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Formulation Development and Evaluation of Taste-masked Moxifloxacin granules for the Treatment of Pediatric Tuberculosis

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ABSTRACT: Fluoroquinolone antibiotic moxifloxacin (MOX) is a second-line therapy for multidrug-resistant tuberculosis (MDR TB) and drug-susceptible TB. Low patient compliance with MOX is caused by taste and odour issues, particularly in the paediatric population. By utilising mannitol, aspartame as a sweetener, and lemon flavour as a flavouring agent, wet granulation was used to create MOX taste-masked granules. One of the major challenges was to get the free-flowing granules so the wet granulation technique was used and desired flow properties were achieved. The flow characteristics and in vitro drug release of the produced granules were assessed. FTIR, DSC, and XRD instrumental analyses were also carried out. Based on the results, it was determined that the flow qualities of the granules from batch F6 were outstanding. The optimised batch demonstrated full medication release in about 10 minutes. In the FTIR and DSC studies, no incompatibility between the drug excipients was observed. According to XRD, the MOX in the final formulation was present in crystalline form. MOX taste-masked granules would be a superior alternative for treating paediatric TB.

Keywords: Tuberculosis, moxifloxacin, dispersible tablets, taste mask, disintegration.

INTRODUCTION

When employing the oral route of administration, bitter, sour, or unsweetened tastes are completely inappropriate, especially when it comes to drugs intended for children. The majority of drugs taken orally, including antibiotics like moxifloxacin, clarithromycin, and, sparfloxacin have a bitter taste. Such drugs are difficult for patients to swallow, which reduces patient compliance and the effectiveness of the treatment (Reddy, 2020). The development of all oral formulations faces the challenge of masking the bitter taste of drugs, which is a requirement for better patient compliance and product value. The process and formulation should be affordable, rapid, and simple, involving the least amount of equipment, processing steps, and excipients while maintaining drug bioavailability (Thakker *et al.,* 2020; Prashanth *et al.,* 2022). Drug bitterness is a significant issue with pediatric and geriatric formulations. Effective taste masking may be achieved using a variety of techniques, including the use of flavours and sweeteners, microencapsulation, complexing with ion exchange resin, using an insoluble prodrug, forming inclusion complexes, gelation, liposomes, multiple emulsions, granulation, and so on (Boateng, 2017). Apart from all these techniques, taste masked granules are also widely utilised in pediatric and geriatric populations. The manufacturing of taste-masked granules is easy and cost-effective, and later it can be converted into suitable dosage forms like capsules, tablets, suspensions, etc., or can be filled in sachets as a finished product. Pawar *et al.* developed and evaluated taste masked granules of satranidazole using the melt granulation technique (Pawar *et al*., 2014). Similarly, Ntemi *et al.* (2019) also developed taste-masked granules of clarithromycin for pediatric and geriatric patients (Ntemi *et al.,* 2019). Nishiyama *et al.* (2016) developed bitter taste-masking granules of lafutidine for orally disintegrating tablets. Taste-masking granules were prepared by coating granules with a taste-masking layer prepared by combining the water-insoluble and soluble polymers, ethylcellulose and hypromellose, respectively (Nishiyama *et al.,* 2016). Shahzad *et al.* (2011) studied and evaluated coated granules to mask the bitter taste of dihydroartemisinin (Shahzad *et al.,* 2011). Considering the potential advantages of the taste-masked granules, it would serve as alternate drug delivery technology for pediatric as well as geriatric patients who have difficulty swallowing solid oral dosage forms.

An estimated 80,000 children without HIV are thought to die from TB each year, and there are between 0.5 and 1 million new cases. TB is a severe health issue for children worldwide. In addition, the number of children with extensively drug-resistant (XDR) and multi-drug-resistant (MDR) tuberculosis is rising alarmingly (Ebonyi *et al.,* 2016). Compared to adult treatments, pediatric TB therapies are still in their infancy. Adult oral immediate-release tablets are commonly unsuitable for children. Several of the second-line TB drugs can also be administered as suspensions or liquid solutions. They, however, provide unique difficulties. Storage, packing, and safe transportation are expensive, liquids are frequently less stable even when refrigerated, masking the taste is difficult, and for chronic diseases

like HIV, practitioners prefer tablet formulations over suspensions. These are all problems associated with liquid dosage form which currently pharmaceutical industry is facing (Nahirya-Ntege *et al.,* 2012).

Due to their effects *in vitro* and *in vivo* activity against *Mycobacterium tuberculosis*, fluoroquinolones are a crucial component of current MDR TB treatment regimens for adults and children. Moxifloxacin (MFX), the fluoroquinolone now believed to be most effective against M. tuberculosis, has an early bactericidal activity similar to that of isoniazid (Qiao *et al.,* 2021). Data demonstrate its therapeutic efficacy in treating pediatric TB. Moxifloxacin is now advised for use in children with multidrug-resistant (MDR) TB at a dose of 7.5–10 mg/kg[3] (Srivastava *et al.*, 2016). However, fluoroquinolones and MOX have unpleasant bitter tastes and odours, which contribute to low patient compliance, particularly in the pediatric population (Zheng *et al.,* 2021). Taste-masked granules of MOX employing flavoring agents and sugars would be the optimum method for the effective treatment of pediatric TB, taking into account all the possible problems of the current treatment alternatives. The difficulties in treating pediatric TB might be solved by the taste-masked granules of MOX.

MATERIALS AND METHODS

Materials: Moxifloxacin HCl (MOX) was obtained as a gift sample from Macleods Pharmaceuticals Ltd. Mumbai, India. Microcrystalline cellulose (MCC 101) was purchased from Maple Biotech Pvt Ltd., Pune, India, aspartame (Ranbaxy, New Delhi, India). Crospovidone was obtained from Concertina Pharma Pvt., Ltd, Hyderabad, India. Mannitol 100 SD, Aspartame, and Sodium chloride were purchased from signet excipients PVT Ltd. Mumbai, India. The lemon flavor was purchased from Bell Flavors and Fragrances.

Methods:

Manufacturing of MOX taste-masked granules: MOX taste-masked granules were manufactured by an aqueous wet granulation method using PVP K-30 as a binder. To mask the bitter taste of the MOX, mannitol 160 C, aspartame as sweeteners, and Lemon flavor as a flavoring agent. The batch composition of the formulations is presented in Table 1. MOX, MCC 101, Crospovidone, Mannitol 160C, and Aspartame were co-sifted through sieve # 40. These all ingredients were properly mixed in a polybag for 15-20 min. PVP K-30 as per batch quantity was dissolved in sufficient quantity of the purified water till a clear solution was obtained. The blend containing MOX was granulated manually with slow addition of PVP K-30 binder solution till granules are formed. The wet granules were dried in a hot air oven at 55-60°C for 35-40 minutes. The dried granules were sized through sieve #30 to get uniform granules. Based on the yield of granules, extra granular material Crospovidone and Lemon flavor were weighed accurately and passed through sieve # 40, and blended with dried granules for 5 min. The final granules were packed in and sealed in sachets and used for further characterization.

Characterisation of granules (Nanjwade *et al.,* 2013):

Angle of repose (θ): For determining the angle of repose, the funnel method was utilised. In the funnel, a weighed quantity of lubricated granules was kept and regulated at a certain height such that the heap of powder just reached the funnel's tip. The heap's diameter was calculated and the following formula was used to calculate the angle of repose.

$$\tan \theta = \frac{h}{r}$$

Where h = Height of the pile and r= radius of the base

Bulk density (BD): Accurately weighed lubricated granules were slowly poured into a measuring cylinder of 50 ml, and the bed was made uniformly without disturbing. The volume was measured in milliliters, and the BD was calculated using the formula below.

$$BD = \frac{\text{Mass of sample in g}}{\text{Volume occupied by sample in ml}}$$

Tapped density (TD): Lubricated granules were taken and weighed accurately and poured into a measuring cylinder placed in a bulk density tester. The initial volume occupied by the sample was noted it was tapped (50-100-250 times) till no change in the volume was observed and noted as tapped volume.TD was determined using the following formula

$$TD = \frac{\text{Mass of sample in gm}}{\text{Tapped volume occupied by sample in ml}}$$

Compressibility Index (CI): The CI was calculated using the formula below.

$$CI = \frac{TD - BD}{TD} \times 100$$

Hausner's Ratio (HR): HR was calculated with the help of the below formula

$$HR = \frac{TD}{BD}$$

Drug content: Granules equivalent to 100 mg of MOX (300 mg) were dissolved in methanol (10 mL) and made up to the volume with phosphate 7.4 buffer. The solution was stirred till the granules get dissolved completely. The solution was filtered through the 0.45-micron filter to get a clear solution and samples were analysed at 240 nm using a UV spectrophotometer and based on absorbance drug content was determined.

***In-vitro* release studies:** Dissolution test apparatus was used (USP type II) to determine the release of MOX in pH 7.4 phosphate buffer (900 ml; 37°C ± 0.5°C) at 50 rpm for 15 min. The samples of 5 ml were taken out at predetermined time intervals (2, 4, 6, 8, 10, 12, and 15 min) and replenished with the same amount of freshly prepared buffer for maintaining the sink condition. By using 0.45 µm filters the samples were filtered to get clear solutions and MOX content was determined using UV spectroscopy at 240 nm (Gohel *et al.,* 2005).

FTIR study: The compatibility of the MOX with other ingredients was determined using FTIR study. The infrared spectra of MOX and optimised formulation of granules were obtained by using FTIR by the potassium bromide pellet method. The dry samples were mixed separately with potassium bromide in 1:99 proportions and triturated and placed in the sample

holder to compress the pellets. The resulting pellets were scanned in the frequency range of 4000-400 cm^{-1}. The spectral analysis was carried out, by the standards absorbance range of the functional groups.

Differential Scanning Calorimetry (DSC) Studies: The DSC analysis of pure MOX and the optimised formulation were performed using the DSC instrument. The small amount of MOX and 2 to 3 mg of granules was accurately balanced in an aluminum pan and it was hermetically sealed with the help of a crimper. The sample pan and reference pan were kept in a DSC analyzer. The sample was heated from ambient temperature 40°C to 400°C, with a heating rate of 10°C/min. Inert atmospheres were provided by purging nitrogen gas flowing at 100 ml/min (Nyavanandi *et al.,* 2023).

X-Ray Diffraction: XRD patterns of pure MOX and optimised granule formulations were recorded with the following settings: Cu Kα radiation with wavelength 1.54 Å, voltage = 45 kV, current = 40 mA. Measurements were made in the 2° range of 10 to 80°.

RESULTS AND DISCUSSION

MOX taste-masked granules were developed using a combination of sweetening (mannitol, aspartame) and flavoring agents (lemon flavor). The flow properties of the developed granules were determined and presented in Table 2. The angle of repose was found between 25.5± 0.110 to 35.26± 0.111 while bulk density ranged between 0.237± 0.015 to 0.453± 0.033 gm/cm^3. The tapped density ranged between 0.246± 0.054 to 0.489± 0.032 gm/cm^3. HR ranged from 1.02± 0.027 to 1.14± 0.029 and CI was found between 2.13± 0.045 to 11.99± 0.039. The granules having angle of repose between 25-30 are considered to have excellent flow properties (Chaudhari and Dave 2015). The HR between 1.00 to 1.11 and CI between 0-10 indicate the excellent flow properties of the powder (Irigoiti *et al.,* 2021). Overall, the flow properties of the granules (F6) were found to be excellent.

***In-vitro* release studies:** The *in vitro* MOX release from developed granules was studied in a pH 7.4 phosphate buffer. **Table 3** and **Figure 1** show the comparative MOX release from different batches of the granules. Batches F3 to F6 showed greater than 80% drug release within 15 minutes. The drug release was found to be dependent on the concentration of the crospovidone. The addition of crospovidone (5 mg/tab to 30 mg/tab) significantly improved the dissolution profile in batches F1 to F6. Crospovidone has a strong capillary action, is highly hydrated, and exhibits significant agglomeration as well as a little propensity towards gel formation. The granules quickly dissolve but produce larger volumes of aggregated particles (Rowe *et al*., 2009). To achieve the therapeutic impact in the treatment of TB, this fast-release pattern is both necessary and preferred.

IR: FT-IR spectra of the pure MOX and optimised formulation F6 are presented in Fig. 2A and 2B respectively. In FTIR spectra of MOX HCl (Fig. 2A) the characteristic peaks were observed at 3522 cm^{-1} (secondary N-H stretching), 1699 cm^{-1} (CO stretching of keto group), 1499 cm^{-1} (OH bending of COOH) and 1617 cm^{-1} (CO stretching). Similar characteristic peaks for MOX were also reported in published literature (Mudgil and Pawar 2013). Similar characteristic peaks with lower intensity and slight shifting were also observed in the IR spectra of the F6 formulation (Fig. 2B). This shows that the MOX drug's characteristic peaks were retained in the final formulation. As a result, no interactions between the drug and the excipients are employed in the granule formulations.

DSC: During the drug development process, DSC helps in the identification of transitions such as melting point, glass transition temperature, and crystallinity. Fig. 3A and B show the DSC thermograms for the pure MOX and the F6 formulation, respectively. At 255.42°C, MOX showed a strong endothermic peak, suggesting that it is crystalline. Misra *et al.* (2011) also found a similar endothermic peak at 255°C with crystalline characteristics (Misra *et al.,* 2011). The optimised formulation F6 showed an endothermic peak at 252.66°C. When MOX was manufactured into granules, the strength of the endothermic peak of the compound decreased, indicating an increase in its amorphous nature.

X-Ray Diffraction: At diffraction angles of 8.44, 10.07, 15.11, and 19.06, distinct sharp peaks of MOX were observed (Fig. 4A). Therefore, the XRD spectrum of pure MOX showed crystal structure. As seen in Fig. 4B, the intensity of the crystalline peaks of the pure MOX drug slightly decreased in the optimised formulation. The high-intensity peaks seen at diffraction angles 32.41 and 35.94 may be due to the other excipients present in the formulation. These findings proved that the MOX in the final formulation also existed in crystalline form.

Table 1: Formula composition of MOX dispersible tablets.

Sr. No.	Name of ingredient	F1	F2	F3	F4	F5	F6
	Intragranular						
1	Moxifloxacin	100.0	100.0	100.0	100.0	100.0	100.0
2	Microcrystalline cellulose (MCC 101)	94.5	89.5	84.5	79.5	74.5	69.5
3	Mannitol 160 C	71	71	71	71	71	71
7	Aspartame	12.5	12.5	12.5	12.5	12.5	12.5
4	Crospovidone	2.5	5.0	7.5	10.0	12.5	15.0
5	PVP K-30	15.0	15.0	15.0	15.0	15.0	15.0
6	Purified water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
	Extra granular						
6	Crospovidone	2.5	5.0	7.5	10.0	12.5	15.0
8	Lemon flavor	2.0	2.0	2.0	2.0	2.0	2.0
8	**Total**	300.0	300.0	300.0	300.0	300.0	300.0

Table 2: Flow properties of the granules.

Batch	Angle of repose (θ)	Bulk Density (gm/cm^3)	Tapped Density (gm/cm^3)	Hausner Ratio	CI
F1	33.11± 0.125	0.237± 0.015	0.246± 0.054	1.04± 0.012	3.66± 0.024
F2	35.26± 0.111	0.278± 0.012	0.287± 0.065	1.03± 0.021	3.14± 0.027
F3	32.11± 0.195	0.296± 0.023	0.31± 0.034	1.05± 0.013	4.52± 0.032
F4	31.27± 0.145	0.301± 0.024	0.351± 0.025	1.02± 0.027	2.13± 0.045
F5	33.45± 0.127	0.345± 0.027	0.392± 0.065	1.14± 0.029	11.99± 0.039
F6	25.5± 0.110	0.453± 0.033	0.489± 0.032	1.08± 0.016	7.36± 0.043

Table 3: Comparative in vitro MOX release from dispersible tablets.

Time (min)	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
2	17	20	26	30	37	46
4	25	32	40	45	50	69
6	34	45	52	59	64	84
8	45	56	67	72	78	97
10	51	65	72	78	85	100
12	60	71	78	84	93	
15	67	75	88	92	100	

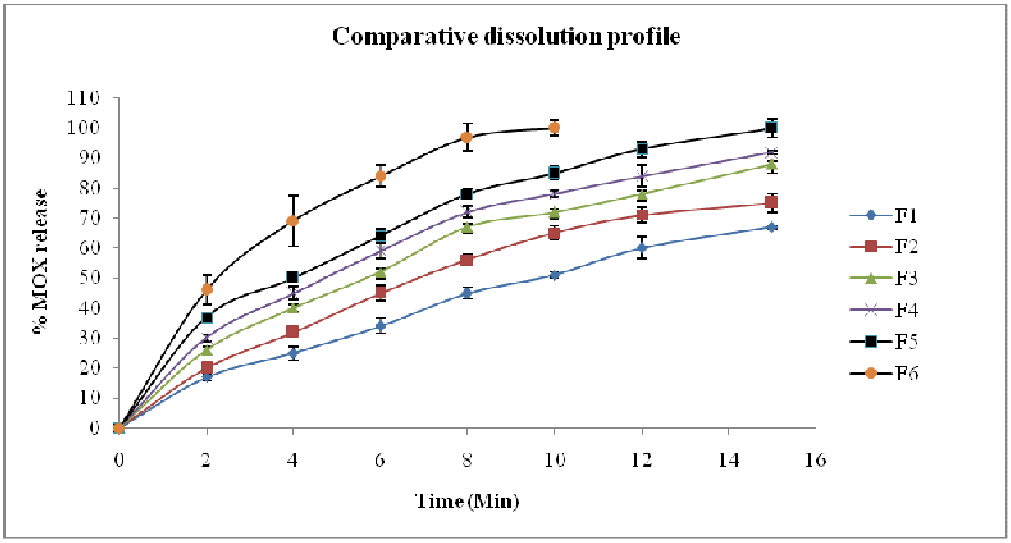

Fig. 1. Comparative *in vitro* MOX release in pH 7.4 phosphate buffer.

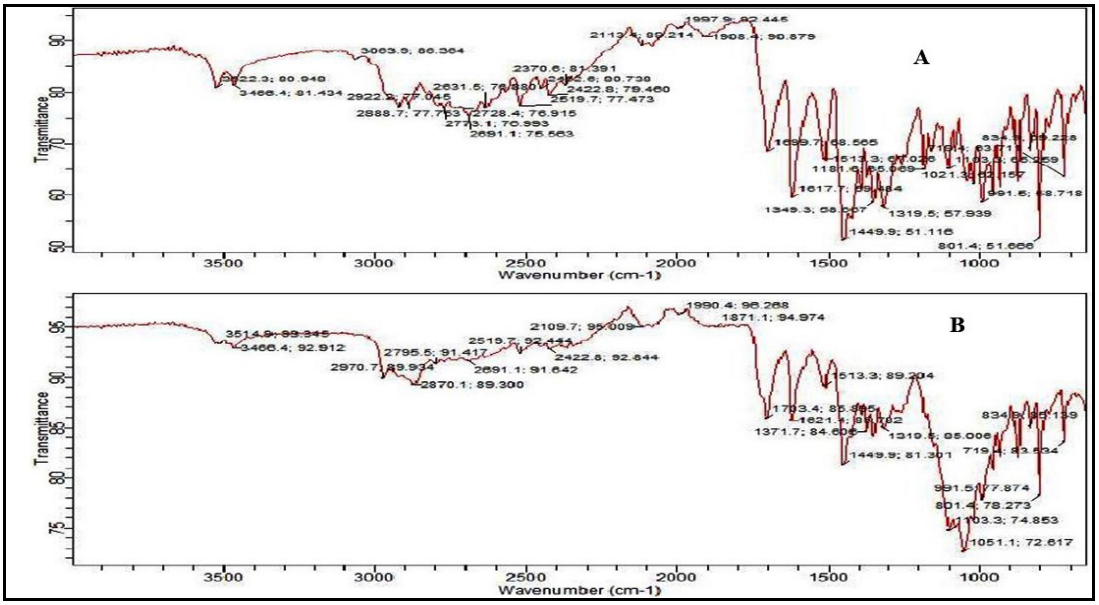

Fig. 2. FTIR spectra of **(A):** Pure MOX and **(B):** Optimised formulation F6.

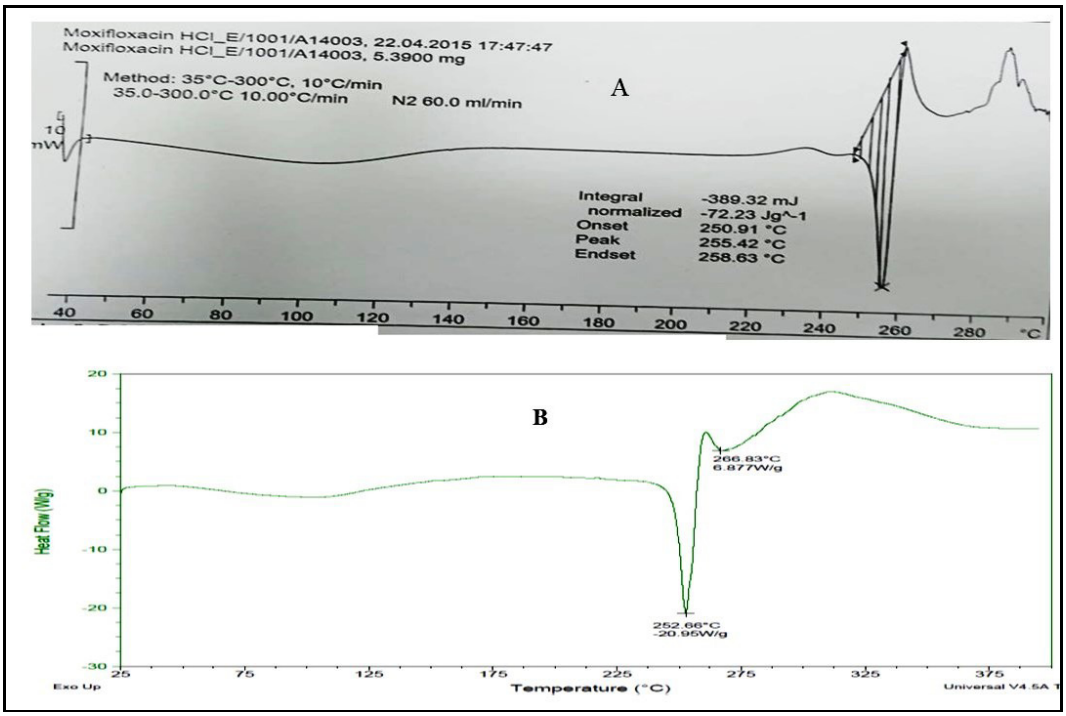

Fig. 3. A: DSC endothermic peak of pure MOX and **B:** optimised formulation F6.

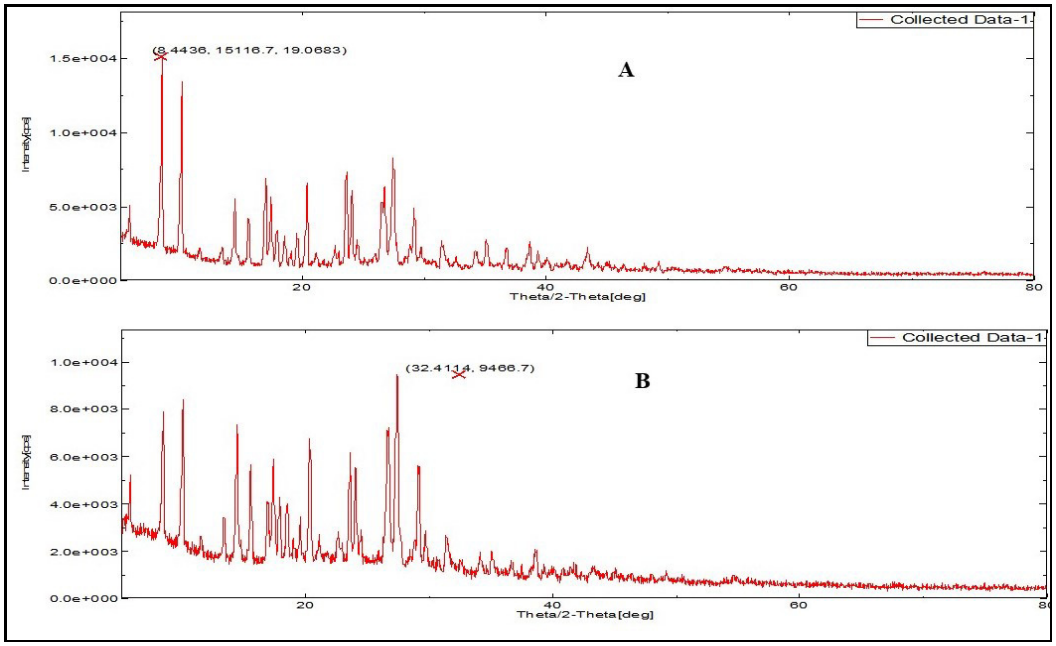

Fig. 4. X-ray diffraction pattern of **(A):** Pure MOX drug and **(B):** optimised formulation F6.

CONCLUSIONS

The present study concludes that the taste-masked granules of the MOX can be successfully developed by using the wet granulation technique by incorporating sugars and flavouring agents. The optimised granules showed excellent flow properties and can be easily filled in suitable packaging material. The optimised batch showed complete drug release within 10 min period. FTIR and DSC studies revealed no drug excipient incompatibility. XRD demonstrated that the MOX in the final formulation was present in crystalline form. The taste-masked granules of the MOX could be a potential alternative for the treatment of pediatric TB.

FUTURE SCOPE

The developed taste-masked granules can be furthermore planned for scale-up batches can also be planned to check the process feasibility.

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Conflict of Interest. None.

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