

FORMULATION AND EVALUATION OF MODIFIED PULSINCAP DRUG DELIVERY SYSTEM OF RIZATRIPTAN BENZOATE

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ABSTRACT

Objective: The objective of the present study was to develop colon targeted pulsatile drug delivery system of Rizatriptan benzoate for the treatment of migraine.

Method: Drug excipient interaction was carried by UV spectroscopy, FT-IR, and DSC. Granules were prepared by wet granulation method. Physicochemical characteristics of Rizatriptan benzoate was carried out by flow properties and drug content. From the obtained results the formulation was selected for further preparation of pulsatile capsule with 100mg hydrogel plug. Prepared pulsincap was coated with 5% CAP. The pulsincap was evaluated for in-vitro dissolution studies and release kinetics.

Results: F6 formulation was optimized. FTIR and DSC has shown no interaction between polymer and Rizatriptan benzoate. Cross-linked gelatine capsule were evaluated and confirmed that 8 hrs formaldehyde treatment was sufficient. 100mg hydrogel plug was optimized. Hardness and thickness of the plug controlled lag time. Granules showed good flow properties and drug content were found to be in the range of 95.4±0.56 to 98.3±0.56 %. The results indicated that drug content was uniform. *In-vitro* release studies revealed that increasing the polymer content resulted in sustained release. Value of *n* in Korsmeyer-Peppas Equation is greater than 1 hence, formulation were follows swelling controlled super case II transport.

Conclusion: Present pulsincap formulation study conclude that optimized F6 batch of Rizatriptan benzoate successfully targeted to colon for the treatment of migraine. Drug release over a period of 5-18 hrs, can be achieved from treated gelatine capsule and hydrogel plug.

Keywords: Pulsatile, Colon-targeted, Migraine, Chronotherapeutic, Rizatriptan benzoate.

INTRODUCTION

Pulsatile drug delivery systems are time-controlled drug delivery system. These systems are design to achieve time specific and site specific delivery of drugs according to the circadian rhythm of the body. Pulsatile release pattern has gained most popular form of controlled drug delivery system because conventional systems with a continuous release are not ideal. Pulsatile systems are beneficial for the drugs having chronopharmacological behaviour [1,2].

Colon-targeted drug delivery systems (CDDS) have been developing as one of the site specific drug delivery systems. Along with various applications in local and systemic delivery of drugs the CDDS would also be advantageous when a delay in absorption is desirable from a therapeutic point of view as for the treatment of diseases that have peak symptoms in the early morning and that exhibit circadian rhythm, such as migraine, rheumatoid arthritis, angina and peptic ulcer [3]. In case of migraine, peak symptoms occur early in the morning due to release of adrenaline in larger quantities during the early morning. Since adrenaline affects blood pressure and the regulation of dilation or contraction of the blood vessels, it may play a role in the migraine attacks. So by developing the pulsatile device for specific colon targeted delivery, plasma peak is obtained at an optimal time, number of doses can be reduced and first pass metabolism can also be avoided. Frequent administration of this drug is necessary due to its short biological half life. Based on the concept that a formulation leaving stomach arrives at the ileocaecal junction in about 6 hours colonic targeting was designed, for achieving the selective delivery of drugs to colon, which is chronopharmaceutical approach for the better treatment of migraine attacks[4]. Rizatriptan benzoate is a selective 5-hydroxytryptamine receptor agonist [N,N-dimethyl-5-(1H-1,2,4-triazol-1-ylmethyl)-1H-indole-3-ethanamine monobenzoate] for the treatment of migraine headaches. It has

biological half-life of 2-3 hours and bioavailability is 45%. It acts on stimulation of presynaptic 5-HT_{1D} receptors, which serves to inhibit both dural vasodilatation and inflammation, direct inhibition of trigeminal nuclei cell excitability via 5-HT_{1B/1D} receptor agonism in the brainstem and vasoconstriction of meningeal, dural, cerebral or pial vessels as a result of vascular 5-HT_{1B} receptor agonism [5,6].

MATERIAL AND METHODS

Rizatriptan Benzoate and HPMC K4M was gift sample from Gen Pharma International Pvt Ltd, Pune India. Methanol was supplied by Qualigens fine chemicals, Mumbai. All other ingredient used was of analytical grade.

Drug -Characterization

UV Spectroscopy

Calibration curve of Rizatriptan benzoate was plotted with water, pH 1.2, 7.4 and 6.8 buffer with different concentration (1, 2, 3, 4, 5 µg/ml). The absorbance of the solution was taken at wavelength 225 nm against the blank solution. (UV spectroscopy 400-200 nm, Shimadzu, Japan 1601)[6].

Fourier Transform Infrared (FT-IR) Spectroscopy

Infrared spectroscopy was used to predict possible drug excipients interaction using a FTIR spectrometer (8400S, Shimadzu, Japan) at 4000-400cm⁻¹[6].

Differential Scanning Calorimetry (DSC)

Thermogram of drug was carried out by using DSC. In this study approximately 5 mg of sample were taken and heated 0°C to 450 °C at heating rate 10°C/min. Thermo gram obtained by using DSC (METTLER DSC 1 STAR SYSTEM, Zürich, Switzerland) [6].

Drug excipient interaction study

Fourier Transform Infrared (FT-IR) Spectroscopy:

The IR spectra of Rizatriptan benzoate, polymer and optimized formulation were recorded with the help of Fourier transform infrared spectroscopy using the range 4000-400 cm^{-1} . The sample was intimately mixed with dry powdered potassium bromide in 1:10 ratio. The mixture was then compressed into transparent disc under high pressure using special dies. The disc was placed in IR spectrophotometer using sample holder and IR spectrum was recorded [6].

Differential Scanning Calorimetry (DSC)

The thermogram of pure drug, polymer and formulation was carried out using DSC. Samples were placed in aluminium crucibles and DSC thermograms were recorded at the heating rate of $10^\circ\text{C}/\text{min}$ in the range of 0°C to 450°C . Air was purged at the rate of $10 \text{ ml}/\text{min}$.

Formulation design [7-10].

Preparation of Cross-Linked Gelatine Capsules

Formalin treatment has been employed to modify the solubility of gelatine capsules. Exposure to formalin vapours results in an unpredictable decreases in solubility of gelatine owing to the cross-linkage of the amino group in the gelatine molecular chain aldehyde group of formaldehyde by Schiff's base condensation.

Method

Hard gelatine capsule of size 0 was taken. Bodies were separated from cap, 25 ml of 15% (v/v) formaldehyde was taken into desiccators and a pinch of potassium permanganate was added to it, to generate formalin vapours. The wire mesh containing the empty bodies of capsule was then exposed to formaldehyde vapours. The caps were not exposed leaving them water-soluble. The desiccators were tightly closed. The reaction was carried out for 12 h after which the bodies were removed and dried at 50°C for 30 min to ensure completion of reaction between gelatine and formaldehyde vapours. The bodies were then dried at room temperature to facilitate removal of residual formaldehyde. These capsule bodies were capped with untreated caps and stored in a polythene bag.

Tests for Formaldehyde Treated Empty Capsules

Various physical tests include identification attributes as visual defect, dimensions, solubility studies of treated capsules, and chemical test were carried out simultaneously for formaldehyde treated and untreated capsules. Variations in dimensions between formaldehyde, treated and untreated capsules were studied. The length and diameter of the capsules were measured before and after formaldehyde treatment, using dial calliper.

Solubility study of treated capsules [9,10].

The capsule bodies were exposed to 15% formaldehyde solution in varying time intervals. Then exposed capsule bodies were dried in hot air oven. The solubility of bodies was tested in 0.1N HCL. The time at which the capsule dissolves or forms a soft fluffy mass was noted.

Qualitative test for free formaldehyde

Standard used is formaldehyde solution and sample solution is formaldehyde treated bodies (about 25 capsules), cut into small pieces and taken into a beaker containing distilled water. This was stirred for 1 hrs with a magnetic stirrer, to solubilise the free formaldehyde. The solution was then filtered into a 50 ml volumetric flask, washed with distilled water and volume was made up to 50 ml with the washings.

Method

1ml of sample solution, 9ml of water was added. One millilitre of resulting solution was taken into a test tube and mixed with 4ml

of water and 5ml of acetone reagent. The test tube was warmed in a water bath at 40°C and allowed to stand for 40 min. The solution was less intensely colored than a reference solution prepared at the same time and in the same manner using 1ml of standard solution in place of the sample solution. The comparison was made by examining tubes down their vertical axis [11].

Optimization of hydrogel plug

The formulation of pulsincap 90mg and 100mg hydrogel plug was prepared by compressing equal amount of HPMC K4M and lactose using 7mm punches and dies on rotary tablet press keeping variation in thickness and hardness values of tablet plug. This plug was then fitted into the body of hard gelatin capsule (containing granules equivalent to 10mg of Rizatriptan benzoate) which was cross linked by exposing the capsule bodies to formaldehyde vapour in desiccator for 12 hours.

Characterization of prepared hydrogel plug

The prepared hydrogel plug evaluation was carried out for hardness, thickness and lag time test. The prepared hydrogel plugs were plugged to capsule bodies containing formulated granules and the cap was closed. The lag time test was conducted using USP II dissolution testing apparatus using 7.4 pH for phosphate buffer for 6 hrs. The drug release was observed.

Preparation of Rizatriptan benzoate granules

Rizatriptan benzoate granules were prepared by wet granulation method. The composition of different formulations used in the study is given in Table 1. The HPMC K4M, were sieved (no.60) separately and mixed with Rizatriptan benzoate. The powders were blended and granulated with PVPK30. Isopropyl alcohol was used as granulating agents. The wet mass was passed through a mesh and granules were dried at 50°C for 1 hr.

Characterization of Rizatriptan benzoate granules formulated with HPMC K4M

The prepared granules were evaluated for different flow properties which include angle of repose, bulk density, tapped density, compressibility index, Hausner's ratio, and drug content. The drug content was evaluated by an UV spectrophotometric method based on the measurement of absorbance at 225 nm.

Formulation of pulsatile (modified pulsincap) drug delivery system:

Preparation of modified pulsincap

Equivalent to 10 mg drug granules were filled in the capsule bodies and plugged with hydrogel plug. The treated body and the cap of the capsules were sealed with a small amount of 5% ethyl cellulose ethanolic solution. The sealed capsules were completely coated with enteric coating (5% CAP) to reduce variability in gastric emptying time, coating was repeated until an expected weight gain of 8-12% was obtained.

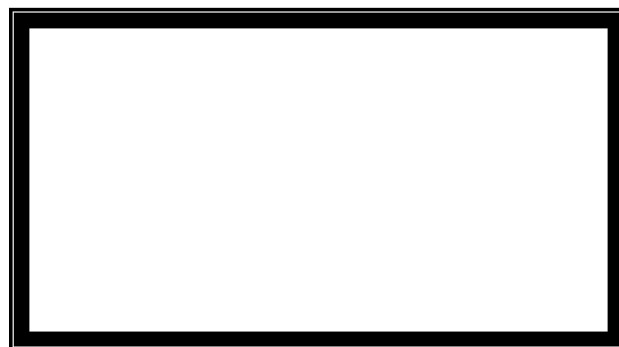


Fig. 1: Overview of designed pulsincap device

Evaluation of modified pulsincap

Thickness of cellulose acetate phthalate coating [14,15].

The thickness of cellulose acetate phthalate coating was measured using screw gauge and expressed in mm.

Weight variation

10 capsules were selected randomly from each batch and weight individually for weight variation.

In-vitro release profile

Dissolution studies were carried out by using USP II dissolution test apparatus (Basket) method. Capsules were placed in a basket so that the capsule should be immersed completely in dissolution media but do not float. In order to simulate the pH changes along the GI tract, three dissolution media with pH 1.2, 7.4 and 6.8 were sequentially used referred to as sequential pH change method. When performing

experiments, the pH 1.2 medium was first used for 2 hrs (since the average gastric emptying time is 2 hrs) then removed and the fresh pH 7.4 phosphate buffer saline (PBS) was added. After 3 hrs (average small intestinal transit time is 3 hrs) the medium was removed and fresh pH 6.8 dissolution medium was added for subsequent hrs. 900ml of the dissolution medium was used at each time. Rotation speed was 50 rpm and temperature was maintained at $37 \pm 0.5^\circ\text{C}$. Five millilitres of dissolution media was withdrawn at predetermined time intervals and fresh dissolution media was replaced. The withdrawn samples were analyzed at 225 nm by UVabsorption spectroscopy.

Drug Release kinetics data

To investigate the possible mechanisms of Rizatriptan benzoate release from the prepared pulsincap, the drug release data were fitted to various models such as Higuchi, Zero-order, First-order, Hixson Crowell and Korsmeyer Peppas kinetics. Model fitting was carried out using PCP DISSO.v 2.08 Software.

Table1: Composition of Rizatriptan Benzoate granules with HPMC K4M

S. No.	Ingredient (mg)	Formulation Code					
		F1	F2	F3	F4	F5	F6
1	Rizatriptan Benzoate	10	10	10	10	10	10
2	HPMC K4M	25	50	75	100	125	150
3	PVPK 30	20	20	20	20	20	20
4	Talc	2.5	2.5	2.5	2.5	2.5	2.5
5	Magnesium Stearate	2.5	2.5	2.5	2.5	2.5	2.5

Table 2: Composition for modified pulsatile device on the basis of design summary

Formulation code	Wt. of empty body (mg)	Wt. of Granules/ capsule (mg)	Hydrogel plug (100 mg)	Total weight of capsule with cap (mg)	Wt. Capsule After cap coating (mg)
F1	59.79	60	HPMCK4M+Lactose	256.22	265.11
F2	60.01	85	HPMCK4M+Lactose	282.17	290.84
F3	59.95	110	HPMCK4M+Lactose	307.79	316.25
F4	59.15	135	HPMCK4M+Lactose	333.02	342.21
F5	59.90	160	HPMCK4M+Lactose	357.42	366.52
F6	60.04	185	HPMCK4M+Lactose	383.28	394.72

Table 3: Drug release kinetics of F1-F6

Formulation Code	Zero order kinetic data		First order kinetic data		Higuchi Matrix kinetic data		Hixson-Crowell kinetic data		Korsmeyer-Peppas Equation-		
	R ²	k	R ²	k	R ²	k	R ²	k	R ²	k	n
F1	0.7461	6.818	0.6010	-0.1912	0.5821	-0.040	0.6592	14.317	0.8451	0.1683	2.306
F2	0.7969	0.650	0.6245	-0.1637	0.630	-0.036	0.6965	14.6203	0.8781	0.1607	2.262
F3	0.8281	6.7270	0.6465	-0.1921	0.6602	-0.039	0.7347	16.004	0.8964	0.1510	2.263
F4	0.8300	5.7141	0.7646	-0.0991	0.6641	0.7799	0.7927	-0.027	0.9010	0.1725	2.228
F5	0.8204	4.7513	0.7027	-0.0822	0.6530	11.8373	0.7494	-0.022	0.9160	0.1674	2.179
F6	0.8690	4.6358	0.7114	-0.0857	0.7047	12.701	0.7799	-0.022	0.9360	0.1692	2.341

RESULTS AND DISCUSSION

Drug Characterization

UV Spectroscopy

From calibration curve UV absorption maximum of drug was found at 225 nm. According to calibration curve correlation coefficient was found to be 0.998 (water), 0.999 (pH 1.2), 0.999 (pH 7.4), 0.997 (pH 6.8). Calibration curve obeyed beer's law in the range of 1-5 µg/ml.

FT-IR spectroscopy

FT-IR spectra of Rizatriptan benzoate shown peaks at 3497 cm⁻¹, 2947 cm⁻¹, 3003 cm⁻¹, 1606 cm⁻¹, 1375 cm⁻¹, 1294 cm⁻¹. These spectra match with standard drug [6].

Differential Scanning Calorimetry (DSC) study

Melting point of drug was measured; and found to be in the range 178-180°C. (figure 2)

Drug excipient interaction study

FT-IR spectroscopy

The IR spectra of drug, polymer, and formulation were reported in figure 2. It was found that there was no chemical interaction between all spectra. Drug shows intense peak at 3497 cm⁻¹, 2947 cm⁻¹, 3003 cm⁻¹, 1606 cm⁻¹, 1375 cm⁻¹, 1294 cm⁻¹, the same peaks with little difference were observed in the formulation [6].

Differential Scanning Calorimetry (DSC)

DSC thermograms of drug, polymer and formulation was studied and it was found that drug shown endothermic peak at 175-180°C. HPMCK4M showed broad peak at 76-78 °C and formulation (F6) shows broad base peak and slight shifting of melting point to 184.29°C (Figure.3). There is no major difference in the melting point of pure drug and formulation. It indicates the absence of chemical interaction between the drug and polymer [6].

Evaluation of Rizatriptan benzoate granules formulated with HPMC K4M

It was found that angle of repose was in the range 21-25°. This showed that granules had good flow properties. Bulk density and tapped density was found to be $0.3797 \pm 0.064 \text{ gm/cm}^3$ to $0.5357 \pm 0.062 \text{ gm/cm}^3$ and $0.4347 \pm 0.042 \text{ gm/cm}^3$ to $0.6120 \pm 0.056 \text{ gm/cm}^3$ respectively. The Hausner's ratio was found to be within the range of 1.115 to 1.151. The Carr's compressibility index (C) was found less than 15% in the range of 10.35-13.14. Result obtained was within the range of 10.35 ± 0.30 to $13.14 \pm 0.26 \%$. All the formulation showed good compressibility. The drug content was found to be in the range of 95.4 ± 0.56 to $98.3 \pm 0.56 \%$. Results indicated that in all the formulation the drug content was uniform [16].

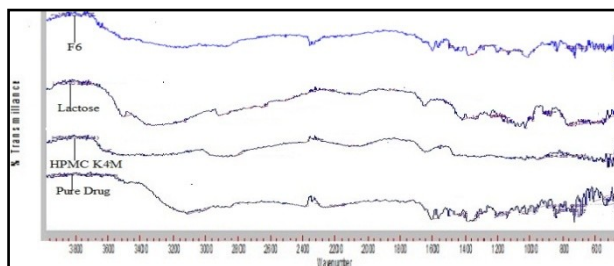


Fig. 2: IR spectra of Pure drug, HPMCK4M, lactose and F6 formulation

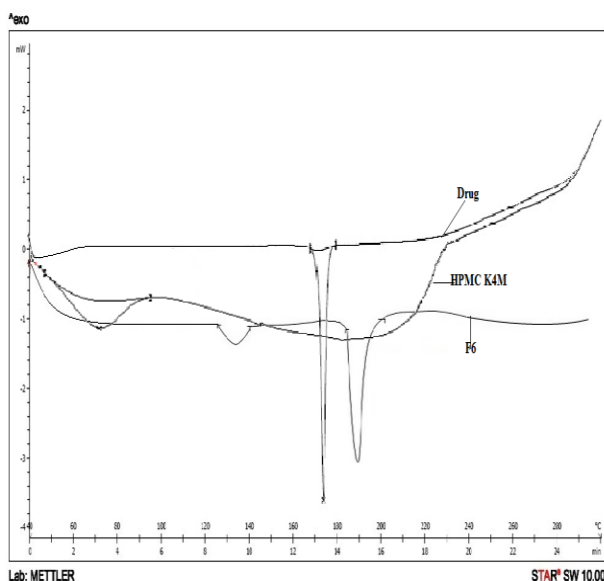


Fig. 3: Differential scanning calorimetry graph of pure drug, HPMCK4M and F6

Evaluation of hydrogel plug

The prepared hydrogel plugs were evaluated by thickness, hardness and lag time. It was found that 90 mg plug showed 4 hrs lag time and 100 mg plug showed 5.5 hrs lag time. Therefore 100 mg plug was optimized.

Evaluation of formulation treated empty capsules

The evaluation of treated empty capsule (cap and body) was carried out by length and diameter of capsules, It showed

Average capsule length

Before formaldehyde treatment (untreated cap and body): 20.85 mm

After formaldehyde treatment (treated body and untreated cap): 19.72 mm

Average diameter of capsule body

Before formaldehyde treatment: 7.12mm

After formaldehyde treatment: 6.84 mm

Average length of capsule body

Before formaldehyde treatment: 17.84mm

After formaldehyde treatment: 16.92mm

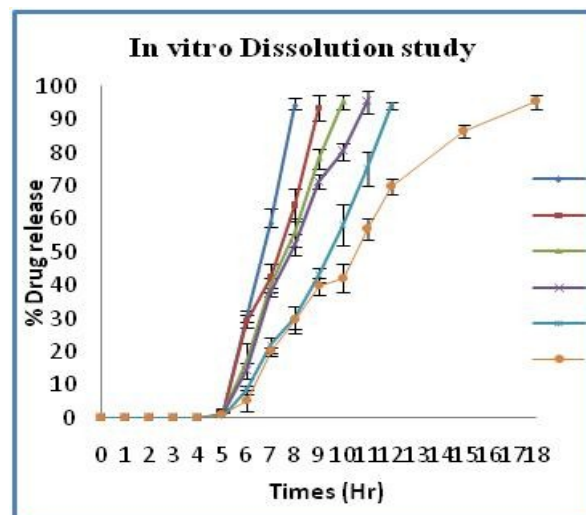


Fig. 4: In vitro Dissolution study

Solubility study for the treated capsules [17]

When the capsules were subjected to solubility studies in 0.1 N HCL for 24 hrs, the observation was found that the normal capsules both cap and body dissolved within fifteen minutes and another formaldehyde treated capsules, only the cap dissolved within 15 minutes remaining body of capsule intact for about 24 hours. Present work concludes that 8 hr formaldehyde treatment is sufficient to sustain the release for 18hr and found that the capsule has maintained the physical stability during the dissolution process.

Quantitative test for free formaldehyde

The formaldehyde capsules were tested for the presence of free formaldehyde. The sample solution was not more intensely colored than the standard solution inferring that less than 20µg free formaldehyde is present in 25 capsule.

Evaluation of modified pulsincap

Weight variation and thickness of coating

The filled capsules pass the weight variation test as their weights are within the specified limits and The thickness of the CAP coating was measured by using screw gauge the values ranged from 0.056-0.071 mm [13,14].

In-vitro release studies [18].

In-vitro drug release profiles from formulation (F6) were found to have very good sustaining efficacy. (Figure 4) During the dissolution studies, it was observed that, the enteric coat of the cellulose acetate phthalate was intact for 2 hours in pH 1.2, but dissolved in intestinal pH, leaving the soluble cap of capsule, which also dissolved in pH 7.4 phosphate buffer and then the exposed polymer plug which absorbed the surrounding fluid, swelled and released the drug through the swollen matrix. After complete wetting of the plug, it formed a soft mass, which was then easily ejected out of the capsule body; releasing the granules into simulated colonic fluid (pH 6.8 phosphate buffer). With all the formulations, there was no drug release in pH 1.2, thus indicating the efficiency of 5% CAP for enteric coating very slight release was observed in pH 7.4 phosphate buffers.

Drug release Kinetics data

Table 3 suggest that kinetics of drug release data with statistical analysis for formulation F1-F6 respectively the model that gives high R^2 value is considered as the best fitted model for the release of data and it was found that all the formulation follows the Korsmeyer-Peppas drug release that the Korsmeyer-Peppas equation of the F6 formulation were fairly linear because ' R^2 ' values near about 1 in all the cases. When percent drug release was plotted against time, linearity was observed for all the pulsincap as shown in figure 4. Value of n in Korsmeyer-Peppas equation is greater than 1 hence, formulation were follows swelling controlled super case II transport.

CONCLUSION

The present study was carried out to develop colon target drug delivery of Rizatriptan benzoate. The main aim of this study was to target drug release for colon to maintain the chrono pharmacological anti-migraine activity. The results obtained from the above study of revealed the following conclusions.

The FTIR and DSC studies indicated that, there was no interaction between polymer and drug. The result for micromeritic properties of granules showed good flow property for physical mixture and the drug content of all formulation. On the basis of drug content, *in-vitro* release, F6 was selected as better formulation designing pulsatile device. During the dissolution studies, it was observed that, the enteric coat of the cellulose acetate phthalate was intact for 2h in pH 1.2, but dissolved in intestinal pH, leaving the soluble cap of capsule, which also dissolved in pH 6.8, and then the exposed polymer plug absorbed the surrounding fluid. After complete wetting of the plug, it formed a soft mass, which was then easily ejected out of the capsule body. Releasing the minor quantity of granules into colonic fluid (pH 7.4) and other released in pH 6.8 buffer solutions. Statistical data showed that the drug release from the formulation follows Korsmeyer-Peppas model. From the present study it can be concluded that optimized F6 batch of Rizatriptan benzoate could be delivered drug in colon targeted system for the treatment of migraine.

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Conflict of interest: None

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