https://doi.org/10.48047/AFJBS.6.13.2024.6525-6532

African Journal of Biological Sciences

Journal homepage: http://www.afjbs.com

Research Paper Open Access

FORMULATION AND EVALUATION OF GLYCEROL GELATIN-BASED ISONIAZID SUPPOSITORIES FOR EFFECTIVE ANTI TUBERCULAR TREATMENT

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Volume 6, Issue 13, Aug 2024

Received: 15 June 2024

Accepted: 25 July 2024

Published: 15 Aug 2024

doi: 10.48047/AFJBS.6.13.2024.6525-6532

ABSTRACT

Globally, tuberculosis (TB) is a great cause of mortality and continues to pose a threat to public health. Given its early bactericidal action, isoniazid (INH) is a crucial first-line treatment for tuberculosis. There is a rising demand for an alternative method of isoniazid administration for the prevention and treatment of tuberculosis in children. Pharmaceutical formulations named suppositories are used to administer medication through the vaginal or rectal mucosa. This study aims to assess the in vitro release of isoniazid from extemporaneously compounded isoniazid suppositories and to optimize the suppository dosage form for this use. Isoniazid suppositories were formulated with a hydrophilic base material called glycerol gelatine, which has a greater impact on drug release than any other base with IP standards. The fusion method is utilized to formulate five batches of isoniazid suppositories, and it calculated their release rates in a pH 7.2 buffered with phosphate. Suppositories for uniform distribution are frequently prepared using the fusion technique. All of the suppositories had a drug content that ranged from 93.15%±0.75 to 102.40%±1.23. An isoniazid suppository based on glycerol gelatine base has been developed with an optimised formulation that can be used as an impromptu combining model in a resource-constrained scenario.

KEYWORDS: Suppositories, tuberculosis, glycerol, gelation, isoniazid.

INTRODUCTION

Isoniazid (INH) has been prescribed to treat tuberculosis (as part of combination therapy) and latent tuberculosis infection[1]. Anti-tuberculosis (TB) chemotherapy is now accessible, but tuberculosis (TB) is still the top infectious agent-related cause of mortality worldwide and a

concern to well-being of the public. The World Health Organization (WHO) estimates that over 10 million individuals worldwide develop TB each year, and around 1.6 million of them die from the disease. Approximately 30,000 new cases of TB and 2,000 fatal cases of TB are reported. INH is occasionally used as part of a combination regimen to treat nontuberculous mycobacterial infections. The medication can be administered in such a way that it reaches all organs, and that it can be extracted from various bodily fluids including caseous material, ascitic fluid, pleural fluid, and cerebral fluid. For susceptible strains of Mycobacterium tuberculosis, INH has both bacteriostatic and bactericidal properties. Mechanism of action—INH's antimicrobial activity is selective for mycobacteria, most likely due to its blocking mycolic acid formation, which interferes with cell wall synthesis and results in a bactericidal effect[2]. In addition, INH inhibits the synthesis of DNA, lipids, carbohydrates, and nicotinamide adenine dinucleotide (NAD). Glycerol gelatine suppositories fall into several classifications according to their preparation, including hydrophilic, lipophilic, and mucoadhesive[3]. Isoniazid (INH) has strong early bactericidal activity, making it a valuable first-line anti-TB drug. In order to ensure medication efficacy, safety, and the reduction of tuberculosis resistance, pharmaceutical analysis and therapeutic drug monitoring of isoniazid are essential for comprehending bioavailability, bioequivalence, and patient follow-up. Currently, the most prevalent kind of resistance to anti-TB medications is resistance to INH, either by itself or in combination with additional drugs. 7.1% of new cases and 7.9% of patients undergoing treatment already had INH resistance in TB cases without concurrent rifampicin (RIF) resistance, according to global data[4].

MATERIALS:

The active pharmaceutical ingredient was isoniazid. Because these suppositories were glycerol-based, we employed glycerol, gelatine, water, and tween 80 as polymers, with zinc oxide as a preservative.

TABLE 1. FORMULATION OF ISONIAZID SUPPOSITORIES

S.NO	INGREDIENT	AMOUNT TAKEN
1.	Isoniazid	100 mg
2.	Gelatine	7000 mg
3.	Glycerol	24 ml
4.	Water	30ml
5.	Zinc oxide	20mg
6.	Tween 80	40 mg

METHODOLOGY:

FUSION METHOD:

This process is frequently employed to get suppositories ready for administration. After melting the suppository base and adding the medication, the mixture is placed into a mould that has been lubricated. Suppositories form and are removed from the suppository mould once they have cooled.

SUPPOSITORY MOULD:

For commercial use, suppository moulds come in a variety of sizes and varieties. A suppository mould with six to twelve chambers of the appropriate shape and size was used. Usually, brass, aluminium, nickel, copper alloy, plastic, stainless steel, or nickel are used to make these moulds.

Figure 1: Suppository mould

The screw that holds the plates together in the middle can be removed to allow the suppository mould to be disassembled diagonally. When the suppositories are being removed, cleaned, and lubricated, the mould is opened. The plates are taken out and dipped into hot water with detergent to remove the mould. The mould is completely dried after being cleaned with water and then the lubricant is applied. Suppositories with uneven surfaces will result from failing to take proper care to ensure that the inside surface of the mould cavities is free of scratches.

METHOD OF PREPARATION:

- ◊ Provide the mould, thorough cleaning and lube it with the proper lubricant. To keep it cool and to drain any extra lubricant on ice, please keep it inverted. It is not required to lubricate the mould when using a synthetic or emulsifying base.
- ◊ Preheat the china dish in a water bath. Consider the medicament's displacement value and add the required amount of gelatine along with glycerol. A provision is included for inevitable waste that may arise during preparation by adding two extra suppositories. When two thirds of the base has melted, remove the china dish from the water bath and stir well until the entire mixture has melted. This method prevents warming of the foundation.
- ◊ Place the weighed amount of powdered medication on an ointment tile, incorporating it with the suppository base. Pour around half of the melted base over it. Use a flexible spatula to combine the ingredients completely. Pour the mixed mixture into the china bowl and mix well until a lumpy consistency forms.

- ◊ To make the bulk pourable, briefly warm the china dish over a water bath while stirring constantly.
- ◊ Transfer the liquefied blend into the suppository mould set over ice. To avoid hollows in the tops of the last suppositories, which happen when cocoa butter shrinks when chilled, completely fill each hole. When adding the material to the cavities, use caution. To guarantee that the medication is dispersed uniformly throughout each suppository, it must be continuously combined.
- ◊ To remove the surplus mass, use a sharp razor or blade after properly setting the mass.
- ◊ Store the mould in a cool area for 10-15 mins.
- ◊ To extract the suppositories, pry open the moulds. Subsequently, use a fresh piece of cloth or filter paper to carefully wipe each suppository. Put wax paper around each packet.

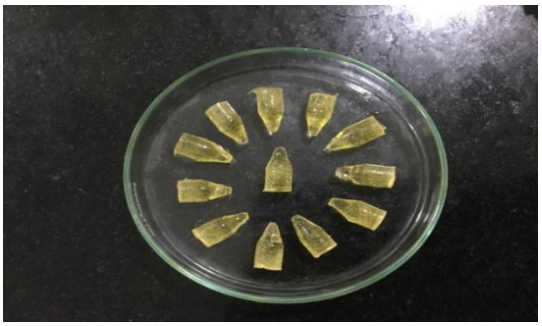

Figure 2: ISONIAZID SUPPOSITORY

EVALUATION PARAMETER OF TABLETS:

HARDNESS (FRACTURE POINT):

A Pfizer hardness tester was used to gauge the suppositories' level of hardness. The hardness of the suppository was determined by the weight needed for it to collapse.

UNIFORMITY OF WEIGHT:

Average weight was established after taking approximately 20 suppositories. Only two individual suppositories should differ by 10%.

% of weight variation = average wt.–average wt. Individual wt. / average wt×100

DISINTEGRATION TEST:

Six suppositories of each kind were subjected to the disintegration test using the USP pill disintegration (Model PTW, Germany) test device. The media used was 750 ml of PH 7.2 phosphate buffer at 37 °C. The amount of time needed for suppositories made with bases that dissolve in water to completely dissolve was calculated.

DISSOLUTION TEST:

900 ml of pH 7.2 phosphate buffer were used for the dissolving test, which was conducted in the USP Rotating Basket dissolving equipment. For 60 minutes, the rotation speed was regulated to 50 revolutions per minute, and the temperature was kept at 37±0.5°C. At predetermined intervals, five milliliter aliquots of the dissolution fluid were taken out of the reservoir and replaced with an equivalent volume of brand-new dissolution buffer media each

time. Samples that were withdrawn were appropriately diluted and examined at 354 nm. Plotting the absorption and concentration from several dilutions resulted in a linear relationship.

RESULTS AND DISCUSSION:

Isoniazid, an antitubercular medication, was made into rectal suppositories utilizing the fusion method using emulsified glycerol-gelatin and glycero gelatine as bases. The prepared suppositories were assessed for invitro dissolution, liquefaction/softening time, weight fluctuation, and appearance. For the preparation, the previously calibrated molds with a 1 gram capacity were utilized. By appearance, there were no fissures or cracks in any of the suppositories. After 45 minutes of in-vitro release testing, it was determined that each formulation had a disintegration time of less than 30 minutes.

TABLE 2: EVALUATION PARAMETERS OF ISONIAZID

Formulation Code	Weight variation (Mg)	Width (Cm)	Hardness (Kg/Cm2)	Disintegration time (mins)	Cumulative drug release percentage
S1	0.876	0.7	3.1	23	98.2829
S2	0.875	0.8	2.8	26	99.27829
S3	0.877	0.8	3.0	24	102.4567
S4	0.879	0.9	2.9	25	93.483409
S5	0.877	0.8	2.9	23	94.23829

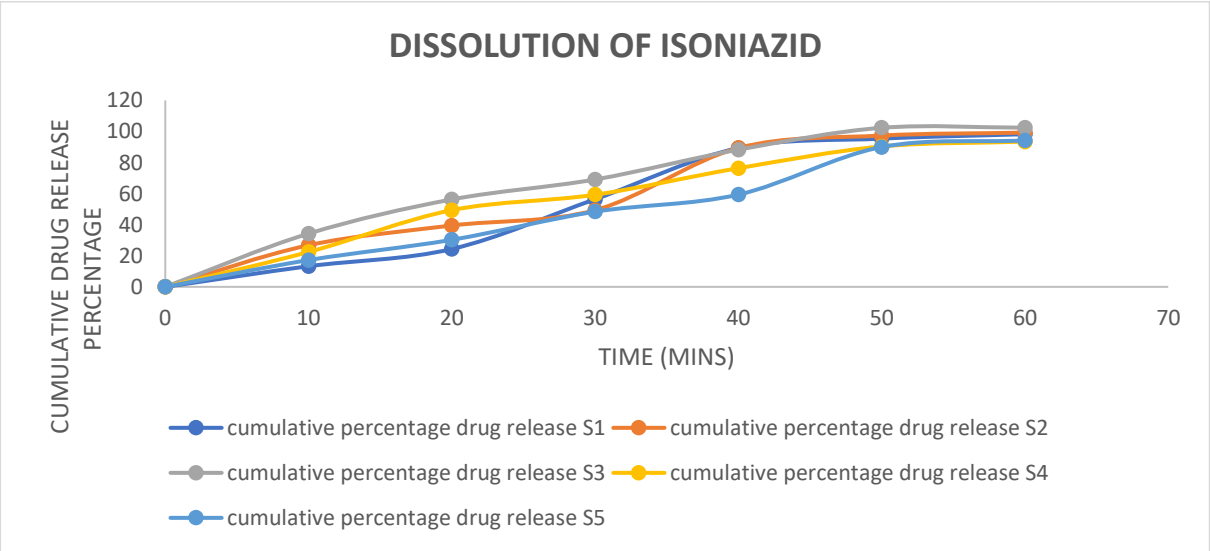

Figure 3: DISSOLUTION GRAPH OF ISONIAZID

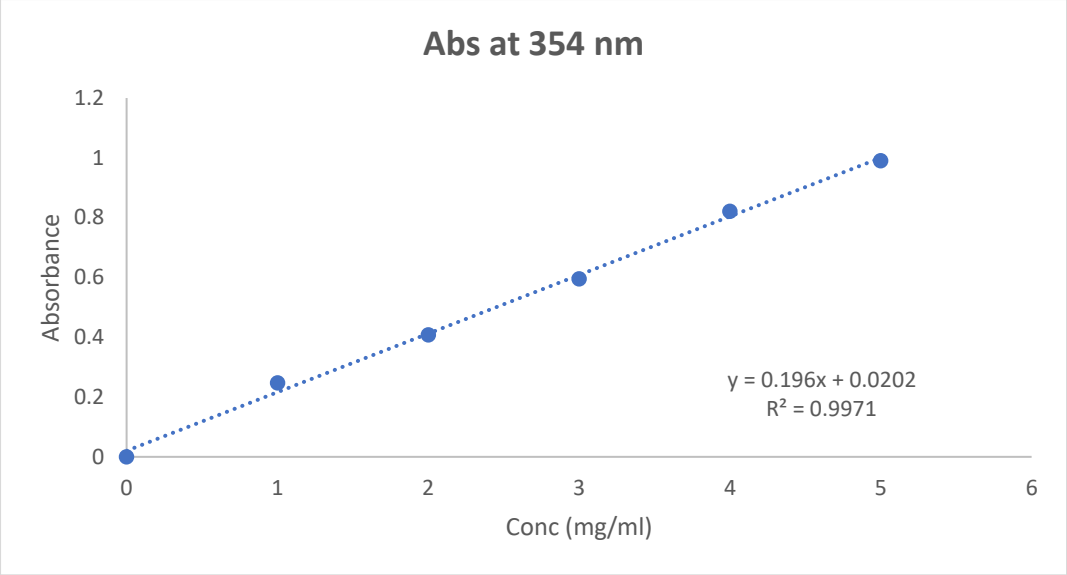

Figure 4: LINEARITY GRAPH OF ISONIAZID

Time	cumulative percentage drug release				
	S1	S2	S3	S4	S5
0	0	0	0	0	0
10	13.28197	26.765467	34.262728	22.437839	17.23839
20	24.37289	39.47389	56.27289	49.373989	30.28299
30	56.3872899	49.372876	69.12538	59.302028	48.38396
40	89.3278391	89.38739	88.2729	76.3839	59.38739
50	95.398739	97.37839	102.3739	90.3839	89.99307
60	98.2829	99.27829	102.4567	93.483409	94.23829

TABLE 3: CUMULATIVE DRUG RELEASE PERCENTAGE OF ISONIAZID SUPPOSITORIES

It was determined that every longitudinal segment of the suppositories was plain and clear. Additionally, the weight homogeneity of the made suppositories was assessed; the findings are shown in the table. According to Indian pharmacopeia, the percentage deviations from the mean weights of all batches fell inside the allowed ranges (mean weight ±5 to ±7.5%). It was discovered that the drug content ranged from 97 to 99%. It was discovered to be within the bounds as well. When the suppositories can tolerate a body temperature of 37°C, it is called the softening period. The emulsified medicated suppositories show no liquefaction at that temperature, despite the disintegration range of 10 to 5 minutes. The various dissolving characteristics were evaluated by conducting in vitro dissolution studies on the suggested formulations in phosphate buffer with a pH of 7.2. The dissolution profiles are displayed in the figures, and the findings are displayed in the table.

CONCLUSION: Research work aimed to characterize isoniazid physiochemically and then use that knowledge to formulate isoniazid with minimal excipients for rectal delivery.

Compared to oral, parenteral, or transdermal administration methods, suppositories have several advantages. All suppositories met acceptable limits regarding weight, hardness, content uniformity, melting temperature, and disintegration time. The suppositories had smooth layers, adequate weights, and an RSD% of less than 5%, which suggested flawless mould calibration and uniform filling. The in-vitro release test yielded appropriate findings for the formulations, offering reliable confirmation of their effectiveness and purity.

AUTHOR'S CONTRIBUTION: All authors endorsed the final version of the manuscript and made contributions to the study and manuscript preparation.

Conflict of interest: Nil
Funding: Nil

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