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Development and Characterization of Nicotinic acid Extended Release Tablets with Hydrophobic Polymer

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ABSTRACT

Nicotinic acid is widely used since long period of time as antihyperlipidemic agent in extended release tablet dosage form with high dose. It is rapidly absorbed in GI tract and undergo extensive metabolism. This leads to high variable plasma drug concentration, which may correlate with the side effects of Nicotinic acid. Available marketed formulation shows good correlation of in-vitro dissolution profile; however in-vivo performance of the formulation shows highly variable plasma concentrations. Available marketed formulation is designed with hydrophilic polymer (HPMC). This erratic in-vivo behaviour of the available marketed formulation may be due to the variability in physiological pH or impact of mobility and composition and volume of GI liquids. Here we worked on the composition as a factor and new formulation is designed with insoluble polymer. This current research is aimed to design a robust matrix tablet with insoluble polymer.

Keywords: Inter-subject Variability, Hydrophilic Polymer, Hydrophobic Polymer, Antihyperlipidemic agent, Matrix Tablet

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INTRODUCTION

Nicotinic acid reduces the low density and very low-density lipoprotein in plasma, and it is one of the oldest drugs in this category. It is used as antihyperlipidemic agent. In today's world most of the people suffered from hyperlipidaemia which caused atherosclerosis and cardiovascular disease [1].

Nicotinic acid inhibits the absorption of dietary cholesterol and indirectly decrease the synthesis of LDL, VLDL which is precursor of cholesterol. Currently Nicotinic acid is available as extended-release tablet formulation with high doe such as 500mg, 750mg, 1000mg. The current marketed formulation is available as matrix tablet comprises of hydrophilic polymer (HPMC) as a release controlling polymer. Being a BCS class I molecule, it is a typical candidate for extended-release formulation. This use of only hydrophilic polymer leads to formation of gel like structure which is a hydrophilic gel to control the drug release. As Nicotinic acid is a BCS class I drug and with high dose only hydrophilic polymer is not sufficient to control the drug release in vivo leading to inter-subject variation of plasma drug concentration[2-5].

In one of the researches, it was shown that similarity factor of in vitro dissolution study in simulated fasted condition (F2 value = 62.83 to 73.20) and in simulated fed condition (F2 = 67.29 to 90.34). However these formulation shows high inter subject variability in Cmax from 44% to 73% in fasted condition and 65.2 to 131.8% in fed condition [6].

This challenge triggers to design a extended release matrix tablets using a insoluble polymer along with the hydrophilic polymer. Hence in current research ethyl cellulose is taken as an insoluble polymer and extended release tablets designed and demonstrated the similar in-vitro dissolution profile.

MATERIALS AND METHOD

Nicotinic acid is a gift sample from Divis laboratories Limited, India, HPMC k15M, HPMC k100M and ethyl cellulose gift sample from colorcon and other excipients such as stearic acid present in the university were used for formulating.

Preparation of extended release Nicotinic acid matrix tablets 1000mg:

Wet granulation technique was used to prepare matrix tablets. Nicotinic acid (API), HPMC K 15 M, HPMC K100M and ethyl cellulose were sifted through #20mesh. Sifted material were mixed and purified water was added as granulating agent and wet mass was produced. Wet mass thus obtained was screened through sieve No. 18. The granules were air dried at room temperature and dried in tray dryer to achieve the LOD. The coarse granules so obtained were again screened using the same sieve to get the sized granules. Stearic acid was sifted through sieve no. 60 and added to

the granules as lubricant. Lubricated blend were compressed with similar size of punches as per RLD size using single punch tablet compression machine (Cadmach).

Table 1: Comparative qualitative composition of the test and reference product

Ingredient	Function	Reference product	Test Product
Core Tablets Composition			
Nicotinic acid	Drug Substance	√	√
Hypromelloses	Rate controlling polymer	√	√
Povidone	Binder	√	x
Stearic Acid	Lubricant	√	√
Ethylcellulose	Rate controlling polymer	x	√
Film-Coating			
Polyethylene glycol	Plasticizer	√	x
FD&C yellow #6	Colorant	√	x
Synthetic red and yellow iron oxides	Colorant	√	x
Titanium dioxide	Opacifier	√	x
Opadry Orange 03B130007	Coating agent	x	√

In vitro release rate studies:

During formulation development, the dissolution method as recommended by FDA for Nicotinic acid ER tablets 1000 mg, i.e., 900mL, water as medium with USP apparatus I (basket) at 100 rpm. The dissolution sampling time point were 1 hour, 3 hours, 6 hours, 9 hours, 12 hours, 15 hours, 20 hours and 24 hours. Figure 4 show the dissolution profile of NIASPAN tablets 1000 mg in water, pH1.2 buffer, pH4.5 acetate buffer, and pH 6.0 phosphate buffers.

The Nicotinic acid ER tablet 1000 mg meets appropriate in-vitro testing(F2＞50) in comparison with the Reference Drug (NIASPAN Tablets 1000 mg), the comparative dissolution profiles have been provided in Table withdrawn and replaced with the same volume pre -warmed (37±0.5°c) fresh dissolution medium. The samples withdrawn were filtered through 0.45 membrane filters, and drug content in each sample was analyzed after suitable dilution by UV/HPLC. The actual content in samples was read from a calibration curve prepared with standard Nicotinic acid. All dissolution studies were carried out induplicate and repeated at least thrice. The same was carried out on marketed product for comparative evaluation.

Rational for selecting the ingredients:

Hypromellose (METHOCELTM K100M Premium):

Hypromellose is a partly O-methylated and O-(2-hydroxypropylated) cellulose. It is available in several grades that vary in viscosity and extent of substitution. Grades may be distinguished by appending a number indicative of the apparent viscosity, in mPa·s, of a 2% w/w aqueous solution at 20℃. In oral products, Hypromellose is primarily used as a tablet binder,(1) in film-coating,(2–

7%) and as a matrix for use in extended release tablet formulations.(8–12%) Concentrations between 2% and 5% w/w may be used as a binder in either wet- or dry-granulation processes. High-viscosity grades may be used to retard the release of drugs from a matrix at levels of 10–80% w/w in tablets. In the current formulation METHOCELTM K100M Premium is used as a matrix rate controlling polymer.

Hypromellose (METHOCELTM K15M Premium):

Hypromellose is a partly O-methylated and O-(2-hydroxypropylated) cellulose. It is available in several grades that vary in viscosity and extent of substitution. Grades may be distinguished by appending a number indicative of the apparent viscosity, in mPa·s, of a 2% w/w aqueous solution at 20℃. In oral products, Hypromellose is primarily used as a tablet binder, in film-coating, and as a matrix for use in extended release tablet formulations. Concentrations between 2% and 5% w/w may be used as a binder in either wet- or dry-granulation processes. High-viscosity grades may be used to retard the release of drugs from a matrix at levels of 10–80% w/w in tablets. In the current formulation METHOCELTM K15M Premium is used as a matrix rate controlling polymer.

Ethyl cellulose:

Ethyl cellulose is partially ethoxylated. The main use of ethylcellulose in oral formulations is as a hydrophobic coating agent for tablets and granules. Ethylcellulose coatings are used to modify the release of a drug, to mask an unpleasant taste, or to improve the stability of a formulation; for example, where granules are coated with ethylcellulose to inhibit oxidation. Modified-release tablet formulations may also be produced using ethylcellulose as a matrix polymer. Drug release through ethylcellulose-coated dosage forms can be controlled by diffusion through the film coating. This can be a slow process unless a large surface area (e.g. pellets or granules compared with tablets) is utilized. In those instances, aqueous ethylcellulose dispersions are generally used to coat granules or pellets. Ethylcellulose-coated beads and granules have also demonstrated the ability to absorb pressure and hence protect the coating from fracture during compression. High-viscosity grades of ethylcellulose are used in drug microencapsulation. Release of a drug from an ethylcellulose microcapsule is a function of the microcapsule wall thickness and surface area. In tablet formulations, ethylcellulose may additionally be employed as a binder, the ethylcellulose being blended dry or wet granulated with a solvent such as ethanol (95%). Ethylcellulose produces hard tablets with low friability, although they may demonstrate poor dissolution. Ethylcellulose was used in the current formulation as a matrix polymer.

Stearic acid:

It is the most commonly used lubricant for tablets. Stearic acid from BASF company Ltd was selected, it is semi-synthetic. The raw materials basis: Coconut oil / palm kernel oil / palm oil / palm stearin /rapeseed oil.

Opadry Orange 03B130007:

Film coated is the most economical method of enhancing the product – improving visual appearance, as well as easing swallow ability, and enhancing the taste and masking objectionable odours. As NIASPAN (Nicotinic acid) Tablets 1000 mg tablet is film-coated, Opadry Orange 03B130007 from Colorcon was selected as a coating material to develop tablets with similar appearance to reference listed drug.

RESULTS AND DISCUSSION

Formulation of granules is the key factor in the production of tablet dosage form involving extended release of drug from matrix type particle. Physical parameters such as area, hardness, and surface Wet granulation method was used for manufacturing the tablets and analytical study was performed (Dissolution study) by UV/HPLC method after manufacturing the tablets.

Reference Listed Drugs (NIASPAN® 1000mg) tablets and test product (Nicotinic acid Extended Release tablets 1000mg) were taken and the dissolution method as recommended by FDA for Nicotinic acid ER tablets i.e., 900mL, water as medium with USP apparatus I (basket) at 100 rpm. The dissolution sampling time point were 1 hour, 3 hours, 6 hours, 9 hours, 12 hours, 15 hours, 20 hours or 24 hours were used for evaluation. Test product is manufactured with similar physical parameters as RLD and evaluated by same dissolution method used for RLD.

Through my research work the impact of insoluble polymer on drug product release profile will present and how reliable to correlate the in-vitro dissolution for highly soluble drug products.

Nicotinic acid ER Tablets 1000 mg, a generic version of the reference drug NIASPAN (1000 mg) Tablets. We used ethyl cellulose as an insoluble polymer and all other ingredients similar to RLD which is given in the comparative composition in the table, to develop a Tablet formulation and manufacturing process that ensures the quality, safety and efficacy of NIASPAN (1000 mg) Tablets.

Initially, the quality target product profile (QTPP) was defined based on the properties of the drug substance, characterization of the Reference Drug product, and consideration of the Reference Drug product label and intended patient population. Nicotinic acid ER Tablets were designed to achieve all of the attributes in the QTPP. However, our investigation during pharmaceutical development focused on critical quality attributes (CQA's) that could be impacted by a realistic

change to the drug product formulation. or manufacturing process. These attributes included physical attributes and drug release.

Nicotinic acid ER Tablets contain the drug substance Nicotinic acid. To match the Reference Drug, Nicotinic acid ER Tablets 1000 mg was manufactured as a, extended-release tablets with rate controlling polymer and other excipients compressed as a tablet. The development process was initiated with the selection of a suitable API source. Two different grades of Hypromellose (HPMC K100 LVCR and HPMC K15M CR) were used in the formulation as a rate controlling polymer along with Ethyl cellulose. The appropriate level of lubricant (Stearic acid) was also identified to produce a robust formulation.

A predictive dissolution method was a key element for the development program. The USFDA recommended dissolution method (USP apparatus I at 100 rpm in 900 ml of water) was used for evaluating the samples.

During formulation development, the dissolution method as recommended by FDA for Nicotinic acid ER tablets 1000 mg, i.e., 900mL, water as medium with USP apparatus I (basket) at 100 rpm. The dissolution sampling time point were 1 hour, 3 hours, 6 hours, 9 hours, 12 hours, 15 hours, 20 hours and 24 hours. Figure 4 show the dissolution profile of NIASPAN tablets 1000 mg in water, pH1.2 buffer, pH4.5 acetate buffer, and pH 6.0 phosphate buffers.

The Nicotinic acid ER tablet 1000 mg meets appropriate in-vitro testing(F2＞50) in comparison with the Reference Drug (NIASPAN Tablets 1000 mg), the comparative dissolution profiles have been provided in table across the different physiological pH range with using ethyl cellulose as insoluble polymer where as the RLD formulation contains only hydrophylic polymers. Dissolution data are demonstrated below

Table 2: Comparison of dissolution profile data of Nicotinic acid Extended Release tablets, 1000mg and NIASPAN Tablets, 1000 mg in water media

Apparatus	**USP-I(basket)**	**Speed**	**100 rpm**
Medium	**Water**	**Volume**	**900 ml**
Time point/hours	**NIASPAN Tablets 1000 mg, RLD**	**Nicotinic acid ER tablets 1000mg, Test**	**Acceptable Ranges(F2≥50)**
0	0	0	F2:98
1	9	9	
3	21	21	
6	36	36	
9	49	48	
12	62	62	
20	88	88	

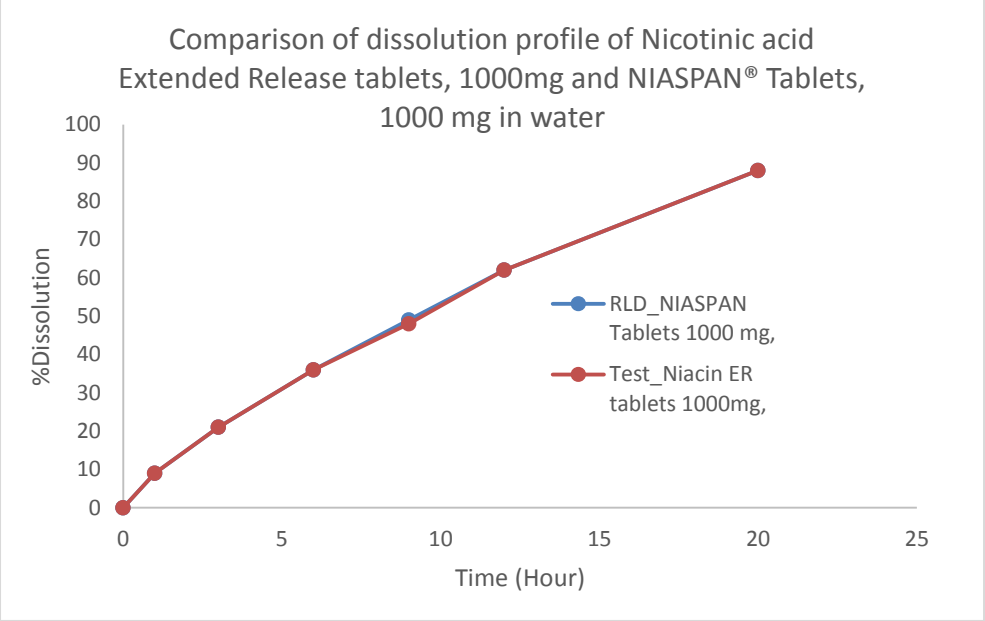

Figure 1 Comparison of dissolution profile of Nicotinic acid Extended Release tablets, 1000mg and NIASPAN® Tablets, 1000 mg in water media

Table 3: Comparison of dissolution profile data of Nicotinic acid Extended Release tablets, 1000mg and NIASPAN Tablets, 1000 mg in pH 1.2 HCl solution

Apparatus	USP-I(basket)	Speed	100 rpm
Medium	pH 1.2 HCl solution	Volume	900 ml
Time point/hours	**NIASPAN Tablets 1000 mg, RLD**	**Nicotinic acid ER tablets 1000mg, Test**	**Acceptable Ranges(F2≥50)**
0	0	0	F2:89
1	16	16	
3	34	33	
6	53	52	
9	69	68	
12	83	81	
20	100	98	

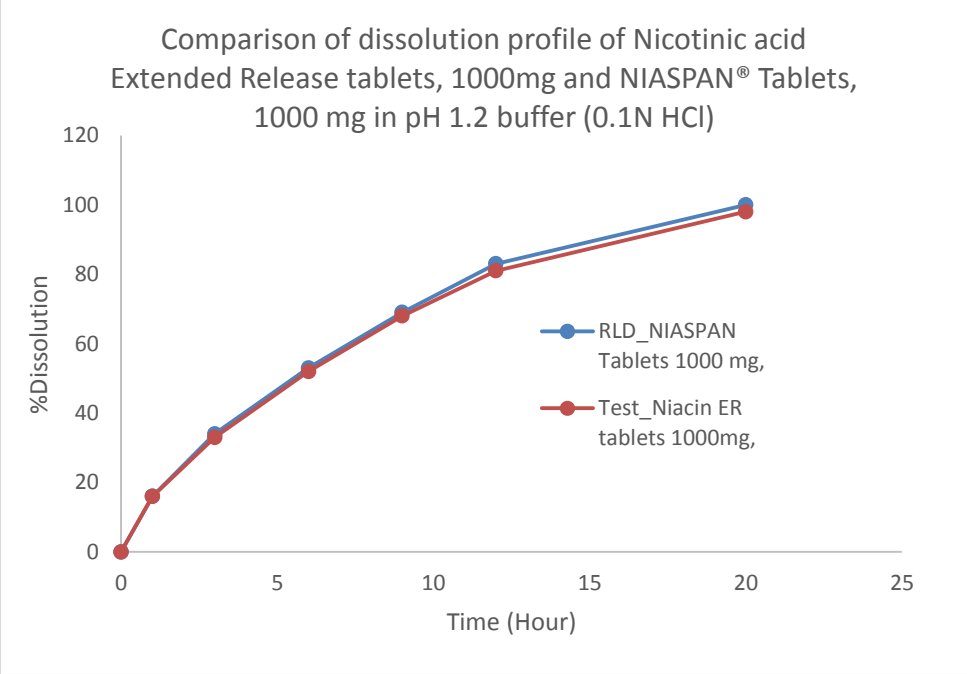

Figure 2: Comparison of dissolution profile of Nicotinic acid Extended Release tablets, 1000mg and NIASPAN® Tablets, 1000 mg in pH 1.2 HCl solution

Table 4: Comparison of dissolution profile data of Nicotinic acid Extended Release tablets, 1000mg and NIASPAN Tablets, 1000 mg in pH 4.5 acetate buffer

Apparatus	USP-I(basket)	Speed	100 rpm
Medium	pH 4.5 acetate buffer	Volume	900 ml
Time point/hours	**NIASPAN Tablets 1000 mg, RLD**	**Nicotinic acid ER tablets 1000mg, Test**	**Acceptable Ranges(F2≥50)**
0	0	0	F2:74
1	10	9	
3	22	21	
6	36	36	
9	48	50	
12	59	63	
20	81	87	

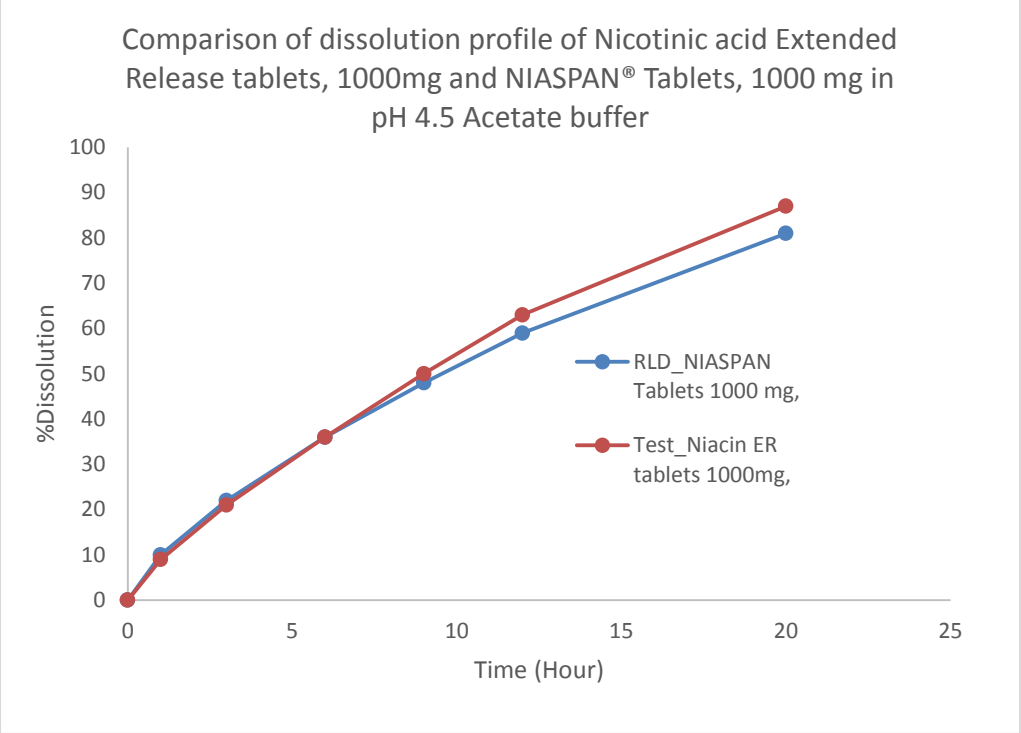

Figure 3: Comparison of dissolution profile of Nicotinic acid Extended Release tablets, 1000mg and NIASPAN® Tablets, 1000 mg in pH 4.5 acetate buffers

Table 5: Comparison of dissolution profile data of Nicotinic acid Extended Release tablets, 1000mg and NIASPAN Tablets, 1000 mg in pH 6.0 phosphate buffer

Apparatus	USP-I(basket)	Speed	100 rpm
Medium	pH 6.0 phosphate buffer	Volume	900 ml
Time point/hours	**NIASPAN Tablets 1000 mg, RLD**	**Nicotinic acid ER tablets 1000mg, Test**	**Acceptable Ranges(F2≥50)**
0	0	0	F2:96
1	8	9	
3	20	20	
6	34	34	
9	46	45	
12	58	57	
20	80	80	

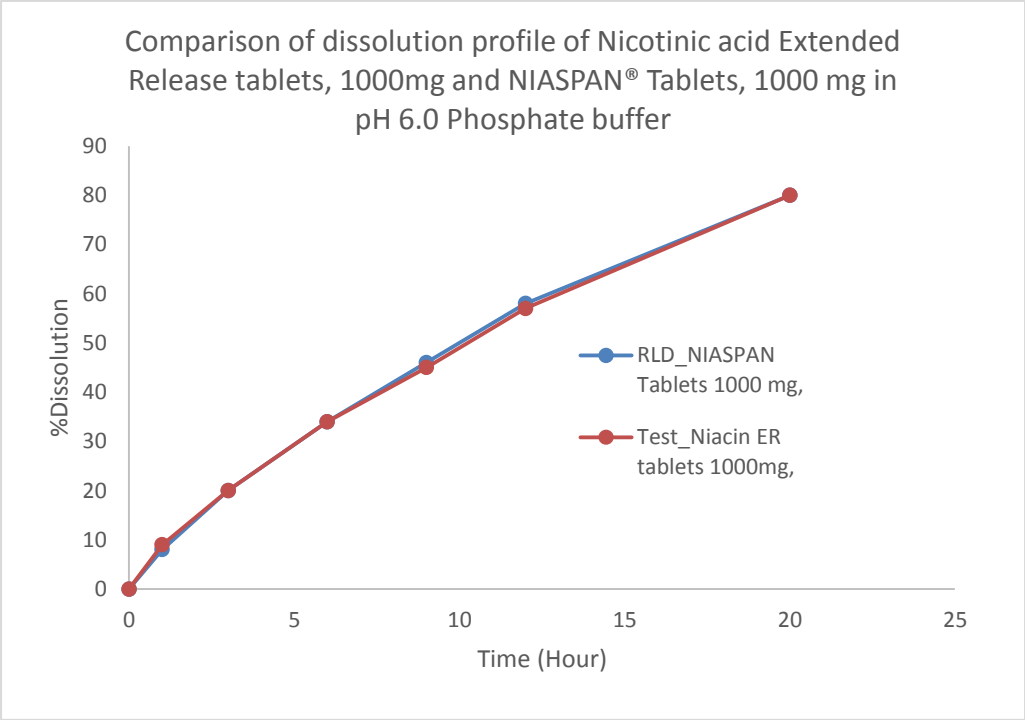

Figure 4: Comparison of dissolution profile of Nicotinic acid Extended-Release tablets, 1000mg and NIASPAN® Tablets, 1000 mg in pH 6.0 phosphate buffer.

CONCLUSION

Through my research work the impact new formulation is designed with use of ethyl cellulose an insoluble polymer along with the similar hydrophylic polymer similar to RLD. The new formulation is found comparable with RLD across the physiological condition which strongly predict similar in-vivo performance. Due to addition of insoluble polymer this technology controls the drug release by erosion and diffusion mechanism rather than only diffusion from hydrophylic gel matrix. This addition property with insoluble polymer probable improve the inter subject variability issues with current marketed formulation with only hydrophilic polymer matrix tablets.

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