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A NEW APPROCH TO FORMULATE AND OPTIMIZETHE POROUS TABLETS CONTAINING LORATIDINE

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ABSTRACT

The objective of the present study is to develop a Loratidine Porous tablets. In this present study an attempt was made to improve on set of action as well as to enhance bio-availability of drug. The present study was carried out to develop porous tablets for oral administration of Loratidine. The major obstacle against Fast disintegrating delivery of Loratidine was its low aqueous solubility, which was overcome by kneading the drug with βCD and tartaric acid in a simple and easy-to-scale-up formulation strategy. Porous structure, aiding rapid disintegration and dissolution of tablets in the oral cavity, was successfully achieved after camphor sublimation from the directly compressed tablets by means of vacuum oven. Therefore, it is reasonable to say the adopted formulation strategy to prepare porous sublingual tablets could be of great potential for drugs suffering from extensive first-pass metabolism. Systematic studies were conducted using different concentration of super disintegrant i.e. Cross Carmellose sodium. All the prepared systems were evaluated for the different properties. Before the preparation of tablets, preformulation studies were conducted like Micromeritic properties to assess flow ability, compressibility properties and solubility studies. And all the formulations gave good results for above preformulation studies. Formulated tablets gave satisfactory results for various physical tablet evaluation parameters like tablet dimensions, hardness, friability, weight variation, wetting time, content uniformity, all the formulations were found within the permissible range.
Then prepared tablets were evaluated for *in-vitro* drug release. Finally it was concluded: Formulation 8: Drug, volatilizing agent and super disintegrant (Ac-Di-Sol) ,which was prepared by direct compression method have good wetting property, lesser disintegration time and faster action when compared to other formulations. so the formulation F8 was taken as a optimized one.

Keywords: Loratidine, Orodispersible Porous tablets, Formulation,

INTRODUCTION

Porous tablets are also known as mouth dissolving tablets, Orodispersible tablets, fast disintegrating tablets, quick disintegrating tablets, fast dissolving tablets, rapid dissolving tablets, oral disintegrating tablets, quick melt tablets or rapid melt tablets. They are defined by the FDA as "*A solid dosage form containing medicinal substances which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue*". In order to accomplish disintegration in under one minute, tablets are composed of special ingredients including super disintegrates such as crospovidone, crosscarmellose sodium or sodium starch glycolate. These materials allow for rapid uptake of water or are manufactured with low compression force to achieve the same effect.

Drug delivery systems (DDS) are a strategic tool for expanding markets/indications, extending product life cycles and generating opportunities. Oral administration is the most popular route for systemic effects due to its ease of administration, pain avoidance, versatility and patient compliance, less expensive to manufacture**.** The oral route remains the perfect route for the administration of therapeutic agents because the low cost of therapy, manufacturing and ease of administration lead to high levels of patient compliance[1-5]. Many patients have difficulty swallowing tablets and hard gelatin capsules and

consequently do not take medications as prescribed. It is estimated that 50% of the population is affected by this problem, which results in a high incidence of noncompliance and ineffective therapy[6-8]. oral tablet administration to patients is a significant problem and has become the object of public attention. The problem can be resolved by the creation of rapidly dispersing or dissolving oral forms, which do not require water to aid swallowing. The dosages forms are placed in the mouth, allowed to disperse or dissolve in the saliva, and then are swallowed in the normal way[9,10].

The concept of Fast Disintegrating Drug Delivery System emerged from the desire to provide patient with more conventional means of taking their medication. It is difficult for many patients to swallow tablets and hard gelatin capsules. Hence they do not comply with prescription, which results in high incidence of non-compliance and ineffective therapy. In some cases such as motion sickness, sudden episodes of allergic attacks or coughing and unavailability of water, swallowing conventional tablets may be difficult. Particularly the difficulty is experienced by pediatric and geriatric patients. Such problems can be resolved by means of Fast Dissolving Tablet. When put on tongue, this tablet disintegrates instantaneously, releasing the drug, which dissolves or disperses in the saliva.

Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablet dosage form[11,12].

As tablet disintegrates in mouth this could enhance the clinical effect of the drug through pre-gastric absorption from the mouth, pharynx and esophagus. This leads to an increase in bioavailability by avoiding first pass metabolism [13-15].

Definition: The Center for Drug Evaluation and Research (CDER), US FDA defined Oral Disintegrating Tablets (ODT) as "A solid dosage form containing medicinal substances, which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue."

A fast disintegrating or dissolving system or tablet can be defined as a solid dosage form that can disintegrate or dissolve within 30 seconds, in the oral cavity resulting in a solution or suspension without administration of water. The fast disintegrating tablets are synonymous with fast dissolving tablets; melt in mouth tablets, rap melts, Porous tablets, Orodispersible, quick dissolving or rapidly disintegrating tablets.

Requirements of fast disintegrating tablet of an ideal FDT [16]

Require no water for oral administration, yet dissolve / disperse/ disintegrate in mouth in a matter of seconds. Have a pleasing mouth feel. Have an acceptable taste masking property.

Be optimum harder and less friable Leave minimal or no residue in mouth after administration Exhibit low sensitivity to environmental conditions (temperature and humidity).

Advantages: [16,17,18] Ease of administration to patients who refuse to swallow a tablet, such as pediatric and geriatric patients and psychiatric patients.

Convenience of administration and accurate dosing as compared to liquids. No need of water to swallow the dosage from, which is highly convenient feature for patients who are traveling and do not have immediate access to water.

Characteristics of fast disintegrating systems: a. Ease of administration, b. Taste of the medicament, c. Hygroscopicity. d. Friability e. Mouth feel.

The key to rapid disintegration for mouth dissolving tablets is the presence of a porous structure in the tablet matrix. Hence. To generate porous matrix, volatile ingredients are used that are later subjected to a process of sublimation. In studies conducted by Heinemann and Rothe, Kitsch et al.,[19] and Roser and Blaire al.,[20] inert solid ingredients that displayed high volatility (e.g., ammonium bicarbonate, ammonium carbonate, benzoic acid, camphor, hexamethonium tetramine, naphthalene, phthalic anhydride, urea, and urethane were compressed along with other excipients into a table.[21,22] The volatile material was then removed by sublimation, leaving behind a porous matrix. Solvents such as cyclohexane and benzene were also suggested for the generation of porosity in the matrix.

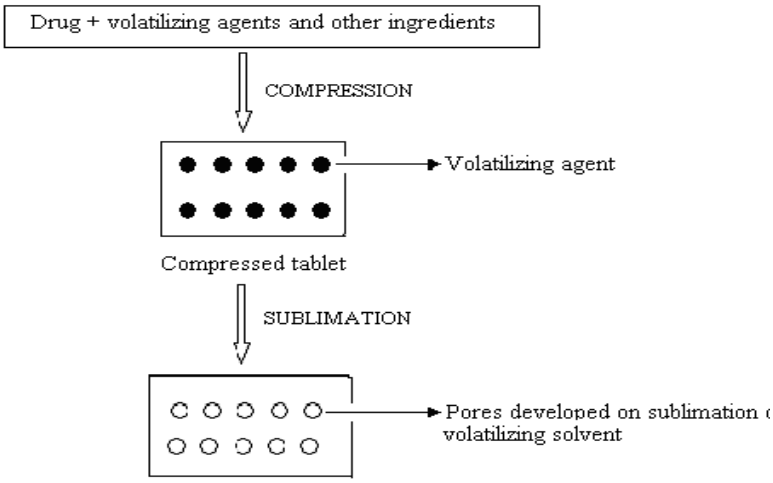


Fig 1: Schematic Diagram of Sublimation Technique for Preparation of FDT

Patented technologies for mouth dissolving drug delivery system[22]

several technologies are available, a few have reached for commercial marketed products such as Flash dose, Flash tab, Oraquick, Orasolv, Zydis and WOW Tab.FDA considers these mouth dissolving tablets as a new dosage form .

Mechanism of tablet disintegration[25]

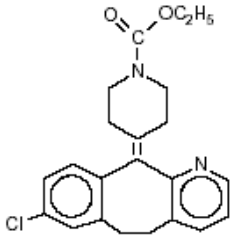
Capillary action (Wicking), Swelling, Due to disintegrating particle/particle repulsive forces, Due to deformation, Due to release of gases.

DRUG PROFILE[23, 24]

Loratadine

Loratadine is a derivative of azatadine and a second-generation histamine H1 receptor antagonist used in the treatment of allergic rhinitis and urticaria. Unlike most classical antihistamines (histamine H1 antagonists) it lacks central nervous system depressing effects such as drowsiness.

Structure



Chemical Formula: $C_{22}H_{23}ClN_2O_2$, **Molecular weight**: 382.89

Clinical Pharmacology: Indication: A self-medication that is used alone or in combination with pseudoephedrine sulfate for the symptomatic relief of seasonal allergic rhinitis. Also used for the symptomatic relief of pruritus, erythema, and urticaria associated with chronic idiopathic urticaria in patients (not for children under 6 unless directed by a clincian).

MATERALS AND METHODS

S. NO	EQUIPMENT NAME	SOURCE
1	DIGITAL WEIGHING MACHINE	SHIMADZU ATY 244
2	TABLET COMPRESSION MACHINE	KARNAVATHI MINI PRESS-II
3	MONSANTO HARDNESS TESTER	CINTEX IND. CORPORATION, MUMBAI
4	FRIABILITY TESTER	ELECTROLAB PVT LTD. INDIA
5	USP DISSOLUTION APPARATUS	LAB INDIA DS 8000
6	DISINTEGRATION APPARATUS	LAB INDIA DT 1000
7	TRAY DRYER	SISCO
8	UV-VIS DOUBLE BEAM SPECTROPHOTOMETER	ELICO SL 164 DOUBLE BEAM SPECTROPHOTOMETER

INGREDIENT DETAILS

S.NO	DRUG/EXCIPIENTS	NAME OF SUPPLIER
1.	LORATIDINE	TORRENT PHARMA
2.	CAMPHOR	SD FINE –CHEM PVT, MUMBAI
3.	MANNITOL	SD FINE –CHEM PVT, MUMBAI
4.	CROSCARMELLOSE SODIUM	SD FINE –CHEM PVT, MUMBAI
5.	MENTHOL	SD FINE –CHEM PVT, MUMBAI
6.	MAGNESIUM STEARATE	SD FINE –CHEM PVT, MUMBAI
7.	TALC	SD FINE –CHEM PVT, MUMBAI

METHODOLOGY

Ultraviolet Visible (UV-visible) spectroscopy: Construction of Calibration Curve

Preparation of Stock Solution: 100 mg of Loratidine was taken in a 100 ml volumetric flask. To that 10 ml of methanol was added and shaken well to dissolve the drug. The solution was made up to the mark with 6.8 PH phosphate buffer solutions.

- From the above solution 1 ml is diluted to 10 ml with, 6.8pH phosphate buffer solutions to give 100 µg /ml concentration.
- From the above solution 1 ml is diluted to 10 ml with, 6.8pH phosphate buffer solutions to give 10 µg /ml concentration.
- The prepared solution i.e., 10 µg/ml concentration was scanned for λ_{max} from 200-400 nm in UV/Visible spectrophotometer.

Evaluation of API and Blend (Pre-compression Parameters): Angle of Repose, Bulk density, Tapped density, Compressibility index and Hausner's ratio:

Compressibility index = 100 × tapped density / bulk density

Hausner's ratio = tapped density / bulk density

In a variation of these methods, the rate of consolidation is sometimes measured rather than, or in addition to, the change in volume that occurs on tapping. For the compressibility index and the Hausner's ratio, the generally accepted scale of flow ability is described in the following table. Flow properties and corresponding Angle of repose, Compressibility index and Hausner's ratio:

Table 1: Flow properties determination

S.No	Flow properties	Angleof repose(θ)	Compressibility Index (%) or Carr's index	Hausner ratio
1	Excellent	25-30	<10	1.00-1.11
2	Good	31-35	11-15	1.12-1.18
3	Fair	36-40	16-20	1.19-1.25
4	Passable	41-45	21-25	1.26-1.34
5	Poor	46-55	26-31	1.35-1.45
6	Very poor	56-65	32-37	1.46-1.59
7	Very very poor	> 66	>38	>1.6

EVALUATION OF TABLETS (Post Compression Parameters): The quantitative evaluation and assessment of a tablets chemical, physical and bioavailability properties are important in the design of tablets and to monitor product quality. There are various standards that have been set in the various pharmacopoeias regarding the quality of pharmaceutical tablets. These include the diameter, size, shape, thickness, weight, hardness, disintegration and dissolution characters.

Drug release: The drug release from the Loratidine tablets was investigated in a USP-II(paddle) apparatus, 900 ml of 6.8pH Phosphate buffer (50 rpm, 37°C). At predetermined time intervals, 5-ml samples were withdrawn and take 1ml sample and diluted to 10 ml and then analyzed with UV spectrophotometry at λmax=242nm.

Dissolution study of Loratidine of fast disintegrating tablets

Bath temperature : 37 ⌖ 0.5°C
Dissolution media : 6.8 pH buffer
Volume of dissolution media : 900 ml
Aliquot withdrawn : 5 ml
Dissolution apparatus : USP type II (paddle)
Revolutions per minute (Speed): 50

FORMULATION DEVELOPMENT OF POROUS TABLETS

Table 2: Excipients in the formulation of porous tablets

Ingredients	Purpose
Mannitol	Diluent
Croscarmellose	superdisintegrants
Camphor	Pore forming agent
Menthol	Flavoring agent
Magnesium stearate	**Lubricant**
Talc	Glidant

Procedure for the preparation of porous tablets by Sublimation technique:

Loratidine: βCD: tartaric acid kneaded solid system prepared in 1:2:2 molar ratios, respectively, that showed the highest solubility and extent of drug dissolution were incorporated in the proposed porous tablets. It was mixed with CCS for 20 minutes using a pestle in a glass morter. Following that, the calculated amount of mannitol was added to the above mixture and blended together for additional ten minutes. Prior to compression, the sublimable material, either camphor or menthol, was added to the tablets mixture and was mixed with for 20 minutes. Lastly, magnesium stearate was incorporated to the previous mixture and mixed for additional 10 minutes. Tablets of 200 mg were prepared using a single punch tablet press machine equipped with 6 mm punch and die. The tablets were then placed in a vacuum oven adjusted at 60°C for 2 hour to eliminate camphor or menthol by sublimation leaving many pores where they previously existed in the compressed tablets[14]. The formed pores or cavities allow rapid penetration of saliva into these tablets leading to fast disintegration when placed in the oral cavity.

Table 3: Composition of Loratidine porous tablets

S.NO.	Ingredient	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
1	Loratidine Kneaded solid system	Eqto 10mg	Eqto 10mg	Eqto 10mg	Eqto 10mg	Eqto 10mg	Eqto 10mg	Eqto 10mg	Eqto 10mg	Eqto 10mg	Eqto 10mg
2	Camphor%	---	10	20	--	--	--	10	20	--	--
3	Menthol%	----	----	--	10	20	--	----	--	10	20
4	Croscarmellose sodium	--	--	--	--	--	10	10	10	10	10
5	Mannitol upto	200	200	200	200	200	200	200	200	200	200

** all the ingredients were taken in mg's*

RESULT AND DISCUSSION

Table 4: Pre Formulation Study

S.NO	API CHARACTERISATION	RESULTS
1	Physical Appearance	a white to slightly pink crystalline powder
2	Melting point	138-148 ºC
3	Bulk density	0.376 gm/ml
4	Tapped Density	0.421 gm/ml
5	Carr's index/Compressibility index	11.9
6	Hausner's Ratio	1.119

Table 5: Solubility Studies

Composition	Solubility (mg/ml)	
	Physical Mixer	Kneading solid systems
Water	0.023	
Lor:bCD:(1:2)	0.02 ± 0.01	0.21 ± 0.08
Lor:bCD:Tar(1:2:1)	2.87 ± 0.1	5.64 ± 0.6
Lor:bCD:Cit(1:2:1)	2.46 ± 0.4	3.93 ± 0.3
Lor:bCD:Tar(1:2:2)	3.45 ± 0.2	7.30 ± 0.8
Lor:bCD:Cit(1:2:2)	2.92 ± 0.3	4.09 ± 0.4

Aqueous solubility (mg/ml ±SD, n=3) at 25°C, relative increment, and dissolution efficiency of Loratidine from the prepared solid systems. (Lor: Loratidine; Tar: Tartaric acid; Cit: Citric acid).

Drug Polymer Interaction Study: From the spectra of Loratidine, combination of Loratidine with excipient, it was observed that all characteristic peaks of Loratidine were present in the combination spectrum, thus indicating compatibility of the drug and excipient.

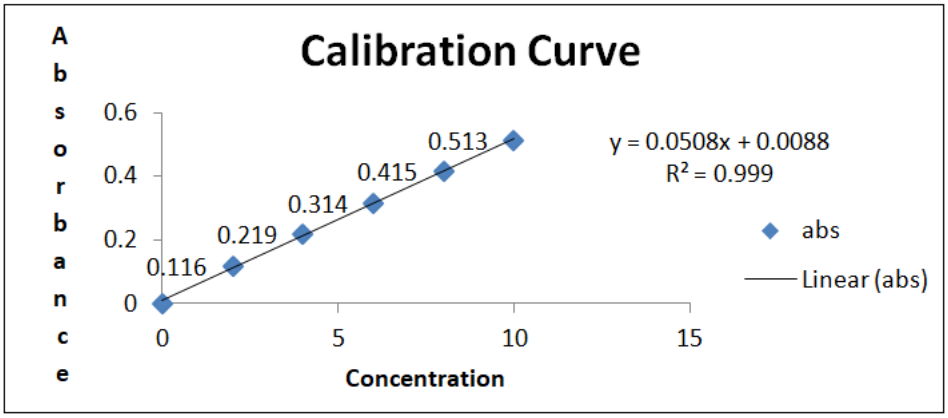


Fig 2: Standard calibration curve for Loratidine

Table 6: FLOW PROPERTIES

Formulation	Bulk density	Tapped density	Carr's Index	Hausner's Ratio	Angle of Repose
F1	0.318	0.389	18.25	1.223	24.93
F2	0.331	0.399	17.04	1.205	24.25
F3	0.329	0.396	16.91	1.203	25.05
F4	0.345	0.409	15.64	1.185	26.40
F5	0.338	0.378	10.58	1.118	28.67
F6	0.389	0.444	12.38	1.141	27.56
F7	0.362	0.410	11.70	1.132	27.66
F8	0.329	0.396	16.91	1.203	28.67
F9	0.337	0.403	16.31	1.195	25.06
F10	0.345	0.409	15.64	1.185	26.40

Evaluation studies of tablets

FORMULATION CODE	WEIGHT VARIATION	HARDNESS Kg/Cm^2	THICKNESS (mm)	FRIABILITY (%)
F1	200±0.13	3.6	1.85	0.15%
F2	200±0.53	3.5	1.9	0.12%
F3	2000±0.69	4.1	1.91	0.14%
F4	199±0.11	3.9	1.95	0.12%
F5	200±0.16	3.5	1.86	0.13%
F6	200±0.17	3.3	1.92	0.12%
F7	201±0.18	3.4	1.91	0.14%
F8	199±0.10	3.8	1.93	0.16%
F9	200±0.03	3.5	1.87	0.15%
F10	200±0.13	3.6	1.85	0.15%

The hardness of the all formulations was found to be 3.3 to 4.1 kg/cm^2 and friability was found to be below 1% indicating good mechanical resistance. The thickness of the tablets was found to be 1.85 to 1.98. All the tablets passed weight variation test, as percentage weight variation was within the pharmacopoeial limits i.e. ±7.5%.

Disintegration time of all formulations: The most important parameter that needs to be optimized in the development of fast disintegrating tablets is the disintegration time of tablets. In the present study disintegration time of all batches were found in the range of 13-447sec fulfilling the official requirements (less than1 min) for disintegrating tablets. Results were showed in table:7.

Table 7: Disintegration and Drug Content

Formulation	Drug content in %	*In-vitro* Disintegration time(sec.+/_S.D)	Wetting Time(sec)
F1	95.69	447.42 ± 12.47	> 300
F2	94.67	62.49 ± 4.15	95.46
F3	96.19	57.12 ± 2.87	73.56
F4	93.67	63.49 ± 4.15	65.78
F5	96.16	47.45 ± 3.18	59.34
F6	94.17	47.45 ± 3.18	48.78
F7	95.18	38.93 ± 5.72	43.76
F8	98.16	13.21 ± 2.24	23.67
F9	96.20	37.45 ± 3.18	35.78
F10	95.16	42.45 ± 2.18	43.8

From the formulations F1 -F10, F8 formulation is having 98.16% drug content, lesser disintegration time (13sec) and wetting time (23sec). so the formulation F8 was taken as optimized one according to this data.

IN VITRO DISSOLUTION STUDIES

Apparatus: I, Solvent: 6.8 pH phosphate buffer Volume: 900 ml, Rpm: 50
Temperature: 37 ± 5˚C,λ_{max}: 242 nm

Table 8: Dissolution Profile of Prepared Formulations

Time	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
0	0	0	0	0	0	0	0	0	0	0
5	10.31 ± 0.06	9.91 ± 0.19	4.99 ± 0.07	14.61 ± 0.08	14.62 ± 0.16	16.83 ± 0.02	14.74 ± 0.03	27.16 ± 0.10	20.68 ± 0.11	16.83 ± 0.23
10	15.89 ± 0.02	14.93 ± 0.11	9.79 ± 0.11	15.98 ± 0.07	16.94 ± 0.19	17.40 ± 0.07	16.81 ± 0.09	45.11 ± 0.09	32.04 ± 0.26	18.41 ± 0.21
20	28.07 ± 0.04	22.83 ± 0.15	14.65 ± 0.14	29.25 ± 0.12	30.26 ± 0.17	31.07 ± 0.19	30.26 ± 0.05	50.55 ± 0.07	49.75 ± 0.12	31.75 ± 0.17
30	43.53 ± 0.09	26.33 ± 0.03	16.96 ± 0.09	47.79 ± 0.06	48.33 ± 0.12	49.29 ± 0.13	48.33 ± 0.05	66.11 ± 0.08	64.34 ± 0.19	49.72 ± 0.12
40	61.59 ± 0.10	44.54 ± 0.07	34.74 ± 0.13	62.40 ± 0.02	62.45 ± 0.20	64.04 ± 0.13	62.45 ± 0.09	83.53 ± 0.09	77.01 ± 0.16	64.38 ± 0.29
50	72.06 ± 0.14	69.68 ± 0.15	67.13 ± 0.12	72.93 ± 0.09	74.11 ± 0.19	75.04 ± 0.03	74.11 ± 0.04	90.64 ± 0.12	82.88 ± 0.20	75.79 ± 0.14
60	83.32 ± 0.09	89.61 ± 0.19	84.55 ± 0.08	94.40 ± 0.19	95.92 ± 0.23	94.47 ± 0.08	95.92 ± 0.04	98.41 ± 0.10	96.86 ± 0.21	96.61 ± 0.23

STABILITY STUDIES: There were no significant changes in physical and chemical properties of capsule of formulation F-8 after 2 months. Parameters quantified at various time intervals were shown:

Table 9: Results of stability studies of optimized formulation F8

Formulation code	Parameters	Initial	1st Month	2nd Month	Limits as per specifications
F8	25˚C/60%RH % Release	98.41	97.87	97.65	Not less than 85%
F8	30˚C/75%RH % Release	98.41	97.89	97.88	Not less than 85%
F8	40˚C/75%RH % Release	98.41	97.88	97.63	Not less than 85%
F8	25˚C/60%RH Assay value	98.41	98.10	98.12	Not less than 90% Not more than 110%
F8	30˚C/75%RH Assay value	98.41	98.11	98.10	Not less than 90% Not more than 110%
F8	40˚C/75%RH Assay value	98.41	98.10	98.10	Not less than 90% Not more than 110%

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CONCLUSION

Finally it was concluded that, Formulation 8: Drug, volatilizing agent and super disintegrant (Ac-Di-Sol), which was prepared by direct compression method have good wetting property, lesser disintegration time and faster action when compared to other formulations. So the formulation F8 was taken as a optimized one.

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