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Mouth Dissolving Film of Antidiabetic Drug: Formulation & Optimization by 3^2 factorial design

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Abstract : The objective of the present study was to formulate and evaluate Mouth Dissolving film of Voglibose. Voglibose with t1/2 4 hrs and absolute oral bioavailability about 60-65%,are Alpha-glucosidase inhibitors that act as competitive inhibitors of enzymes needed to digest carbohydrates: specifically alpha-glucosidase enzymes in the brush border of the small intestines. The films were prepared using solvent casting method using HPMCe-15, PVA as polymer and Polyethylene glycol 400 as plasticizer. HPMCe-15 was selected as polymer on the basis of their film forming property and inertness, while Aspartame is used as a sweetening agent, Pineapple flavor is used as a flavouring agent and to analyse the usefulness of DOE in the development and optimization of a Mouth Dissolving film of a model drug employing 3^2 full factorial statistical design. The drug-polymer compatibility study was carried out to determine the interactions, if any between the drug and the polymers used in the study. The FTIR and DSC study revealed that, polymers and excipients used were compatible with drug. Evaluation of mouth dissolving film for physical appearance, surface texture, thickness measurement, weight uniformity, drug content, folding endurance, surface pH, *In vitro* disintegration time, % Moisture Content, % Moisture uptake, % Moisture uptake as well as *Ex-vivo* permeation studies. Formulation MDF3 disintegrated in 27.46±0.5 seconds. The formulation MDF3 showed maximum % drug release of 94.68±1.02% in 10 minutes and concluded that MDF3 was superior and effective in achieving patient compliance. Optimized MDF3 batch when subjected to stability at 40± 2^0C temperature with relative humidity 75±5% for three months, indicating there was no degradation and change in film.

Keywords : Voglibose, Mouth dissolving Film, HPMCe15, PVA, PEG 400, FTIR, DSC, SEM, 3^2 Factorial Design.

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Introduction

The conventional delivery system shows various problems like gastro intestinal irritation, very low concentration of drug in blood and incomplete absorption of drug from gastro-intestinal tract, and mainly poor patient compliance[1,2]. To avoid such problem and to achieve maximum therapeutic efficacy[3,4], preparation of mouth dissolving film of water soluble drug is better alternative which gives improved patient compliance and rapid onset of action due to disintegration of film in saliva and pre-gastric absorption of drug. In present study attempt has been made to develop mouth dissolving film of antidiabetic (Voglibose) drug and its optimization by 3^2 Factorial design with objectives to avoid first pass metabolism effect with rapid onset of action as well as to formulate stable, effective and optimum dosage from by studying effect of different excipients in the formulation so as to improve specific distribution of the drug.

Materials and Methods

Materials

Voglibose was received as gift sample from ZIM Laboratories Ltd. Pharma Nagpur. Hydroxy Propyl Methyl Cellulose 15cps (Hyperomellose) from S. D. Fine Chem Ltd. Mumbai, whereas Poly vinyl alcohol, Aspartame and PEG-400were procured from Loba Chemicals, Mumbai.

Methods

Organoleptic Properties

Organoleptic properties such as colour, odour, appearance and melting point were determined.

Estimation of Voglibose by UV Spectrophotometer

UV spectroscopic determination of $\lambda_{max}$of Voglibose

Stock solution of Voglibose sample was prepared by dissolving 0.5 mg of Voglibose in 100 mL of phosphate buffer pH6.8 to get 100µg/ml. Then these solutions were scanned on UV in the wavelength range from 200-400nm.

Standard Calibration Curve of Voglibose

A series of working solutions of concentration ranging from 5.0-30.0 µ/mL were prepared from stock solution. $\lambda_{max}$was observed from the absorption spectrum. The absorbance of the solution was measured against pH 6.8 phosphate buffer as blank on UV spectrophotometer at 282 nm. Calibration curve was plotted by concentration on X-axis and absorbance on Y-axis. The calibration curve was used for the estimation of drug content in formulation and for e*x-vivo* diffusion studies[5].

Drug Excipient Compatibility Study by Fourier Transform Infrared Spectroscopy

Voglibose, polymers and physical mixture of drug and polymers were further characterized by FT-IR spectrophotometer FTIR-8400S, CE (Shimadzu, Japan). The samples were previously triturate and mixed thoroughly with potassium bromide in 1:100 (Sample:KBr) ratio. KBrdiscs were prepared by compressing the powders at a pressure of 5 tons for 5 min in hydraulic press[6,7]. Scans were obtained at are solution of $4cm^{-1}$ from 4000 to $400cm^{-1}$.

Preparation of mouth dissolving film

Mouth-dissolving films of Voglibose were prepared by the solvent-casting method[8,9]. The polymer (HPMCe-15) was weighed accurately and soaked in sufficient amount of distilled water for 2hrs. PVA was weighed accurately, dissolved in sufficient amount of distilled water and heated at 60^0C with continuous stirring until uniform dispersion was formed. Both the polymer solutions were mixed together. The soaked polymers was made to a uniform dispersion. Aqueous solution I was prepared by adding plasticizer to above polymeric solution and was allowed to stir. Aqueous solution II was prepared by dissolving Voglibose in specific

proportion in remaining amount of distilled water. Both aqueous solutions I and II were mixed and was subjected to sonication for removal of air bubbles. The solution was then casted on film former machine at 40-45 ^{0}C temp of machine until films were totally dried. The dried films were cut in desired size and were evaluated and these dried films, wrapped in aluminum foil, labeled and stored in desiccator for further evaluation.

Dose calculation for Voglibose[10]

Since the dose of Voglibose is 0.3 mg. Therefore amount Voglibose required in 4cm^2 of film is 0.3 mg.

Area of square	= (side)^2
Total Area of film	= 0.3×40 cm^2= 12cm^2
Area of drug loaded film	= 2×2 cm= 4cm^2
4cm^2 contains	= 0.3 mg
(12) cm^2 contains	= 1000mg of MTS

Optimization of Mouth Dissolving film by factorial design[10]

The objective of the present investigation was to observe the combined effect of the concentration of Polymer as well as the concentration of Plasticizer on the disintegration time, *In-vitro* % drug release and folding endurance for obtaining the optimized oral dispersible film. (Dependent Responses /objective functions.)To reduce the computational complexities, the components were subjected to 2 independent variables namely,

Concentration of Polymer(X1) = 2, 4, 6%

Concentration of Plasticizer (X2) = 2, 3, 4%

The approximate appropriate levels of these independent variables were chosen from the data selection of polymer and plasticizer.

It is assumed that the independent variables affects the responses in a linear as well as quadratic manner and a possibility of interaction effect of independent variables are also taken into consideration. This assumption is necessary to develop a mathematical model which can be tested for significance of contribution of various independent variables. Hence, it becomes essential to use a factorial design with 3 levels to estimate curvature in response (i.e. 3^2 factorial with total no. of experiments = 9). To save time, single block design with zero (0) replication has been preferred. The experimental grid was coded for ease of representation in Table 2 and Table 3.

6.12 Analysis of Mouth Dissolving film data by design expert software

The obtained data was subjected to statistical analysis for the purpose of:

i. Assessment of suitable Model

To evaluate the significant factors and their contribution, significance is tested using ANOVA and is represented with surface response chart. To get clarity for this purpose, confidence level is set to 95 % with level of 0.50.

ii. Selecting Significance Level of Independent Variables

A typical problem in product development is to find out a set of conditions or levels of input variables that produces the most desirable product in terms of response on output variable. The general procedure involves predicting response on dependent variable by finding the observed response using equation based on level of independent variables and finding the level of X variable that simultaneously produces most desirable response on Y variable. The modelling provides the significance levels of various factors. With this, it becomes possible to ignore insignificant effects which can be pulled together in error term.

iii. Representation of Effect of Individual Independent Variable

The best representation of the effect of individual independent variable can be done by mean plot. Hence, mean plots of X_1, and X_2 were generated. These provide the idea of extent of direction of effect which was helpful in setting optimization limit**.**

iv. Converting Developed Model for Predictability

After the development of model generated for every response function, desirability profiling was done. The relationship between predicted responses on one or more dependent variables and the desirability of response is called desirability function. Profiling of desirability of response involves specific desirability function for each dependent variable by assigning predicted value as score from zero (very undesirable) to one (very desirable). Desirability profile consists of a series of graphs, one for each independent variable of overall desirability score at different level of one independent variable whereby the levels of other independent variables were held to a constant at specific value.

Evaluation of Mouth Dissolving film[11-14]

Physical appearance and surface texture

This parameter was checked simply by visual inspection of films and evaluation of texture by feel or touch.

Thickness measurement

The thickness of each film was measured at five different locations (centre and four corners) using Digital VernierCalliper, with an accuracy of 0.001. Data was represented as a mean ± SD of triplicate determinations.

Weight uniformity

The film (4 cm^2) was cut at three different places. The weight of each film strip was taken on a digital weighing balance. Average weight and weight variation was calculated.

Drug content

The area of 2 × 2(4cm^2) of the prepared film was cut from different area of each film and dissolved in 100 mL of simulated saliva with occasional shaking. Filtration was carried out to remove insoluble residue. The absorbance is measured on double beam UV spectrophotometer (Shimadzu UV-1700) at 282nm.

Folding endurance

The folding endurance was expressed as the number of folds (number of times the film is folded at the same place) required to break the specimen or to develop visible cracks. This also gives an indication of brittleness of the film. A strip of 2 × 2 cm diameter (an area of 4 cm^2) was subjected to folding endurance by folding the film at the same place repeatedly several times until a visible crack was observed, and the values were reported

Surface pH

Surface pH of the films was determined in order to investigate the possible side effects due to change in pH *in vivo*, since an acidic or alkaline pH may cause irritation to the buccal mucosa. The film was placed in a Petri dish and moistened with 1 ml of distilled water and kept for 1 h. pH was noted with the electrode of the pH meter. The average of three determinations for each formulation was done.

***In vitro* disintegration time**

The film size required for dose delivery (2×2 cm^2) was placed in a glass petridish containing 10 ml of distilled water. The time required for the film to break was noted as *in vitro* disintegration time. Test was

conducted in triplicates.

% Moisture Content

This test was also carried to evaluate the integrity of films at dry condition. Film of 4 cm^2 area was cut and weighted accurately and kept in a desiccator containing activated silica. The films were weighed regularly until a constant weight was obtained. Percentage moisture content of film was determined as follows.

$$\textbf{Percent moisture content} = \frac{\textbf{[Initial weight-Final weight]}}{\textbf{Final weight}} \textbf{ X 100}$$

% Moisture uptake

The dried films were weighed and placed in a desiccator containing 200ml of saturated solution of potassium chloride (84% relative humidity) at room temperature. The percentage moisture uptakes of the films were calculated. The percent moisture uptake was calculated by using the following formula,

$$\textbf{Percent moisture uptake} = \frac{\textbf{[Initial weight-Final weight]}}{\textbf{Final weight}} \textbf{ X 100}$$

***In-vitro* dissolution study**[15]

The phosphate buffer pH 6.8 was taken as the dissolution medium to determine the drug release. The dissolution profile of quick release films of Voglibose was carried out in USP type I (basket apparatus) (Electolab, Mumbai) containing 900 ml of the phosphate buffer pH 6.8. The film was placed in the basket, maintained at 37±0.5°C and the agitation speed was 50 rpm. Aliquots (5 ml) of the dissolution medium were withdrawn at 1, 2, 4, 6, 8, 10 and 12 minutes time intervals and the same amount was replaced with the fresh medium. Samples were assayed spectrophotometrically at 284 nm. The cumulative percentage drug release was expressed as each value is the mean ± SD, n = 3 determinations.

***Ex-vivo* permeation studies throughgoatbuccal mucosa of Mouth Dissolving Film** [15]

Ex-Vivo diffusion study of Voglibose was performed using Franz diffusion cell (receptor compartment volume containing 45 mL, radius 2.4 cm).The receptor compartment was filled with 6.8 pH phosphate buffer and magnetic bead was placed inside the cell. The buccal pouch of the freshly killed goat was procured from the local slaughter house. The buccal mucosa was excised and trimmed evenly from the sides and then washed in 6.8 pH phosphate buffer and used immediately. Contact with the diffusion medium was ensured by removing bubbles and adjusting level of medium. 20 mg of Voglibose was accurately weighed and uniformly spread on the mucosa. The donar compartment is fixed with rubber. Then assembly was held over magnetic stirrer by means of a stand. The solution was stirred for a 30 min and 1 ml of samples from receptor compartment was withdrawn at suitable time interval which was then replaced with 1 ml of pH 6.8 phosphate buffer. The percentage of Voglibose permeated was determined by measuring the absorbance in UV Visible spectrophotometer at 282 nm. Same procedure was followed for optimized MDF3 batch.

Differential Scanning Calorimetry (DSC)[17]

Thermal properties of pure Voglibose and the optimized formulation were analyzed using DSC [8]. The samples were heated in a hermetically sealed aluminum pans. Heat runs for each sample were set from 30^0C to 350^0C at a heating rate of 10^0C/min, using nitrogen as blanket gas.

Scanning Electron Microscopy (SEM)[17]

Morphology of optimized formulation MDF3 was characterized by using Scanning Electron Microscopy.The samples weremounted on scanning electron microscope stubs with double-sided carbon tape and observed under 370701-14, S-3700, Scanning Electron Microscope.

Stability study[17]

The optimized formulation (MDF3) was evaluated for stability studies and stored at 40^0C± 2^0C/75% ± 5% RH) for 3 months and were analyzed for physical appearance, disintegration time, folding endurance and *in-vitro* release rate after 1 month for three months. It was found that films retained its physical appearance and there was no much significant change in the values of disintegration time, drug content and *in-vitro* release studies.

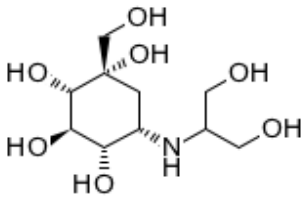


Fig. 1 Structure of Voglibose

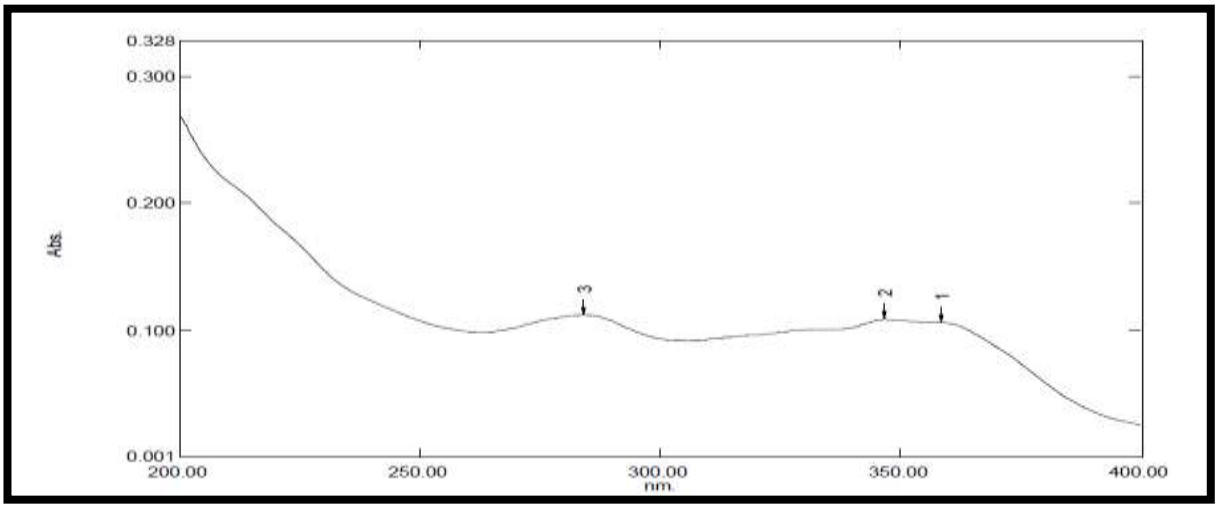


Fig. 2: Absorption spectra ofVoglibose (λ_{max}) in pH 6.8 Phosphate buffer

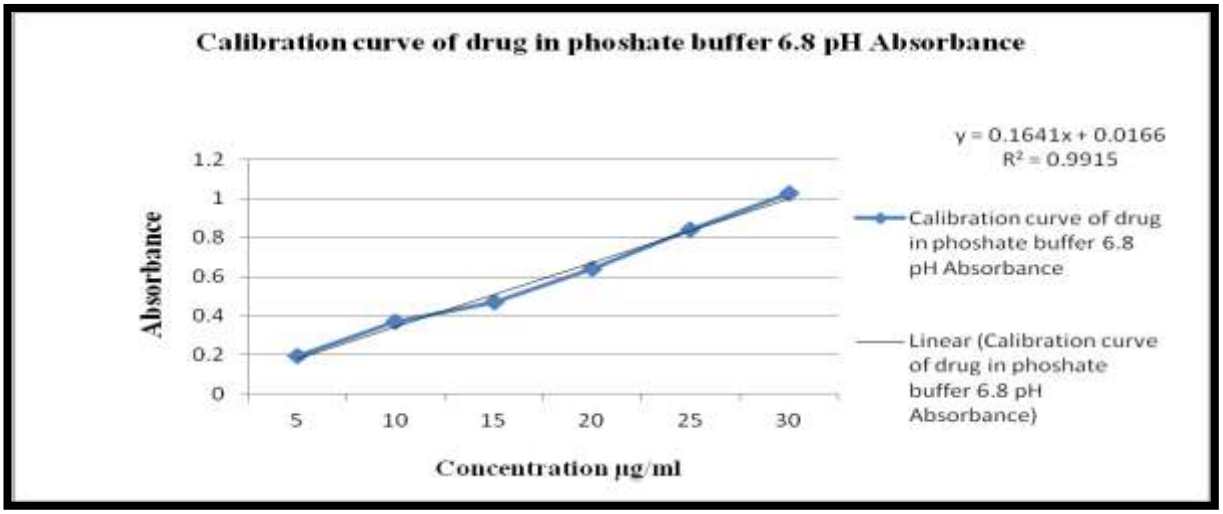


Fig. 3: Standard calibration curve for Voglibose in Phosphate buffer pH 6.8 at λ_{max}282nm

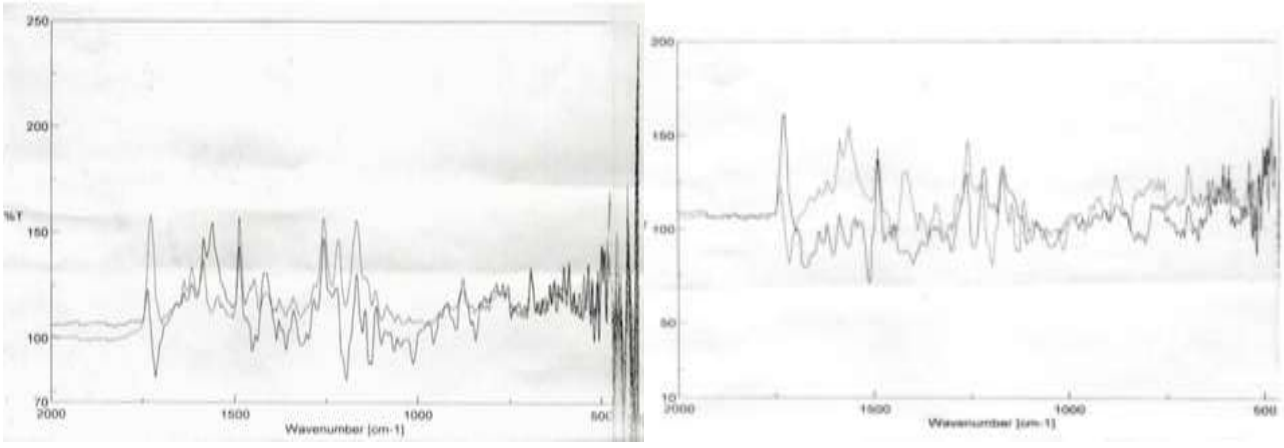
Results and Discussion

Voglibose(Fig. 1) was evaluated for as colour, odour, appearance and melting point and melting point was found to be complied with specifications given in the Indian pharmacopoeia. Voglibose was observed to be white to off white colored powder, odorless and tasteless powder with melting point of 210^0C-212^0C. The solution of 10µg/ml in Phosphate buffer pH 6.8was prepared and scanned in the range of 200-400 nm and wavelength maxima (Fig.2) was found to be 282 nm. Standard calibration curve of Voglibose (Fig. 3) and absorbance values of different concentrations of Voglibose were determined (Table 1).

Table 1: Absorbance Values of Different Concentration of Voglibose in Phosphate Buffer Ph 6.8

Concentration (µg\ml)	Absorbance
0	0
5.0	0.196±0.07
10.0	0.368±0.03
15.0	0.472±0.03
20.0	0.639±0.06
25.0	0.839±0.01
30.0	1.029±0.04

The interaction studies of drug with polymers suggest no incompatibility revealed from FTIR studies. Voglibose showed retention of basic characteristics peaks as shown in FTIR of drug and excipients. The typical FTIR curves as shown in Fig.4[A], [B] and [C].



[A] **[B]**

[C]

Fig. 4: FTIR of [A] Voglibose and poly vinyl alcohol, [B] Voglibose and HPMCe-15,[C] Voglibose and PEG-400

Fig. 5: Mouth Dissolving film of Voglibose

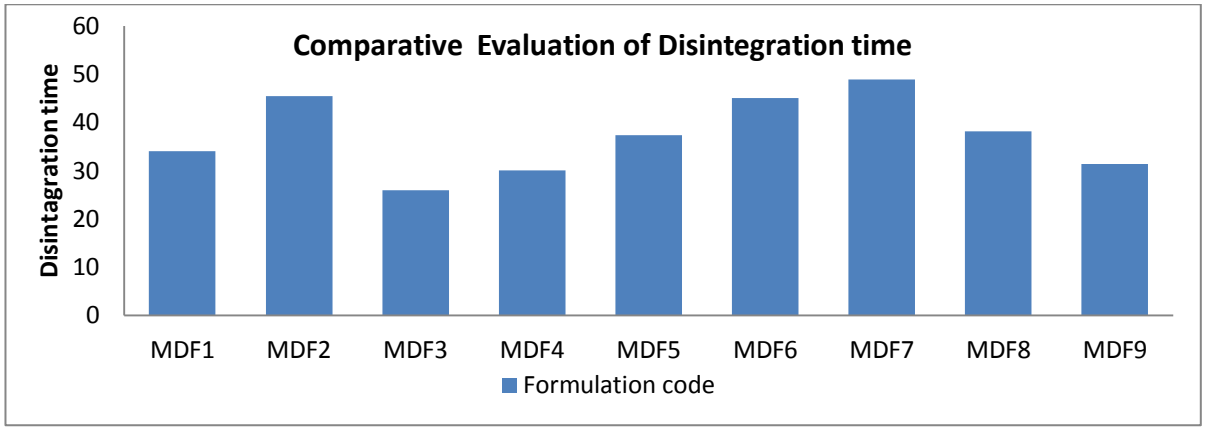


Fig. 6: Comparative Evaluation of Disintegrating Time

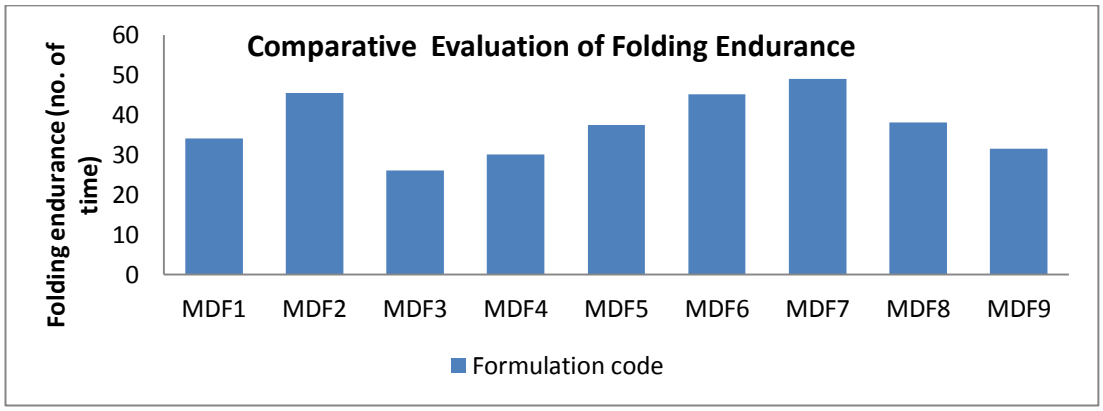


Fig. 7: Comparative Evaluation of folding endurance

The films of Voglibose were prepared in various batches MDF1 – MDF9 (Table 2) with usefulness of DOE in the development and optimization using two variablesi.e Concentration of HPMC-15 and Concentration of PEG 600 (Table 3 and Table 4, Table 5 & Table 6) were studied at three levels i.e Disintegration time (Table 7, Table 8), In-vitro % drug release (Table 9, Table 10) and Folding endurance (Table 11, Table 12 & Table 13) thus, a 3^2 full factorial design (Table 5) was applied and nine different formulations were developed by solvent casting method. Prepared batches were evaluated for physical appearance as a transparent with smooth surface texture (Fig. 5) whereas weight uniformity in the range of 22.13±0.18mg to 26.54±0.20 mg, maximum surface pH 6.80±0.14, thickness from 0.023±0.0057 mm to 0.036±0.0011 mm, drug content 91.73±0.29% to 97.29±0.32%, moisture content 1.98±0.12% to 2.68±0.18% and moisture uptake2.20±0.09% to 3.48±0.02% as shown in Table 14, Fig. 6 and Fig. 7.

Table 2: Formulation of Voglibose Mouth Dissolving Film as Per 3^2 Factorial Design

Batches code	Voglibose (mg)	Polymer HPMCe15:PVA	Polyethylene Glycol 400 (ml)	Aspartame (mg)	Pineapple Flavour (mL)	Water (ml)
MDF1	0.3	400:200	0.5	10	Qs	20
MDF2	0.3	400:200	1	10	Qs	20
MDF3	0.3	400:200	1.5	10	Qs	20
MDF4	0.3	600:300	0.5	10	Qs	20
MDF5	0.3	600:300	1	10	Qs	20
MDF6	0.3	600:300	1.5	10	Qs	20
MDF7	0.3	800:400	0.5	10	Qs	20
MDF8	0.3	800:400	1	10	Qs	20
MDF9	0.3	800:400	1.5	10	Qs	20

Table 3: Formulation Factors, Concentrations and Levels

Coded Values	Actual Values (%)		Response		
	X_1 (Conc. of HPMC-15)	**X_2 (Conc. of PEG 600)**	**Y_1**	**Y_2**	**Y3**
-1	2	2	Disintegration time(sec)	*In-vitro* %drug release (%)	Folding endurance (No. of times)
0	4	3			
+1	6	4			

Table 4: Factor Combination as Per the Experimental Design for Preparation of Mouth Dissolving Film

Variable level	Batch code								
	MDF1	**MDF2**	**MDF3**	**MDF4**	**MDF5**	**MDF6**	**MDF7**	**MDF8**	**MDF9**
X1	0	+1	-1	-1	0	+1	+1	0	-1
X2	-1	0	+1	-1	0	-1	+1	+1	0

Table 5: Composition and Responses of Full Factorial Batches Mdf1 To Mdf9

			Responses		
Formulation Code	**Variable in coded form**		**Disintegration time(sec)**	***In-vitro* drug release (%)**	**Folding endurance (No.of times)**
	X_1(%)	**X_2(%)**			
MDF1	0	-1	34.00±0.35	88.69 ±1.02	146
MDF2	+1	0	45.50±0.15	86.71±1.42	160
MDF3	-1	+1	26.00±0.14	94.68±1.02	172
MDF4	-1	-1	30.05±0.42	94.25±1.03	154
MDF5	0	0	37.41±0.23	91.57±0.89	149
MDF6	+1	-1	45.15±0.12	88.73±1.12	143
MDF7	+1	+1	49.00±0.12	85.56±1.32	166
MDF8	0	+1	38.13±0.26	92.72±1.18	162
MDF9	-1	0	31.41±0.14	93.12±1.36	169

Coded Value	**Actual Value (%)**	
	Amount of HPMCe-15 (X_1)	Amount of Polyethylene glycol 400(X_2)
-1.000	2	2
0.000	4	3
+1.000	6	4

Table 6: Design Summary

Factor	Name	Units	Type	Low Coded	High coded	Mean
X_1	HPMCe-15	%	Numeric	-1=2	1=6	4
X_2	Polyethylene Glycol 400	%	Numeric	-1=2	1=4	3

Table 7: Response Summary

Response	Name	Units	Observations	Analysis	Mini-mum	Maxi-mum	Mean
Y_1	Disintegration time	Seconds	9	Polynomial	26	49	37.18
Y_2	In-vitro % drug release	%	9	Polynomial	85.56	94.68	90.67
Y_3	Folding endurance	No. of times	9	Polynomial	143	170	157.77

Table 8: Anova for Disintegration Time

Source	Sum of square	Degree of freedom	Mean square	F value	P value	Level of significance
Model	437.33	5	87.47	11.58	0.0355	Significant
A-conc.of HPMCe-15	416.67	1	416.67	55.15	0.0051	
B-conc.of Polyethylene glycol 400	2.67	1	2.67	0.3529	0.5943	
XY	16.00	1	16.00	2.12	0.2416	
X_1	2.00	1	2.00	0.2647	0.6424	
X_2	0.0000	1	0.0000	0.0000	1.0000	
Residual	92.81	3	7.56			
Cor total	460.00	8				

Table 9: Anova for *In-Vitro* % Drug Release

Source	Sum of square	Degree of freedom	Mean square	F value	P value	Level of significance
Model	74.13	2	37.06	14.57	0.0050	Significant
HPMCe-15	73.85	1	73.85	29.03	0.0017	
B-conc. of Polyethylene glycol 400	0.2774	1	0.2774	0.1090	0.7525	
Residual	15.26	6	2.54			
Cor total	89.39	8				

Table 10: Anova for Folding Endurance

Source	Sum of square	Degree of freedom	Mean square	F value	P value	Level of significance
Model	707.33	2	353.67	12.32	0.0075	Significant
A-conc.of HPMCe-15	66.67	1	66.67	2.32	0.1783	
B-conc. of Polyethylene glycol 400	640.67	1	640.67	22.32	0.0032	
Residual	172.22	6	28.70			
Cor total	879.56	8				

Table 11: Optimization of Mdf Formulation

Constraint			
Name	**Goal**	**Lower limit**	**Upper Limit**
HPMCe-15	Minimum	2	6
Polyethylene glycol 400	Minimum	2	4
Disintegration time	Minimum	26	49
In-vitro %drug release	Maximum	85.56	94.68
Folding endurance	In range	143	170

Table 12: Solutions for Numerical Optimization of Mouth Dissolving Film

Sr. No	Conc. Of HPMCe-15	Conc. of Polyethylene glycol 400 (%)	Disintegration time(sec)	*In-vitro* %drug release (%)	Folding endurance (No. of times)	Desirability	
1	2	2	27	94.58	165	0.947	Selected
2	2	2.10	28	94.83	168	0.910	
3	2	2.28	29.46	94.86	172	0.896	

Table 13: Comparison Of Predicted And Experimental Value

Responses	Design expert MDF3	
	Predicted	Experimental
Disintegration time(sec)	27	27.46
In-vitro %drug release (%)	94.58	94.68
Folding endurance (No. of times)	165	168

Table 14: Evaluation of Mouth Dissolving Film

Batches Code	Drug content (%)±SD	Moisture content (%)±SD	Moisture uptake (%)±SD	Weight uniformity (mg) ±SD	Surface pH ±SD	Thickness (mm) ±SD
MDF1	94.03±0.24	1.89±0.17	3.05±0.20	24.45±0.5	6.67±0.08	0.023±0.0017
MDF2	91.73±0.29	2.68±0.18	2.44±0.14	23.40±0.10	6.65±0.12	0.033±0.0037
MDF3	95.28±0.28	1.97±0.10	2.20±0.09	22.13±0.18	6.80±0.14	0.020±0.0000
MDF4	92.23±0.40	2.09±0.08	2.52±0.04	23.43±0.26	6.76±0.17	0.036±0.0011
MDF5	97.14±0.37	1.79±0.22	2.25±0.19	23.65±0.63	6.54±0.18	0.023±0.0047
MDF6	97.29±0.32	3.26±0.15	2.36±0.15	22.75±0.28	6.80±0.14	0.036±0.0017
MDF7	97.18±0.52	2.45±0.06	3.48±0.02	24.65±0.53	6.53±0.12	0.026±0.0051
MDF8	94.45±0.48	1.98±0.12	2.45±0.08	26.54±0.20	6.66±0.21	0.043±0.0021
MDF9	95.94±0.87	1.26±0.14	2.82±0.12	24.02±0.28	6.59±0.17	0.040±0.010

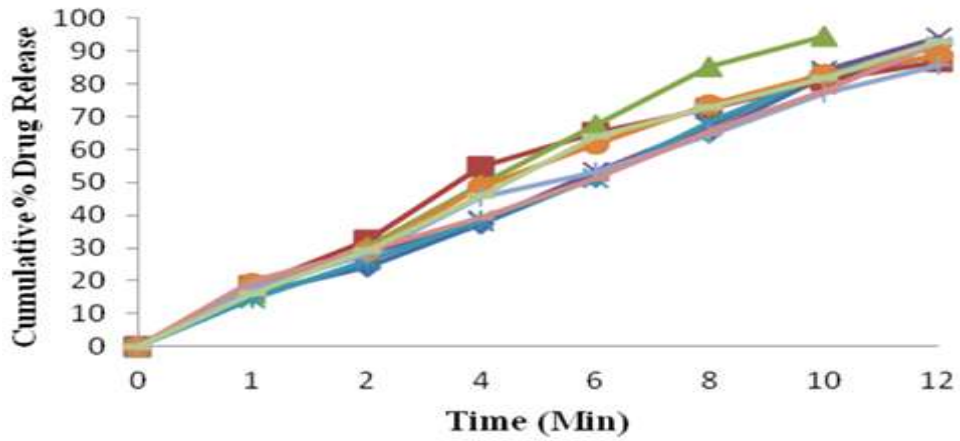


Fig. 8:*In-vitro* release profile of Voglibose in pH 6.8 Phosphate Buffer

Fig. 9: Permeation study assembly

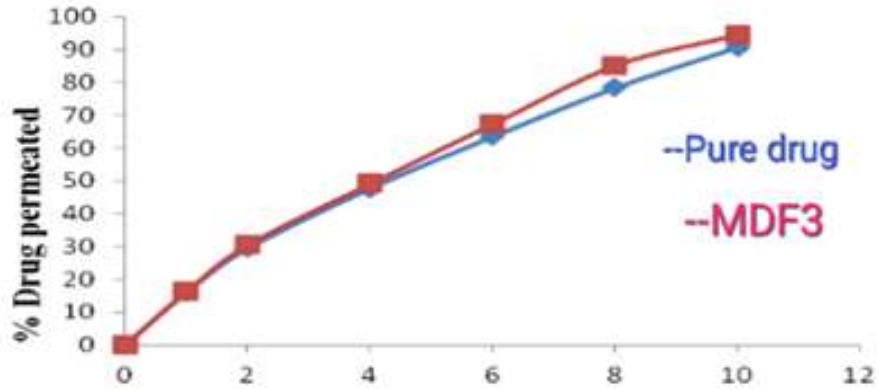


Fig. 10: *Ex-vivo* permeation study

Table 15: In-Vitro Drug Release Study of Voglibose Mouth Dissolving Film (MDF1-MDF9)

Time (min)	Percentage drug released								
	MDF1	**MDF2**	**MDF3**	**MDF4**	**MDF5**	**MDF6**	**MDF7**	**MDF8**	**MDF9**
0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
1	16.20± 1.10	18.41± 0.89	16.30 ± 1.2	17.31± 1.53	14.39 ±1.14	19.29± 0.35	17.54± 1.4	20.01± 0.28	16.08± 1.6
2	24.32± 0.32	32.25± 1.01	30.50 ± 1.25	28.41± 1.4	26.21± 1.26	29.11± 1.5	28.12± 1.2	29.4 ±1.49	29.30± 1.5
4	37.20± 1.02	54.78± 0.32	49.20 ± 1.35	38.32± 0.97	38.41± 1.74	48.73± 0.56	45.42± 1.09	39.25± 1.21	45.70 ±1.51
6	51.60± 1.26	65.23± 0.85	67.40 ± 1.22	53.40± 1.12	51.36± 1.1	61.57± 1.16	53.13± 0.48	51.37± 1.32	64.13± 1.6
8	65.60 ±1.41	72.58± 1.13	85.30 ± 1.58	67.32± 1.17	68.43± 0.24	73.71± 1.09	64.45± 0.90	65.45± 0.98	73.08± 1.24
10	82.03± 1.32	81.06± 1.36	94.68± 1.02	84.12 ±0.96	83.08 ±1.21	83.01± 1.78	77.11± 1.2	78.04± 1.15	81.67± 1.42
12	88.69 ±1.02	86.71± 1.42	-----	94.25 ±1.03	91.57 ±0.89	88.73± 1.12	85.56± 1.32	92.72± 1.18	93.12± 1.36

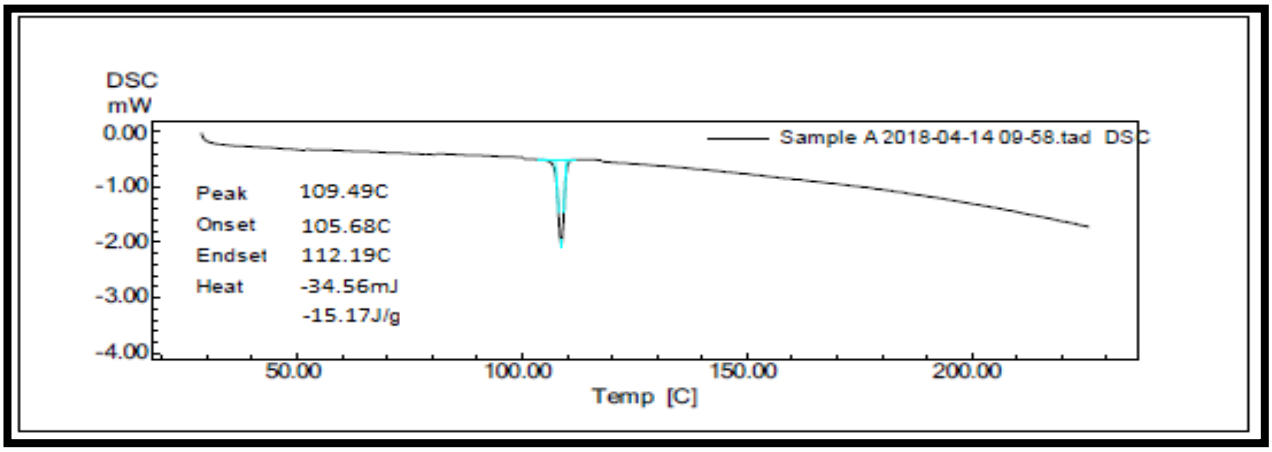
Table 16: *Ex-Vivo* Drug Permeation Data of Optimized Formulation Mdf3

Time (min)	Pure drug (% drug permeated)	MDF3 (% drug permeated)
0	0	0
1	16.11	16.30
2	29.51	30.50
4	47.76	49.20
6	63.56	67.40
8	78.43	85.30
10	90.8	94.68

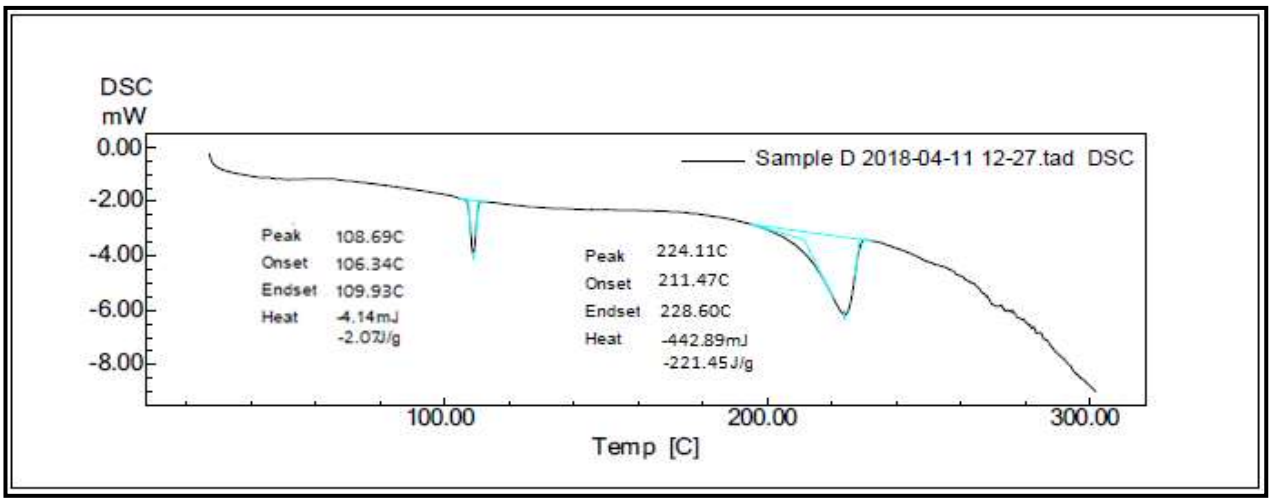
In vitro dissolution study of prepared film namely MDF1-MDF9 (Table 15, Fig. 8) were carried out. Batch MDF3 releases Voglibose early i.e. within 10 minutes in 94.68±1.02 %, whereas all other releases Voglibose up to twelve minutes and hence MDF3 promisingly considered as optimized batch. Ex-vivo

permeation study using Franz diffusion cell (assembly set up in Fig. 9), revealed increased in permeation of Voglibose (94.68%) from MDF3 than Voglibose per se as shown in Table 16 and Fig. 10.

Differential scanning calorimetry (DSC) can be used to investigate and predict physicochemical interaction between components in a formulation thus helps in selecting suitable chemically compatible excipients. Any interaction would be indicated in the thermogram of a mixture by the appearance of one or more new peaks or the disappearance of one or more peaks corresponding to those of the components. Any polymorphic change in the drug causes changes in the melting point, bioavailability and release kinetics. The DSC thermogram of Voglibose (Fig 11A) records endothermic peak corresponding to the melting point of drug (109.49^0C) whereas Voglibose Loaded optimized formulation, MDF3 (Fig 11B), showed lesser melting point (108.69^0C), suggesting the possibility of interaction. Scanning Electron Microscopy of MDF3 was homogenous with rough surface, which may be due to the presence of drug on surface (Figure 12).



[A]



[B]

Fig. 11: DSC Chromatogram of [A] Voglibose[B] Drug Loaded optimized formulation

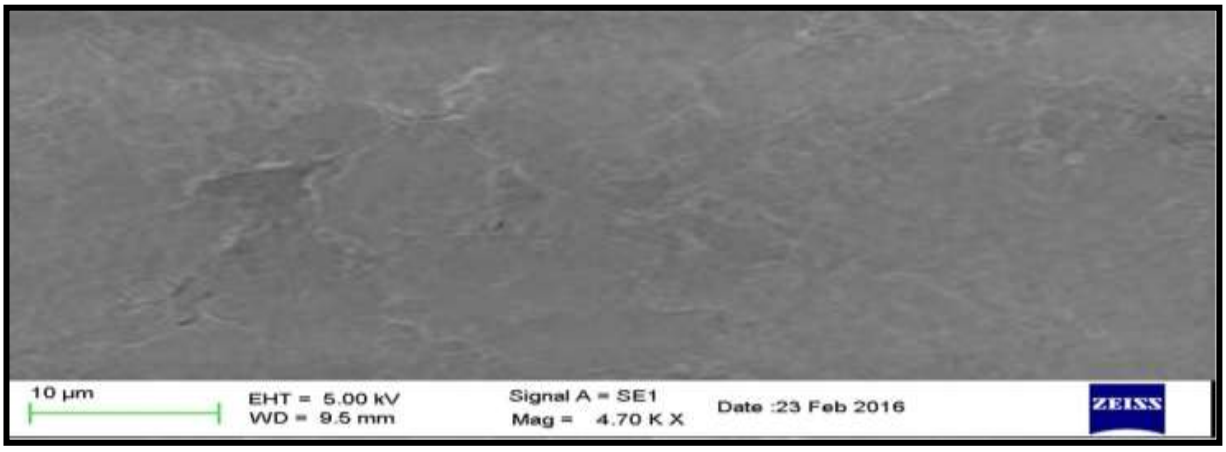


Fig. 12: Scanning electronic microscopy of MDF3

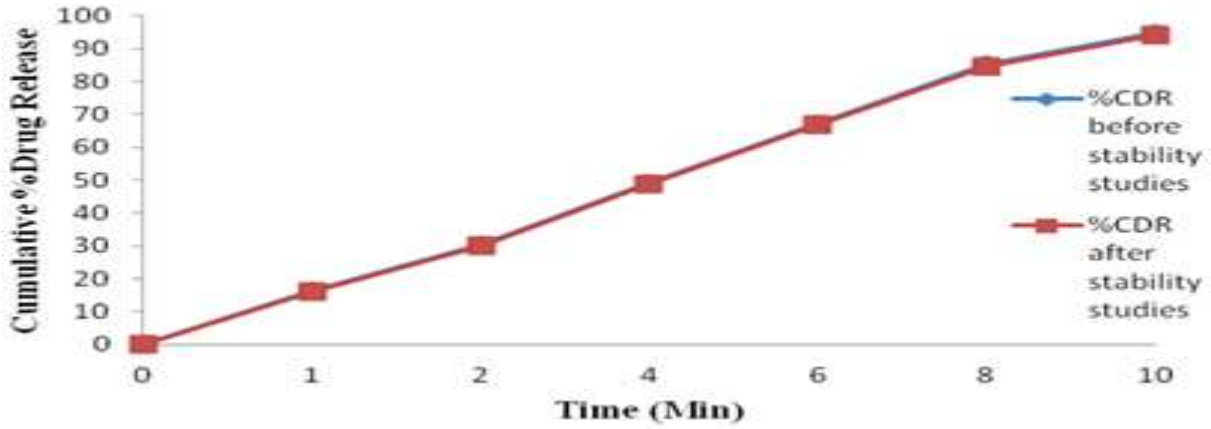


Fig. 13: Drug release profile of formulation MDF3 after stability studies

Films retained its physical appearance and there was no much significant change in the values of disintegration time, drug content and *in-vitro* release studies and folding endurance as shown from stability studies. The results were shown in Table 17 & Figure 13. This indicates that the oral films are stable at 40^0C 75%RH.

Table 17:Stability Studies Of Optimized Formulation (Mdf3)

Parameters	**0 month**	**1 month**	**2 month**	**3 month**
Description	Transparent	Transparent	Transparent	Transparent
Disintegration Time	27.46	28.10	27.16	27.01
Folding endurance	168	167	165	160
Drug content (%)	95.28	95.19	94.16	94.06
% CDR	94.68	93.88	94.19	94.18

Conclusion

Mouth Dissolving films of Voglibose in the treatment of diabetes can be formulated, analysed and optimized by 3^2 full factorial statistical design successfully using HPMC-15 as film forming polymer PVA as integrity enhancer and polyethylene glycol 400 as a plasticizer, showed rapid onset of action by avoiding first pass metabolism effect with improved specific distribution of the drug.

Moreover, Formulations prepared by such polymers can be considered as promising mouth dissolving film to bring promising approach for the delivery of Voglibose for the treatment of Diabetes.

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