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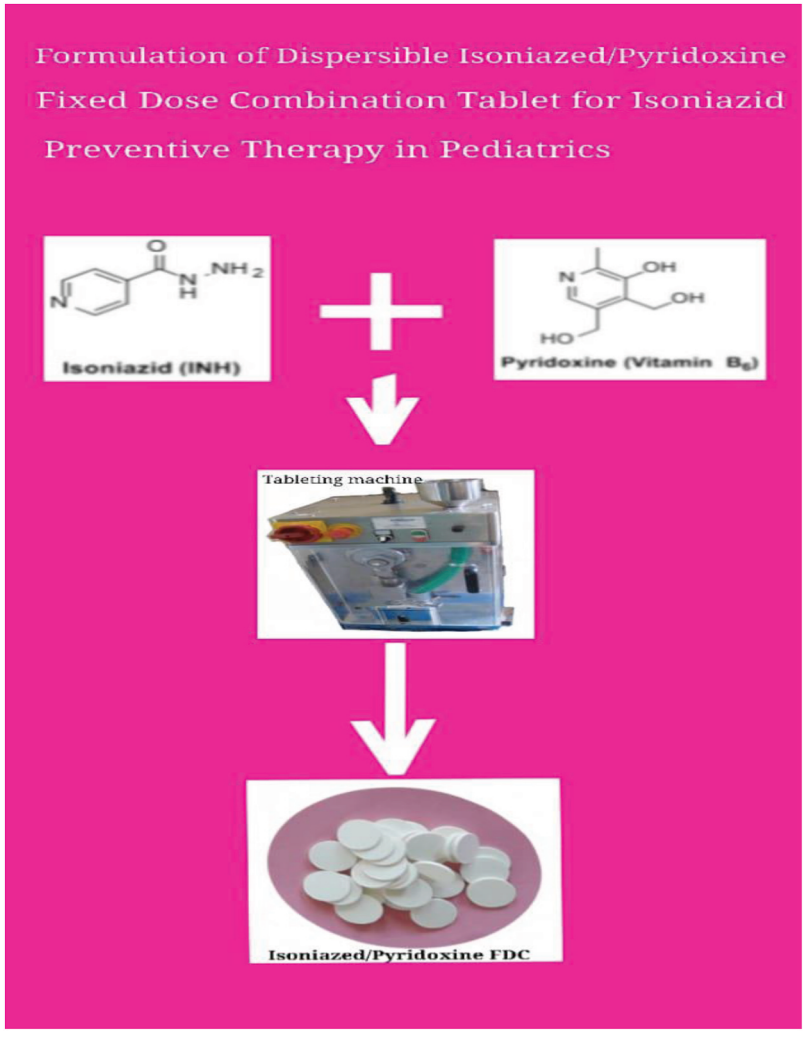

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PHARMACEUTICAL SCIENCE | RESEARCH ARTICLE

Formulation of dispersible isoniazid/pyridoxine fixed-dose combination tablets for isoniazid preventive therapy in pediatrics

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Additional information is available at the end of the article

Objective: Oral dispersible isoniazid 50 mg/pyridoxine 6.25 mg fixed-dose combination (FDC) tablets were formulated for Isoniazid Preventive Therapy in pediatrics weighing less than 5 kg. Significance: The Kenyan clinical market lacks age-appropriate isoniazid/pyridoxine formulations for pediatrics whose dose requirements are catered extemporaneously. The proposed oral dispersible FDC tablets would improve the treatment outcomes of the drug combination by ensuring accurate dosing, reduce pill burden, prolonged shelf life, and circumvent individual drug stock-outs. Method: Nine batches of isoniazid/pyridoxine FDC tablets with an average weight of 125 mg differing in the composition of three superdisintegrants were formulated. Pre-formulation studies were done on the powder blend using Fourier transform infra-red spectroscopy before the blend was directly compressed. Pharmaceutical parameters of the tablets were assessed against compendial specifications. Results: Pre-formulation studies showed no predictable incompatibilities between the drugs and excipients. All batches complied with compendial specifications for weight uniformity, hardness and disintegration, while three batches complied with the friability test. Only Batch Nine tablets containing croscarmellose and sodium starch glycolate superdisintegrants in the ratio of 3:5 complied with the assay specification. Batch Nine tablets contained 96% of isoniazid and 95% of

ABOUT THE AUTHOR

The Formulations and Drug Delivery Group in the Department of Pharmaceutics and Pharmacy Practice focuses on the design and preparation of suitable dosage formulations that are age-appropriate and site-directed. The formulated drug products include tablets, capsules, oral liquid and parenteral fluids. Our focus is mainly on pediatric medicines informed by the fact that age-appropriate pediatric dosage formulations are deficient in the clinical market hence dose requirements are catered for extemporaneously. The proposed oral dispersible fixed-dose combination tablets would improve the treatment outcomes of the drug combination by ensuring accurate dosing, reduce pill burden, prolonged shelf life, and circumvent individual drug stock-outs.

PUBLIC INTEREST STATEMENT

Tuberculosis (TB) is an infectious disease that is transmitted through sputum droplets from an infected person. It is one of the major killer diseases in children. According to the World Health Organization (WHO) statistics, in 2015, 7,000 children in Kenya were TB-infected and the deaths recorded were highest among the under 5 years. One TB control measure advocated by the WHO is the administration of isoniazid to individuals at high risk of developing active TB. It is recommended that patients on isoniazid be given daily pyridoxine to counter isoniazid side effects. The most preferred dosage form for pediatrics is dispersible tablets. In cases where more than one drug is administered, it is advisable to use fixed-dose combinations to enhance patient compliance. This study sought to formulate oral dispersible tablets of isoniazid 50 mg and pyridoxine 6.25 mg for the prevention of TB in paediatrics under 5 kg.

pyridoxine complying with the United States Pharmacopeia (USP) 2016 monograph limits of 90–110% and 95–115% of the labelled isoniazid and pyridoxine, respectively. In the in-vitro dissolution studies, 88.7% and 105.3% of isoniazid and pyridoxine contained in Batch Nine tablets dissolved within 30 min complying with the USP 2016 specifications for dissolution test. Conclusion: The isoniazid/pyridoxine FDC incorporating croscarmellose sodium and sodium starch glycolate superdisintegrants was the most successful formulation since the formulated tablets complied with all the evaluated compendial specifications implying potential clinical utility of the formulation.

Subjects: Bioscience; Pharmaceutical Science; Pharmacy

Keywords: Tuberculosis; isoniazid preventive therapy; isoniazid; pyridoxine; dispersible tablets; superdisintegrants

1. Introduction

Tuberculosis (TB) is an infectious disease caused by the bacillus *Mycobacterium tuberculosis* that is transmitted through sputum droplets from an infected person (Pai et al., 2016; Peter et al., 2016). On inhalation, infectious droplets migrate through nasal passages to the alveoli in the lungs where the bacteria establish pulmonary TB. Some of the bacteria may spread to other body parts like the bones and brain via the blood stream resulting in extra-pulmonary TB. In most cases, the immune system kills the bacteria, but in other cases, macrophages ingest and suppress the bacteria resulting in latent TB. The risk of developing active TB in individuals with latent TB infection is 5–10%, with a wide incubation period ranging between eight weeks to decades (Peter et al., 2016). Tuberculosis is a major global health challenge and is currently ranked as the leading cause of death from a single infectious disease worldwide, ranking above human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) since 2013 (World Health Organization, 2017).

The global burden of TB is huge. According to the Global TB Report 2017, there were estimated 10.4 million TB incidences resulting in approximately 1,700,000 deaths globally in 2016 with highest mortality occurring in South-East Asia and Africa. The daily-adjusted life-years lost due to TB morbidity and mortality is 40 million (World Health Organization, 2017). Not surprising, TB is one of the major killer diseases in children. According to the World Health Organization (WHO) statistics, a million children suffer from TB and 140,000 deaths are reported annually (TB Alliance, 2017). Further, according to the TB Alliance, 7,000 children in Kenya were TB infected in 2015 with mortality rate and multidrug-resistant tuberculosis (MDR-TB) cases being highest among the under 5 years (TB Alliance, 2017). There currently are ongoing concerted efforts to halt the spread of TB with its attendant morbidity and mortality. One method advocated by the WHO as a control measure for TB is the prophylactic use of Isoniazid Preventive Therapy (IPT).

Isoniazid Preventive Therapy entails the administration of isoniazid (INH, Figure 1) to individuals at high risk of developing active TB (WHO, 2011). Indications for IPT include HIV-positive patients who have been in contact with sputum-positive TB patients, all pediatrics under 5 years (both HIV-

Figure 1. Chemical structures of isoniazid and pyridoxine.

positive and HIV-negative) who have been in contact with sputum-positive TB patients, and prisoners in congested cells. To mitigate the development of isoniazid induced neuropathy (Arbex et al., 2010), it is recommended that patients on INH be given daily prophylactic pyridoxine (vitamin B_6, Figure 1). Isoniazid is available in the Kenyan clinical market as 100 mg and 300 mg tablets, while pyridoxine is available as 25 mg and 50 mg tablets. Administration of IPT to young children is hindered by their inability to swallow tablets.

The WHO cites a lack of appropriate dosage form of medicines for pediatrics in developing countries as a contributing factor for high morbidity and mortality. This can be reduced by focusing on the development of the right dosage forms for pediatric use (Ivanovska et al., 2014). Formulation of medicines for pediatrics is both cost-intensive and challenging, manifested by dire deficiency of age-appropriate dosage forms and off-label use of medicines in this patient subpopulation (Nunn & Williams, 2005; Samuel & Daniel, 2011). There is therefore a need to come up with a formulation that is stable and can be administered to children of all age groups at the correct dose. *Per-oral* is the preferred route of drug administration. When compared against parenteral routes, it offers advantages of convenience since the patients can self-administer the drugs, it is not painful, it is less expensive, it is safer, and the tablets can be manufactured in different pharmaceutical shapes which improves the aesthetic appeal of the tablet (Jissa & Emmanuel, 2014; Verma et al., 2010).

Whereas liquids are a convenient alternative to tablets for pediatric oral formulations, they are hamstrung by several limiting factors such as poor palatability, physicochemical instability, bulkiness, and in some cases, the need for special storage conditions (Ivanovska et al., 2014). Therefore, the most preferred dosage form for pediatrics is the dispersible tablets, designed to disperse rapidly in liquid just before administration (WHO Inter-Agency Task Team, 2016). For APIs that are soluble in water, the drugs can be formulated by this method. Since dispersible tablets disintegrate within seconds, this leads to faster bioavailability of the drug compared to the conventional oral dosage forms. Dispersible tablets can be formulated by the use of appropriate disintegrants and water-soluble excipients (Chotaliya & Chakraborty, 2012; Rewar et al., 2014).

Disintegrants are drug excipients that facilitate the disintegration of tablet matrix once the tablet is in an aqueous environment. Commonly used disintegrants include starch, povidone and cellulose. Superdisintegrants are chemically modified disintegrants with greater disintegration efficiency at much lower concentrations (Desai et al., 2016). Superdisintegrants have the ability to fasten tablet disintegration and hence increase drug dissolution. The quantity of superdisintegrant required is minimal compared to the natural disintegrants and they have minimal effect on the flow rate of the powder as well as compressibility (Pahwa & Gupta, 2011). Usually, the percentage of superdisintegrants used is 1–10% of the total weight of the tablet (Mohanachandran et al., 2012). The percentage range of crospovidone, croscarmellose sodium and sodium starch glycolate used is 1–3%, 2–5% and 4–6%, respectively.

In cases where more than one drug is administered, it is advisable to use fixed-dose combination (FDC) formulations to enhance patient compliance. This study therefore aimed to formulate FDC oral dispersible tablets of isoniazid 50 mg/pyridoxine 6.25 mg for IPT in pediatrics weighing less than 5 kg using varying concentrations of three superdisintegrants, namely croscarmellose sodium, crospovidone and sodium starch glycolate (Desai et al., 2016; Zhang, 2010). The tablets were then evaluated for compendial compliance as specified in the British Pharmacopoeia 2009 (B. P., 2009) and the United States Pharmacopeia 2016 (USP, 2016).

2. Experimental

2.1. Materials

Isoniazid and pyridoxine were obtained from Kobian Kenya Limited. Microcrystalline cellulose, mannitol, crospovidone, sodium starch glycolate, magnesium stearate and colloidal anhydrous silica were gift samples from Regal Pharmaceuticals. Croscarmellose sodium and strawberry flavour were gift samples from Elys Chemical Industries (Nairobi, Kenya). Sodium saccharin was a gift sample from Laboratory & Allied (Nairobi, Kenya). All materials were of pharmaceutical grade.

The following equipment were used in the study: AUW 20 analytical balance (Shimadzu Co., Japan), IR Prestige 21 Fourier-Transform Infrared (FTIR) spectrophotometer (Shimadzu, Japan), type iEP-1 single station automatic tablet press (Inweka, India), Scheulinger 2E electronic tablet hardness tester (Erweka, Germany), friability tester (Erweka, Germany), UV-1800 UV/Vis spectrophotometer (Shimadzu Co.), disintegration apparatus (Erweka, Germany) and DS 8000 dissolution tester type 2 (Lambindia, Germany).

2.2. Procedures

2.2.1. Compatibility studies

Pressed disks of the drugs, the excipients and the physical binary mixture of the drugs and the excipients in potassium bromide were prepared and the IR spectra obtained at 4000–400 cm^{-1} electromagnetic spectrum range using FTIR spectroscopy.

2.2.2. Preparation of tablets

A total of nine tablet batches were formulated. The batches were designed in such a manner as to contain two of the three studied superdisintegrants, microcrystalline cellulose as binder, mannitol as a filler, magnesium stearate as a lubricant, colloidal anhydrous silica as a glidant, sodium saccharin as a sweetener and strawberry flavor as a flavoring agent. The amounts required to produce 100 tablets per batch were calculated. The ingredients were passed through a 710 µm sieve before mixing and the resultant powder blend evaluated for pre-compression parameters before compression into tablets using a single station automatic tablet press.

The tablets in each of the nine batches contained 50 mg isoniazid, 6.25 mg pyridoxine, 25 mg microcrystalline cellulose, 29.375 mg mannitol, 1.25 mg magnesium stearate, 0.625 mg colloidal anhydrous silica, 1.25 mg sodium saccharin and 1.25 mg strawberry flavor with an average tablet weight of 125 mg. The ratios of superdisintegrants incorporated in each of the nine tablet batches are shown in Table 1.

2.2.3. Evaluation of powder blend

The flow properties of the powder blend were evaluated by calculating the angle of repose, bulk density, tapped density, compressibility index (CI) and Hausner's ratio (HR).

Table 1. Ratios of the superdisintegrants used in the study

1:1 (5 mg, 5 mg)	3:5 (3.75 mg, 6.25 mg)	3:5 (3.75 mg, 6.25 mg)
Batch 1 Crospovidone: Croscarmellose sodium	**Batch 4** Croscarmellose: Crospovidone	**Batch 7** Crospovidone: Croscarmellose
Batch 2 Crospovidone: Sodium starch glycolate	**Batch 5** Sodium starch glycolate: Crospovidone	**Batch 8** Crospovidone:Sodium starch glycolate
Batch 3 Croscarmellose Sodium: Sodium starch glycolate	**Batch 6** Sodium starch glycolate: Croscarmellose	**Batch 9** Croscarmellose:Sodium starch glycolate

2.2.4. Evaluation of the tablets

The compressed tablets were evaluated on their physical appearance, weight uniformity, hardness, friability, drug content, disintegration, dissolution, thickness and diameter (Chandrasekhar et al., 2013; Nag et al., 2015; Shah et al., 2008).

2.2.5. Disintegration test

One tablet was placed in each of the six tubes of the disintegration apparatus basket assembly and immersed in a water bath whose temperature was maintained at 25°C. The time it took for each of the tablets to disintegrate was noted. The disintegration time for all the batches was noted (B.P., 2009, Shukla & Manvi, 2010).

2.2.6. Assay for drug content

Isoniazid standard (10 mg) and pyridoxine standard (12.5 mg) were dissolved separately in 100 mL 0.1M HCI to make standard stock solutions (100 µg/mL and 125 µg/mL, respectively). A working standard solution was prepared by pipetting 10 mL and 1 mL of isoniazid and pyridoxine stock solution, respectively, into a 100 mL volumetric flask and made to volume using 0.1M HCI. The working standard mixture thus contained 10 µg/mL isoniazid and 1.25 µg/mL pyridoxine. The absorbance of standard mixture was determined spectrophotometrically at 263 nm and 292 nm for isoniazid and pyridoxine, respectively.

Twenty tablets were weighed and pulverized to a fine powder. A powder weight equivalent to 50 mg of isoniazid (corresponding weight of pyridoxine was 6.25 mg) was weighed, dissolved in 100 mL 0.1M HCI, the solution filtered, and the filtrate diluted further to produce a solution containing nominal 10 µg/mL isoniazid and 1.25 µg/mL pyridoxine. The absorbance of the resulting solution was determined spectrophotometrically at 263 nm and 292 nm. The absorbance values for the standard mixture and the samples were used to calculate the label claim using Equation 1 (Nag et al., 2015; Pawar et al., 2012).

$$TA/SA \times WS/TW \times DT/DS \times P/100 \times AWT/LC \times 100\% \quad (1)$$

where TA is the absorbance of the test sample, SA is the absorbance of the standard mixture, WS is the weight of the standard, TW is the weight of the test sample, DT is the dilution of the test sample, DS is the dilution of the standard, P/100 is percentage potency of the standard, AWT is the average weight of 20 tablets, LC is the label claim.

2.2.7. Dissolution

The dissolution of the isoniazid/pyridoxine dispersible tablets was determined using USP dissolution test apparatus type 2 in 900 mL 0.1 N HCl dissolution medium for 1 h at 50 rpm. The medium was maintained at 37 ± 0.5°C. A 20 mL aliquot was withdrawn at various intervals (5,10,15,30,45, 60 min) for quantitation of drug release and replaced with an equivalent volume of the dissolution medium. The sampled aliquots were filtered, appropriately diluted and analysed spectrophotometrically at 263 nm and 292 nm for isoniazid and pyridoxine, respectively. The absorbances were used to calculate the drug content in the FDC (Nag et al., 2015) using Equation (2).

$$TA/SA \times WS/TW \times DT/DS \times P/100 \times VDM/TW \times AWT/LC \times 100\% \quad (2)$$

where TA is the absorbance of the test sample, SA is the absorbance of the standard, WS is the weight of the standard, TW is the weight of the test sample, DT is the dilution of the test sample, DS is the dilution of the standard, P/100 is percentage potency of the standard, VDM is the volume of the dissolution medium, TW is the tablet weight, AWT is the average weight of 20 tablets, and LC is the label claim.

Table 2. Pre-compression parameters of the powder blends for the batches

Batch	Angle of repose (°), n = 3	Bulk density (g/mL)	Tapped density (g/mL)	Compressibility index (%), n = 3	Hausner's ratio, n = 3
1	40.8 ± 0.69	0.59	0.78	23.67 ± 0.58	1.31 ± 0.01
2	31.67 ± 0.58	0.57	0.69	17.33 ± 0.115	1.21 ± 0.0058
3	31.67 ± 0.58	0.625	0.833	23.67 ± 0.115	1.33 ± 0.0058
4	31.67 ± 0.58	0.52	0.69	23.67 ± 0.115	1.33 ± 0.0058
5	32.67 ± 0.58	0.57	0.83	30.67 ± 0.115	1.45 ± 0.0058
6	29.33 ± 0.58	0.625	0.833	24.33 ± 0.115	1.33 ± 0.0058
7	39.6 ± 0.53	0.52	0.74	29.8 ± 0.173	1.42 ± 0.0058
8	37.4 ± 0.35	0.63	0.83	23.67 ± 0.577	1.3 ± 0.0058
9	23.67 ± 0.58	0.568	0.694	18.17 ± 0.058	1.22 ± 0.0058

2.3. Results and discussion

2.3.1. Compatibility studies

Examination of the FTIR spectra did not reveal any discernible drug-excipient incompatibilities indicating that the formulation was predictably compatible.

2.3.2. Powder blend properties

The angle of repose was in the range 23.6–40.8° indicating fair to excellent powder flow. The compressibility index and Hausner's ratio values (Table 2) indicated that the powder properties ranged from poor to fair. This indicates that there might be a need to further investigate the optimal concentration of the glidant in future studies.

2.3.3. Post-compression parameters

The weight of the tablets ranged from 120.1 mg to 126.55 mg. All the nine batches complied with the BP specifications that recommend a deviation of ≤ 7.5% from the tablet average weight for not more than two tablets for tablets with an average mass between 80 mg and 250 mg (B.P., 2009).

2.4. Appearance of formulated tablets

The tablets were smooth, circular, shiny and white in colour with the diameter being 10 mm and the thickness ranging from 1.1 mm to 1.2 mm.

The hardness of the tablets was between 20 N to 35 N. Batch 3 tablets had the highest value of 34.6 N while batch 1 had the lowest value of 21.5 N. The percentage friability of batches 2, 3 and 9 was below 1% (Table 3) indicating the ability of these tablets to resist mechanical stress.

Table 3. Post-compression parameters of the formulated tablets

Batch	Tablet weight (mg), mean±SD	Hardness (N), mean±SD	Friability (%)	Disintegration time (sec), mean±SD
1	124.25 ± 2.37	21.5 ± 4.22	1.2	6.5 ± 1.05
2	124.76 ± 2.73	28 ± 9.45	0.8	10 ± 3.35
3	125.56 ± 3.44	34.6 ± 12.67	0.8	35.67 ± 5.79
4	124.67 ± 2.88	29.8 ± 10.61	1.2	11.67 ± 1.63
5	125.48 ± 3.22	23.7 ± 5.70	1.2	8.83 ± 2.93
6	126.55 ± 1.92	30.9 ± 6.05	1.2	39.83 ± 6.68
7	120.1 ± 3.43	22.4 ± 5.27	1.2	6.33 ± 2.33
8	124.53 ± 3.93	26 ± 4.4	1.2	12.5 ± 2.26
9	124.84 ± 3.04	30.4 ± 6.74	0.8	62.83 ± 5.27

Table 4. Mean percentage drug content and uniformity of content of the formulated tablets

Batch	Percent content (RSD) n = 3		Uniformity of content (RSD) n = 3	
	Isoniazid	Pyridoxine	Isoniazid	Pyridoxine
1	94.4 (0.37)	84.3 (0.69)	97.2 (0.26)	88.5 (1.41)
2	96.9 (0.18)	86.3 (0.67)	107.3 (0.51)	100.4 (0.61)
3	98.2 (1.21)	89.0 (1.26)	104.3 (1.63)	98.6 (2.19)
4	93.0 (1.63)	86.7 (3.33)	102.4 (3.21)	92.4 (3.15)
5	95.0 (0.43)	85.6 (1.21)	100.7 (5.17)	96.6 (5.16)
6	88.3 (0.35)	78.3 (2.95)	99.3 (1.85)	93.8 (1.48)
7	95.0 (0.36)	84.9 (1.84)	102.6 (1.72)	93.4 (1.58)
8	90.8 (0.76)	84.3 (1.81)	99.2 (3.76)	91.7 (3.93)
9	96.0 (0.10)	95.0 (0.00)	101.6 (1.92)	102.7 (3.01)

n = Number of samples per batch.

Disintegration time is the time taken for a tablet to disintegrate when it comes into contact with fluids. Disintegration could be a rate-limiting step in drug dissolution and hence absorption. Batch 9 tablets which contained croscarmellose and sodium starch glycolate superdisintegrants had the longest disintegration time of 62.83 sec. This could be because of the formation of the viscous gel layer by sodium starch glycolate which slows the permeation of water (Setty et al., 2008). Batch 7 tablets which contained crospovidone and croscarmellose superdisintegrants had the shortest disintegration time (6.33 sec). For dispersible tablets, the BP specifies that for a tablet to comply, it should disintegrate within 3 min (B.P., 2009). Disintegration time can be reduced by using a combination of wick-type superdisintegrants such as crospovidone which acts by rapid capillary action that disrupts the physical bonds between the particles, and swelling-type superdisintegrants such as croscarmellose which act by swelling and breaking the matrix from within (Setty et al., 2008).

2.4.1. Assay and content uniformity of formulated isoniazid pyridoxine dispersible tablets

The mean percentage content and uniformity of content of the nine batches are presented in Table 4. The USP 2017 specifies that isoniazid and pyridoxine tablets should contain no less than 90% and not more than 110% isoniazid and no less than 95% and not more than 115% pyridoxine of

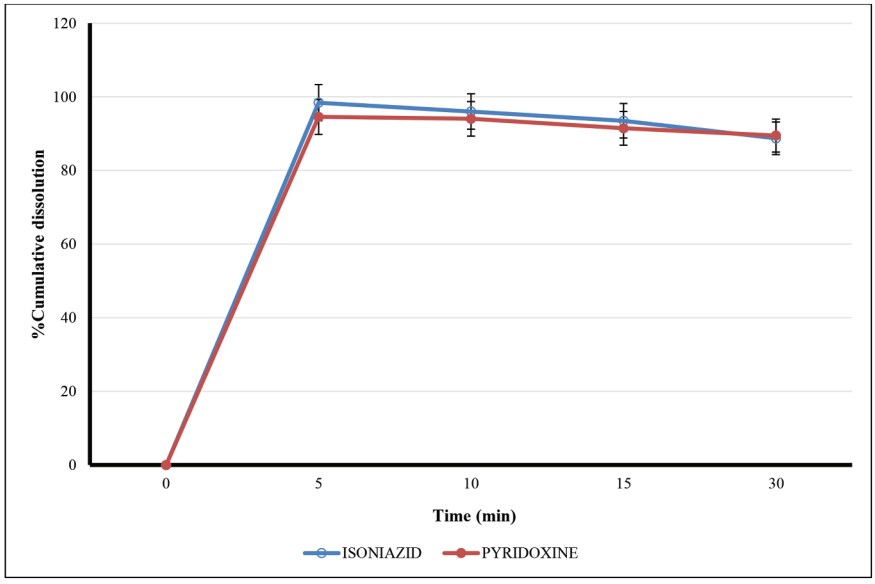

Figure 2. Dissolution profile of Batch Nine tablets.

the label claim. Tablet Batches 2, 3, 5 and 9 complied with the USP specifications for content uniformity but only Batch 9 tablets complied with the USP specification for drug content.

2.4.2. Dissolution test

The USP 2016 specifies that not less than 80% and 75% of the labelled amount of isoniazid and pyridoxine, respectively, should be released in 45 min (USP, 2016). The dissolution test was carried out on Batch Nine tablets only since it is the only batch that complied with all the other pharmacopoeial specifications. Percentage cumulative dissolution was plotted against time as presented in Figure 2. The dissolution profile of Batch Nine tablets indicated that the tablets complied with the dissolution specification of the USP (2016) having dissolved within 30 min (USP, 2016; Vaghela et al., 2011; World Health Organization, 2011; Yasir et al., 2010). The percentage cumulative concentration of isoniazid and pyridoxine in the dissolution medium achieved maxima within 5 min which is consistent with release characteristics for dispersible tablets.

3. Conclusion

The formulation of dispersible isoniazid/pyridoxine FDC tablets for pediatric use was successful. Batch Nine tablets, comprising croscarmellose sodium and sodium starch glycolate (3:5 ratio) as super-disintegrants, complied with all the pharmaceutical tests. Further optimization and stability studies are recommended before the product is considered for upscaling and evaluation for clinical utility.

List of abbreviations

API–Active Pharmaceutical Ingredients
BP–British Pharmacopoeia
FDC–Fixed-Dose Combination
FTIR–Fourier transform infra-red
HIV–Human Immunodeficiency Virus
INH–Isoniazid
IPT–Isoniazid Preventive Therapy
RSD–Relative Standard Deviation
SD–Standard Deviation
TB–Tuberculosis
USP–United States Pharmacopeia
UV–Ultraviolet
WHO–World Health Organization

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Declarations

Ethics approval and consent to participate: N/A

Availability of data and material

All data obtained during this study are included in this article.

Competing interests

The authors declare that they have no competing interests.

Cover image

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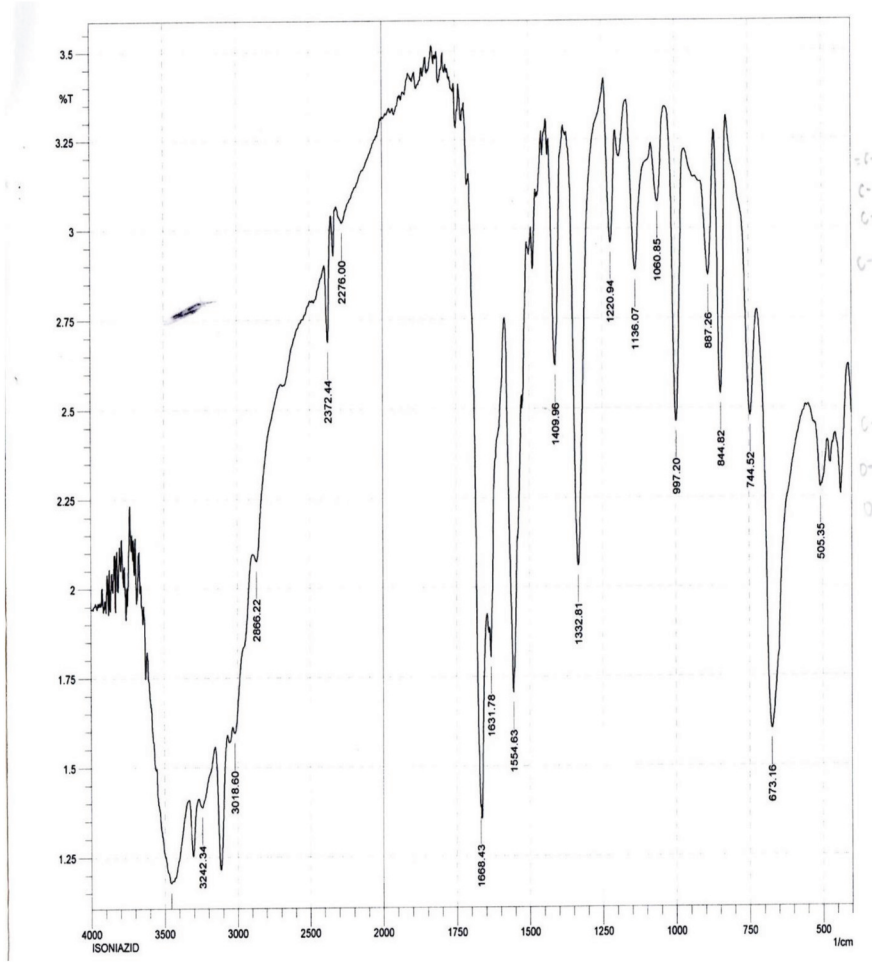
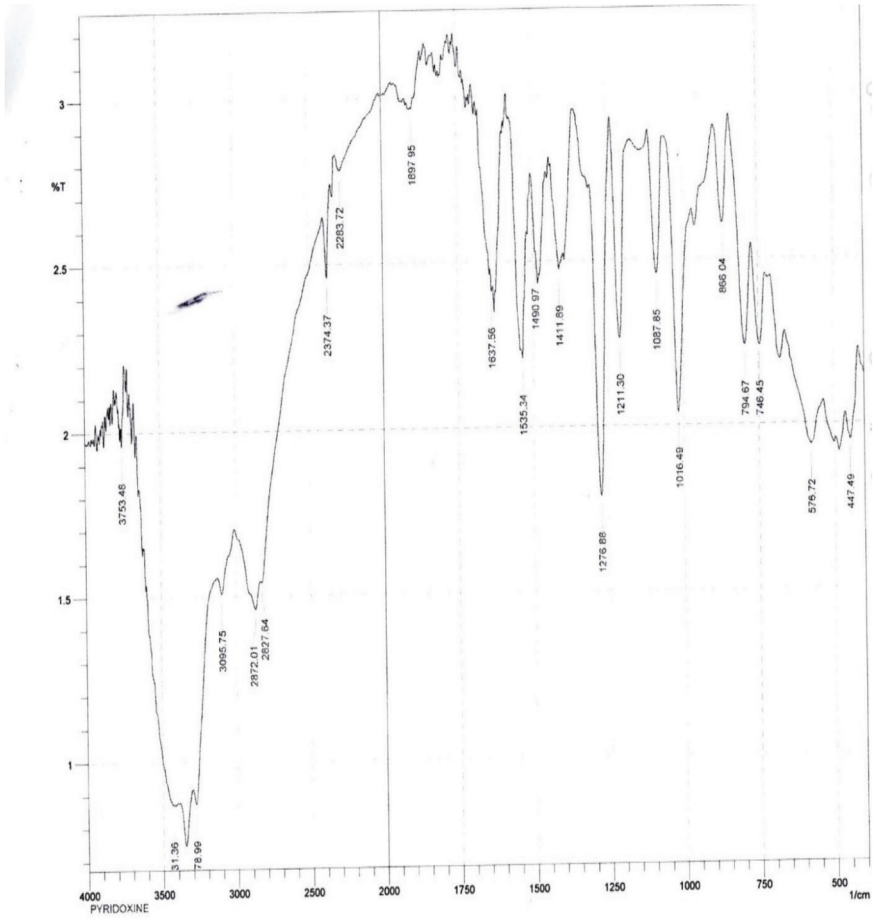
APPENDICES

Appendix 1. FTIR spectrum of isoniazid.

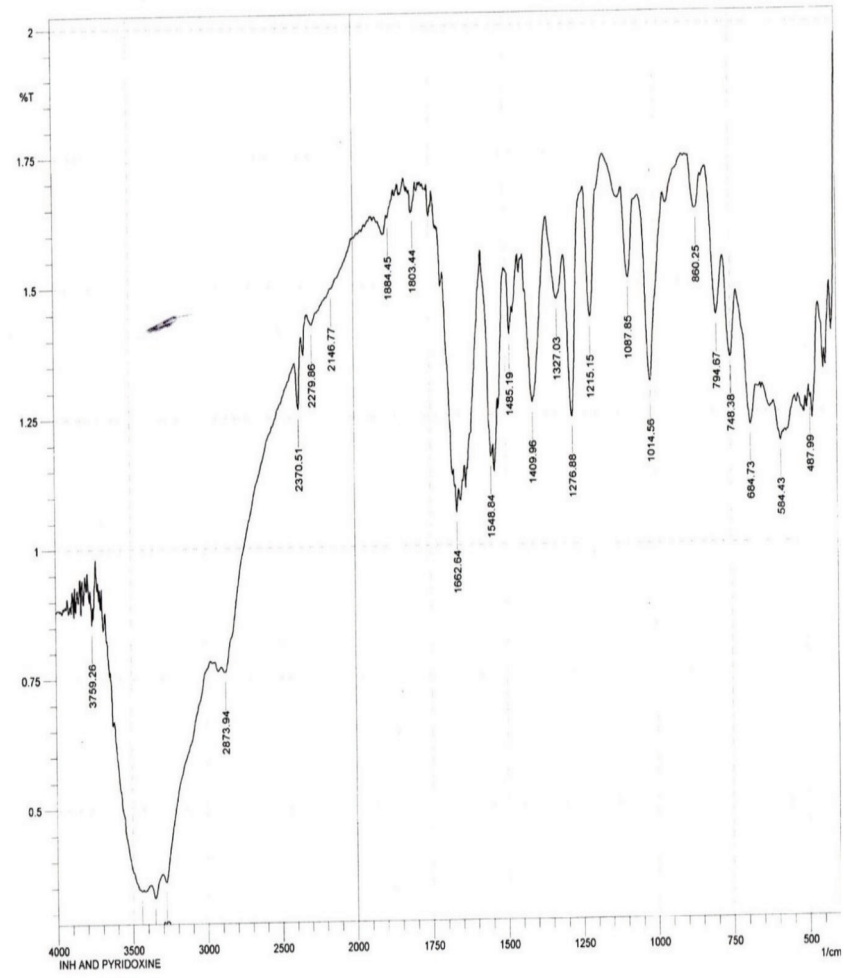
APPENDICES



Appendix 2. FTIR spectrum of pyridoxine.



Appendix 3. FTIR spectrum of isoniazid and pyridoxine combination.



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