Formulation and Evaluation of taste masked Dry Syrup Containing Tedizolid

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***Abstract*—993Oral routes of drug administration have wide acceptance up to 50-60% of total dosage forms. Many active pharmaceutical ingredients taste bitter and thus are not favoured by children, as well as many adults leading to non-adherence in many cases. Background: An attempt was made to develop a palatable reconstitutable dry syrup formulation of Tedizolid using ion exchange resin technology for effective taste masking while maintaining optimal therapeutic efficacy. Methods: Drug-resin complexes were prepared using the batch method with various ion exchange resins. Formulations were evaluated for taste masking efficiency, physicochemical properties, drug content uniformity, viscosity, sedimentation rate, redispersibility, and in vitro drug release characteristics. Accelerated stability studies were conducted to determine shelf life. Results: Indion214 resin demonstrated superior drug loading capacity of 83.87% among tested resins. The optimized formulation containing 3% guar gum as a suspending agent exhibited excellent taste masking properties, satisfactory viscosity (350-450 cPs), optimal sedimentation volume (0.85-0.95), complete redispersibility (<15 strokes), and high drug content uniformity (98.5-101.2%). In vitro drug release showed >85% within 45 minutes in gastric pH. Conclusion: The developed Tedizolid dry syrup successfully addressed the taste challenge while maintaining desirable physicochemical and release characteristics, making it a promising formulation for paediatric use.**

***Index Terms*—Dry syrup, Ion exchange resin, Taste masking, Tedizolid,**

1 INTRODUCTION

Severe bacterial infections caused by multidrug resistant bacteria are posing major health problems across the globe.[1] Unfortunately, the effectiveness of available antibacterial agents is diminishing, as the microorganisms are evolving new mechanisms of resistance and rapidly spreading them via mobile genetic elements such as plasmids and integrons.[2] Tedizolid phosphate, approved in 2014, is a second-generation Synthetic oxazolidinone antibacterial[3].Tedizolid phosphate is a prodrug used for the treatment of acute bacterial skin and skin structure infections caused by certain susceptible bacteria, including Staphylococcus aureus (including methicillin-resistant strains (MRSA) and methicillin-susceptible strains), various Streptococcus species, and Enterococcus faecalis.[4] Tedizolid inhibits bacterial protein synthesis by binding to the 23S ribosomal RNA of the 50S subunit, preventing the formation of the functional 70S ribosomal complex. This action blocks bacterial translation and ultimately inhibits protein synthesis, leading to bacteriostatic activity against susceptible gram-positive bacteria.[5] Despite its proven clinical efficacy across various infection types including nosocomial pneumonia, complicated skin and soft tissue infections, and resistant tuberculosis, the inherent intensely bitter taste of Tedizolid creates substantial challenges for paediatric administration. The problem of bitterness in pharmaceutical formulations extends beyond mere discomfort, as it can lead to poor medication adherence, treatment failures, and potential development of antibiotic resistance. This is particularly crucial in paediatric populations where taste acceptance often determines the success of antimicrobial therapy.[6] While Tedizolid is available in various dosage forms including tablets, intravenous injections, and oral suspensions, the commercial oral suspension still presents taste-related challenges.

Ion exchange resins are water-insoluble, cross-linked polymer containing salt forming groups in repeating position on the polymer chain. The unique advantage of ion exchange resins for complexation is their fixed positively or negatively charged functional groups attached to water insoluble polymer backbones. These groups have an affinity for oppositely charged counter ions, thus absorbing the ions into the polymer matrix.[7]

Taste-masking technologies have evolved significantly, with ion exchange resins emerging as a particularly effective approach for bitter drugs.[8] These resins form complexes with drug molecules that remain stable at salivary pH, preventing release and subsequent taste perception, while dissociating in gastric pH to ensure proper drug absorption.[9,10]Dry syrup formulations offer additional advantages in terms of stability, convenience, and patient acceptability, particularly in resource-limited settings.[11]This study aimed to develop a stable, palatable dry syrup formulation of Tedizolid using ion exchange resin technology, with comprehensive evaluation of its physicochemical properties, stability, and release characteristics to ensure optimal therapeutic performance.

2 MATERIALS AND METHODS

2.1 Materials

Tedizolid API was obtained as a gift sample (Cubist Pharmaceuticals, Inc). Various ion exchange resins including Kyron T-104, T-134, T-154, T-314, Indion204, and Indion214 were procured from reputable suppliers. Suspending agents including xanthan gum, guar gum, and sodium carboxymethyl cellulose (CMC) were of pharmaceutical grade. Other excipients including sucrose, methylparaben, propylparaben, citric acid, sodium citrate, flavours, and colours were of compendial quality. All chemicals and reagents used in analytical studies were of analytical grade.

2.2 Preparation of Drug-Resin Complexes

The batch method was employed for the formation of drug-resin complexes. Precisely weighed quantities of ion exchange resins were dispersed in distilled water to form a uniform slurry. Tedizolid was separately dissolved in a suitable solvent and added gradually to the resin slurry under continuous mechanical stirring. The mixture was agitated for a predetermined time at controlled temperature to allow complete drug loading. The resulting complex was separated by filtration, washed with distilled water to remove uncomplexed drug, and dried in a hot air oven at 40°C for 12 hours. The dried complex was sieved through appropriate mesh size and stored in airtight containers until further use.[12]

2.3 Optimization of Drug Loading

Drug loading efficiency was optimized by varying critical parameters including resin:drug ratio, pH of the medium, temperature, stirring time, and particle size of the resin. The percentage drug loading was determined by extracting the drug from a known quantity of complex using 0.1N HCl and analyzing the solution spectrophotometrically at 256 nm. The optimized complex was characterized by Fourier Transform Infrared Spectroscopy (FTIR) to identify any potential interactions between the drug and resin.

2.4 Formulation of Dry Syrup

The taste-masked drug-resin complex was incorporated into the dry syrup formulation using the formula presented in Table 1. The dry syrup was prepared by geometric dilution and thorough mixing of all ingredients. The mixture was passed through a sieve (#60 mesh) to ensure uniform particle size distribution and packed in airtight containers.

Table 1: Composition of Tedizolid Dry Syrup Formulation

Sr No	Ingredients	Quantity per 5 mL	Function
1	Tedizolid equivalent to	100 mg	Active pharm. ingredient
2	Indion 214 resin	q.s.	Taste masking agent
3	Guar gum	3% w/v	Suspending agent
4	Sucrose	60% w/v	Sweetener
5	Methylparaben	0.1% w/v	Preservative
6	Propylparaben	0.02% w/v	Preservative
7	Citric acid	0.05% w/v	pH adjustment
8	Sodium citrate	0.1% w/v	Buffer
9	Flavour	q.s.	Flavouring agent
10	Colour	q.s.	Colouring agent
11	Purified water	q.s. to 5 mL	Vehicle

2.5 Evaluation of Dry Syrup[13,14]

The formulated dry syrup was evaluated for the following parameters:

Taste Evaluation: The taste was evaluated by a panel of 6 trained human volunteers using the sip and spit method after obtaining ethical clearance. The bitterness score was recorded on a scale of 0 (no bitterness) to 5 (strong bitterness)

Physical Parameters: The reconstituted syrup was evaluated for colour, odour, and appearance.

Viscosity: The viscosity of the reconstituted suspension was determined using a Brookfield viscometer (LV model) at 10 rpm using appropriate spindle.

Sedimentation Volume: The sedimentation volume was determined by transferring 50 mL of the reconstituted suspension to a graduated cylinder and allowing it to stand for 7 days. The sedimentation volume (F) was calculated as F = Vu/Vo, where Vu is the ultimate volume of sediment and Vo is the initial volume of suspension.

Redispersibility: The redispersibility was measured by counting the number of strokes required to redisperse the sediment after standing for 7 days.

Drug Content Uniformity: The drug content was determined by extracting the drug from a known quantity of formulation and analyzing spectrophotometrically at 256 nm.

In vitro Drug Release Studies: The drug release profile was studied using USP Type II dissolution apparatus at 50 rpm in 900 mL of 0.1N HCl maintained at 37±0.5°C. Samples were withdrawn at predetermined time intervals and analyzed spectrophotometrically at 256 nm.

Stability Studies: The optimized formulation was subjected to accelerated stability studies as per ICH guidelines at 40±2°C/75±5% RH for 3 months. Samples were evaluated for physical appearance, drug content, and dissolution characteristics at monthly intervals.

2.6 Statistical Analysis

All experiments were conducted in triplicate and results expressed as mean ± standard deviation. Data were analyzed using one-way ANOVA followed by Tukey's post-hoc test with $p<0.05$ considered statistically significant.

3 RESULTS AND DISCUSSION

3.1 Selection and Optimization of Drug-Resin Complex

The successful taste masking of Tedizolid depended significantly on the selection of appropriate ion exchange resin and optimization of complexation parameters. Among the various resins evaluated, Indion 214 demonstrated superior drug loading capacity (83.87%) compared to Kyron series resins and Indone 204 (ranging from 68.81% to 81.43%). This superior performance might be attributed to the optimal swelling characteristics and ionic capacity of Indion 214 resin which facilitated more efficient drug-resin interaction.

The optimization studies revealed that the drug loading efficiency was highly dependent on the resin:drug ratio, with 1:1 ratio providing the optimal complexation without excess free drug. The pH of the medium significantly influenced complexation, with pH 6.0 providing optimal conditions for drug-resin interaction. The complexation efficiency increased with stirring time up to 4 hours, beyond which no significant improvement was observed. Temperature also played a crucial role, with 40°C proving optimal for the complexation process.

Table 2: Evaluation of Different Resins for Drug Loading Capacity

Resin Type	Drug Loading Efficiency (%)	Complexation Efficiency
Kyron T-104	68.53 ± 1.32	Good
Kyron T-134	72.36 ± 1.45	Moderate
Kyron T-154	79.34 ± 1.87	Good
Kyron T-314	77.84 ± 2.15	Good
Indion 204	80.12 ± 1.31	Good
Indion 214	83.87 ± 1.24	Excellent

FTIR studies confirmed the formation of drug-resin complex without any chemical interaction, as the characteristic peaks of Tedizolid were preserved in the complex, though with slight shifts in wave numbers and reduced intensity.

3.2 Evaluation of Dry Syrup Formulation

The formulated dry syrup exhibited excellent physicochemical properties with pleasant characteristics acceptable for paediatric administration. The results of comprehensive evaluation are presented in Table 3.

Taste Evaluation: The taste evaluation revealed complete masking of bitterness, with the optimized formulation scoring 0 (no bitterness) on the bitterness scale compared to pure drug solution which scored 4 (strong bitterness). This confirmed the effectiveness of Indion 214 resin in masking the bitter taste of Tedizolid.

Physical Parameters: The reconstituted syrup had a pleasant pink color (due to added colorant), characteristic strawberry flavor, and uniform appearance without any visible particulate matter.

Viscosity: The viscosity of the reconstituted suspension was found to be 377±17 cPs, which provided optimal flow characteristics for easy pourability while maintaining adequate suspension of particles. The formulation containing 3% guar gum showed better viscosity characteristics compared to those with gellan gum or CMC.

Sedimentation Volume: The sedimentation volume ratio was determined to be 0.88±0.02, indicating good suspension characteristics with minimal settling. These values close to 1 indicate excellent suspension stability.

Redispersibility: The formulation exhibited excellent redispersibility, requiring only 11±2 strokes to completely redisperse the sediment, which is well within acceptable limits (<15 strokes).

Drug Content Uniformity: The drug content was found to be 98.5±1.2% of the labeled claim, indicating excellent uniformity and compliance with pharmacopeial requirements (90-110% of labeled claim).

Table 3: Evaluation Parameters of Optimized Tedizolid Dry Syrup

Parameter	Results	Specification
Appearance	Fine, free-flowing powder	Free-flowing powder
Color of reconstituted syrup	Pink	As desired
Odor	Characteristic strawberry	Pleasant
Taste	No bitterness (Score 0)	No bitterness
Viscosity (cPs)	377±17	350-450
Sedimentation volume (F)	0.88 ± 0.02	>0.85
Redispersibility (no. of strokes)	11 ± 2	<15
Drug content (%)	98.5±1.2 %	90-110%
pH of reconstituted suspension	5.5 ± 0.4	4.5-6.5

3.3 In vitro Drug Release Studies

The drug release profile from the optimized formulation showed that less than 5% of the drug was released at salivary pH (6.8) within 5 minutes, confirming effective taste masking2. However, in gastric pH (0.1N HCl), the formulation exhibited rapid and complete drug release with >85% drug released within 45 minutes, ensuring proper absorption and therapeutic efficacy. The drug release followed first-order kinetics with the mechanism of release being ion exchange driven by the pH environment.

The rapid drug release in gastric pH can be attributed to the displacement of drug molecules from the resin complex by hydrogen ions in the acidic environment, followed by dissolution of the free drug.

3.4 Stability Studies

The accelerated stability studies indicated that the formulation remained physically and chemically stable throughout the study period of 3 months. No significant changes were observed in color, odor, taste, drug content, or dissolution characteristics. The drug content remained between 98.5-101.2% of initial value, and dissolution characteristics showed no significant variation ($f2 > 50$). The slight decrease in pH (from 5.2 to 4.9) was within acceptable limits and did not affect product performance.

Based on the stability data, the shelf life of the formulation was projected to be 24 months when stored at room temperature (below 30°C) in tightly closed containers. The stability of Tedizolid in aqueous solution has been previously established, with studies showing that it maintains >95% potency for 34 days at 25°C in various intravenous fluids, supporting our findings10.

4 CONCLUSIONS

The study successfully developed a palatable dry syrup formulation of Tedizolid using Indion214 ion exchange resin for effective taste masking. The optimized formulation contained 3% guar gum as suspending agent and exhibited excellent physicochemical properties, taste masking efficiency, and drug release characteristics. The formulation demonstrated satisfactory stability under accelerated conditions, suggesting adequate shelf life for commercial viability.

The taste-masked dry syrup addresses a critical need in paediatric therapy by improving medication adherence without compromising therapeutic efficacy. The successful application of ion exchange resin technology presents a viable approach for taste masking of other bitter drugs in paediatric formulations. Future studies should focus on long-term stability testing, in vivo bioavailability studies, and clinical trials to establish bioequivalence with existing formulations.

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