stomach by the portal vein. Therefore, first-pass metabolism is avoided by absorption through the oral cavity. Typically, the tablets are flat, tiny, and gently compacted to maintain their softness. For the medications to be rapidly absorbed, the pill needs to disintegrate rapidly.

It is made to dissolve in a tiny amount of saliva. To keep the tablet in place, the patient should refrain from eating, drinking, smoking, and possibly speaking after it has been inserted beneath the tongue. Additionally, since saliva may contain dissolved drugs, it is best to avoid swallowing it. In order to prevent salivary stimulation, bland excipient is utilized. Rapidly dissolving or disintegrating tablets can be made using a variety of methods.

One method for achieving rapid tablet disintegration is direct compression, which calls for the addition of a super disintegrant to the formulation or the use of excipient that are extremely soluble in water. Direct

compression is the best technique for drugs that are sensitive to heat and moisture since it eliminates the need for heat or water during the formulation process.

IDEAL PROPERTIES OF SUBLINGUAL TABLETS:

- No flavor of bitterness.
- The dosage is less than 50 mg.
- The molecular weight is little to moderate.
- Good stability in water and saliva.
- Maybe not completely ionized at the pH of the oral cavity.
- Sublingual dose forms are appropriate for drugs that undergo substantial first pass metabolism, which results in poor bioavailability.
- Parenterally prepared drugs are not administered.
- It should be less bioavailable.

MATERIALS AND METHODS:

Bumetanide was provided by Olan S.P.A, Mannito SD 200 and Pearlitol Flash was Roquette, Sodium Starch Glycolate and Sodium Stearyl Fumerate was JRS Pharma, Sucralose was JK Sucralose, Magnesium Stearate was Avantor, Peppermint Flavor was Firemenish, Capsil orange Flavor was Colorcon.

Preformulation Studies:

Determination of Absorption Maxima:

A solution of Bumetanide containing the concentration 5 µg/ ml was prepared in water in UV spectrum was taken using Double beam UV/VIS spectrophotometer. The solution was scanned in the range of 200 – 400 nm.

Preparation calibration curve For Bumetanide:

25 mg of Bumetanide drug was accurately weighed and dissolved in 250 ml volumetric flask and 5 ml taken in another 100 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 water.

The absorbance of standard solution was determined using UV/ VIS spectrophotometer at 220nm. Linearity of standard curve was assessed from the square of correlation coefficient (r2) which determined by least-square linear regression analysis.

Drug Excipient Compatibility Study for Using Fourier Transform Infrared Spectroscopics Studies (FTIR):

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.

Formulation of Bumetanide Sublingual Tablets by Direct Compression Method:

1. The manufacturing process involved excipients like Mannitol SD 200 and Pearlitol Flash co-sifted through # 30 ASTM mesh and divided into two equal parts.
2. Bumetanide was sifted through #30 ASTM mesh. In the using polybag, the sifted Bumetanide and co-sifted excipients was blended for 10 minutes for using hand blend method.
3. Sodium Starch Glycolate was sifted through #30 ASTM mesh was blended for 5 minutes.
4. Sucralose was sifted through #30 ASTM mesh was blended for 5 minutes.
5. Capsil Orange Flavor was sifted through #30 ASTM mesh was blended for 5 minutes.

6. Finally Sodium Stearyl Fumerate was sifted through # 60 ASTM mesh and blended along with the bulk of the blend in polybag for 5 minutes.
7. The tablets were prepared by using direct compression method.

INGREDIENTS	FUNCTION	F1	F2	F3	F4	F5	F6
Bumetanide	API	0.5	0.5	0.5	0.5	0.5	0.5
Mannitol SD200	Filler, Binder	79.62	39.07	38.98	38.98	38.98	38.98
Pearlitol Flash		-	39.07	38.98	38.98	38.98	38.98
Sodium Starch Glycolate	Super Disintegrant	4.25	4.25	4.25	4.25	4.25	4.25
Sucralose	Artificial sweetener	0.2	0.4	0.4	0.4	0.4	0.4
Magnesium Stearate	Lubricant	0.43	-	-	-	-	-
Sodium Stearyl Fumerate		-	1.72	1.72	1.72	1.72	1.72
Lemon	Flavour	-	-	0.17	-	-	-
Peppermint		-	-	-	0.17	-	-
Orange		-	-	-	-	0.17	0.17

Pre Compressional evaluation of powder blend:
Solubility Studies:

Solubility of Bumetanide was determined in Ethanol, with heat as needed, yielding a clear to slightly hazy, colourless to yellow solution.

Biopharmaceutical Classification System

BCS Class	Solubility	Permeability
I	High	High
II	Low	High
III	High	Low
IV	Low	Low

Bulk density:

A known quantity of powder blend (20 gm) was poured into the 35 ml measuring cylinder, carefully leveled the powder without compacting, apparent volume, (Vo) nearest graduated unit was taken as reading. Bulk density all powder blends were calculated in gm/ml or gm/cm^3, by using formula,

$$\text{Bulk Density (Vo)} = \frac{\text{Weight of Powder (g)}}{\text{Bulk Volume of Powder (mL)}}$$

Tapped density:

Tapped density was achieved by mechanically tapping a measuring cylinder containing a powder sample. (USP Tap Density Apparatus) Weighed quantity of powder (20 gm) was poured into 35 ml measuring cylinder freely without compacting, bulk density was calculated. Then measuring cylinder was fixed on USP Tap Density Apparatus and mechanically tapped for fixed interval of tapping 10, 500 and 1250. Cylinder dropping distance is 3 ± 2 mm at a normal rate of 1250 drops/minute. After completion of tapping, volume of powder was observed (Vf). Tapped density was calculated in gm/ml, by using formula,

$$\text{Tapped Density (Vd)} = \frac{m}{Vf}$$

Carr's compressibility index and Hausner's ratio:

Type of flow of powder was assessed by determining the Carr's Index (%) and Hausner's ratio using formula as given below,

$$\text{Carr's Compressibility index (\%)} = \frac{\rho 2 - \rho 1}{\rho 2} * 100$$

Where, ρ2 – tapped density,
ρ1 – Bulk density

$$\text{Hausner ratio} = \frac{Vo}{Vf}$$

Where, Vo – Bulk Volume,
Vf – Tapped Volume

Powder blends of all preliminary trial were evaluated for micromeretic properties by using above mentioned tests.

Hausner's and Carr's Index ratio Acceptance Limits

Hausner's Ratio	Types of Flow	Carr's Index (%)
1 – 1.11	Excellent	10
1.12 – 1.18	Good	11 – 15
1.19 – 1.25	Fair	15 – 20
1.26 – 1.34	Passable	21 – 25
1.35 – 1.45	Poor	26 – 31
1.46 – 1.54	Very poor	32 – 37
> 1.60	Very, very poor	> 38

Angle of Repose (θ):

A funnel was fixed to the brim. For measuring angle of repose, some quantity of powder blend was taken. Blend was allowed to flow smoothly through the orifice under gravity. The radius of base of powder cone was measured. Height of the pile was kept constant to 2 cm measured. The frictional force in a loose powder was measured by using following formula,

$$\tan(\theta) = \frac{h}{r}$$

Where, is the angle of repose?
h is height of pile
r is radius of the base of pile

Angle of Repose Acceptance Limits

Angle of Repose (°)	Types of Flow
25 – 30	Excellent
31 – 35	Good
36 – 40	Fair
41 – 45	Passable

46 – 55	Poor
56 – 65	Very poor
> 66	Very, very poor

Post Compressional evaluation of Sublingual tablets:

General Appearance:

The formulated tablets are evaluated for general appearance. Viz., color, odour, shape.

Thickness:

Ten tablets were chosen at random from the formulation. Using a Vernier Caliper, the crown thickness of each tablet was measured.

Hardness Test:

An Erweka hardness tester was used to assess the hardness of ten tablets that were chosen at random from the formulation. Kg/cm2 or Newton (N) is the units of measurement.

Friability test:

Initially 6.665 grams tablets were weighed [W (initial)] and transferred to Labindia Friabilator. The Friabilator was operated at 25 rpm for 4 mins or run up to 100 revolutions. The tablets were dusted to remove surface particle and weighed again [W (final)].

The percentage friability was then calculated by formula,

$$F = \frac{W\,(initial) - W\,(final)}{W(initial)} * 100$$

Weight Variation Test:

To check for weight variance, twenty tablets were chosen at random from the batch and weighed separately. The U.S. Pharmacopoeia permits a little amount of fluctuation in a tablet's weight.

Weight variation for percentage deviation

Average weight of a tablet	Percentage deviation
Less than 130mg	± 10%
More than 130mg to Less than 324mg	± 7.5%
324mg or more	± 5%

In-vitro disintegration test:

Six tablets from the formulation were chosen at random. A 1000 ml beaker was filled with 900 ml of purified water. The temperature was kept at 37 ± 2°C. The amount of time needed for the tablet to completely dissolve was recorded after it was placed inside.

In-vitro dissolution test:

In vitro dissolution study was conducted for the formulation using USP type-II (Paddle) apparatus. Six tablets were randomly selected for test. The dissolution test was performed using 900 ml of water at 50 rpm and 37°C ± 0.5°C temperature. Sampling interval were 5, 10, 15, 20, 30, and 45min. 10 ml of aliquots were periodically withdrawn and the sample volume was replaced with an equal volume of fresh dissolution medium. On end of each particular time, withdraw 10 milliliter of the solution from each dissolution vessel. Pass the solution across 0.45 µm PVDF Syringe filter and solution was injected to HPLC.

In-vitro Drug Release Kinetics:

To analyze the In-vitro release data various kinetic models were used to describe the release kinetics. The zero order rate describes the systems where the drug release rate is independent of its concentration. The first order describes the release from the system where release rate is concentration dependent. Higuchi described the release of drugs from insoluble matrix as a square root of time dependent the release from the systems where there is a change in surface area and diameter of particles. The Koresmeyer-peppas describes the mode of release of drug from swellable matrics.

Release Kinetics Models

Release Kinetics Model	Equation
Zero Order	Qt = Q0 + K0.t
First Order	In Qt = In Q0 + K0.t
Hixson-Crowell	Q0 1/3 – Qt 1/3 + K. t
Higuchi	Q = KH. t ½
Korsmeyer-Peppas	Mt / M0 = a. tn

Qt is amount of drug release at time t,
Mt is drug release at time t,
M0 is total amount of drug in dosage form,
F is fraction of drug release at time t,
K0 is zero order release rate constant,
Q0 is Initial amount of drug in the solution (Most times, Q0 = 0)
KH is Higuchi's square root of time release rate constant,
Km is constant depend on geometry of dosage form and
n is diffusion exponent values indicating the mechanism of drug release.
Fitness of release profiles to linear equations is assessed by comparing the coefficients of determination (r) values. **(Harris Shoaib *et al.*, 2006: Praveen Kumar Mandapali *et al.*, 2012).**

Diffusion exponent values indicating drug release mechanism

S. No.	Diffusion exponent value (n)	Drug release mechanism
1.	< 0.5	Fickian release
2.	0.5 to 1.00	Non-Fickian transport
3.	1.00	Case II transport
4.	> 1.00	Super case II transport

The In-vitro data are fitted to the above mathematical models and the applying data are,

- ✓ Cumulative % drug release vs. time for zero order kinetic.
- ✓ Log cumulative of % drug remaining vs. time for first order kinetics.
- ✓ Cumulative % drug release vs. Square root of time for Higuchi model.
- ✓ Log cumulative % drug release vs. log time for Korsmeyer-Peppas model and
- ✓ Cube root of drug % remaining in matrix vs. time for Hixson-Crowell cube root time.

Selection of best formulation:

The best formulation is selected in accordance with the results obtained from Sublingual behavior, In-vitro drug release studies.

Stability Study:

The product was packaged in two distinct configurations and kept at 40°C and 75% relative humidity for six months, as advised by the ICH. Samples were removed after 15 days intervals, and their thickness, hardness, assay, water by Kf, disintegration time, and in-vitro drug release profile were assessed.

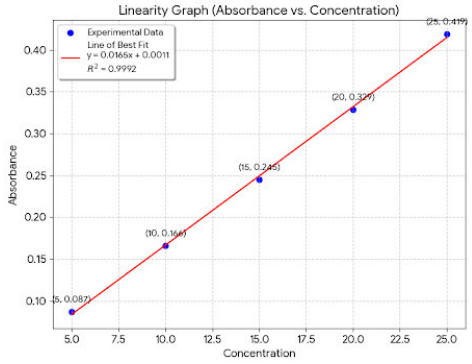
RESULTS AND DISCUSSION

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 0.999 in water.

Absorbance vs. Concentration

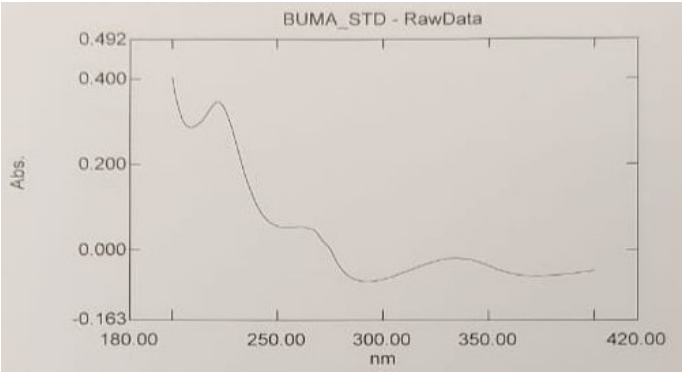
S. No.	CONCENTRATION (µg/ml)	ABSORBANCE
1.	5	0.087
2.	10	0.166
3.	15	0.245
4.	20	0.329
5.	25	0.419



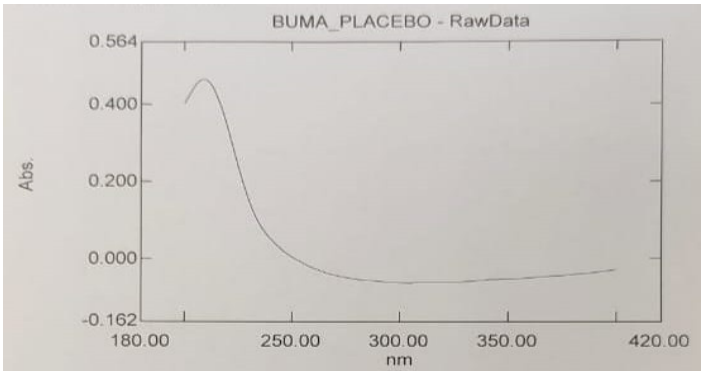
Absorbance vs. Concentration

Estimation of Absorption maximum (λ max) for Bumetanide by Ultrviolet Spectroscopy (UV):

The absorption maximum (λ max) of Bumetanide was estimated by scanning the drug solution (5 µg/ml) between 200 – 400 nm regions on UV spectrophotometer. The obtained spectrum showed that the absorption maximum (λ max) was 220 nm in Water. The result was shown in Figure. 30.



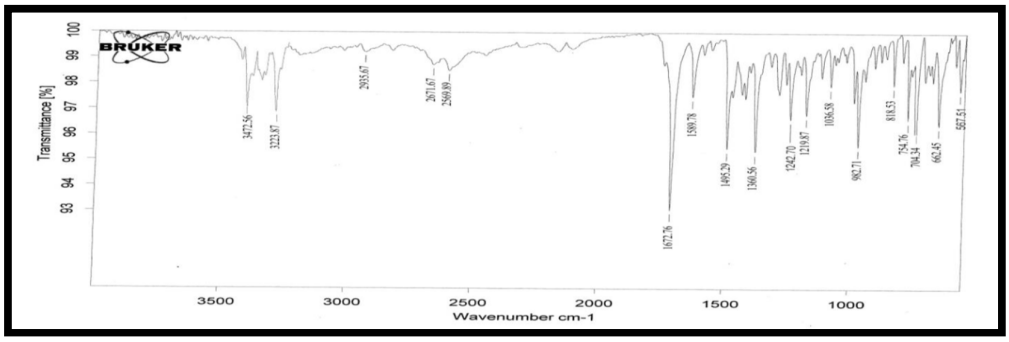
Bumetanide tablet by Ultrviolet Spectroscopy



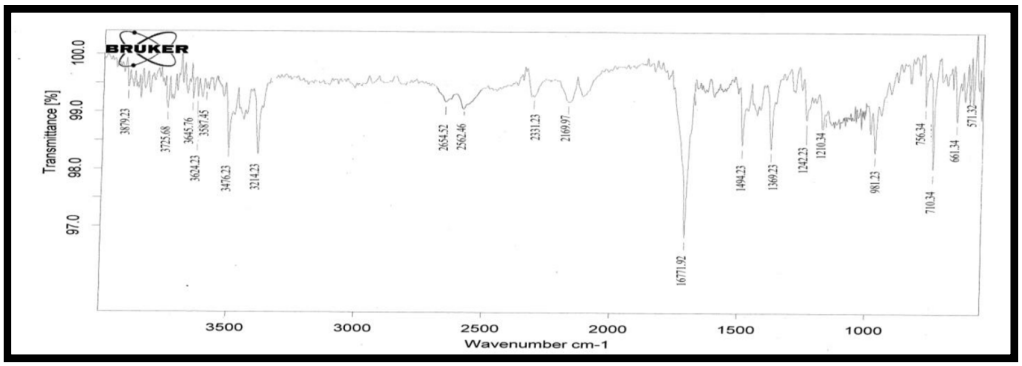
Bumetanide placebo by Ultraviolet Spectroscopy

Drug Excipients Compatibility Study for Using FTIR Spectroscopy:

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. 32 shows the IR spectrum of pure Bumetanide while Figures. 33 show the compatibility between the drug and Magnesium Stearate respectively.



FTIR spectra of Bumetanide



FTIR spectra of Bumetanide and Magnesium Stearate

Pre Compressional Evaluation Of Powder Blend:

Solubility Studies:

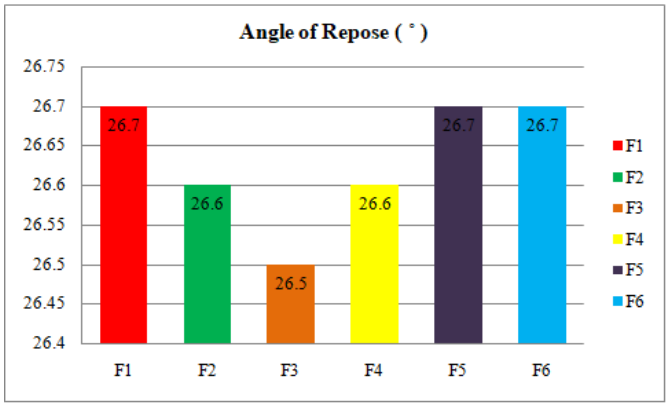
It is also soluble in Acetone and Acetonitrile and Alkaline solutions.

It is a slightly soluble in Chloroform and in Ether.

It is a very slightly soluble in Water.

Angle of Repose (θ):

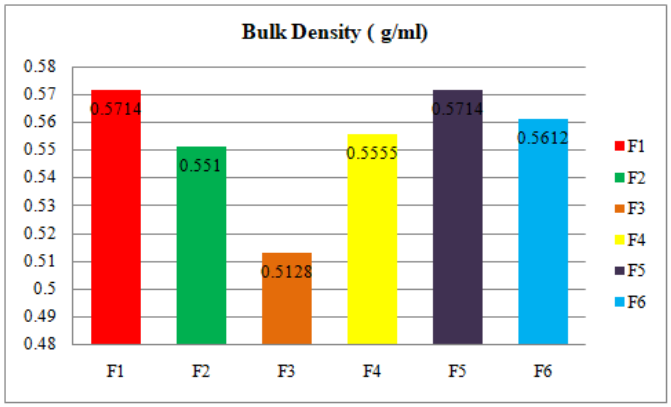
The values obtained for angle of repose for final blend are tabulated in Table. 12. The values were found to be 25°. This indicates good flow property of the powder blend.



Angle of Repose

Bulk Density (gm/ml):

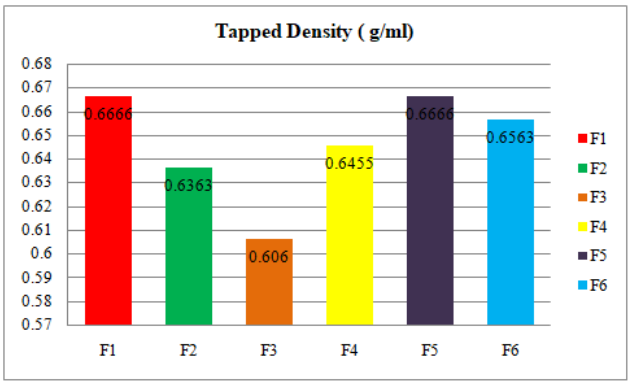
The bulk density of powder blends was in the range of 0.5128 to 0.5714 gm/ml, which indicates the powder blends were not bulky. The results were shown in the Figure. 35.



Bulk Density

Tapped Density (gm/ml):

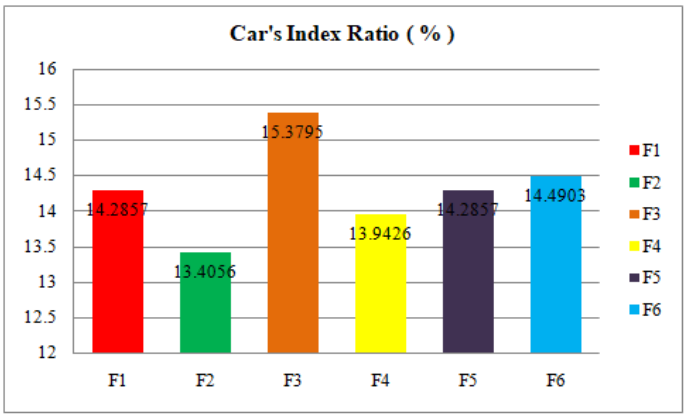
The tapped density of powder blends was in the range of 0.6060 to 0.6666 gm/ml, which indicates smaller particles to occupy the voids between larger particles. The results were shown in the Figure. 36.



Tapped Density

Compressibility Index (%):

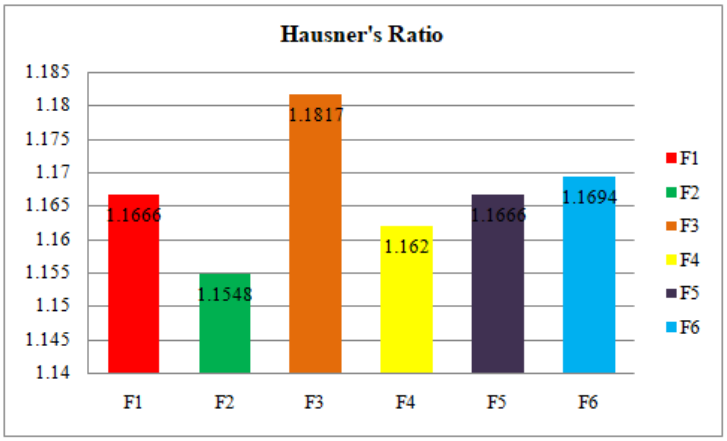
Compressibility index were found to be in between 13.4056 to 15.3795 which indicates that the powder blend have good flow property for direct compression. The results were shown in Figure. 37.



Carr's Index ratio

Hausner's Ratio:

The Hausner's ratio of powder blend was found to be in the range of 1.1548 to 1.1817 which indicates good flow properties of powder blend. The results were shown in the Figure. 38.



Hausner's ratio

Pre Compressional Evaluation of Powder Blend

METHOD	BULK DENSITY (g/ml)	TAPPED DENSITY (g/ml)	CARR'S INDEX (%)	HAUSNER'S RATIO	ANGLE OF REPOSE (°)
F1	0.5714	0.6666	14.2857	1.1666	26.7
F2	0.5510	0.6363	13.4056	1.1548	26.6
F3	0.5128	0.6060	15.3795	1.1817	26.5
F4	0.5555	0.6455	13.9426	1.1620	26.6
F5	0.5714	0.6666	14.2857	1.1666	26.7
F6	0.5612	0.6563	14.4903	1.1694	26.7

Particle Size Distribution

	ASTM Sieve #	% Retained
Particle Size Distribution	20	0
	40	0
	60	1
	80	4
	100	12
	140	51
	200	7
	Pan	25

Post Compressional Evaluation of Sublingual Tablets:

Shape of the tablet:

Each formulation batch's tablets had a round shape and no cracks when examined under a microscope.

Weight Variation Test:

The percentage weight variations for all formulations were shown in Table 14. All the tablets passed weight variation test as the % weight variation was within the pharmacopoeial limits of ± 5%, ± 7.5% & ± 10% of the weight. The weight of all the tablets were found to be uniform with low standard deviation values.

Thickness:

Vernier calipers were used to measure the tablet's length and thickness. For this test, ten drugs were chosen at random, and the average value was recorded. The values of thickness were tabulated in Table 14.

Hardness:

The measured hardness of tablets of each formulations were shown in Table 14. This ensures good handling characteristics of all batches.

Friability Test:

The values of friability test were tabulated in Table 14. The % friability was less than 1% in all the formulations ensuring that the tablets were mechanically stable.

In *vitro* disintegration test:

The values of tablet disintegrations were tabulated in Table 14. The disintegration sec's was less than 30 sec in all the formulations ensuring that the tablets were easy to orally disintegrate.

Post Compressional Evaluation of Sublingual Tablets

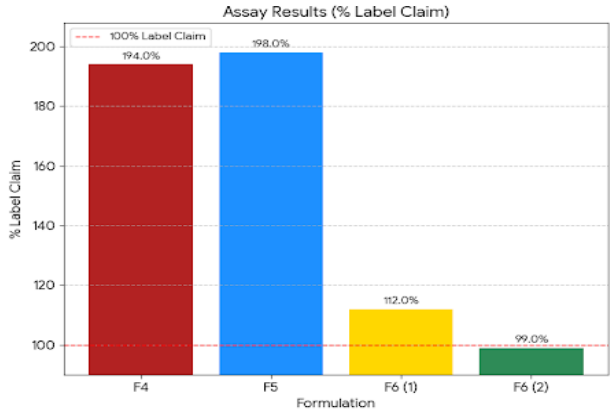
METHOD	WEIGHT (mg)		THICKNESS (mm)	HARDNESS (kp)	DISINTEGRATION TIME (sec)	FRIABILITY (%)
	Min	Max				
F1	84 - 86		2.6	4.1	6 – 10	0.97
F2	84 - 86		2.5	4.2	6 – 9	0.12
F3	84 - 86		2.7	4.0	7 – 10	0.13
F4	84 - 86		2.5	4.2	7 – 10	0.12
F5	84 - 86		2.5	4.2	7 – 10	0.12
F6	84 - 86		2.5	4.2	7 – 10	0.12

Assay:

The percentage of assay for F6 was found to be in the ranges from 97% to 104%, which is within acceptable limits, showed that the drug was uniformly distributed in all formulations. Hence the percentage of assay of all formulations complies with official monograph as per USP. The results were shown in Figure. 39.

Drug Content

S. No	Batch No	Sample No. of Unit	Sample Abs	Content in mg per Tablet	% Label Amount	
1.	F4	10	0.769	0.97	194.00	194.00
		10	0.769	0.97	194.00	
2.	F5	10	0.781	0.99	198.00	198.00
		10	0.781	0.99	198.00	
3.	F6	10	0.474	0.56	112.00	112.00
		10	0.474	0.56	112.00	
4.	F6	10	0.420	0.49	98.00	99.00
		10	0.421	0.50	100.00	



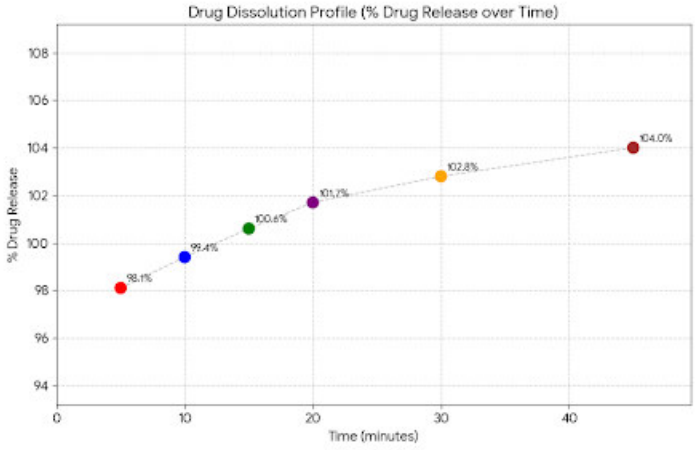
% Drug Content

In-vitro Dissolution Study:

In vitro dissolution study was conducted for all the formulation using USP type-II (Paddle) apparatus. Six tablets were randomly selected for test. The dissolution test was performed using 900 ml of Water at 50 rpm and 37°C ± 0.5°C temperature. Sampling interval were 5, 10, 15, 30 and 45 min. 10 ml of aliquots were periodically withdrawn and the sample volume was replaced with an equal volume of fresh dissolution medium. On end of each particular time, withdraw 10 milliliter of the solution from each dissolution vessel. Pass the solution across 0.45 µm PVDF Syringe filter and solution was injected to HPLC. The in-vitro drug release profile of tablet from each formulations were shown in Table16.

Dissolution Study (F6)

Tablet strength (mg)		% Dissolution - Mean, Range, % RSD (USP-II, 50 rpm, water)					
		5 min	10 min	15 min	20 min	30 min	45 min
0.5	Mean (%)	98	99	101	102	103	104
	Min to Max	97.3 to 99.1	98.6 to 100.2	99.7 to 101.3	100.8 to 102.5	101.9 to 103.6	103.0 to 104.7
	% RSD	0.77	0.63	0.67	0.68	0.69	0.67



% Drug release

In-vitro release kinetics studies:

The release data (1-12hrs) were analysed as per Zero order, First order, Hixson crowns well, Higuchi's and Peppas equation models to know the pattern of drug release and mechanism of drug release from the matrix tablet. **(Nirav Patel et al., 2013).**

KorsmeyerPeppas model was found to be the best fitted in all dissolution profile having higher correlation coefficient (R2 value). The values of n (diffusion exponent) were estimated by linear regression of log cumulative % drug release Vs log time (t) of different formulations. The 'n' value could be used to characterize different release mechanisms as follows, **(Gupta Amit M. et al., 2011).**

S. No.	Diffusion exponent value (n)	Drug release mechanism
5.	< 0.5	Fickian release
6.	0.5 to 1.00	Non-Fickian transport
7.	1.00	Case II transport
8.	> 1.00	Super case II transport

The 'n' value of Koresmeyer-Peppas model of all formulations was between 0.929 to 0.998. The R2 value of best formulation F6 was 0.998. Therefore, the most probable mechanism that the release patterns of all formulations followed was Non-fickian diffusion.

The drug release mechanism was sustained by both diffusion as well as polymer relaxation process. The rate of drug permeation out of the matrix was supposed to be proportional to the rate of solvent entry and broadening of the diffusion path length due to swelling of the matrix as a result of polymer hydration and subsequent strand relaxation.

The kinetic studies of all the formulations showed that the Zero order plots were fairly linear as indicated by their high regression values compared to Zero order plots. Therefore it was as certained that drug release from the all formulations followed Zero order kinetics (0.991 to 0.997). Formulation F6 showed the closest linearity to unity (r2= 0.996).

Selection of best formulation:

From the above results, F6 was selected the best formulation based on following character,

Disintegrating time: 10 seconds

In-vitro release profile: 99.0 %

In-vitro release kinetics: Zero order kinetics (r^2 = 0.996)

EVALUATION OF STABILITY STUDIES FOR BEST FORMULATION (F6)

Stability studies were carried out by using selected formulation i.e. F6. The formulation is kept in accelerated stability condition at 40°C temperature and 75% relative humidity for a period of six months as per ICH guidelines. The samples were withdrawn at every 15 days intervals and evaluation was carried out for appearance, thickness, hardness, assay, water by Kf, disintegration time, and in-vitro drug release studies (60 days) were assessed. The results were shown in Table.17.

Evaluation of Stability Studies

Formulation Parameters	Initial	15 days	30 days	45 days	60 days
Average weight (mg)	85.4	86.0	85.8	85.1	85.6
Thickness (mm)	2.5	2.6	2.4	2.5	2.5
Hardness (Kp)	4.1	4.0	3.9	4.2	4.1
Disintegrating time	9 sec	10 sec	9sec	9sec	9 sec
Drug content (%)	99.1 %	98.9 %	99.0 %	99.3 %	99.5 %
% Drug release	98.2	99.1	99.3	98.8	98.9

SUMMARY & CONCLUSION

In this research work, we have successfully developed and commercialized a drug product of Bumetanide in the form of Sublingual Tablets. BCS Class II drug (Low Soluble & High Permeable); API exhibited relevant density, flow, compressibility, moisture content & particle size distribution values suitable for direct blending and compression process. Based on prototype formulation trials, formula optimization and organoleptic evaluation, the final composition was finalized which include 0.5 percent Sucralose, 2 percent Sodium Stearyl Fumerate, 5 percent Sodium Starch Glycolate, 45.9 percent Mannitol SD 200, and 45.9 percent Pearlitol Flash (a co-processed excipient of 80 percent D-Mannitol and 20 percent Maize Starch) and 0.2 percent Capsil Orange Flavor. The maximum daily dose (MDD) of Bumetanide is 10 mg per day. The composition was checked for the IIG compliance and was found to comply with the regulatory requirements.

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