

## Evaluation of Liquisolid Compacts Using Response Surface Methodology

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### Abstract

Liquisolid Compacts technique has potential to develop sustained release formulations. It involves conversion of liquid drug (either solution or suspension) in non-volatile solvent into free-flowing, non adherent, dry looking and readily compressible powder. In the present work, an attempt was made to develop such formulation of Diltiazem HCl and evaluation using Response surface methodology. Liquisolid compacts were prepared by dissolving Diltiazem HCl in Polyethylene Glycol 400. Then a binary mixture of carrier-coating material, Avicel and Aerosil, was added to liquid medication under continuous mixing in mortar. The HPMC K4M was used as adjuvant for sustaining the drug release. The pre-compression studies for all the formulations were also carried out. The Liquisolid compacts were evaluated in-vitro dissolution studies. Statistical Evaluation: The experimental data was evaluated using Design Expert Software. The % Drug Concentration, ratio of Carrier to Coating material and amount of HPMC K4M are taken as three factors. Response Surface methodology was used to study the influence of the each factor on the response. The present investigation showed that Polyethylene Glycol 400 has important role in release retardation of drug in Liquisolid compacts. The reduction in Tg can be reason for same. The Response surface methodology showed that all the factors were significantly affect the release at 16 hrs.

**Keywords:** Liquisolid compacts, Carrier, Coating material, HPMC K4M, Response surface methodology

### Introduction

Sustained release dosage form maintains therapeutic blood or tissue levels of the drug for extended period of time with minimized local or systemic adverse effects. Further, they are economic and show greater patient compliance. Various approaches have been used by researchers to sustain drug release in the form of tablets, among which control of drug dissolution rate is one of the best and most successful approach due to its simplicity and low cost.[1]

Liquisolid system is novel technique developed by Spireas et al.[2] It involves conversion of liquid drug (either solution or suspension) in non-volatile solvent into free-flowing, non adherent, dry looking and readily compressible powder. This is done by blending it with calculated amount of carrier and coating materials. The drug is adsorbed and absorbed on carrier material while coating materials is essential to provide flowable powder mixtures. Previously this method has been used for enhancing the dissolution rate of poorly water soluble drugs. [3-9] If the hydrophobic carrier is used instead of the hydrophilic carrier, it

can be used as sustained release system.[10, 11] Because of its low cost, simple formulation technique and capability of industrial production serve to be advantages of this technique. [12]

Diltiazem hydrochloride (DHL) is calcium channel blocker and is an effective agent in hypertension and angina (variant & classical angina). Its use extent in the management of angina pectoris, arrhythmia and hypertension. The half-life of the drug is about 4.5 hours and the usual oral dosage regimen is 60 to 360 mg. The drug is freely water soluble and hence judicious selection of release retarding excipients is necessary to achieve a constant in vivo input rate of the drug. As a result of its short half-life and to reduce frequent administration of dosage form and to improve patient compliance, a sustained-release formulation DHL is desirable.[13]

The objective of present study is to evaluate the Liquisolid compacts by using Response Surface Methodology (RSM). Also, attempt was made to study the influence of formulation factor on drug release as formulation characteristics. In this study, The Design Expert® Software (DXT 8.0.4.1 version, Stat-ease Inc) is used to analyze the experimental data. The experimental data was fitted into the Historical data option of RSM. This is used to

evaluate the data that is already generated. The software gives a mathematical model which is highly significant and used to navigate within design space. The model is also useful to predict the response at various levels of the formulation factors.

## Materials and methods

### Materials

DHL is obtained as a gift sample from the ACE Pharma, Mumbai. Avicel pH 102 was kindly gifted by Reliance Cellulose Products Ltd. HPMC K4M was obtained as a gift sample from Colorcon Asia Pvt. Ltd. Aerosil 200 and Polyethylene Glycol 400 (PEG 400) and other ingredients are of analytical grade.

### Solubility Studies

Solubility Studies of DHL was carried out in PEG 400. For this saturated solution of DHL was prepared by adding excess of DHL to the PEG 400 and shaking on the shaker (Joshi Scientific Cop. India) for 48 Hrs at 37°C. The Solutions were filtered through a 0.45 micron filter. One ml of the above solution was diluted with water up to 100ml. One ml of this solution was removed and further diluted to 100ml with distilled water. This solution was analyzed by UV-spectrophotometer at a wavelength of 237 nm (Systronics 2201 UV-Vis Spectrophotometer).

### Application of Mathematical model

To calculate the amount of carrier and coating material and to maintain acceptable flowability and compressibility, the mathematical model described by Spireas et al was used. In this study, Polyethylene Glycol 400 was used as liquid vehicle; Avicel PH 102 and Aerosil 200 were used as the carrier and coating materials, respectively. Concentration of the drug in Polyethylene Glycol 400 was taken as 50 % and 60 % w/w. The carrier to coating material ratios were taken as 2 and 3.

Flowable liquid retention potential ( $\Phi$  value) of powder excipients was used to calculate the required ingredient quantities. Therefore, carrier to coating ratios ( $R$ ) and liquid load factors ( $L_f$ ) of the formulations are related as follows:

$$L_f = \Phi + \Phi (1/R) \quad (1)$$

Where,  $\Phi$  and  $\Phi$  are the values of carrier and coating materials, respectively and they are constant. Liquid load factor ( $L_f$ ) is defined as the ratio of the weight of liquid medication ( $W$ ) over the weight of the carrier powder ( $Q$ ) in the system, which should be possessed by an acceptably flowing and compressible Liquisolid system.[14, 15] That is,

$$L_f = W/Q \quad (2)$$

Where,  $W$  is amount of drug in liquid vehicle  
The ratio  $R$  of powder is defined as,

$$R = Q/q \quad (3)$$

Where,  $R$  is the ratio between the weights of carrier ( $Q$ ) and coating ( $q$ ) materials present in the formulation.

Hence to calculate the required weights of carrier ( $Q$ ) and coating ( $q$ ) a material first from equation 1,  $L_f$  was calculated at the different levels of  $R$ . By using equation 2 amount of  $Q$  was determined and  $q$  was determined by using equation 3. Liquisolid compacts were formulated as shown in Table 1.

### Preparation of Liquisolid Compacts

For the preparation of Liquisolid compacts of solid drug, non-volatile solvent PEG 400 was employed to prepare the drug solution or suspension having different drug concentrations (50 % w/w and 60 % w/w). The desired quantities of solid drug and PEG 400 were accurately weighed in a 20 ml glass beaker and then heated to with constant stirring, until a homogeneous drug solution was obtained. Selected amounts ( $W$ ) of the resulting hot liquid medications were incorporated into calculated quantities of carrier and coating materials. During the first stage, the system was blended at an approximate mixing rate of one rotation per second for approximately one minute in order to evenly distribute the liquid medication into the powder. In the second mixing stage, the liquid/powder admixture was evenly spread as a uniform layer on the surfaces of the mortar and left standing for approximately five minutes to allow the drug solution or liquid drug to be absorbed in the interior of the powder particles. In the third stage, the powder was scraped off the mortar surfaces by means of an aluminium spatula. Then, HPMC K4M was added to this mixture and blended with mortar. This gives final formulation which was compressed into tablets using single punch tablet compression machine.

### Differential Scanning Calorimetry (DSC)

Thermogram of the sample of Liquisolid was recorded using Differential scanning calorimeter (STARe SW 10.00). Samples were placed in Aluminium pans and the lids were crimped. Thermal behaviour of the sample was investigated under Nitrogen gas at scanning rate of 200°C/min over the range of 40-300°C.

### In vitro drug release studies

The developed Liquisolid compacts ( $n=3$ ) were subjected to release studies using USP type I dissolution apparatus at 100 rpm with a constant temperature water bath at  $37 \pm 0.5$  °C. Dissolution medium used was pH 1.2 (900 ml) for first 2 hours and pH 6.8 (900 ml) for next for remaining hours. The samples were withdrawn (10 ml) at different time interval and replaced with an equivalent amount of fresh medium. After filtration through Whatman filter paper 0.45 micron concentration of Diltiazem Hydrochloride was determined spectrophotometrically at 237 nm (Systronics 2201 UV-Vis Spectrophotometer, India).

### Statistical analysis of the data and its validation

The Design Expert® Software (DXT 8.0.4.1version, Stat-ease Inc) was used to analyze the experimental data and obtain the polynomial model. The experimental data was fitted into the



Historical data option of the RSM. This was used to evaluate the data that was already generated.

Here, the Drug Concentration (% w/w) in liquid vehicle ( $X_1$ ), the ratio of the carrier to coating material ( $X_2$ ) and amount of HPMC K4M ( $X_3$ ) were independent variables, whereas % drug release at the 2 hrs ( $Y_1$ ) and % drug release at the 16 hr ( $Y_2$ ) were dependent variables. The factors their actual values were shown in the Table 2. Polynomial models for factors were generated for two the response variables ( $Y_1$  and  $Y_2$ ) by means of multiple linear regression analysis. In order to validate the polynomial equations, one optimum checkpoint and two random check points were selected by intensive grid search, performed over the entire experimental domain. Values of two responses were predicted for the each factor and two additional random check points covering the entire range of experimental domain. These predicted values were compared with the resultant experimental values and percentage prediction error was calculated.

## Results and Discussion

### Application of Mathematical model for design of Lquisolid systems

According to Lquisolid hypothesis of Spireas et al., drug candidate dissolved in liquid nonvolatile vehicle and incorporated into carrier material having porous structure and closely matted fibers in its interior, phenomenon of both adsorption and absorption occurs. Thus, the drug in the form of liquid medication is first get absorbed in the interior of particles of carrier and after saturation of this process it gets adsorbed into internal and external surfaces of carrier. The Lquisolid systems get desirable flow properties due to the Coating materials such as, Aerosil 200, which have high adsorptivity and greater surface area. Mathematical model equation for Avicel PH 102 and Aerosil 200 in PEG 400 can be given according to values of Phi ( ) as given by Spireas et.al.[16]

$$L_f = 0.005 + 3.26 (1 / R)^7$$

Based on this equation,  $L_f$  is calculated by using different  $R$  values.

### Solubility of DHL in PEG 400

Determination of solubility is most important aspect in formulation of Lquisolid systems. The solubility of Diltiazem Hydrochloride in PEG 400 was found to be 60.024mg/ml.

### Differential Scanning Calorimetry (DSC)

The DSC study showed (Figure 1) that the glass transition temp ( $T_g$ ) of the carrier material found to be decrease (62.46 °C) towards the lower side in the Lquisolid formulation than the physical mixture (70 °C).

### *In vitro* dissolution studies

The results of in vitro drug release from Lquisolid compacts were shown in the Figure 2. In Lquisolid, the drug is absorbed and adsorbed on the surface of the carrier material. After exposure to dissolution medium the drug which is present on the surface of the carrier material dissolves in the dissolution medium. This might be the reason of the initial burst release from the formulation. Formulation with higher amount of the Avicel (F3 and F4) showed decrease in the initial burst release than other, since more amount of drug was absorbed than adsorbed at the surface of the carrier material.

The mechanism of release prolongation of drug from the Lquisolid compacts was likely because of the efficient encapsulation of the drug particles by hydrophobic material. The major difference between the Lquisolid compacts and other dosage forms is the presence of the Liquid vehicle, which act as plasticizer. This liquid vehicle reduces the glass transition temp of the polymer material by changing intermolecular bonding between polymer chains and imparting flexibility. At the temperature above  $T_g$ , a better coalescence of the polymer material which gives a fine network and a matrix with lower porosity and high tortousity. This leads to the restricted leaching of the drug from the Lquisolid compacts. As the concentration of the drug in the Liquid vehicle increases the decrease in the drug release is seen because less amount of drug is available in molecular state. But effect of this is less prominent than the effect of the hydrophobic carrier material. Thus, F3 and F4 batches showed more retarding drug release than others, while F5 and F6 showed maximum amount of drug release at the end of 16 hrs. Further, the concentration of the HPMC K4M also contributes to the release retardation of the drug from the compacts. Thus, F6 showed more retarding effect than F5.

### Analysis of Data using Response Surface Methodology

Design Expert® Software (DXT 8.0.4.1version, Stat-ease Inc) was used to analyze the data. The statistical evaluation of data gave a polynomial regression equation that fitted to data was as follows

$$Y = b_0 + b_1X_1 + b_2X_2 + b_3X_3 \quad 8$$

Where,  $b_0$  was the intercept representing the arithmetic mean of all the quantitative outcomes of eight experimental runs;  $b_1$  to  $b_3$  were the estimated coefficients from the observed experimental values of  $Y$ ;  $X_1$ ,  $X_2$  and  $X_3$  were the values of each factors drug concentration (% w/w), ratio of carrier to coating material and amount of HPMC. The equation represents the quantitative effect of factors ( $X_1$ ,  $X_2$  and  $X_3$ ) upon the each of the responses;  $Y_1$  and  $Y_2$ . Coefficients with one factor represent the effect of that particular factor. A positive sign in front of the terms indicates



Table 1. Formulation design of Liquisolid Compacts

Formulation Batch	Drug solution % w/w	Ratio R = Q/q	Wt. of drug solution in gm	L <sup>f</sup>	Avicel PH 102 (Q) in gm	Aerosil 200 (q) in gm	HPMC K4M in gm
F1	50	2	0.240	1.635	0.147	0.073	0.050
F2	50	2	0.240	1.635	0.147	0.073	0.075
F3	50	3	0.240	1.091	0.220	0.073	0.050
F4	50	3	0.240	1.091	0.220	0.073	0.075
F5	60	2	0.200	1.635	0.122	0.061	0.050
F6	60	2	0.200	1.635	0.122	0.061	0.075
F7	60	3	0.200	1.091	0.183	0.061	0.050
F8	60	3	0.200	1.091	0.183	0.061	0.075

\* Liquid load factor

Table 2 Factors with their actual values

Sr.No.	Factors	Level of factor in actual values	
1	Drug concentration in liquid vehicle (% w/w)	50	60
2	Ratio of Carrier to Coating material	2	3
3	Amount of HPMC K4M	50	75

Table 3 AVOVA Results of release at 16 hr

Source	Sum of Squares	df	Mean Squares	F value	p-value probe > F
Model	552.65	3	184.22	23.60	0.0053
A-A	64.47	1	64.47	8.26	0.0453
B-B	379.91	1	379.91	48.67	0.0022
C-C	108.27	1	108.27	13.87	0.0204
Residual	31.22	4	7.81		
Core Total	583.87	7			
"Pred R-Squared"			0.7861		
"Adj R-Squared"			0.9064		
Adeq Precision			13.575		

Table 4 The experimental and predicted values of responses R1 and R2 for optimum formulation and two check points

Responses	A,B,C	Optimum formulation 60,2,50	Check point 1	Check point 2
R1 release at 2 hrs	Experimental value	31.55	14.13	29.79
	Predicted value	31.82	14.36	29.93
	% PE *	-0.86	-1.63	-0.47
R2 release at 16 hrs	Experimental value	92.19	66.24	89.34
	Predicted value	91.58	65.87	88.89
	% PE *	0.66	0.56	0.50

\*%PE= (Experimental value- Predicted value) / Experimental Value \* 100

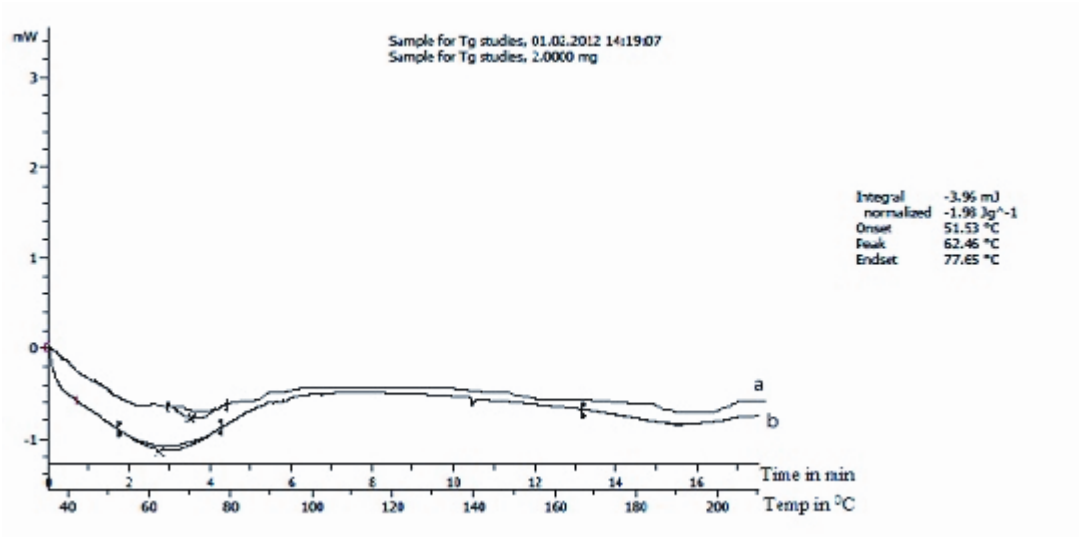


Figure 1. Tg study of a) Physical Mixture b) Liquid Formulations.

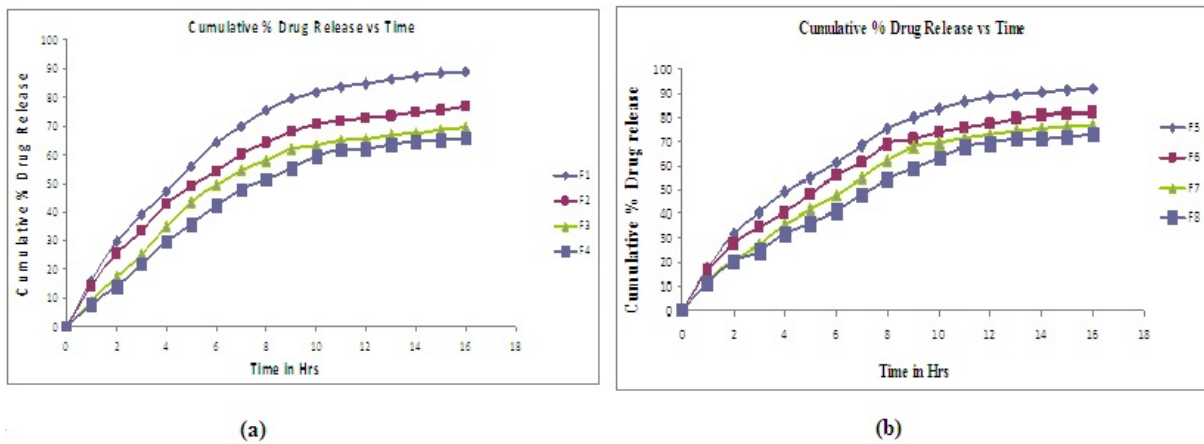


Figure 2. In vitro drug release of Liquid compact (a) of Formulation F1 to F4 (b) of Formulation F5 to F8.

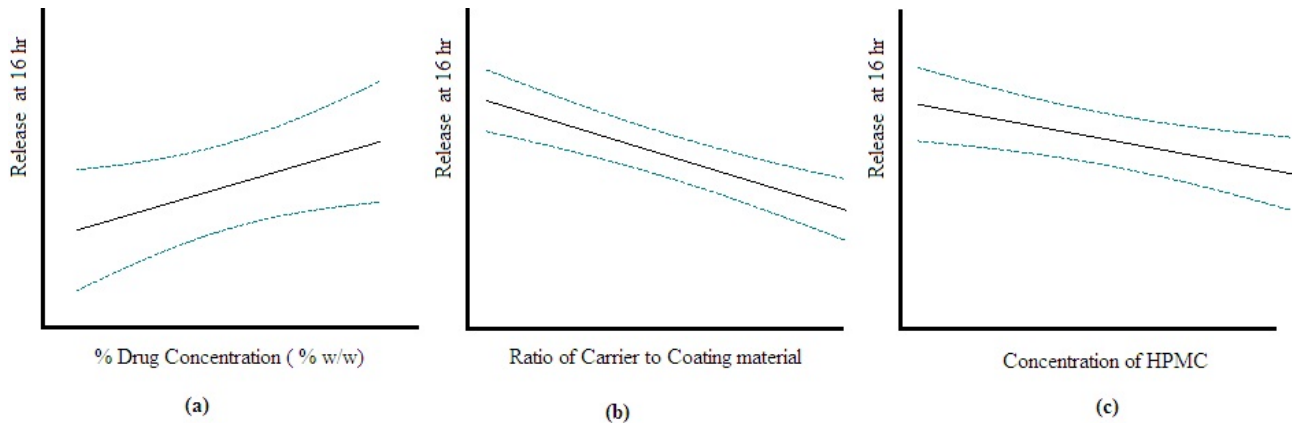


Figure 3. Influence of (a) % Drug concentration (b) Ratio of Carrier to coating material (c) HPMC concentration on % drug release at 16 hrs.





synergistic effect while negative sign indicates antagonistic effect of the factors. The significance of the model was estimated by applying analysis of variance (ANOVA), at 5% significance level. A model is considered significant if the  $p$ -value is less than 0.05.

### Influence of Formulation Factor on % Drug release at 16 Hrs

Out of all the Liquisolid formulations, the drug release at the end of the 16 hrs should be maximum. Hence, in the evaluation of Liquisolid compacts, release at the end of 16 hrs is also important parameter.

The influence of formulation factors of Liquisolid compacts on release at 16 hrs was given by equation 10. This was the linear polynomial equation generated as significant mathematical model by the software. The significant level of the model was explained with the help of ANOVA results shown in Table 3.

Release at end of 16 Hrs (R2) =  $+99.79750 + 0.56775X1 - 13.78250X2 - 0.29430X3$       9

From the Table 3 Value of "Prob > F" for model, is less than 0.05 and The Model F value of 23.60 implies that the model is significant. The Values of "Prob > F" for X1, X2 and X3 are also less than 0.05 or between 0.05-0.10, that is they are significant model terms. Thus, they will contribute in generating the response Y2.

From the Table 3, the "Pred R-Squared" of 0.7861 is reasonable agreement with "Adj R-Squared" of 0.9064, their difference should not greater than 0.2, and this may indicate a good fitting of the model. Thus, the polynomial equations can also be used to draw conclusions considering the magnitude of coefficient and the mathematical sign it carries, that is, positive or negative. "Adeq Precision" measures the signal to noise ratio. A ratio greater than 4 is desirable. A ratio of 13.575 indicates an adequate signal. This model can be used to navigate the design space.

The positive coefficient of variable X1, i.e. Drug Concentration (% w/w) in case of response i.e. % drug release at 16 hrs indicated that as the concentration of drug in liquid vehicle was increased; the % drug release was also increased. The relationship between the variables was further elucidated by using the response surface plot shown in Figure 3. It was observed from the figure that as the drug concentration in liquid vehicle increases the drug release also increases and vice versa.

The negative coefficient of variable X2, i.e., ratio of Carrier to Coating material in case of response i.e. % drug release at 16 hrs indicates that as ratio of Carrier to Coating material was increased; % drug release value was decreased. The relationship between the variables was further elucidated by using the response surface plot shown in Figure 3. It was observed from the

figure that as the ratio of carrier to coating material increases, drug release decreases and vice versa.

The negative coefficient of variable X3, that is, HPMC in case of response, i.e. % drug release at 16 hrs indicated that as the concentration of HPMC was increased; the % drug release value was decreased. The relationship between the variables was further elucidated by using the response surface plot shown in Figure 3. It was observed from the figure that as the amount of HPMC K4M increases, drug release decreases and vice versa.

### Optimization of the Formulation

The optimized formulation was obtained with the help of the above developed mathematical model by applying the constraints to the two responses as follows,

R1 i.e. % drug release at 2 hrs which should be above 30 % and

R2 i.e. % drug release at 16 hrs which should be above 90%

The experiments were carried out according to the composition obtained for optimum formulation. The optimum formulation was evaluated for the dissolution profile. In order to evaluate the reliability of the developed mathematical model, two additional check points were taken estimated by use of generated model covering the entire experimental domain. Table 4 gives the levels of each factor, Drug concentration in % w/w (A), ratio of Carrier to coating material (B) and amount of HPMC K4M (C) of optimum formulation and two random check points with their experimental values, predicted values and percentage prediction error.

### Conclusion

The present study showed that Liquisolid technique can be adopted for the optimization of the sustained release formulation of the Diltiazem HCL using Polyethylene glycol 400 and HPMC K4M. The FT-IR studies show compatibility between Drug and excipients. The data analyze by RSM shows that F5 formulation is optimized formulation among all the batches.

### Acknowledgement

Authors are thankful to ACE Pharma, Mumbai, Reliance Cellulose Products Ltd. and Colorcon Asia Pvt. Ltd. for providing the Diltiazem HCL, Avicel PH 102 and HPMC K4M.

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