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Formulation and evaluation of tofacitinib citrate floating tablet

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Abstract

The present research work done with an objective of preparation and evaluation of floating tablets of Tofacitinib Citrate drug with Hydroxy propylene methyl cellulose (HPMC), Polyox N-60K, Carbopol 934 P and Guar gum polymers. Floating tablets were based on effervescent approach using sodium bicarbonate a gas releasing agent. Direct compression method was used in present study for preparation of tablets. Effect of polymers was evaluated by studying drug release and floating time. In-vitro drug release profile indicates that sustained nature increased by increasing the concentration of polymer. The formulation containing Polyox N-60K and Carbopol 934 P in combination was optimized as it showed drug release up to 12hrs. Optimized formulation F18 was found stable during stability condition up to 1 month.

Keywords: Tofacitinib Citrate, Floating Tablets, Carbopol 934 P.

1. Introduction

The majority of clinical applications still prefer oral drug administration as the primary route. Certain drugs possess ideal characteristics that promote good absorption, which is crucial for optimizing the therapeutic benefits they offer. Oral delivery of drugs is highly favored due to its ease of administration, patient compliance, and formulation flexibility. However, the transit time from the mouth to the colon can vary significantly within the range of 8-10 hours. The residence time in the stomach plays a vital role in determining gastrointestinal transit. Controlled oral drug delivery systems aim to continuously release the drug within an absorption window, ensuring prolonged and sufficient bioavailability. Floating dosage units are particularly beneficial for drugs that act locally in the proximal gastrointestinal tract. They are also advantageous for drugs that have poor solubility or are unstable in intestinal fluids. Examples of floating systems include floating tablets and floating capsules.

Effervescent floating drug delivery system:

A gastro-retentive dosage form is designed to release the drug slowly in the stomach and upper gastrointestinal tract, allowing for better absorption. There are several methods proposed to control the drug's residence in the upper part of the gastrointestinal tract, including the use of a floating drug delivery system. This system, along with high-density drug delivery systems, bioadhesive systems, swelling and expanding drug delivery systems, modified shape systems, and other delayed gastric devices, can help drugs with specific absorption windows or those that act locally in the stomach. These systems are also beneficial for drugs that are poorly soluble or unstable in intestinal fluid. The floating drug delivery system, in particular, remains buoyant in the stomach without affecting the gastric emptying rate for an extended period. Two different technologies, non-effervescent and effervescent systems, have been utilized in the

development of the floating drug delivery system based on the mechanism of buoyancy. In non-floating drug delivery systems, the drug is mixed with gel-forming agents or hydrocolloids that swell upon contact with gastric fluid after oral administration. This swelling helps maintain a stable shape and a bulk density of less than unity within the outer gelatinous barrier. The matrices system is prepared using swellable polymers and components such as sodium bicarbonate, citric acid, or stearic acid.Approaches for gastric retention:

For developing floating tablets of tofacitinib citrate to achieve gastric retention, you could consider several approaches:

1. Floating Systems: Utilize polymers or excipients that reduce tablet density, such as hydrocolloids (e.g., hydroxypropyl methylcellulose), to enable buoyancy in the gastric fluid.

2. Gas Generating Agents: Incorporate effervescent agents like sodium bicarbonate or citric acid to generate gas upon contact with gastric fluid, promoting tablet buoyancy.

3. Swelling Systems: Use swellable polymers like sodium alginate or polyethylene oxide, which increase in size upon hydration, thus delaying gastric emptying.

4. Mucoadhesive Systems: Employ mucoadhesive polymers such as carbopol or chitosan, which adhere to the gastric mucosa, prolonging gastric residence time.

5. Coating Techniques: Apply gastroretentive coatings like ethyl cellulose or cellulose acetate phthalate to delay tablet disintegration and dissolution in the stomach.

6. Floating System (Low Density Approach):These systems are referred to as hydrodynamically balanced systems (HBS/FDDS). They possess a bulk density lower than that of gastric fluid (<1.004 gm/ml). The specific gravity of gastric fluid is around 1.004-1.010 g/cm3 as per the “Documenta Geigy,” allowing the FDDS to float in the stomach without impacting the gastric emptying rate for an extended duration. This oral dosage form (capsule or tablet) is formulated to extend the duration of the dosage form's presence in the gastrointestinal tract.

Non effervescent floating drug delivery system

1.Colloidal gel barrier systems: Colloidal gel barrier systems are designed with a hydrodynamically balanced system (HBSTM) that includes drug along with gel-forming or swellable cellulose type hydrocolloids, polysaccharides, and matrix-forming polymers. These systems typically have high levels (20 to 75% w/w) of one or more gel-forming highly swellable cellulose type hydrocolloids like hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), hydroxypropyl methyl cellulose (HPMC), sodium carboxymethyl cellulose (NaCMC), as well as polysaccharides and matrix-forming polymers like polycarbophil,

polyacrylates, and polystyrene. These components are usually incorporated into tablets or capsules. When the system interacts with gastric fluid, the hydrocolloid hydrates and creates a colloidal gel barrier on its surface. This gel barrier helps regulate the rate of fluid penetration into the device, thereby controlling the release of the drug.

2.micro sporous compartment system: The micro porous compartment system involves enclosing a drug reservoir within a compartment that has pores on its top and bottom surfaces. The walls of the drug reservoir compartment are sealed to avoid direct contact with the gastric mucosal surface. When in the stomach, the floatation chamber filled with air allows the delivery system to float above the gastric

contents. Gastric fluid enters through the pores, dissolves the drug, and transports it continuously across the intestine for absorption.

3. Alginates beads: Alginate beads have been created as a form of multiple unit floating dosage. To produce these beads, a solution of sodium alginate is dropped into a calcium chloride solution, resulting in the formation of spherical beads with a diameter of approximately 2.5
mm. These beads are then separated, rapidly frozen in liquid nitrogen, and subjected to freeze drying at a temperature of -40 °C for a duration of 24 hours. This process leads to the development of a porous system within the beads, enabling them to maintain their floating force for a period exceeding 12 hours.

4. Hollow microspheres: Hollow microspheres, also known as micro balloons, were fabricated using a novel emulsion solvent diffusion technique. In this method, ibuprofen was loaded into the outer polymer shells of the microspheres. The process involved pouring a solution of the drug and an enteric acrylic polymer, dissolved in a mixture of ethanol and dichloromethane, into a vigorously stirred aqueous solution of polyvinyl alcohol (PVA). The temperature of the PVA solution was carefully maintained at 40°C. As the dichloromethane evaporated, gas was generated within the dispersed polymer droplets, resulting in the formation of internal cavities within the polymer microspheres, which encapsulated the drug.

5. Volatile liquid-based systems:To maintain the gastric retention time (GRT) of a drug delivery system, one approach is to include an inflatable chamber that holds a volatile liquid such as Ether or Cyclo-pentane. This liquid undergoes gasification at body temperature, leading to the inflation of the chamber within the stomach. These systems are designed as osmotically controlled floating systems, comprising a hollow deformable unit that can transition from a collapsed state to an expanded state. After a prolonged period, it can then revert back to its collapsed position.

6. Gas production systems:These floating delivery systems employ a bubbly reaction between carbonate/bicarbonate salts and citric/tartaric acid to release CO2, which becomes trapped in the gel-like hydrochloride layer of the system. As a result, the system's specific gravity decreases, allowing it to float on top of the chyme.

1. Dependence on Gastric Conditions: Non-effervescent FDDs rely on gastric conditions for dissolution and absorption, which can be altered by factors such as food intake or concurrent medication use, leading to unpredictable drug delivery.

2. Limited Compatibility: Certain active pharmaceutical ingredients may not be suitable for formulation into non-effervescent FDDs due to stability or solubility issues, limiting their applicability for some drugs.

Excipients are inactive ingredients used as carriers for the active ingredients in a pharmaceutical product. These may be classified into the following categories:

1. Binders
2. Diluents (filler)
3. Antiadherents
4. Disintegrants
5. Coloring Agent
6. Glidants and lubricants
7. Preservative
8. Sorbents
9. Sweeteners

1. Binders :

To promote cohesive compacts during direct compression and ensure the tablet remaining intact after

compression. To promote granulation (i.e. as granulator) to ensure free flowing properties of the particles. Binders are used either in a solution or in a dry form depending on other materials in the formulation & the method of preparation. The binding action is more effective when the binder is in a solution form than if it was dispersed in a dry form and moisten with the solvent.

Eg. Materials commonly used as binders include starch, lactose, methylcellulose, HPMC

2. Diluents (filler):

A filler, such lactose, is included to increase the size of the tablet. This is necessary as often the amount of 'active ingredient' is so tiny that the tablet would be too small to handle without it. Diluent adds bulk to make the tablet with practical size for compression and to be easily handled.

Requirements for a good filler:

1. Chemically inert, biocompatible, cheap.
2. Non-hygroscopic.
3. Good biopharmaceutical properties. (water soluble or hydrophilic).
4. Good technical properties (compactability)
5. Have an acceptable taste.

3. Antiadherents:

Many powders are prone to adhere to the punches ″sticking" or ″picking″, which is affected by the moisture content of the powder. - Such adherence specially occurred if the tablet punches have markings or symbols. Examples of antiadherents: -Mg stearate -Talc -Starch

4. Disintegrant is added to tablet formulation:

To facilitate tablet disintegration (break up) when it contacts fluids in the GIT and thus promotes rapid drug dissolution. Substances routinely included in tablet formulations and in many hardshell capsule formulation. To promote moisture penetration and dispersion of the matrix of the dosage form in dissolution fluids to expose primary drug particles.

Examples for disintegrants Common disintegrants include: - Starch and its derivatives (Sodium Starch Glycolate). - Cellulose and its derivatives (MCC,HPMC, CMC)

5. Colouring agent:

They are added to the tablet formulation to provide product identification and acceptable appearance. - All colorants used in pharmaceuticals must be approved and certified by the FDA. - Colorants are often accomplished during coating, but can be also included in the formulation prior to compaction. In the latter case, the colorant can be added as a soluble dye (wet granulation process) or insoluble lakes (direct compression).

6. Glidants and lubricants:

They have overlapping functions:

A- Glidants promote the flow of the tablet granules or powder by reducing friction between particles,

B- Antiadherents reduce sticking or adhesion of the tablet granules or powders to the faces of the punches or the die walls, e.g. Mg stearate, talc and starch.

C- Lubricants reduce the friction occurs between the walls of the tablets and the walls of the die cavity when the tablet is ejected, e.g. Mg stearate, waxes and talc.

They improve the rate of flow of the tablet granulation, prevent adhesion of the tablet material to the surface of the dies and punches, reduce interparticle friction, and facilitate the ejection of the tablets from the die cavity.

Examples for Glidants: - They are used in the formulation for direct compression. - They are also added to the granules before tableting to ensure proper flowability of the tablet mass for high production speed.

Mg stearate is mainly used as lubricant but also can be used as glidants

7. Sweetners:

Sweeteners are substances added to foods, beverages and pharmaceuticals to provide sweetness without adding significant calories or affecting blood sugar levels. Sweetners are used in tablet to mask bitter test.

Sweetening agents should have the following ideal properties

1. They are required to be effective when used in small concentration.
2. They must be stable at a wide range of temperature to which the formulations are likely to be exposed
3. Prolonged use of these agents containing preparations should not produce any carcinogenic effects
4. They should have very low or non-calorific value.
5. They should be compatible with other ingredients in formulations.
6. They should not show batch to batch variations.
7. They should be readily available and inexpensive.

Plan of work :

1. Selection of project tittle.
2. Literature survey.
3. Selection of suitable excipient and method .
4. Preformulation study :
   a) bulk density and tap density
   b) carr's index
   c) hausner's ratio
   d) angle of repose
5. procedure (weight granulation)
6. Evaluation tests:
   a) weight variation test
   b) hardness
   c) thickness
   d) friability test
   e) disintegration test
7. Results and conclusion

Drug profile :

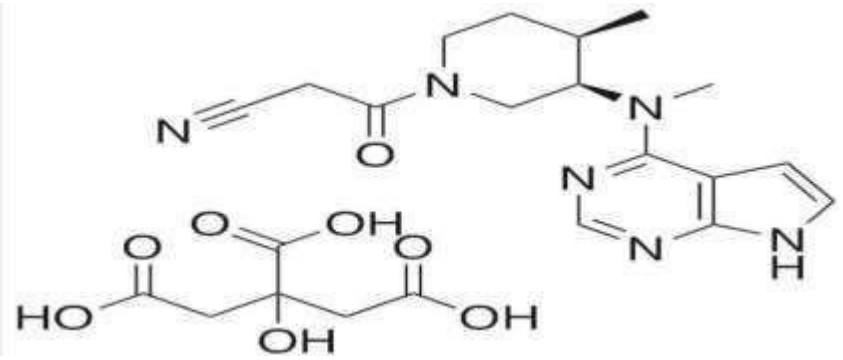

Fig no 1.Tofacitinib citerare

Background :-

Tofacitinib is an inhibitor of Janus kinases, a group of intracellular enzymes involved in signalling pathways that affect hematopoiesis and immune cell function. It is approved by the FDA for treatment of moderate to severe rheumatoid arthritis that responds inadequately to methotrexate or in those who are intolerant to methotrexate. Besides rheumatoid arthritis, tofacitinib has also been studied in clinical trials for the prevention of organ transplant rejection, and is currently under investigation for the treatment of psoriasis. Known adverse effects include nausea and headache as well as more serious immunologic and hematological adverse effects. Tofacitinib is marketed under the brand name Xeljanz by Pfizer.

tofacitinib citrate: Tofacitinib is an inhibitor of Janus kinases, a group of intracellular enzymes involved in signalling pathways that affect hematopoiesis and immune cell function. Tofacitinib is indicated for the treatment of adult patients with moderately-to-severely active rheumatoid arthritis (RA), active psoriatic arthritis, To controlled rheumatoid arthritis patients receiving 5mg or 10mg of tofacitinib twice daily Common known adverse effects of tofacitinib include headaches, diarrhea, nausea, and upper respiratory tract infection. Before initiations of tofacitinib patients should be tested for latent infections of tuberculosis, and should be closely monitored for signs and symptoms of infection (fungal, viral, bacterial, or mycobacterial) during therapy. Therapy is not to be started in the presence of active infection, systemic or localized

Sr.no.	**Properties**	**Tofacitinib Citrate**
1	IUPAC Name	3-[(3R,4R)-4-Methyl-3-[methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]piperidin-1-yl]-3-oxopropanenitrile
2	Appearance	White to off white powder
3	Colour	
4	Molecular formula	C22H28N6O
5	Molecular weight	312.377 g/mol
6	Melting point	198-202° C (dec.)
7	Log p	1.15
8	Category	Janus kinase (JAK) inhibitor
9	Dissociation constant	8.46
10	BSC class	Class III (high aqueous solubility and moderate permeability)
11	Half life	3 hours.
12	Synonyms	CP-690550, Xeljanz, Tasocitinib, (3R,4R)-4-Methyl-3-(methyl-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)-ß-oxo-1-piperidinepropanenitrile citrate salt
13	Bioavailability	74% oral absorption (absolute bioavailability), with peak plasma concentrations (T max) achieved in 0.5-1 hour.
14	Solubility	Freely soluble in N,N-Dimethylacetamide, slightly soluble in water, and very slightly soluble in ethanol (99.5% ethanol)

Mechanism of action :
Rheumatoid arthritis is a condition where the immune system mistakenly attacks the body's own tissues, leading to inflammation and joint damage. This is caused by an imbalance of pro- inflammatory cytokines such as IL7, IL15, IL21, IL6, IFN-alpha, and IFN-beta. These cytokines signal the immune cells to cause tissue inflammation and joint damage through the janus kinase signalling pathway. Tofacitinib is a medication that specifically targets and inhibits janus kinases (JAKs), which are involved in the cytokine signalling pathway. By blocking JAKs, tofacitinib prevents the phosphorylation and activation of STATs, which are important for the transcription of cells involved in hematopoiesis and immune cell function. By inhibiting the JAK-STAT pathway, tofacitinib reduces the inflammatory response in rheumatoid arthritis.

Absorption: 74% oral absorption (absolute bioavailability), with peak plasma concentrations (T max) achieved in 0.5-1 hour. Administration with fatty meals does not alter AUC but reduces Cmax by 32%.

Toxicity
Minimum lethal dose in rat: 500 mg/kg. Maximum asymptomatic dose in non human primate: 40 mg/kg. Lymphatic, immune system, bone marrow and erythroid cell toxicity was seen in animal studies involving rate and monkeys. Doses used in these studies ranged from 1mg/kg/day to 10mg/kg/day, over a duration of 6 weeks to 6 months. Lymphopenia, neutropenia, and anemia is seen in human subjects and may call for an interruption or discontinuation of therapy if severe. Reduced female fertility in rats was seen at exposures 17 times the maximum recommended human dose. Fertility may be impaired in human females and harm may be caused to unborn child. Carcinogenic potential is seen, however evidence for dose dependency is lacking. Because the janus kinase pathway plays a role in stimulating the production of red blood cells and is involved in immune cell function, inhibition of this pathway leads to increased risk of anemia, neutropenia, lymphopenia, cancer and infection. Lymphopenia, neutropenia, and anemia in human subjects may call for an interruption or discontinuation of therapy if severe. Role of JAK inhibition in the development of gastrointestinal perforation is not known.

Volume of distribution
Vd= 87L after intravenous administration. Distribution is equal between red blood cells and plasma.

Protein binding:40%, mostly bound to albumin**.**

Metabolism: Metabolized in the liver by CYP3A4 and CYP2C19. Metabolites produced are inactive.

Route of elimination:
70% metabolized in the liver by CYP3A4 (major) and CYP2C19 (minor). Metabolites produced are inactive. 30% renally eliminated as unchanged .

Materials AndMethod:

Sr.no	Drug name	Quantity
1	Tofacitinib citrate powder	5mg
2	Hpmc	31.25g
3	Carbopol 934	6.25g
4	Citric acid	18.75g
5	Magnesium streate	9.4g
6	Lactose	29.4g
7	Sodium bicarbonate	25g
8	Starch	15.62g

Preformulation studies :

1) bulk density and tap density :

The Drug (W) was precisely weighed and then cautiously transferred into a 10 ml graduated cylinder to determine its initial volume (Vo). Subsequently, the graduated cylinder was tapped 100 times, and the resulting volume (Vf), known as the tapped volume, was measured. The bulk density and tapped density were then computed using the prescribed formulas.

Where, w =120 g
V0 = 155 ml
Vf = 130 ml

1. Bulk density = W/V0
= 120/155
=0.77 gm/ml

2. Tapped density = W/ Vf
= 120/130
= 0.92 gm/ml

2) Carr's index:

It was obtained from bulk and tapped densities. It was calculated by using the following formula.

% Carr's index = (Tapped Density – Bulk Density ÷ Tapped Density) × 100

= (0.92- 0.77 ÷ 0.92) ×100

= (0.15÷0.92) ×100

=16.30%

3) Hausner's ratio:

Hausner's ratio is a number that is correlated to the flow ability of a powder. It is measured by ratio of tapped density to bulk density.

Hausner's ratio = (Tapped density ÷Bulk Density)

= 0.92 ÷ 0.77

= 1.19

4) Angle of repose:

Angle of repose of powder was determined by the funnel method. Accurately weight powder blend was taken in the funnel. Height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the powder blend. Powder blend was allowed to flow through the funnel freely on to the surface. Diameter of the powder cone was measured and angle of repose was calculated using the following equation.

$\tan \theta = H/R$

Where,

D = diameter of the circle D1 = 8cm

D2 = 7.7cm

D3 = 8cm D4 = 8.2cm

R = radius of the circle R1 = 4cm

R2 = 3.8cm

R3 = 4cm R4 = 4.1cm

Average radius = R1+R2+R3+R4 / 4

= 4+3.8+4+4.1 / 4

= 15.9 / 4

= 3.98cm

Hight of pile taken in this (H) = 2 cm Avarage radius of the circle (R) = 3.98cm

Angle of repose,

$$\text{Tan } \theta = H/R$$

$$\theta = \tan^{-1} H/R$$

$$= \tan^{-1}(2/3.98)$$

$$= \tan^{-1}(0.51)$$

$$\theta = 27.02$$

Procedure :

1) **Drug and Excipient Selection:** Choose appropriate excipients such as binders, diluents, disintegrants, and lubricants. Tofacitinib should be in a stable form suitable for wet granulation.

2) **Wet Granulation:** Mix the tofacitinib with wetting agents and binders to form granules. Common wetting agents include 0.1% Normal HCL (preparation of 0.1N HCL is 2.1 ml conc. HCL dissolve in 250 ml distilled water)

3) **Granule Drying:** Dry the granules to remove excess moisture. Proper drying is crucial to prevent issues like capping or sticking during tablet compression.

4) **Particle Sizing:** Mill the dried granules to achieve the desired particle size distribution.

5) **Blend Uniformity:** Blend the milled granules with other excipients to ensure uniform distribution of the drug throughout the formulation.

6) **Tablet Compression:** Compress the blend into tablets using a tablet press. Adjust compression parameters to achieve the desired tablet hardness and disintegration properties.

7) **Coating (Optional):** Apply a coating to the tablets for taste masking, protection, or modified release properties if needed.

8) **Quality Control:** Perform quality control tests to ensure the tablets meet specifications for hardness, friability, dissolution, and content uniformity.

Throughout the process, it's important to monitor critical parameters such as moisture content, particle size distribution, and blend uniformity to ensure the final product's quality and stability. Additionally, adhere to regulatory guidelines and good manufacturing practices (GMP) throughout the formulation process.

Fig no 3: granules of the mix samples

Fig no 4: tofacitinib tablet

Results:

1. Weight variation test:

Weight variation test was performed by taking 20 tablets of each batch and weighed using a balance. The average weight and standard deviation were recorded

Tablet	Tablet weight	Tablet	Tablet weight
1	0.47	11	0.46
2	0.45	12	0.47
3	0.46	13	0.47
4	0.48	14	0.46
5	0.45	15	0.46
6	0.47	16	0.49
7	0.50	17	0.48
8	0.47	18	0.42
9	0.46	19	0.45
10	0.45	20	0.39

Total weight of 20 tablet = 9.20 g Average weight of 20 tablet =0.46g

Now findout limits :

Limit = % deviation allowed/100 X average weight
= 5 /100 X 0.46
= 0.02

Upper limit = average weight +limit
= 0.46+0.02
=0.48

Lower limit = average weight – limit
= 0.46 - 0.02
= 0.44

Interpretation : no more than two tablet should outside the upper and lower limit so tablet will the pass weight variation test

2. Hardness

The hardness of ten tablets was determined using the Monsanto hardness tester and the average values were calculated.

Tablet no.	Hardness (kg/cm2)
1	5.13
2	4.72
3	5.26
4	4.76
5	5.14
6	5.07
7	4.58
8	5.15
9	5.42
10	5.29

3. Thickness

The thickness of the tables was determined by using digital Vernier calipers. Three tablets were used, and average values were calculated.

Tablet no.	Thickness
1	5.51
2	5.59
3	5.47
4	5.52
5	5.49
6	5.56
7	5.51
8	5.49
9	5.54
10	5.50

4. Tablet friability

The friability of the tablets was measured in a Roche Friabilator. Tablets of a known weight (W0) or a sample of 10 tablets are dedusted in a drum for a fixed time (100 revolutions) and weighed (Wf) again. Percentage friability was calculated from the loss in weight as given in equation as below. The weight loss should not be more than 1 %. Determination was made in triplicate.

W0 = 4.65 g Wf = 4.42g

% friability = W0 –Wf / W0 X 100

= 4.65-4.42 / 4.65 X 100

= 0.23 / 4.65 X 100

= 4.94

Conclusion :

The current investigation aimed to develop an Effervescent floating drug delivery system for Tofacitinib citrate utilizing HPMC K4M and Carbopol 934 polymers as carriers. Tofacitinib citrate, classified as a BCS class II drug due to its low solubility and high permeability, exhibits an oral bioavailability of less than 55% and a biological half-life of approximately 3-5 hours. These characteristics make it suitable for a gastro retentive drug delivery system. Following the procurement of the drug sample, it underwent FTIR characterization for identification purposes. Subsequently, the compatibility of the drug with all excipients was assessed, revealing no alterations in functional groups. The physical properties of Tofacitinib citrate tablets, including hardness, friability, average weight, and thickness, were found to meet standard references. The floating lag time of all nine tablet formulations indicated a total floating time exceeding 12 hours within one minute.

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