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Original Article

DEVELOPMENT OF FLOATING GASTRORETENTIVE DRUG DELIVERY SYSTEM BASED ON A NOVEL EXCIPIENT FOR METFORMIN HYDROCHLORIDE USING MIXTURE DESIGN

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ABSTRACT

Objective: The present study aimed to develop a new SR metformin hydrochloride (MH) gastroretentive formulation with novel excipient (NE), which has better floatation and can be prepared with more simple pharmaceutical techniques for the treatment of diabetes Mellitus.

Methods: A gastro-retentive floating matrix tablet (GFT) formulation of MH was prepared using various concentrations of PEO (Polyox WSR-303) and hydroxypropyl methylcellulose K100M (HPMC K100 M) and Floating agent (novel excipient) to achieve desirable TFT, FLT and drug release. The wet granulation method was selected using isopropyl alcohol as a binder for the preparation of tablets. D-optimal non-simplex mixture design was used for the selection of suitable polymer concentrations and floating agents. Release kinetics was used to determine the mechanism of drug release.

Results: It was observed that GFT with optimum quantities of PEO, HPMC K100M, and the floating agent showed 100 % of drug release in 24h with FT up to 24h and minimum FLT of less than 2 min. Formulation with an *in vitro* release profile slower to the marketed sample was prepared.

Conclusion: A sustained-release (GFT) of MH tablets using PEO, HPMC K100M, and an effervescent system was successfully prepared. A GFT formulation with an *in vitro* release profile slower to the marketed sample that releases MH for 24h may suitable for once-daily dosing can be prepared.

Keywords: Novel excipient, Drug release, Floating drug delivery system, Mixture design, HPMC, PEO, Total floating time, Floating lag time, FDDS

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INTRODUCTION

Oral administration is the most common route for drug delivery due to ease of administration and full control of administration by the patient, together with a high degree of flexibility on dosing. Floating drug delivery system (FDDS) can prolong gastric residence time (GRT), resulting in increased absorption of the drug and high bioavailability and enhance the solubility of drugs that are less soluble in high pH environment. Gastroretention would also facilitate local drug delivery to the stomach and proximal small intestine. Thus, gastro retention improved therapeutic activity and substantial benefits to patients [1-4].

In the current study, MH was examined as a model drug, which is a disubstituted biguanide and is an orally administered hypoglycemic agent [5]. Due to its ability to lower blood glucose levels, it is widely used to treat non-insulin-dependent type 2 diabetes mellitus (T2DM). It lowers blood glucose concentration and glycosylated hemoglobin A_{1c} levels by inhibiting hepatic gluconeogenesis and improves the insulin sensitivity of peripheral tissues without causing hypoglycemia or weight gain, in contrast to other antidiabetic drugs. These pharmacological advantages have made MH the first choice for the treatment of T2DM. MH is freely soluble in water and its absolute bioavailability is 50 to 60%. This Low systemic bioavailability is due to incomplete absorption of MH. The absorption site for MH is the proximal part of the small intestine where the gastrointestinal absorption is complete after 6 h It is poorly absorbed in the stomach, jejunum, and ileum [5]. Furthermore, MH requires the administration of two or three daily doses to maintain adequate therapeutic concentrations because it has low oral bioavailability and short plasma half-life. Nevertheless, conventional GFT formulations should not be encouraged because the drug absorption is site-dependent in the GIT and more than 30 % of the administered dose is excreted unchanged in the feces. Considering the inverse correlation between medication adherence and dosing frequency, a GFT (SR) formulation designed for once-daily dosing was deemed suitable for MH in terms of improving the compliance and gastrointestinal tolerability. To increase the bioavailability of MH, it would be beneficial to develop a floating gastro-retentive matrix tablet with prolonged gastric retention time and gradual drug release of the drug at the absorption site [6, 7].

This work shows that the novel excipient-NE (calcium derivative) along with other polymers, is a suitable pharmaceutical excipient for the FDDS. The NE has recently introduced a porous microparticle with a nanostructured, lamellar surface, low apparent density, and shows promising properties in the field of oral delivery. Due to its unique properties, NE holds promise in the preparation of FDDS [8, 9].

The present study aimed to develop a new gastro retentive formulation with NE and gradual release of MH, which has short FLT and good floating and swelling abilities and with close to 100% drug release within 24h. Matrix tablets of swellable designs were prepared using a combination of polymers and NE by wet granulation method. The effect of combining two polymers on floating properties and release characteristics of MH was also evaluated and the formulation was optimized with the help of response surface design (D-optimal non-simplex mixture screening design). Also, the formulation to be prepared with a slower release profile is suitable to retard the C_{max}, increase the T_{max} and enhance the bioavailability as compared to the faster release profile of the marketed product, which releases 90% of the drug in about 10h. In particular, an extended-release formulation that releases MH for 24h may be suitable for once-daily dosing [10, 11].

MATERIALS AND METHODS

Materials

MH (gifted from Lupin, Pune) served as the model drug and hydroxypropyl methylcellulose (methocelK100 M), microcrystalline cellulose, stearyl alcohol (gift sample from Lupin, Pune,). NE and

citric acid (gifted from Ipca Labs, Mumbai, India), PEG (polyox™ WSR 303, The Dow chemical company, Midland, Michigan), for wet-granulation, isopropyl alcohol (Avantor, India) were used.

Methods

Formulation of floating tablets of MH

After the initial developmental trials, it was observed that the critical quality attributes (TFT, FLT, and dissolution) are controlled by the type of floating agent, polymer type, and its concentration. So, the formulation was selected for DOE studies to optimize the effects of variables on formulation and it is decided to use HPMC K100M and PEO to formulate an FDDS of MH. Tablets were compressed with round flat-faced die punches of 19 mm diameter. All trials were taken according to table 2 [12].

The required amounts of NE, PEO, HPMC, MCC, citric acid, stearyl alcohol, and MH were weighed and mixed in a mortar and pestle for 10 min. afterward, isopropyl alcohol was added to the mixture to form a paste. The obtained slurry was dried and passed through #18sieve and dried in a hot air oven at 50℃ for the 90 min; dried granules were lubricated with magnesium stearate (sieved through #40 mesh. The blended powder was compressed with 200N in hardness [13, 14].

Experimental design

In particular, when the measured response is assumed to depend only on the proportions of the ingredients present in the formulation, it is possible to use experimental mixture design. In the present study, an 11-run D-optimal non-simplex screening mixture design was applied to the evaluation of critical quality attributes in a complete tablet formulation. Design with 3 levels, 4 factors were applied to initial screening and optimize the proposed formulation. D-optimal Non-simplex screening mixture design was preferred as the choice of experimental design considering its requirement of fewer numbers of experimental runs for three or four independent variables than full factorial design. Therefore, different formulation trials were randomized and presented in below table 2, the randomization was provided by the design-expert software (version 11.0.0, Stat-Ease, Inc., Minneapolis, MN, USA); lower and upper limits of pharmaceutical formulation excipients were proposed based on literature search, preliminary screening trials and provided as design constraints in table 1. independent variables NE as a floating agent, PEO and HPMC K100M CR both as release modifying polymer and MCC as diluent) were evaluated having amount ranging from 400 mg to 600 mg for NE and PEO/HPMC having amount ranging from 170 mg to 250 mg and MCC amount ranging from 20 mg to 380 mg each inadequate concentration ranges, because of their different specific functions in tablet production. All other formulations and processing variables were kept constant throughout the study and dependent variables (FLT, TFT and dissolution at 3h, 10h, and 24h) were pointed out because for floating SR tablets a balance for having tablets with short FLT, extended floating time and extended dissolution profile is of great importance and poses a significant challenge for formulation development and optimization. The layout of the experimental design is given in Table. Each tablet had 500 mg of MH and fixed amounts of citric acid (20 mg), stearyl alcohol (50 mg), and magnesium stearate (10 mg) to analyze the effect of independent variables on tablet properties. In the present experimental design 4 factors evaluated at 3 levels with experimental trials being performed at all 8 possible combinations with limited experiments and 3 replications at the center point's altogether, 11 experimental runs that are illustrated in table 2. Other composition and manufacturing conditions were kept constant for all experimental runs [15-17].

Table 1: Experimental range and levels of the independent variables

Variable	Range and level (mg/tab)		
	-1	**0**	**+1**
A: NE	400	500	600
B: PEO	170	210	250
C: HPMC K100M (HPMC)	170	210	250
D: Diluent (MCC)	20	200	380

Table 2: MH gastro-floating GFT tablet optimization trials

Formulation codes	F-9	F-4	F-10	F-5	F-11	F-1	F-8	F-7	F-6	F-2	F-3
Experimental run order	9	4	10	5	11	1	8	7	6	2	3
Ingredients ↓	**Mg/tablet**										
MH	500	500	500	500	500	500	500	500	500	500	500
NE	400	600	400	600	600	400	600	400	500	500	500
PEO(Polyox™ WSR-303)	170	170	250	250	250	170	170	250	210	210	210
HPMC K100M	170	170	170	250	170	250	250	250	210	210	210
Stearyl alcohol	50	50	50	50	50	50	50	50	50	50	50
Citric acid	20	20	20	20	20	20	20	20	20	20	20
Microcrystalline cellulose (MCC)	380	180	300	20	100	300	100	220	200	200	200
Magnesium Stearate	10	10	10	10	10	10	10	10	10	10	10
Isopropyl alcohol	q. s	q. s	q. s	q. s	q. s	q. s	q. s	q. s	q. s	q. s	q. s
Total	1700	1700	1700	1700	1700	1700	1700	1700	1700	1700	1700

Finally, the calculated empirical models were plotted as contour diagrams for revealing the optimal formulation [17]. Data obtained from the evaluation of tablets were used to generate response surface plots. Linear models were used for data fitting. The best fit model with a significant p-value was selected for statistical analysis.

For each response, the model suggested by the software was used to fit the data and the mathematical equation suggested by the software was solved to get the optimal points. A four-factor model was used to assess the relationship between the studied variables with the FLT, TFT, and dissolution with a linear model for responses.

Optimization of response factors was performed for minimizing the floating lag time FLT while maximizing the floating time and desired dissolution profile. The solution provided by the software with the greatest desirability was chosen as the optimum condition [18, 19].

All responses were fitted to linear models, which were statistically validated by performing an analysis of variance (ANOVA). The statistical parameters used in evaluating and selecting the best-fitted model were the p-value of the model, lack-of-fit test p-value, coefficient of determination (R^2), adjusted R^2, predicted R^2, adequate precision, and predicted residual sum of squares (PRESS) [20].

Table 3: D-optimal non-simplex screening design for buoyant tablets containing MH

Formulation code	Novel excipient-NE (mg) *X1*	-PEO (mg) X2	HPMC-methocel K100M CR (mg) X3	MCC-microcrystalline cellulose (mg) X4
F-1	400	170	250	300
F-2	500	210	210	200
F-3	500	210	210	200
F-4	600	170	170	180
F-5	600	250	250	20
F-6	500	210	210	200
F-7	400	250	250	220
F-8	600	170	250	100
F-9	400	170	170	380
F-10	400	250	170	300
F-11	600	250	170	100

Selection and characterization of optimized formulation

The optimized formulation was selected based on responses, namely: FLT, (TFT), and *in vitro* drug release from GFT tablets using non-simplex D-optimal mixture design. The optimized formulation was then subjected to the following characterization [21-23].

Evaluation parameters

Post compression parameters

Compressed tablets were also tested for FLT, TFT, and *in vitro* drug release behavior [24, 25].

***In vitro* buoyancy studies**

The *in vitro* floating behavior of the tablets was determined by FLT. It is generally assumed that as FLT increases, the tablet may attach to the lower part of the stomach and be unable to float, leading to an increase in the chances of gastric emptying. Therefore, FLT may be an important factor affecting gastric retention time, requiring minimization.

These tests are usually performed in simulated gastric fluid or 0.1N HCl maintained at 37℃, by using a beaker containing 200 ml of 0.1N HCl as the dissolution medium. The time between the introduction of the dosage form and its buoyancy in 0.1N HCl and the time during which the dosage form remain buoyant were measured. The total duration of time by which the dosage form remains buoyant is called TFT [26, 27].

***In vitro* drug release study**

The release of MH from the GR tablets was studied using the USP dissolution apparatus I (rotating basket). The dissolution test was performed using 900 ml of 0.1Nhydrochloric acid. The temperature was maintained at 37±0.5 °C. The rotation speed was 100 RPM. Five milliliters were withdrawn at predetermined time intervals of 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, and 24h from each basket and the medium was replenished with 5 ml of fresh dissolution medium each time. The samples were filtered and diluted to a suitable concentration with 0.1N hydrochloric acid. Samples were analyzed by using UV/visible spectroscopy at 232 nm. The percentage of drug release was plotted against time to determine the release profiles [28, 29].

Kinetic modeling of drug release

The *in vitro* dissolution of the optimized batch of MH floating tablets was carried out. The dissolution profile of optimized batch and the marketed formulation was fitted to zero-order, first-order, Higuchi, Hixson–Crowell, and Korsmeyer–Peppas models to ascertain the kinetic modeling of drug release and the model with the highest correlation coefficient was considered to be the best model. The reading was then processed for dissolution data using DD Solver V1 software [30-32]

Fourier transform infrared spectroscopy (FTIR): interaction studies

The primary objective of this investigation was to identify the drug-using FTIR spectrophotometer. For FTIR the sample was sent into the laboratory and the results presented in results and discussion. The IR spectra were recorded for MH and powdered tablets of the optimized formulation using KBr pellets (by mixing with KBr) by FTIR. The scanning range was 4000 cm^{-1} to 400 cm^{-1}. IR spectra were recorded and compared [33, 34].

Comparison of optimized formulation with carbophage XR 500 mg marketed tablet

Carbophage XR (Merck specialties Pvt Ltd, India) tablets of 500 mg dosage strength, designed to release MH over a 12h period. This commercial product is a matrix tablet that contains cellulosic polymers and drugs; therefore, the SR matrix controls the drug release to give sustained release. *In vitro* drug release profile of developed MH, GFT tablets were compared with the drug release profile of marketed formulation tablets under similar experimental conditions. The data obtained from *in vitro* drug release was not subjected to the similarity factor analysis between marketed product and optimized formulation since the purpose of the target dissolution profile was to attain a slower release profile than the marketed formulation to achieve slow and extended-release [35, 36]

RESULTS AND DISCUSSION

Floating matrix tablets based on a floating agent in combination with the hydrogel polymers is one of the commonly used approaches to prepare floating delivery systems. Floating tablets which contained polymers and floating agent immersed in simulated gastric fluid demonstrated carbon dioxide generation and floating properties. MCC (avicel®PH 101) was incorporated as a filler excipient to maintain tablet weight constant. It also improves compressibility properties and has a very porous structure with this substance, more air would be present in the tablets and this could help the tablets to float. Additionally, this water-insoluble filler was incorporated also to counterbalance the faster solubility of the drug in the presence of the hydrophilic polymer and to provide a stable monolithic matrix. Also, sometimes release from a matrix made up of a high concentration of HPMC is incomplete and MCC addition could increase the release rate at a later stage. The presented formulation combination was also used by Buamgartener *et al.* (2000) for Pentoxyfiline and had found similar effect for floating dosage form. For gastro retentive drug delivery, it is essential to have short FLT and TFT in drug release, and accordingly, tablets were manufactured for controlling the drug release.

Selection of floating agent

Initial screening trials were fabricated with highly porous NE of calcium derivative, which allowed the manufacture of tablets with an inherently low density. The NE has recently introduced a porous microparticle with a nanostructured, lamellar surface. The inherently low apparent density of the NE (approx. 0.6g/cm^3) enabled a mechanism of floatation. Due to its unique properties, it offers the possibility to compact tablets that can be further processed at a relative density<1. NE and citric acid (CA) were used as a gas-forming mixture. The CA is intended to provide an H+donor when contacted with gastric fluid which will evolve CO_2 for flotation and also negate the effect of the difference in acidity *in vivo*. NE is carbonate salt hence generates CO_2 in the presence of dissolution medium (0.1N HCl). The gas generated is trapped and protected within the gel formed by hydration of the polymer, thus decreasing the density of the tablet, and so the tablet becomes buoyant [37].

Selection of polymers

Preliminary trials were fabricated by wet granulation using different grades of PEO as a swelling agent. The PEO matrix is a swellable and gel-forming complex made of drugs, PEO, and other excipients. PEO hydrates very fast and swells in the gastric fluid to a size that can be retained in the stomach even in the fed stage. It has a slippery characteristic that promotes retention of the tablet in the stomach in the fed state while gastric content tries to pass through pyloric sphincters. PEO alone may not help to sustain drug release for a longer duration. It rather necessitates the use of another polymer with higher gel strength to retain its matrix integrity. This is the reason why the use of other polymers such as HPMC along with PEO is required; stronger gel strength will result in the desired drug release rate and floating duration in the stomach.

Selection of combination of polymers

It is important to rationally select the appropriate polymers, to achieve the desirable floating behavior with strength and must be resistant to peristaltic force inside the stomach and remain floating for a reasonably long time. Additionally, the dosage form would act as a drug reservoir, releasing the drug slowly over a long time. In this context, the selection of the matrix polymer is of great importance. PEO swells rapidly but is unable to retain its swelling matrix for a longer period. Its rapid swelling helps to decrease the effective density of the gel matrix below 1 gm/ml, which is important for the floating of the system. MH is soluble in different media according to saturated solubility data. Therefore retardant must be incorporated in the formulation to sustain drug release. HPMC, a hydrophilic matrix acts as a retardant and can form a gel barrier to retard the drug release when it hydrates in the fluid. HPMC, on the other hand, provides integrity in the gel matrix when combined with PEO and helps to retard the drug release of a highly water-soluble drug-like MH. Rajanin Shakya et al., Wei He et al. has also found similar effect of HPMC K100M for Ofloxacin GFT and MH GFT, respectively. This is the reason why the combination of HPMC and PEO at 1:1 was selected for this study.

To reduce the density of the tablets and improve the floating properties, a lipophilic excipient, stearyl alcohol was further added to the formulations. It has a relative density lower than 1, decrease the water intake, and improve the floating properties. The fatty excipient within the formulations could have also slowed down the penetration of the medium. It was observed that polymers in the matrix undergo simultaneous swelling, dissolution, and diffusion into the bulk medium, resulting in erosion and reduction of the matrix strength. It is also considered that the gas bubbles dissipating.

Optimization trials using experimental D-optimal screening non-simplex mixture design

Several formulation variables were considered towards the fulfillment of critical quality attributes. The preliminary study of the developed tablets without NE resulted in longer FLT (data not shown). Therefore, considering the importance of effervescence along with polymer swelling, NE act as a floating agent within the formulation. The level of the independent variables was selected based on the initial screening experiments followed by their observations (data not shown). The D-optimal mixture design was used to optimize the GFT formulation. The peculiar characteristic of a mixture design is that the single components cannot be changed independently of one another since their sum must add up to 100%. This means that mixture factors are expressed as the fraction of the total amount and their experimental ranges lie between 0 and 100%. In the present case, where the excipient mixture composition had to be optimized, the experimental range lay between 0 and 65.88% (w/w)-1120 mg since 1700 mg tablets were prepared with a constant drug content of 500 mg, citric acid 20 mg, stearyl alcohol 50 mg and magnesium stearate 10 mg corresponding to 580 mg: 34.12% (w/w) of the tablet weight.

NE(X1), PEO(X2), and HPMC (X3) and MCC (X4) were chosen as the independent variables, as listed in table 3. FLT (Y1), TFT(Y2) and percentage of drug released in (dissolution) at 3h, 10h, and 24h (Y3, Y4, Y5) were chosen as response variables because they were considered as critical factors for floating sustained release dosage form to improve oral absorption of site-specific absorption drugs.

Table 4: D-optimal screening design observed response values for different buoyant tablets

Run order	Dependant variables (Responses)				
	(FLT) (S) Y1	(TFT) (h) Y2	Dissolution*		
			3h drug release R_3 (Y3)	10h drug release R_{10} (Y4)	24h drug release R_{24} (Y5)
Run-1	240±8	22±0.2	43±0.31	69±0.54	101±0.88
Run-2	105±7	23.7±0.3	44±0.33	70±0.57	100±0.77
Run-3	94±5	24.6±0.3	46±0.41	69±0.71	101±0.91
Run-4	65±7	18±0.3	59±0.52	79±0.70	101±0.87
Run-5	55±7	26.5±0.4	35±0.28	65±0.59	96±0.73
Run-6	90±8	25±0.7	48±0.42	72±0.70	100±0.77
Run-7	200±14	27±0.5	36±0.31	64±0.57	94±0.71
Run-8	75±8	22±0.4	43±0.42	69±0.71	100±0.92
Run-9	185±11	16±0.5	58±0.48	79±0.73	100±0.59
Run-10	180±13	22±0.5	42±0.40	69±0.58	100±0.50
Run-11	50±5	22.2±0.7	41±0.39	68±0.57	100±0.82

* Values are represented as mean of 3

D-optimal non-simplex Screening design minimizes the determinant of the matrix of the independent variables. They are built algorithmically to provide the most accurate estimates of the model coefficients. Obtained response values of individual trial formulations were fitted inappropriate option of the software to find the best-fitted model. After due consideration, the best-fitted model for responses Y1, Y2, Y3, Y4, and Y5 was found to linear. This allowed the choice of the best model from the linear model based on the F-value derived from ANOVA, and the R^2, predicted R^2, and adjusted R^2. The *P*values of less than 0.05 were considered to be statistically significant. In cases of getting insignificance models (P>0.05), the model reduction was performed to get a significant one.

The statistic was applied to find out the mathematical relationships among independent variables with a particular response variable. The obtained results of MLRA analysis to find out the quantitative effects of independent variables on five response variables are provided in below equation 1 to 5.

For FLT

1/√ (FLT) = 0.1740*A+0.1188*B+0.0380*C+0.0694*D (Equation 1)

For FT

Floating time = 18.31*A+39.71*B+39.26*C+17.55*D (equation 2)

For dissolution at 3h

(Dissolution 3h)^1 = 56.18*A+1.50*B+8.25*C+56.63*D (equation 3)

For dissolution at 10h

Dissolution 10h= 77.52*A+43.77*B+46.02*C+77.52*D (equation 4)

For dissolution at 24h

Dissolution 24h = 102.78*A+87.70*B+89.95*C+102.33*D (equation 5)

From the above equations 1 to equation 5, it is evident that independent variables (first-order) have a positive effect for all five responses. On the other hand, higher-order terms have positive effects on all response variables.

Analysis of variance (ANOVA) was the selected statistical test to ensure that the developed model was statistically significant (table 5). Using a 5% significance level, a model was considered significant if the *p*-value (significance probability value) is less than 0.05. In table 6, individual models, including several important terms (marked in bold) were found to be less than 0.05. The nature of the interaction between independent variables to the response variables is qualitatively diagnosed by the respective sign of the coefficient representing individual independent variables and their combination in the equation; a positive sign indicates a synergistic effect while an antagonistic effect is represented by a negative one.

Table 5: ANOVA summary results

Response	Model p-value	Lack of fit (p-value)	R^2 values	Predicted R^2 values	Adjusted R^2 values	Adeq. Precision
FLT	0.0001	0.4311	0.9779	0.9351	0.9684	26.3694
TFT	0.0025	0.1324	0.8560	0.7130	0.7943	11.1427
Dissolution 3 h (D3h)	0.0007	0.3070	0.9006	0.6945	0.8581	13.3228
Dissolution 10 h (D10h)	0.0007	0.4223	0.8989	0.6913	0.8555	13.0730
Dissolution 24 h (D24h)	0.0337	0.0988	0.6899	0.0427	0.5570	6.7812

The selected model was significant since the *p*-value (significance probability value) is less than 0.05. The F value for FLT, TFT and D3,D10,D24 were found to be 103.28,13.87, 21.15,20.74, and 5.19 respectively indicating that the models are significant. (Not shown in the table, taken from statease software). The response observations for FLT were found to be significant model terms. The lack of fit F values for FLT, TFT, D3,D10,D24 was found to be 0.4311, 0.1324, 0.3070,0.4223, and 0.0988, respectively (table 5) suggesting that the lack of fit is significant. In all cases, the adjusted R^2 values are in reasonable agreement with the predicted R^2 values (0.9351 and 0.9684 for FLT, 0.7130 and 0.7943 for TFT, 0.6945 and 0.8581for D 3h, 0.6913 and 0.8555 for D10 h and 0.0427 and 0.5570 for D 24h). D24h R^2 value is less due to close values of dissolution at 24h. In all the cases precision values were in the range 6–26 indicating an adequate signal and that the model can be used to navigate within the design space.

FLT (Y1)

Any floating dosage form should initiate floating immediately or after a minimum lag period to bypass the peristaltic movement and escape out from the stomach to the small intestine and in turn, helps in better drug absorption.

Various formulation variables such as effects of concentration of NE, release modifying polymers (PEO and HPMC), and diluent (MCC) influenced the floating behavior of the present study. The floating tablets were composed of NE and citric acid as a floating agent and combination of PEO and HPMC as a swelling matrix. Upon contact with the acidic medium, *i.e.* 0.1 N HCl, the fluid permeates into the matrix and initiates an effervescence reaction. Liberated CO_2 is entrapped within the polymeric network. Consequently, the polymer matrix swells rapidly and the swollen tablet achieves a required density, which initiates it to float, reaches on the surface, and remains buoyant for a long time as long as it maintains the required buoyancy.

The effects of independent variables on FLT (Y1) are presented by 2-D contour plots in fig. 1,2. FLT was found to be inversely related, not exactly proportional to the concentration of NE when the other two independent variables are present in equal proportion with changing concentration fig. 1, 2; however, from figures, it is evident that NE significantly influenced FLT with 400 mg produced the highest value of FLT. This value may be considered as a requirement for minimum effervescence to equilibrate gravitational force with buoyancy force exerted on the tablet while floating. The effect of polymers (B,C) on FLT, at a variable amount of NE (A), is also evident in fig. 2. As it is noticeable that the lower level of A and the entire range of D provide significant changes in FLT. In some formulation where HPMC concentration is more 250 mg/tab, the TFT is high, the reason may be HPMC could form gel barriers around the tablet after hydration, which slowed down further hydration of the tablet and retained the carbon dioxide inside the gel for a longer floating duration. Without the swollen gel, the carbon dioxide may leave the tablet more rapidly as the gastric contents move, leading to a relatively shorter floating duration, it was found that increasing the amount of HPMC could prolong both the FLT and the TFT, and decrease the rate of drug release. The results are in agreement with the findings of Veronika Eberle (2014) for Caffeine (highly water-soluble drug) Gastro floating tablets, the difference being concentration of novel excipient used, which has been finalized based on suitability for studied formulation.

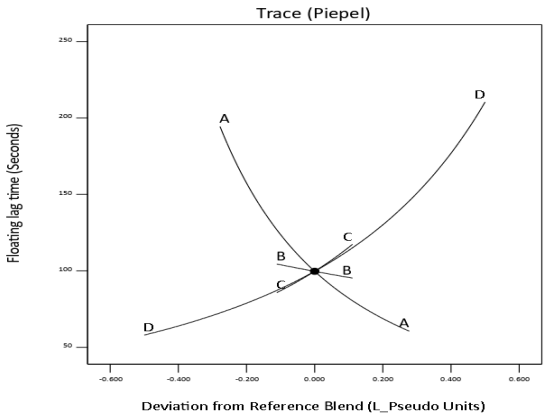

Fig. 1: Trace plot for the response FLT using reference mixture

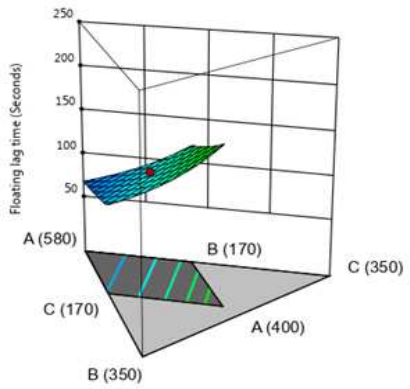

Fig. 2: Three-dimensional response surface plot for the effect of the component indicating response FLT

The above two fig. illustrate the effects of the component proportion change on the response FLT using a reference mixture. It is possible

to depict that the novel ingredient significantly reduces the FLT as the concentration increased. The MCC increases the FLT as the concentration increases. This effect could be explained by the point that NE exhibits a highly porous meshwork with a lamellar surface structure to interlock particles tightly, entrapped air in the porous FCC particles ensures low density of the tablet and provide floatation of the dosage form and tablet relative density<1. MCC causes delays in FLT due to an increase in the strength of the matrix tablets.

Therefore, NE was proposed as an effective independent variable to get minimum floating lag time. The data demonstrate that NE, PEO, and HPMC affect the FLT. It may also be concluded that the low level of (amount of PEO and HPMC K100M) and the high level of NE causes short floating time and as the concentration of Polyox WSR 303 and HPMC K100M increases, the density of the system increases and the FLT of the tablet increases. It may also occur due to the increasing hydrophilic nature of the polymer (PEO), allowing penetration of liquid through pores formed on the surface of the tablet due to PEO.

Floating time (TFT) (Y2)

The designed floating dosage form should maintain the buoyancy for a sufficient period. Long flotation maintained the dosage form in the upper GIT by prohibiting them from trans-locating to the lower GIT, therefore providing local drug absorption and a therapeutic effect in the stomach.

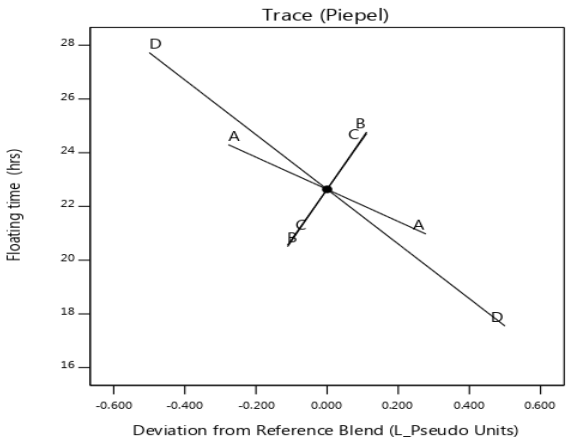

Fig. 3: Trace plot for the response floating time using reference mixture

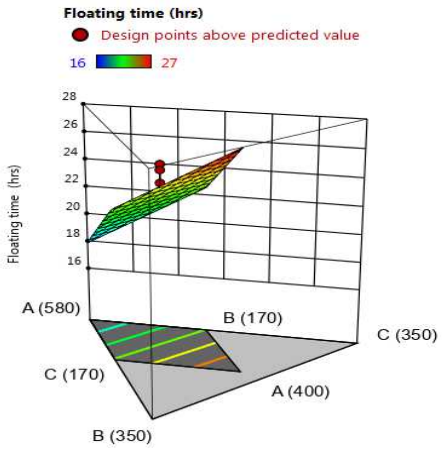

Fig. 4: 3-D response surface plot for the effect of the components indicating response floating time

The above two fig. illustrate the effects of the component proportion change on the response floating time using a reference mixture. It is possible to depict that the novel ingredient significantly reduces the floating time as the concentration increased. Compact density increased to slightly higher than 1 g/cm^3 during floating time measurement in 0.1N HCl. The penetration of liquid into porous FCC particles was slowed down due to the gelation-layer formation of the polymer substances after contact with water. The observation is in agreement with Veronika in the patent (AU2013328718A1) when the pores are exposed to gastric fluid due to high concentration of excipient, water can enter the pores and fill them up and even propagate deep into the pores, particularly when the pores are interconnected due to the lamellar surface structure which interlock particles tightly. As a consequence, the inherent density will increase and that will decrease the floating capability of the tablet and thus provoking the sinking of tablets at a later stage. It is seen that as the amount of PEO and HPMC polymer increases, TFT also increases. It is increased due to swelling of the tablet, which keeps it intact for a longer period.

The observations are in line with the Faria Senjoti *et al.* with respect to PEO WSR 303 and HPMC K100M, who had used MH as model drug.

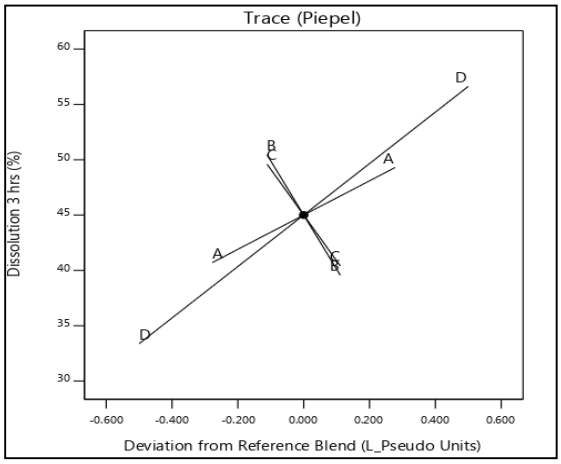

Fig. 5: Trace plot for the response dissolution at 3h using reference mixture

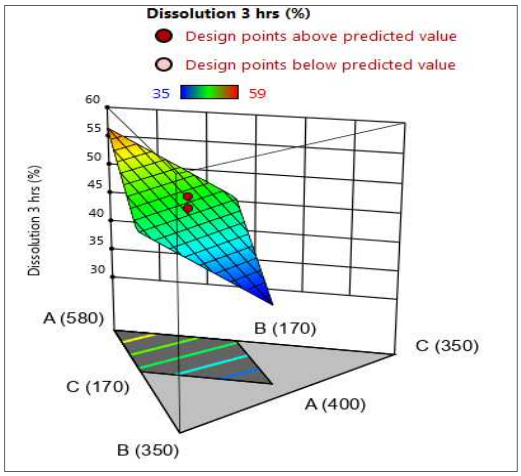

Fig. 6: 3-D response surface plot for the effect of the components indicating response dissolution at 3h

The above two fig. illustrate the effects of the formulation change on the response dissolution at 3h. It is possible to depict that the novel ingredient and MCC significantly increases the dissolution as the concentration increased. The MCC increases the dissolution as the concentration increases due to porous nature and weakened matrix

due to the disintegrating nature of MCC. This effect could be explained by the point that NE exhibits a highly porous meshwork.

The data demonstrate that NE, PEO, and HPMC affect the dissolution at 3h. It may also be concluded that the low level of (amount of PEO and HPMC K100M) and the high level of NE causes faster dissolution and as the concentration of polyox WSR 303 and HPMC K100M increases, the density of the system increases and dissolution of the tablet slows down. The high value of drug release at the initial period can be further explained by the high water solubility of MH. The rapid swelling and hydrophilic nature of PEO helps in rapid contact between drug (located near the periphery) and water. This might allow MH that is located at the outer surface of the tablets to get released quickly. The data demonstrate that NE, PEO, and HPMC affect the floating time. Based on the observations, it can be postulated that the novel ingredient and MCC significantly reduce the floating time as the concentration increased. The polymers increase the floating time as the concentration increases due to thicker hydrogel formation.

Gharti *et al.* also found that similar behavior for Ranitidine, which is highly water-soluble drug. They have reported that at higher concentrations of HPMC K100M and the PEO the viscosity affects drug release. The result of the present study is also supported by those of the previous study by Gharti *et al.*

Dissolution at 10h

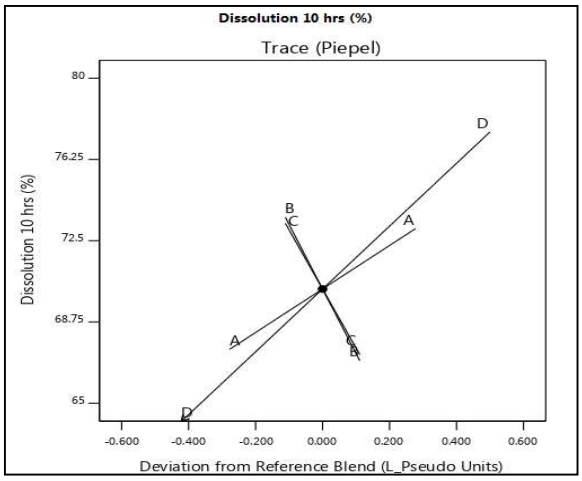

Fig. 7: Trace plot for the response dissolution at 10h using reference mixture

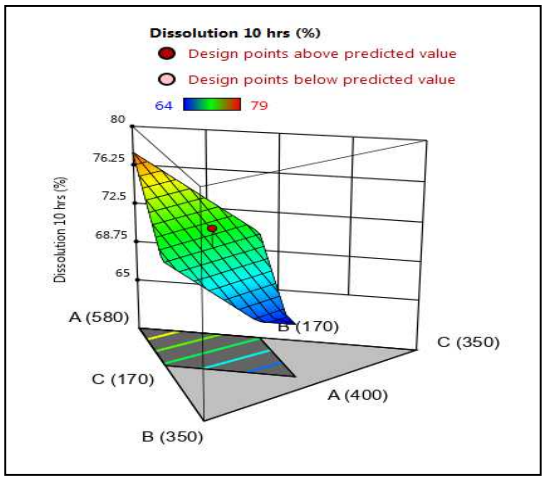

Fig. 8: 3-D response surface plot for the effect of the components indicating response dissolution at 10h

The above two fig. depict the effects of the formulation change on the response dissolution at 10h. It is possible to depict that the novel ingredient and MCC significantly increases the dissolution as the concentration increased. The MCC increases the dissolution as the concentration increases due to porous nature and weakened matrix, but it is slow as compared to 3h dissolution. The contribution of independent variables on dissolution was quite straight forward as detected by the two figures.

The data demonstrate that all 4 independent variables affect the dissolution at 10h. It may also be inferred that as the concentration of PEO and HPMC K100M increases, the density of the system increases and the dissolution of the tablet slows down. The increased retardation is due to swelling of the tablet, which keeps it intact for a longer period. On contact with the dissolution medium, very hydrophilic and swelling nature of HPMC and PEO within the tablet causes the transformation to a gel-like structure. Viscous nature and thickness of gel determine the drug release. HPMC and PEO of higher viscosity grade are characterized by a slower hydration rate and by a stronger resistance to erosion compared to the corresponding polymers of lower viscosity.

The swelling behavior of PEO is retained but balanced against the erosion behavior of HPMC K100M, which modulates the extent and progress of swelling. The gel layer formed by HPMC could also lengthen the diffusion path of drugs, realizing sustained release of Drugs.

Dissolution at 24h

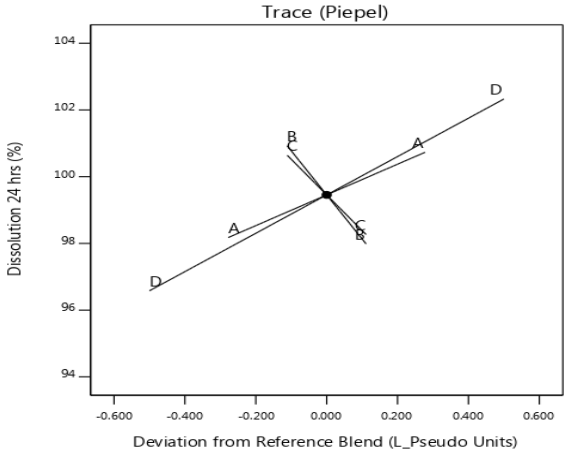

Fig. 9:Trace plot for the response dissolution at 24h

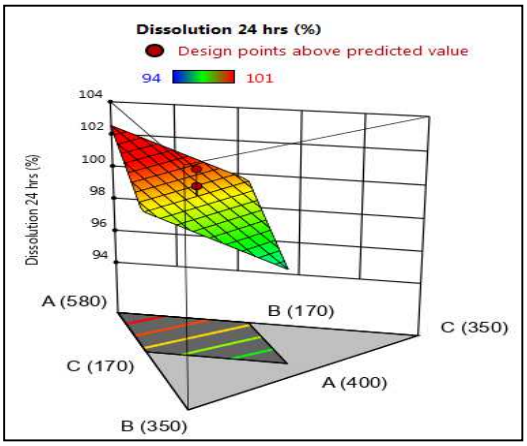

Fig. 10: 3-D response surface plot for the effect of the components indicating response dissolution at 24h

The above two fig. illustrate the effects of the factors on the response dissolution at 24h. It is possible to denote that the novel ingredient significantly reduces the FLT as the concentration increased. This has been attributed to greater extension or exercise of hydration and dissolution of the polymeric matrix as the drug release is subject to limitation. The increasing release restriction given by increasing PEO and HPMC proportions modifies the release mechanism from diffusion toward a relaxation and erosion controlled process. Every restriction of drug release is associated with an extended time of matrix exposition to dissolution medium to release a given quantity of the drug. It may also be concluded that the low level of (amount of PEO and HPMC K100M) and the high level of NE helps in attaining a faster extent of drug release i.e. close to 100%.

Table 6: Constraints: to find out optimized solutions to achieve targeted dissolution profile

Name	Goal	Lower	Upper
A: Novel Excipient	is in range	400	600
B: Polyethylene Oxide	is in range	170	250
C: HPMC	is in range	170	250
D: MCC	is in range	20	380
Floating lag time	is in range	50	240
Floating time	is in range	23	27
Dissolution 3h	is target = 45	35	59
Dissolution 10h	is target = 70	64	79
Dissolution 24h	is target = 99	94	101

Selection of the optimized formulation

The point prediction option of the software was utilized to select the optimized formulation out of 11 trial formulations prepared according to D-optimal mixture design. The optimized composition of the present formulation was selected at the minimum values of Y1 and maximum value of Y2, whereas the defined value of Y3. After a thorough evaluation by the software, it was found that formulation F-2 with the NE (A) 500 mg, PEO and HPMC(B, C) 210 mg and MCC(D) 200 mg is the optimized formulation. From this optimization study formulation batch, F-2 has followed criteria for optimized batch and has given desirable results, so formulation Batch F-2 is an optimized formulation. The results of this investigation show that the D-optimal mixture design for optimization and a mathematical model is suitable.

The optimized formulation gave FLT, TFT, and dissolution at3h, 10h, and 24h, values of 105s, 23.7h and 45%, 77%, 100%, respectively.

Drug release kinetics

Drug dissolution from solid dosage forms has been described by kinetic models in which the dissolved amount of drug (Q) is a function of the test time (t).

Table 9: Kinetic modeling of drug release

Correlation coefficient values and kinetics of drug release based on dissolution profiles of MH tablets						
Code/Batch	**Zero-order**	**First-order**	**Higuchi**	**Hixson crowell**	**Korsmeyer peppas**	
	R^2	R^2	R^2	R^2	R^2	n
Marketed formulation	0.1512	0.9921	0.8869	0.9703	0.9549	0.350
Test formulation	0.4175	0.9447	0.9665	0.8916	0.9930	0.399

In the present study, the dissolution data of marketed and test batch was fitted to first-order, Higuchi, zero-order, and Korsmeyer-peppas models. As clearly indicated in the above table values, both the formulations didn't follow zero-order release kinetics. The model that best fitted the release data was evaluated by the correlation coefficient (R^2). The best fit with higher correlation (R^2>0.98) was found with the Korsmeyer peppas equation for Test batch formulation and the first order for marketed formulation. The diffusion mechanism of drug release for test and the marketed formulation was further confirmed by Korsmeyer-peppas plots that showed fair linearity (R^2 values between 0.95 and 0.99), with slope values less than 0.5, indicating that the drug release mechanism from the selected tablets was diffusion controlled. This finding was following other reported works.

Comparison of optimized formulation F-2 with the marketed formulation

The comparative *in vitro* dissolution study of F-2 and marketed formulation was shown in fig. 11. This study showed that the optimized formulation has a controlled release over 24h. Marketed formulation (carbophage XR 500 mg tablet) released the drug 90% in 10h, whereas the prepared formulation F-2released only 70% at 10h.

Table 10: Comparative release profile

Time (h)	Marketed batch*	Test Batch
0	0	0
1	25	22
2	41	37
3	55	44
4	60	53
6	73	60
8	81	66
10	90	70
12	99	75
16	100	84
20	100	92
24	100	100

* Result is presented as mean and number of times (n) =3

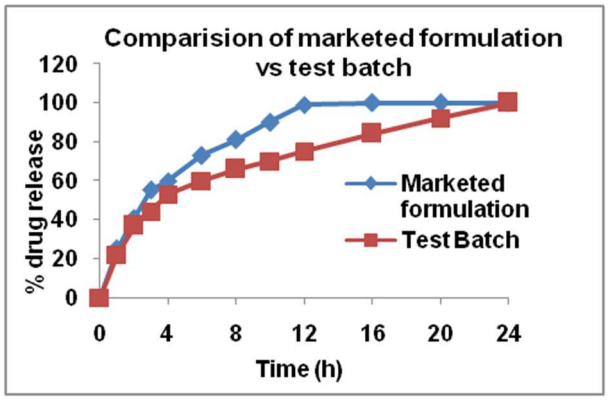

Fig. 11: Comparative release profile of marketed tablet vs test batch

Evaluation parameters of drug and final formulation

Fourier transforms infrared spectroscopy (FTIR)

Interaction studies by FTIR spectroscopy were carried out and presented in the below table. FTIR spectrum of pure MH in fig. 12 exhibits entire characteristic peak N-H stretching, C=N stretching, C-N stretching, and C-H bending at 3367.66 cm^{-1}, 1623.11 cm^{-1}, 1058.27 cm^{-1}, and 1473.3 cm^{-1} respectively when compared with the reported reference spectrum of the drug. These distinctive drug peaks were present in the FTIR spectrum of optimized tablet formulation F-2. As the identical principle peaks were observed in all the cases, hence it shall be confirmed that interactions do not exist between the drug and other excipients after formulating into tablets.

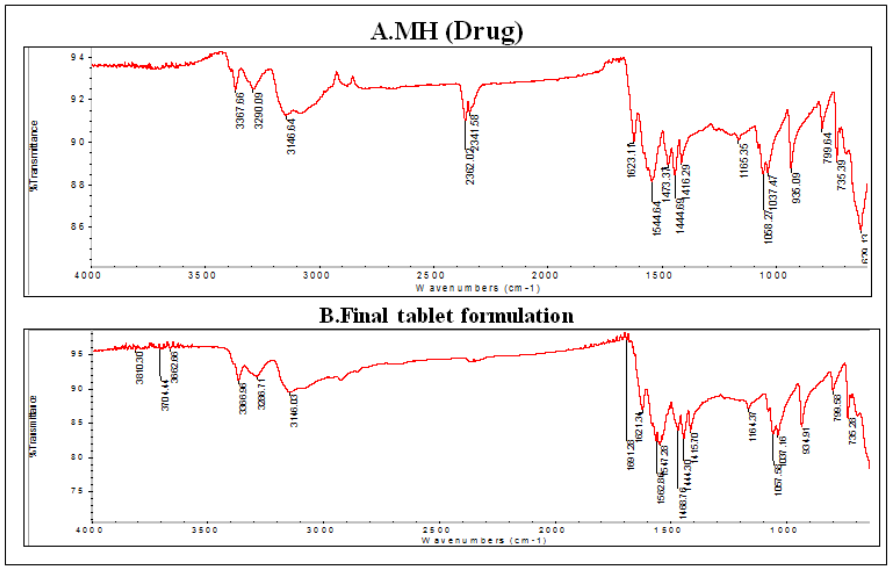

Fig. 12: Comparative FTIR spectra of drug and final tablet formulation

CONCLUSION

The NE, along with other polymers selected as the release modifiers, are more reliable as it released the drug slowly, extending the release over a longer period using D-optimal screening mixture design. PEO component of the matrix limits the initial release of the drug and imparts gastric retention through swelling, while the HPMC component lowers the amount of PEO required while still allowing the swelling to occur. Hence, using PEO and HPMC in combination would be beneficial in achieving prolonged gastro retention along with sustained delivery of highly soluble drugs like MH. It is noteworthy that NE has the potential for the development of a series of novel excipients for floating drug delivery systems. We have demonstrated that floating tablets based on NE with another polymer can efficiently control drug release *in vitro*. NE has markedly improved the floatation of the tablets *in vitro* and reduced process complexity as compared to the polymers commonly used now. Formulated tablets gave satisfactory results for TFT, FLT, and *in vitro* drug release. Moreover, the high swelling capacity of this polymer helped in maintaining the buoyancy with the minimal utilization of gas-evolving excipients such as citric acid. Formulated floating tablets best fitted to the Korsmeyer-Peppas model and diffusion-controlled mechanism. In the future, *in vivo* floating experiments and bioavailability tests will be carried out to prove there tention efficacy of floating systems based on novel excipient, which may eventually lead to promising applications to floating drug delivery systems. Therefore optimized formulation may become a logical way to improve the effectiveness of site-specific therapy against diabetes. However, there is further need for investigation for clinical acceptance of this novel drug delivery system.

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AUTHORS CONTRIBUTIONS

I, Rajesh Pawar, have provided research conception and method, conducted the experiment in the laboratory and authored the manuscript. I, Dr. Swati Jagdale conducted, guided, evaluated the experiments in the laboratory and I, Deeraj Randive, analyzed the obtained data, guided for DOE studies.

CONFLICTS OF INTERESTS

The author(s) declare that there is no conflict of interest.

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