EJPMR, 2026, 13(5), 295-302 **Research Article** **Impact Factor: 8.158**

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

ISSN (O): 2394-3211
ISSN (P): 3051-2573
Coden USA: EJPMAG

FORMULATION AND EVALUATION OF MICROSPONGES LOADED CAPSULE OF BENFOTIAMINE

Tushar Lavari[1]*, Bhakti Shah[2], Dr. Shailesh T. Prajapati[3]

[1*]Department of Pharmaceutics, Shree Swaminarayan Sanskar Pharmacy College, Zundal, Gandhinagar-382421.
[2]Assistant Professor, Department of Pharmaceutics, Shree Swaminarayan Sanskar Pharmacy College, Zundal, Gandhinagar-382421.
[3]Principal, Shree Swaminarayan Sanskar Pharmacy College, Zundal, Gandhinagar-382421.

***Corresponding Author: Tushar Lavari**

Department of Pharmaceutics, Shree Swaminarayan Sanskar Pharmacy College, Zundal, Gandhinagar-382421.

DOI: https://doi.org/10.5281/zenodo.19885560

How to cite this Article: Tushar Lavari[1]*, Bhakti Shah[2], Dr. Shailesh T. Prajapati[3]. (2026). Formulation and Evaluation of Microsponges Loaded Capsule of Benfotiamine. European Journal of Pharmaceutical and Medical Research, 13(5), 295–302.

Article Received on 28/03/2026 **Article Revised on 18/04/2026** **Article Published on 01/05/2026**

ABSTRACT

Objective: The goal of this study was to formulate, develop, and evaluate a microsponge-based capsule formulation of Benfotiamine using Box-Behnken design for enhanced solubility, protect from rapid metabolism, and controlled release of the drug. This approach aimed to improve the therapeutic efficacy of benfotiamine, which suffers from low solubility, and to optimize its delivery for better patient compliance in managing diabetic neuropathy. **Materials and Methods:** Benfotiamine-loaded microsponges were prepared using the quasi-emulsion solvent diffusion technique with ethyl cellulose and PEG 4000. A BBD was employed to optimize the formulation, with three independent variables: drug to polymer ratio, concentration of plasticizer, and stirring speed. The formulations were evaluated for production yield, entrapment efficiency, particle size, and drug release properties. **Result and Discussion:** The optimized formulation, based on the results from the BBD, demonstrated significant improvements in entrapment efficiency and particle size, with a gradual and sustained release of Benfotiamine. The formulation exhibited favorable characteristics, such as enhanced solubility and bioavailability, with a good correlation to the theoretical model derived from the Box Behnken analysis. The microsponge formulation was stable, showing no significant changes in drug content during stability studies. **Conclusion:** The microsponge-based capsule formulation of Benfotiamine developed through BBD offers an efficient method for enhancing drug solubility, providing sustained release, and improving patient compliance. The study demonstrates the potential of microsponge drug delivery systems to optimize the pharmacokinetic profile of Benfotiamine, making it a promising strategy for the treatment of diabetic neuropathy.

INTRODUCTION

Diabetic neuropathy (DN) is one of the most common and serious chronic complications of diabetes mellitus. It primarily involves peripheral nerve dysfunction resulting from prolonged hyperglycemia and metabolic disturbances associated with diabetes.[1] Benfotiamine is a lipid-soluble derivative of thiamine (vitamin B1), which helps to manage diabetic neuropathy.[2] The oral delivery of benfotiamine faces challenges such as rapid metabolism so,to maintain therapeutic level for a long period the sustained drug release is necessary.[3] The microsponges delivery system is an effective approach to address this challenges by incorporating benfotiamine into porous, polymeric microspheres that control and sustain drug release. When drug is delivered orally microsponge system protect benfotiamine from premature degradation in GIT which enhancing it's stability and efficacy.[4-5] Capsule dosage forms provide an effective vehicle for delivering these microsponges.

Box-Behnken Design (BBD), a statistical optimization technique, is ideal for pharmaceutical formulation development. It allows efficient screening of formulation parameters and their interactions with minimal experimental runs.[6]

MATERIALS AND METHODS

Benfotiamine is provided as gift sample by Coax Pharmachem and excipients were Ethyl cellulose, PEG 4000, PVA and Dichloromethane was provided by oxford lab fine chem LLP.

Preformulation studies

Determination of Absorbance Maxima of Benfotiamine[7]

100 mg of Benfotiamine was weighed and transferred to 100 ml of volumetric flask. The drug was dissolved in minimum quantity of methanol and the volume was made up to 100 ml using Solvent to obtain a stock solution of 1000µg/ml (stock solution I). 10 ml of this stock solution was again diluted with Solvent up to 100 ml to obtain a solution of 100µg/ml(stock solution-Ⅱ). 1 ml of this stock solution was again diluted with solvent upto 10 ml to obtaion a solution of 10 µg/ml. UV Spectrum of 10µg/ml was recorded over the wavelength range 200-400 nm using UV-Visible spectrophotometer.

Drug excipients compactibility study by FTIR study [8-9]

Infrared spectroscopy was conducted using FT-IR spectrophotometer and the spectrum was recorded in the wave number region of 4000 to 400 cm^{-1}.

Method of Preparation of Microsponges[10]

Quasi-emulsion solvent diffusion method was used.

Internal Phase: Polymer (Ethyl Cellulose) was dissolved in 10ml of dichloromethane. Benfotiamine was added and mixed well until it gets dissolved completely and to which PEG 4000 was added to facilitate plasticity. The solution was sonicated for 20 minutes.

External phase: Accurately weighed PVA is added to distilled water to form clear solution. 0.5% w/v solution was prepared.

The internal phase was added drop wise to external phase and stirred for 2 hours at room temperature.

The mixture was filtered to separate microsponges and were dried in an air heated oven at 40ºC for 12 hr and stored for subsequent investigation.

Table 1: Formulation table for design batches.

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
Internal Phase								
Benfotiamine(mg)	150	150	150	150	150	150	150	150
Ethyl Cellulose(mg)	300	300	150	300	300	300	300	150
PEG 4000(mg)	200	150	150	150	100	150	200	200
Dichloromethane(ml)	10	10	10	10	10	10	10	10
External Phase								
Polyvinyl Alcohol(mg)	500	500	500	500	500	500	500	500
Distilled Water(ml)	100	100	100	100	100	100	100	100
Stirring Speed(rpm)	800	600	400	600	400	600	400	600

Table 2: Formulation table for design batches.

Ingredients	F9	F10	F11	F12	F13	F14	F15	F16	F17
Internal Phase									
Benfotiamine (mg)	150	150	150	150	150	150	150	150	150
Ethyl Cellulose (mg)	150	300	450	450	450	300	150	450	300
PEG 4000(mg)	150	150	200	150	100	150	100	150	100
Dichloromethane (ml)	10	10	10	10	10	10	10	10	10
External Phase									
Polyvinyl Alcohol (mg)	500	500	500	500	500	500	500	500	500
Distilled Water (ml)	100	100	100	100	100	100	100	100	100
Stirring Speed(rpm)	800	600	600	400	600	600	600	800	800

Evaluation of Microsponges[11-13]

Percentage Yield

$$Production\,Yield = \frac{Practical\ yield}{Theoritical\ yield} \times 100$$

Entrapment Efficiency

$$DDE\% = \frac{Actual\ Drug\ Content}{Theoretical\ Drug\ Content} \times 100$$

Particle Size Analysis

$$dav = \sum nd / \sum n$$

Surface Morphology

Scanning Electron Microscopy of optimized microsponge formulation was carried to determine the surface morphology. The sample was mounted directly

onto the SEM sample holder using double sided sticking tape and images were recorded at different magnifications at acceleration voltage of 10 kV using scanning electron microscope.

Preparation of microsponges loaded Capsules

The optimised microsponges were filled into "1" sizes capsule each containing 150mg equivalent of Benfotiamine.

Table 3: Preparation of Benfotiamine Microsponge Capsules.

Optimized Formulation	Benfotiamine Microsponge (equivqlent to 150 mg)	Lactose(mg)	Magnesium Stearate(mg)
F16	182.92	22.3	0.96

Evaluation of Microsponges loaded capsule[14-15]

Weight Variation

The weight variation test was performed to ensure uniformity of capsule fill weight. A sample of at least 20 capsules was individually weighed, and the average weight was calculated. The deviation of each capsule from the average was compared with pharmacopeial limits (±10% for capsules weighing ≤300 mg and ±7.5% for capsules >300 mg). Excessive variation indicated poor filling consistency in manufacturing.

Disintegration test

The disintegration test was carried out to verify that capsules disintegrated within the required time frame for effective drug release. The USP disintegration apparatus was used, where capsules were placed in a basket and immersed in a dissolution medium such as 0.1N HCl (pH 1.2) for gastric release and phosphate buffer (pH 6.8) for intestinal release, maintained at 37±0.5°C. The time taken for complete disintegration (excluding shell fragments) was recorded, with a typical limit of ≤30 minutes for HPMC capsules.

Dissolution test

The dissolution test was performed to determine the rate and extent of drug release. The test was conducted using the USP dissolution apparatus (Type I - Basket or Type II - Paddle) with a suitable dissolution medium at 37±0.5°C and a set rotation speed (50–100 rpm). Samples were withdrawn at predefined intervals, filtered, and analyzed using UV spectrophotometry. The drug release profile was then compared with pharmacopeial standards to ensure proper bioavailability.

In-vitro drug release

In-vitro release rate studies of microsponges were carried out by filling equivalent amount of microsponge in capsules placed in the basket containing phosphate buffer pH 6.8 was used as medium and rotated at 50 rpm. Samples was withdrawn and determined spectrophotometricaly.

Stability Study[16]

A stability study was conducted to assess the stability profile of the developed formulation under accelerated conditions (40°C ± 2°C / 75 ± 5% RH). The study aimed to evaluate the drug-excipient compatibility and predict the formulation's behaviour under long-term storage conditions. Since the stability assessment depends on the stage of development, early studies focused on understanding the drug substance's inherent stability and potential interactions with excipients. The stability program was designed based on the dosage form and formulation requirements. Accelerated stability studies provided an efficient method to observe potential degradation pathways, ensuring that the formulation remains chemically and physically stable under challenging environmental conditions.

RESULT AND DISCUSSION

Organoleptic Characters of Benfotiamine

The drug sample of Benfotiamine was assessed for organoleptic properties, including color, odor, taste, and appearance, under controlled conditions to ensure accuracy. Observations were compared with reference standards to confirm identity and suitability for formulation development.The result is as per table 4.

Table 4: Organoleptic character.

Property	Observation
Colour	Off White
Odor	Odorless
Taste	Slightly Bitter
Appearance	Fine Powder

Melting point determination of Benfotiamine

The melting point of Benfotiamine was determined using a capillary tube method. A small sample was placed in a sealed capillary tube and gradually heated in a melting point apparatus. The temperature range at which the substance transitioned to a liquid was recorded, ensuring precise measurement. The melting point of drug is determined as shown in table 5.

Table 5: Melting point.

Parameter	Reference	Observation
Melting Point (℃)	164-169℃	165℃

Solubility Study

Solubility of Benfotiamine was assessed by adding excess drug to 10 mL of different solvents:water, phosphate buffer (pH 6.8), methanol, and dichloromethane in separate flasks. Each flask was continuously shaken for uniform mixing. After equilibration, the solutions were filtered to remove undissolved drug particles. The filtrates were appropriately diluted and analyzed using a UV-visible spectrophotometer at a suitable wavelength to determine solubility levels. The result of solubility study of drug is as per table 6.

Table 6: Solubility of Benfotiamine.

Solvent	Observation	Inference
Water	0.67 mg/ml	Extremely low Soluble
Phosphate buffer (pH 6.8)	~2.5 mg/ml	Slightly Soluble
Methanol	90 mg/ml	Soluble
Dichloromethane	75 mg/ml	Soluble
Propylene Glycol	~1 mg/ml	Slightly Soluble
DMSO	~50 mg/ml	Soluble

Absorption Maxima of Benfotiamine

The maximum absorption of drug in phosphate buffer at 242nm which is shown in fig.1 and on it's based we form the calibration of Benfotiamine which is shown in fig.2.

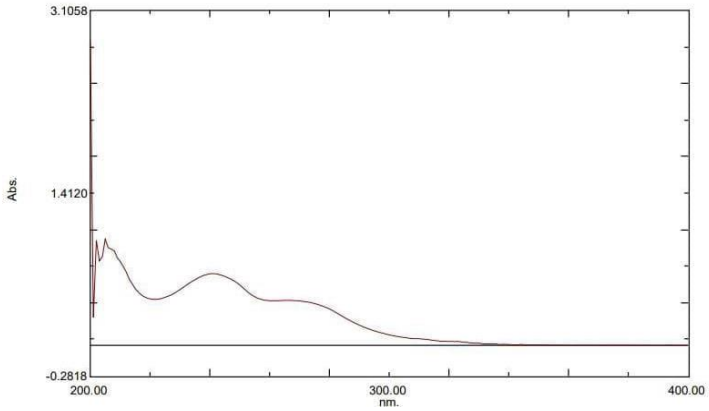

Fig. 1: Absorption maxima of drug.

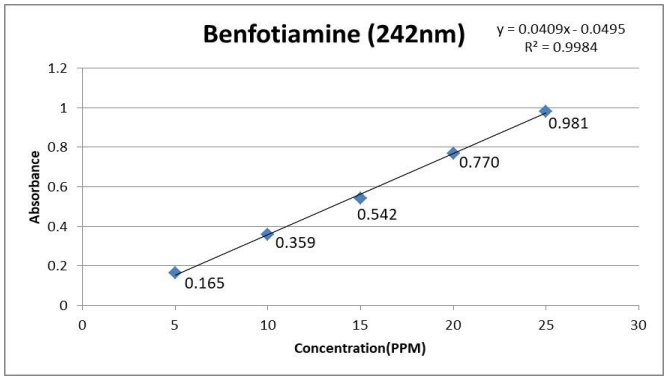

Fig. 2: Calibration Curve.

FTIR Study

Infrared spectroscopy was conducted using FT-IR spectrophotometer and the spectrum was recorded in the wave number region of 4000 to 400 cm-1. The procedure consisted of dispersing the sample (drug alone, mixture of drug and excipients and the optimized formulation) in Potassium bromide and compressed into discs by applying a pressure of 5 tons for 5 minutes in a hydraulic press. The pellet was placed in the light path and the spectrum was recorded which is shown in fig.3.

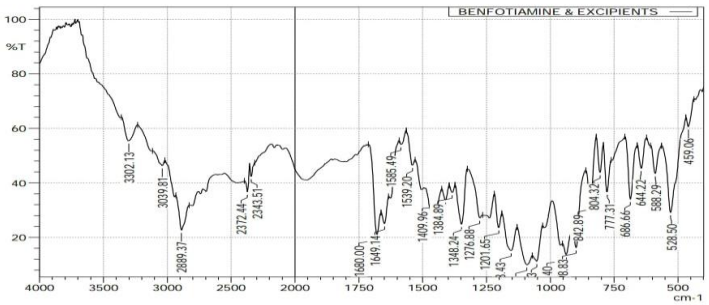

Fig. 3: FTIR of Benfotiamine + Excipients.

Evaluation of Microsponges

As we discuss the method and the equations of evaluation parameter in method and material section we find out the result as per table 7.

Table 7: evaluation of microsponges.

Batches	Practical Yield (%)	Entrapment Efficiency (%)	Particle Size (um)
F1	67.68	78.32	32.11
F2	71.94	82.26	29.91
F3	51.47	64.28	43.85
F4	72.36	81.7	29.79
F5	65.44	76.51	33.15
F6	71.96	81.91	29.9
F7	51.96	65.44	42.45
F8	51.27	64.4	43.55
F9	65.75	76.67	33.19
F10	71.96	81.91	29.9
F11	69.53	79.6	31.83
F12	68.73	78.84	32.48
F13	72.92	81.29	29.5
F14	71.96	81.91	29.9
F15	65.22	75.2	33.56
F16	**74.44**	**83.54**	**29.34**
F17	71.14	80	29.34

Scanning Electron Microscopy

Images were recorded at different magnifications at acceleration voltage of 10 kV using scanning electron microscope which are shown in fig.4.

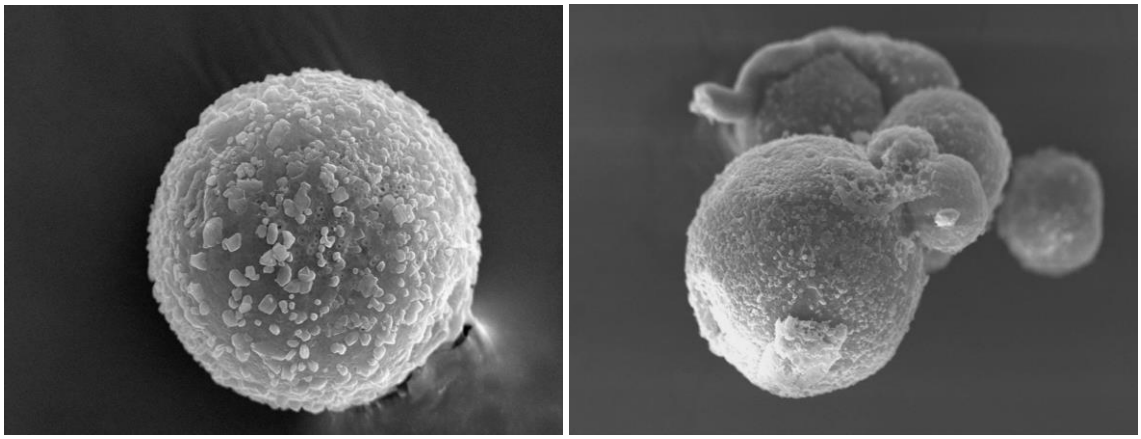

Fig. 4: SEM of microsponges.

Graphical Evaluation

Contour plots were generated for each independent variable (Drug to polymer ratio, Concentration of PEG 4000 and Stirring Speed) to visualize their individual effects on the selected responses, such as percentage yield, entrapment efficiency and particle size. These plots displayed constant contours (z-slices), enabling a two-dimensional representation of the three dimensional response surface. Additionally, 3D surface quadratic plots were created for each variable, providing a deeper insight into their interaction with the responses and highlighting the influence of different factor levels. The 3D plots are shown from fig5-7.

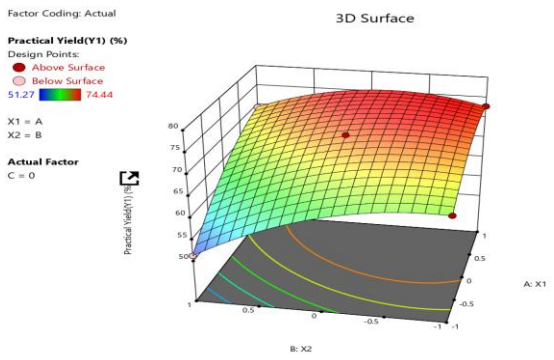

Fig 5: 3D surface plot showing effect on response Y1 % yield.

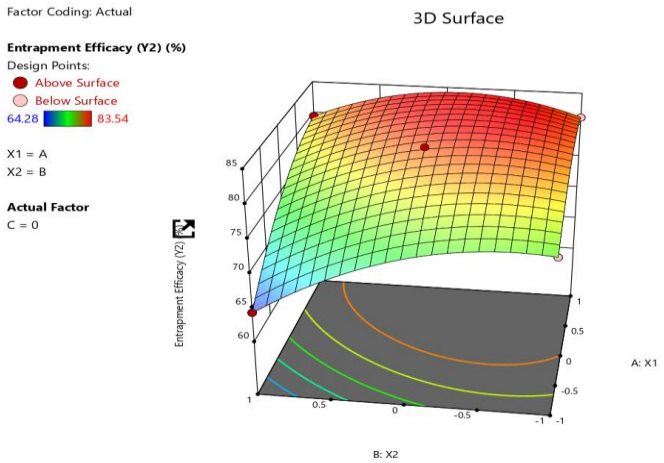

Fig 6: 3D surface plot showing effect on response Y2 Entrapment efficiency.

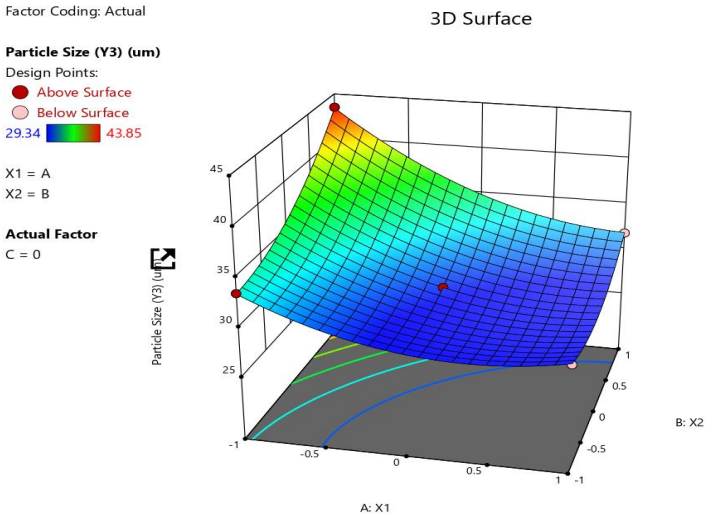

Fig. 7: 3D surface plot showing effect on response Y3 Parctical size.

Check point batch analysis

To validate the accuracy of the design model, a check point batch was selected from the overlay plot for evaluation which is shown in fig.8. This batch was formulated and tested within the experimental domain to ensure model reliability. The observed experimental values of the response parameters were quantitatively compared to the predicted values, and the percentage bias was calculated to assess the deviation between them. The close agreement between experimental and predicted values confirmed the adequacy of the model, ensuring the reliability of the optimization process which is shown in table.8.

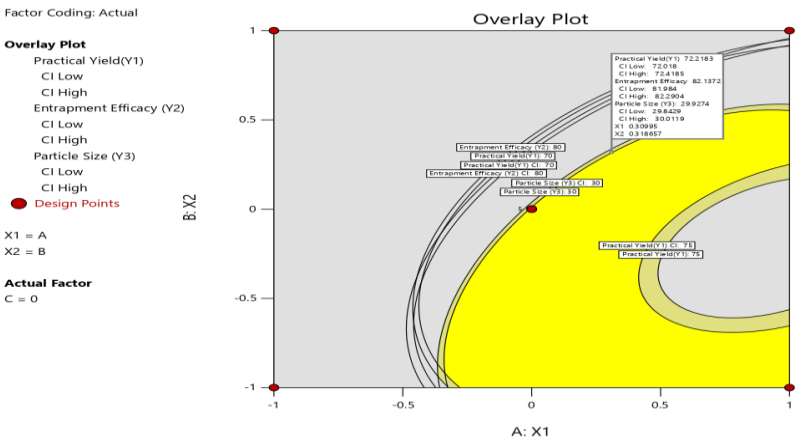

Fig. 8: Overlay plot of checkpoint batch.

Table 8: Result of Check point batch.

Independent Variable			Dependent Variable		
X1	**X2**	**X3**	**Y1**	**Y2**	**Y3**
Benfotiamine:Ethyl cellulose (mg)	Concentration of PEG 4000 (mg)	Stirring Speed (rpm)	Practical Yield (%)	Entrapment Efficiency (%)	Partical Size (um)
Coded Value: 0.309	Coded Value: 0.318	Coded Value: 0	Predicted Value: 72.21	Predicted Value: 82.13	Predicted Value: 29.92
Actual Value:150:346.35	Actual Value:165.9	Actual Value:600	**Observed Data:72.75**	**Observed Data:82.80**	**Observed Data:29.22**

Result of preformulation studies for capsule batch F16

By using the standard formula for performulation study of capsule we observed this result which is shown in table 9.

Table 9: Result of Preformulation study for capsule.

Parameter	Result	Flow characteristics
Angle of Repose (◦)	25.6	Good flow
Compressibility (%)	14.23	Fairly Compressible
Hausners's ratio	1.17	Good flow
Bulk density(g/cm^2)	0.395	-
Tapped density(g/cm^2)	0.489	-

Evaluation of microsponges loaded Capsules of batch F16:

By using the method as we diacuss previously we evaluate batch F16 for weight variation and disintegration time whose result is given in table 10.

Table 10: result of evaluation of capsule.

Parameter	Result
Weight variation	Average weight 217.8 mg
Disintegration time	14.7 min

Dissolution test

At 8 hour 97.1±1.3 % drug release is there which is shown in fig.9.

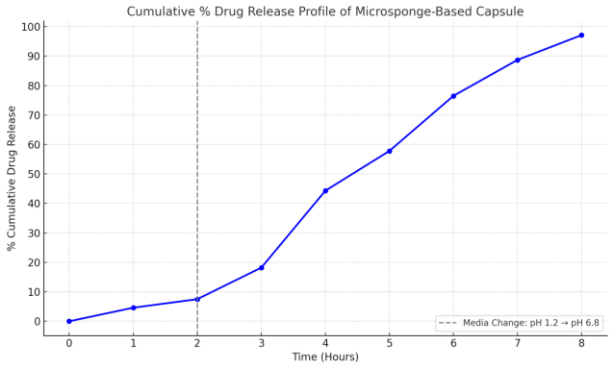

Fig. 9: Graphical representation %CDR of microsponges based capsule.

In vitro drug release

Ratio of in vitro drug release is shown in fig.10

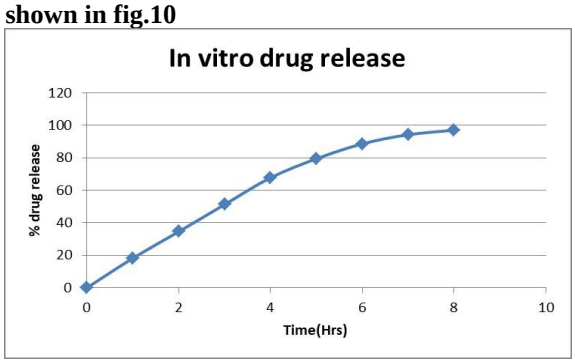

Fig 10: Graphical representation of in vitro drug release.

Stability Study

A stability study was conducted to assess the stability profile of the developed formulation under accelerated conditions (40°C ± 2°C / 75 ± 5% RH). The condition of drug is shown in table.11.

Table 11: Result of stability study.

Conditions	**40℃±2℃/ 75 ± 5 % RH**	
Evaluation parameters	**Initial observation**	**After 1 month**
Appearance	White powder in capsule	white powder in capsule
Disintegration time (min) (n=3)	14.7± 0.5	15.2±0.3
%CDR in phosphate buffer pH6.8 (8hrs) (n=3)	97.1± 1.3	96.3± 0.46

CONCLUSION

In conclusion, the microsponge-based capsule formulation of Benfotiamine successfully demonstrated enhanced drug solubility and sustained release characteristics. This approach offers a promising and patient-compliant alternative to conventional oral tablet formulations, improving therapeutic outcomes in the management of diabetic neuropathy.

ACKNOWLEDGEMENT

The Author would like to immensely grateful to lord shree Swaminarayan and Aacharyas of Swaminarayan sect shree Ajedraprasadji maharaj and shree Madhvedraprasadji maharaj for his divine grace and blessings and we like to thank Shree Swaminarayan Sanskar Pharmacy College, Zundal, Gandhinagar to provide facility, resources and environment to conduct the work and complete it easily.

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