DEVELOPMENT AND EVALUATION OF POLYMERIC SCAFFOLD CONJUGATED AMBROXOL HYDROCHLORIDE ORODISPERSIBLE TABLETS

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(Received 18 January 2025) (Accepted 12 August 2025)

ABSTRACT

The current research aimed to develop orodispersible tablets (ODTs) of ambroxol hydrochloride using Amberlite® IRP69 and IRP64 polymeric scaffolds. The taste-masking orodispersible complexes were prepared in various ratios of Amberlite® IRP64. The physicochemical properties of the complexes were characterised using FTIR spectroscopy, particle size analysis, solubility and *in vitro* taste evaluation. The best results were obtained using a 1:3 drug-resin ratio, which effectively masked the taste of ambroxol hydrochloride. The prepared ODTs had a weight variation between 250.2 ± 0.18mg and 250.7 ± 0.22mg, thickness between 2.48 and 2.68 mm, friability between 0.32 ± 0.06% and 1.5 ± 0.05%, and specific hardness between 2.85 ± 0.2 and 4.31 ± 0.7 kg cm^{-2}, with a disintegration time of 62 to 46 seconds. The ODTs showed 92.86% drug release within 30 minutes, which is essential for a faster onset of action. The Amberlite® IRP64 ion exchange resin complexes effectively masked the taste without compromising the drug release.

Keywords: Nanocomplex, Amberlite® IRP64, Polymer, ambroxol hydrochloride, orodispersible tablets

INTRODUCTION

Orodispersible drug delivery systems (ODDS) were developed to provide patients with an easy way to take their medications. Patients often struggle with swallowing due to physical changes[1]. Children, the elderly, and those who prefer a simple dosage form will benefit from a solid tablet that can dissolve, disintegrate, or suspend in the mouth's saliva[2]. When applied to the tongue, the tablets dissolve immediately, releasing medication that dissolves or disperses in saliva. ODTs rapidly break down or diffuse in the oral cavity. These dosage forms are also called rapidly dissolving, orodispersible, and dispersible tablets[3,4]. ODTs are solid forms that dissolve rapidly in the mouth[5]. This procedure increases the amount of drug that the body can absorb through the mouth, throat, and oesophagus. ODTs can be swallowed without water, making them convenient for people who have difficulty in swallowing[6,7]. This provides greater safety and compliance, as there is no risk of physical blockage and airway choking. Additionally, the pleasant mouth feel helps mask any unpleasant taste of medications, particularly for young children[8-10].

The strong expectorant and mucokinetic properties of ambroxol hydrochloride originally derived from the ayurvedic medicinal plant *Adhatoda vasica* allow it to stimulate bronchial secretion[11,12]. In addition to directly depolymerising mucopolysaccharides, it also breaks the fibre network of tenacious sputum by freeing lysosomal enzymes[13]. It is used to treat coughs and as an expectorant for several respiratory conditions, such as bronchitis and asthma[14]. If there are mucus plugs present, it is especially beneficial. Viral diseases, like the common cold, are the most frequent triggers in paediatrics[15,16]. The paediatric patient finds it challenging to take a tablet-style dosing form because of sore throat symptoms. From the standpoints of dose monitoring and stability, liquid dosage forms have certain limitations[17]. Therefore, an effort was made to prepare an ambroxol hydrochloride fast-disintegrating

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https://doi.org/10.53879/id.63.01.15406

tablet to boost patient compliance and convenience, while shortening the lag. For paediatric patients, fast-disintegrating pills would therefore be the perfect dosage form. As a result, an attempt was made to manufacture an ambroxol tablet that would dissolve quickly[18].

To the best of our knowledge, this study represents the first systematic comparative evaluation of Amberlite® IRP64 and IRP69 resins for the taste masking of ambroxol hydrochloride in orodispersible tablets. Additionally, we optimised the drug-to-resin ratio and pH-dependent drug loading efficiency, providing new insights into the ion-exchange mechanisms affecting palatability and drug release. Our formulation uniquely integrates resin selection, superdisintegrant optimisation, and *in vivo* taste evaluation using animal models, which has not been previously reported in a single study framework. This comprehensive approach aims to enhance paediatric patient compliance through improved palatability and fast disintegration.

MATERIALS AND METHODS

Chemicals and Reagents

The chemicals and reagents used in this study included ambroxol hydrochloride; sodium hydroxide; Sunset Yellow FCF microcrystalline cellulose 101 (Yarrow Chem Products, Maharashtra); MCC Sanaq (Pharmatrans Sanaq Ag Pharmaceuticals, Delhi); Amberlite® IRP64 (Ion Exchange India Limited, Maharashtra); mannitol; potassium dihydrogen ortho phosphate; menthol crystal natural (Central Drug House, Maharashtra); magnesium stearate; talcum powder (Himedia Laboratories Private Limited, Maharashtra); hydrochloric acid (Rankem Laboratory Chemicals, Maharashtra).

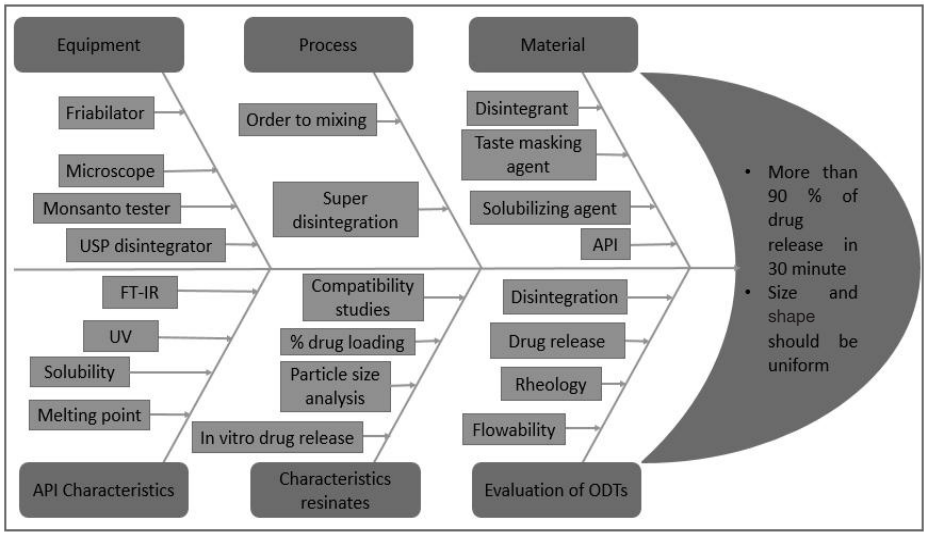

Fig. 1: Fishbone diagram of taste-masked ODTs of ambroxol hydrochloride manufacturing process

Experimental overview

A stepwise experimental approach was followed for the development of taste-masked ODTs of ambroxol hydrochloride. Fig. 1 shows the flow diagram summarising the formulation strategy ODTs.

Identification of the drug

Calculating the melting point of ambroxol HCl

The medication was placed in a fused capillary tube and stored in a digital melting point device (Perfit, India, MODEL REC 2802582). The device was used to record the melting point temperature of the medication[19].

UV analysis of drug identification

The λ-max of the drug was determined by a UV-visible spectrophotometer.

Determination of functional groups by FT-IR

KBr discs were prepared by means of hydrostatic pressure of 6-8 tons using a KBr press. Then, FT-IR spectra were recorded in the scanning range of 400-4000 cm^{-1} (IP 2010).

Creating a standard plot in various media

10 mg of ambroxol hydrochloride was dissolved in 10 mL of a buffer solution to create the standard stock solution. The mixture was then sonicated for 15 minutes to produce a 1 mg mL^{-1}, or 1000 µg mL^{-1}, stock solution. The drug's standard λ_{max} was used for scanning, and a standard plot was created[19].

Preformulation studies

Drug solubility

Solubility is usually determined in different solutions, such as water, 0.1 N acidic buffer, and phosphate buffers (pH 6.8). The drug material was added to this solution until a saturated solution formed. The mixture and filtrate were taken and the absorbance was determined. The concentration of a drug varies in different solutions[20].

Determination of the partition coefficient for the drug

The aqueous and organic layers were separated after ambroxol hydrochloride (20 mg) and 25 mL of n-octanol were added to 25 mL of water in a separating funnel and shaken for 30 min. After the aqueous layer was appropriately diluted, absorbance at 244 nm was noted[21, 22].

$$\text{Partition coefficient} = \frac{\text{Drug concentration in } n\text{-octanol}}{\text{Drug concentration in distilled water}} \quad (1)$$

Preparation of drug resin complex (Resinates)

Amberlite® IRP64 and IRP69 were initially pre-treated with 1N hydrochloric acid (HCl) and 1N sodium hydroxide (NaOH) to remove impurities and activate the resin. Drug-resin complexes were prepared using varying drug-to-resin ratios: 1:1, 1:2, 1:3, and 1:4. For each batch, 0.6 g of ambroxol hydrochloride was mixed with the appropriate amount of resin in 50 mL of deionised water. The mixture was stirred continuously for 6 h using a magnetic stirrer to facilitate ion-exchange interaction. After stirring, the resinates were filtered, thoroughly washed with deionised water to remove unbound drug, and dried in a hot air oven at 60 °C until constant weight was achieved[23].

Evaluation of ambroxol HCl resinate

Drug resins compatibility studies

Ambroxol hydrochloride and resin were mixed in a 1:1 ratio and these mixtures were stored in preserved vials for one month at room temperature at 25 °C. A mixture of ambroxol hydrochloride and resin was scanned by FT-IR[22].

Determination of % drug loading

In a 100 mL volumetric flask, an exact weight of 25 mg of ambroxol hydrochloride resinate was introduced. It was solvated and made up the volume of 100 mL by adding 0.1 N HCl. To determine the drug loading, 1 mL of this solution was saved and put in a 10 mL volumetric flask. The absorbance was then measured[24].

$$\%\ \text{Drug loading} = \frac{\%\text{Weight of ambroxol hydrochloride in resinates}}{\text{Weight of resinates}}\ \text{X}\ 100 \quad (2)$$

Effect of the resin ratio of ambroxol HCl on drug loading

There are two ways to obtain resin: the batch approach and the column analysis. Accurately measured amounts of pre-treated resin (0.6, 1.2, 1.8, and 2.4 g) were combined with 50 mL of deionised water containing 0.6 g ambroxol hydrochloride to obtain drug-resin ratios of 1:1, 1:2, 1:3, and 1:4. The mixture was stirred for 6 h on a magnetic stirrer to facilitate drug loading. The resin was then filtered and washed with deionised water, and the drug-loading efficiency was determined using a UV spectrophotometer set to 244 nm to measure the amount of unbound drug in the filtrate. Finally, the resinate was dried in a hot air oven at 60 °C until its moisture content was less than 5 %[25].

pH impact on drug loading

Buffer solutions prepared according to Indian Pharmacopoeia (IP) requirements, ranging in pH from 1.2 to 7. A 2.4 g sample of pre-treated resin was added to a series of 100 mL beakers, each containing 0.6 g of ambroxol hydrochloride and 50 mL of buffer solution at pH 1.2, 4.0, 6.8, and 7.0, respectively, to achieve a 1:4 ratio. The mixture was shaken for 6 h using a magnetic stirrer to allow for the maximum amount of loading. Whatman filter paper (e.g., 11µm) was then used to filter the residue, and deionised water was used to wash the residue. Lastly, drug-loading efficiency was computed and the quantity of unbound medicine in the filtrate was determined by a UV spectrophotometer at 244 nm[24].

Particle size analysis

The particle size distribution of ambroxol hydrochloride was analysed using optical microscopy. The stage micrometre was calibrated to facilitate the measurements. The average particle size was determined by randomly measuring the diameters of 300 particles[26].

$$\text{Mean diameter} = \frac{\sum n \times d}{\sum n} \quad (1)$$

where, d = mean size range and n = number of resinates

In vitro drug release study of resinates

A USP Type II dissolution apparatus was used to dissolve ambroxol hydrochloride resinates. The dissolution medium was maintained at 37 ± 0.5°C and consisted of 900 mL of 0.1 N hydrochloric acid. 30 mg of ambroxol hydrochloride resinates was carefully weighed, the drug-resinate complex was placed in the dissolution vessel, and swirled at 100 rpm. 5 mL samples were taken out and swapped out for an equivalent volume of fresh dissolving media at different intervals. The drug's concentration was measured at different time points using UV-visible spectroscopy, with absorbance recorded at 244 nm. The drug's released concentration was calculated using a standard calibration curve[27].

Table I: Composition of ambroxol HCl ODTs

Ingredient (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Equivalent amount of ambroxol hydrochloride: 30 mg	120	120	120	120	120	120	120	120	120
Sodium starch glycolate	10	20	30	10	20	30	10	20	30
MCC Sanaq	60	50	40	-	-	-	-	-	-
Microcrystalline cellulose 102	-	-	-	60	50	40	-	-	-
Microcrystalline cellulose 101	-	-	-	-	-	-	60	50	40
Mannitol	50	50	50	50	50	50	50	50	50
Magnesium stearate	2	2	2	2	2	2	2	2	2
Menthol	4	4	4	4	4	4	4	4	4
Talc	2	2	2	2	2	2	2	2	2
Sunset Yellow FCF	2	2	2	2	2	2	2	2	2
Total	250	250	250	250	250	250	250	250	250

Experimental choices

Selection of resin

Amberlite® IRP64 was selected over IRP69 for the final formulation based on comparative evaluation. Amberlite® IRP64 demonstrated higher drug loading efficiency (98.26%) compared to IRP69 (96.55%). *In vivo* taste evaluation using a rat model confirmed that IRP64 provided superior taste masking, with significantly improved palatability compared to IRP69. Furthermore, drug release studies showed that IRP64 resinate (A8 batch) achieved approximately 90% drug release within 60 min, indicating an optimized release profile. Based on superior drug loading, effective taste masking, and optimized drug release, Amberlite® IRP64 was selected for the final formulation.

Selection of drug: resin ratio

Trial batches (A1-A8) were set to contain drug and resin in the ratio of 1:1 to 1:4 for each of the Ion exchange resin (IER) by batch process in Table I with Amberlite® IRP69 and Amberlite® IRP64. Based on drug loading efficiency, resinate complex A8, having a ratio of 1:4 (with Amberlite® IRP64), was finalized for further study. Prepared resinates were evaluated for % drug loading, particle size and *in vitro* drug release study.

Selection of pH

The drug loading of resinate was also affected by changing the pH of the solvent. The effect of pH on drug loading was evaluated by using different pH solutions (pH 1.2 to 7). Maximum drug loading was observed at pH 7.0 for Amberlite® IRP64, indicating efficient ion-exchange interaction under mildly basic conditions.

Preparation of ambroxol HCl ODTs

Ambroxol hydrochloride tablets were made up of superior disintegrants and direct compression method was used various excipients, as shown in Table I. The following steps were used in the direct compression method; Ambroxol hydrochloride drugs : resin complex was weighed and other excipients were also weighed. After mixing properly, they were placed to compress in a punching machine (A2563/3001, Cadmach, Ahmedabad)[17].

Evaluation of ambroxol HCl ODTs

Common appearance

The common appearance, such as its visual uniqueness, is necessary. The size of tablets, taste, exterior quality, physical flaws, and reliability influence consumer acceptance.

Width

The widths of orally disintegrating tablets were measured using a calliper.

Rigidity

The Monsanto hardness tester was used to determine the tablet's rigidity. The tablets were adjusted between rigid and moving jaws. The range was set to zero; the weight was slowly increased until the tablet was broken.

This load was used to calculate the rigidity of tablets. Rigidity was expressed in kg cm^{-2} [28].

Friability

This includes calculating the mechanical resistance of the tablets. A friability testing machine was used to determine the degree of friability. A previously weighed tablet was placed in the friabilator. For a least 4 min. or 100 cycles, tablets were rotated in the friabilator. The tablets were sprayed and weighed once more after the test, and the weight loss of the tablets was calculated using friability and reported as percentage[29].

$$F\% = \frac{\text{Initial weight - Final weight}}{\text{Initial weight}} \times 100 \quad \text{..... (4)}$$

Weight dissimilarity test

20 tablets were arbitrarily selected and the gross weight was calculated. The % dissimilarity of gross weight was measured.

In vitro disintegration time

Disintegration testing was performed in a USP disintegrator by placing six tablets in each tube and the time required for total disintegration was recorded[29].

Drug assay

It was carried out for five tablets. Each tablet was triturated in a mortar & pestle. A % mg equivalent blend was weighed, added to a phosphate buffer solution with a pH of 6.8, diluted as needed, and the absorbance was measured using a spectrophotometer at 244 nm. The reading was taken in triplicate, and the regular drug substance was calculated[30].

In vitro drug release studies

The dissolution study was performed using 900 mL of 0.1 N HCl for the initial 2 h, followed by a pH 6.8 phosphate buffer solution, with the USP-II apparatus operating at 100 rpm. The environmental temperature was maintained at 37±0.5°C. Specified volume (5 mL) samples were collected in a volumetric flask, volumetricized, and absorbance was recorded at a wavelength of 244 nm, and % release was calculated[31,32].

Kinetics of drug release (curve fitting analysis)

The following four data treatment models were fitted with the outcomes of release profiles acquired for each formula. Plots were created for cumulative medication release over the square root of time (Higuchi model), the amount of drug remaining over time (First order kinetic model), cumulative drug release over time (Zero order kinetic model), and log-transformed cumulative drug release over log time (Korsmeyer-Peppas equation)[33-38].

$$At = A_0 - K_0 t \quad \text{.....(5)}$$

Where K_0 = *zero-order rate constant, At = drug release at time t, and* A_0 = *initial drug concentration*

The first-order kinetic model describes the logarithm of the cumulative proportion of medication remaining over time.

$$\text{Log } C = \log C_o - 2.303Kt\ldots \quad \text{.....(6)}$$

Where K denotes the first-order rate constant, C represents the amount of drug remaining at time t, and C_0 denotes the initial amount of the drug.

Drug release cumulative % against time square root (Higuchi model)

$$Q = Kt1/2 \quad \text{.....(7)}$$

Log time versus log cumulative percent medication released (Korsmeyer-Peppas equation)

In vivo taste assessment

Taste masking was assessed using a variety of techniques, including an e-tongue, an animal model, and a human taste panel. Because of its many benefits, this study investigated the *in-vivo* taste aversion (Bata) paradigm to evaluate the taste masking of the unpleasant drug ambroxol hydrochloride. A lab-scale manufactured lickometer was used to create the Bata model. Stainless steel 316 and acrylic glass were used in the construction of the lickometer. The mounted camera on the top side was used to watch the action[39].

For the investigation, four rodent groups were selected. There were three rodents in each group. Prior to the trial, rats were denied water for a whole day. The investigation lasted for 60 minutes. Solution was administered to one group, formulation solution to the second, marketed formulation (Mucolite 30 mg) to the third, and water to the fourth. Each solution's concentration was equal to 10 mg mL^{-1} of ambroxol hydrochloride. For every group, the lick ratio was computed[40].

Statistical analysis

All studies were carried out in triplicate, and mean ± SD was used to report the findings. The data was evaluated using the one-way ANOVA test.

RESULTS AND DISCUSSION

Identification of drug

Melting point

Ambroxol hydrochloride's melting point was determined to be 233.73 ±0.95 °C. The medication can be deemed sufficiently pure for use in the current inquiry based on the melting point observation. 233–234.5 °C is the melting point according to the Merck Index.

Determination of the λ_{max} (wavelength of maximum absorbance) in various media

The ambroxol hydrochloride solution was scanned in a UV double beam spectrophotometer between 200 and 400 nm to determine the wavelength of maximum absorbance in three different media: distilled water, pH 6.8 phosphate buffer solution, and pH 1.2 acidic buffer (Table II).

Table II: UV visible spectroscopy scans maximum absorption ambroxol hydrochloride in different media

S. No.	Medium	λ_{max} (observed)	λ_{max} (reported in USP)
1.	Distilled water	243.5 nm	244 nm
2.	pH 6.8 phosphate buffer	244 nm	244.2 nm
3.	pH 1.2 acidic buffer	244 nm	245 nm

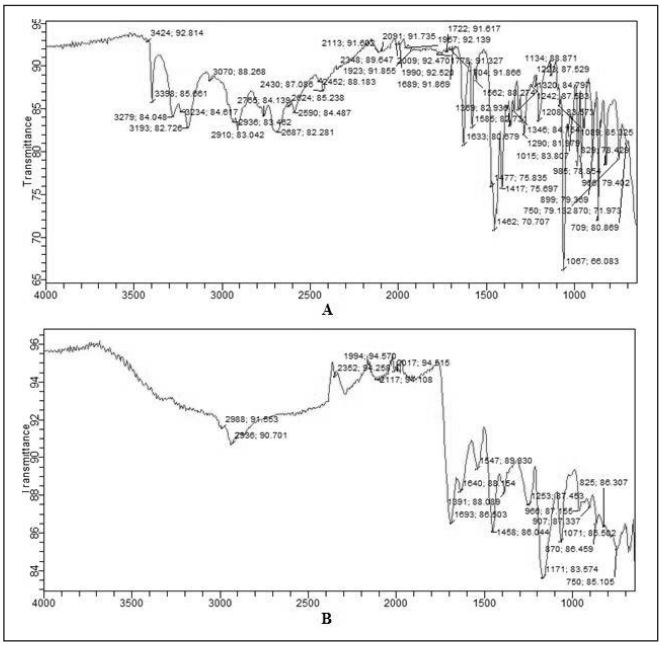

Fig. 2: FT-IR spectra A) pure ambroxol hydrochloride and B) ambroxol hydrochloride with Amberlite IRP64 complex stored at room temperature

FT-IR Analysis

Ambroxol hydrochloride exhibited characteristic absorption bands at 3424 cm^{-1}, 3234 cm^{-1}, 2910 cm^{-1}, 1624 cm^{-1}, 1585 cm^{-1}, 1417 cm^{-1}, 1276 cm^{-1}, and 656 cm^{-1}. Fig. 2A displays the infrared spectrum of ambroxol hydrochloride. The drug's identification was confirmed by the identical peaks and functional groups found in the standard drug and resin complex IR spectra, leading to the conclusion that the drug is pure and free of contaminants.

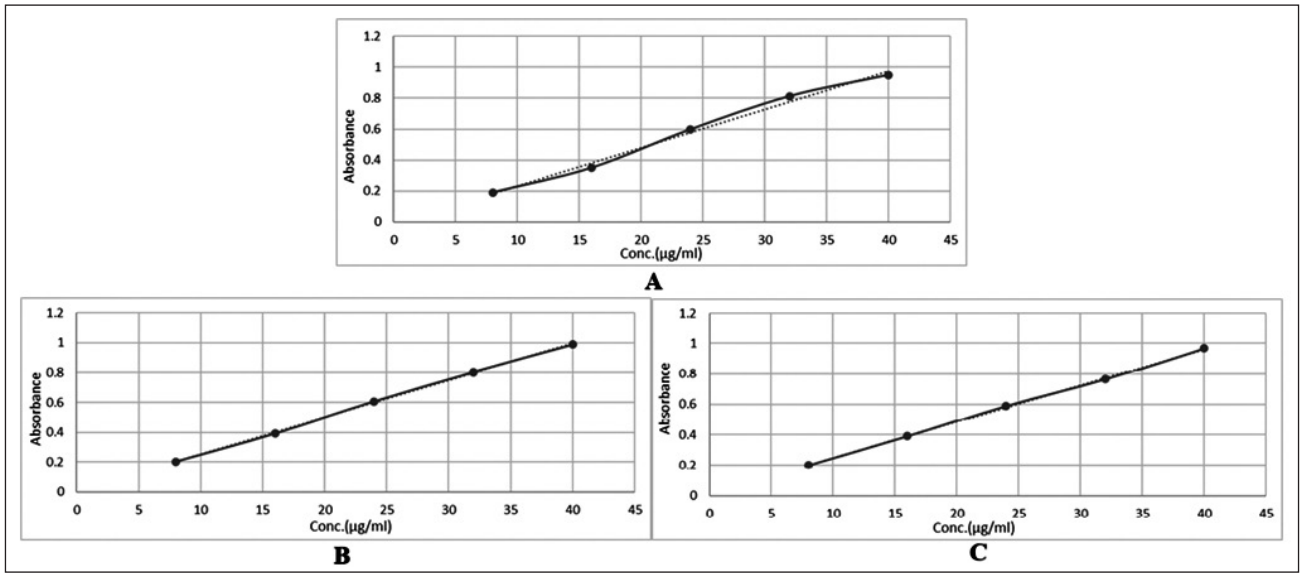

Fig. 3: Curve plot of ambroxol hydrochloride A) pH 1.2 acidic buffer B) pH 6.8 phosphate buffer C) distilled water

Standard drug plots in various media

Ambroxol hydrochloride standard plots were made using distilled water, 6.8 phosphate buffer, and 1.2 acidic buffer, among other solvents. The results show the standard curve of ambroxol hydrochloride in the aforementioned medium, obeying Beer's law; the linear regression equation for ambroxol hydrochloride in these solvents can be used because the R^2 values were found to be between 0.990-0.999 (Fig. 3), which are fairly close to 1.

Preformulation studies

Measuring drug solubility in various media

Ambroxol hydrochloride was found to be soluble in distilled water and pH 1.2 acidic buffers, among other media. Table III displays the solubility study findings. Ambroxol hydrochloride is the least soluble in water and most soluble in pH 6.8 phosphate buffer.

Table III: Solubility of ambroxol hydrochloride in different media

S. No.	Solvent	Solubility (mg mL^{-1})
1.	pH 1.2 acidic buffer	1.429
2.	Distilled water	1.208
3.	pH 6.8 phosphate buffer	13.02

Drug partition coefficient

The results indicate that ambroxol hydrochloride has a partition coefficient of 7.872±0.0173 (n=3) log P=1.95, which is almost similar to the log P-value of 2.65 (drugbank.com) which indicates that the drug is hydrophilic.

Evaluation of ambroxol hydrochloride resinates

Drug-resin compatibility studies

The infrared spectrum of ambroxol hydrochloride and the drug resin complex (resinate) has shown characteristic absorption bands of various functional groups. The Amberlite® IRP64 resin containing ambroxol hydrochloride showed characteristic absorption bands at 2988 cm^{-1}, 1547 cm^{-1}, 1253 cm^{-1}, and 668 cm^{-1}. Fig. 2B displays the infrared spectrum of the Amberlite® IRP64 resin containing ambroxol hydrochloride. The drug's identification is confirmed by the identical peaks and functional groups found in the formulated drug IR spectra, leading to the conclusion that the drug is compatible with the tested resin.

Calculate the percentage of drug loading

Table IV displays the % drug loading of ambroxol hydrochloride resinate in various batches. The A8 batch (drug and resin ratio: 1:4) had the greatest drug loading percentage reaching 98.26 %.

Effect of resin ratio on drug loading

A batch procedure was used to create the resinates. Using different drug-to-resin ratio concentrations, the initial trial batches of resinates were produced at 500 rpm for 6 h. Thus, out of all preliminary trial batches, the best batches were selected based on the results of their % drug loading. The results indicate that the 1:4 ratio using Amberlite® IRP64 (batch A8) achieves better drug loading compared to the other ratios listed in Table IV.

Table IV: Trials batches with Amberlite® IRP69 and Amberlite® IRP64

Batch	Super-disinte-grant	Drug & resin ratio	Swelling time (min.)	Stirring time (min.)	% drug loading
A1	IRP69	1:1	30	360	93.42± 1.01
A2	IRP69	1:2	30	360	93.91± 0.06
A3	IRP69	1:3	30	360	95.18± 0.04
A4	IRP69	1:4	30	360	96.55± 1.74
A5	IRP64	1:1	30	360	93.04± 0.12
A6	IRP64	1:2	30	360	94.08± 0.41
A7	IRP64	1:3	30	360	95.11± 0.34
A8	IRP64	1:4	30	360	98.26± 1.17

Impact of pH on drug loading

Table V displays the results of percentage drug loading as a result of changing the pH of the buffer solutions. The drug loading increased when we changed the pH from 1.2 to 7. In pH 1.2 and 4, slight heat is provided for the dissolution of the drug, but in water, it is freely soluble. Thus, for preparing resins, aqueous media were used. Depending on the drug loading, 1:4 ratios were

selected and, depending on the drug release, Amberlite® IRP64 was selected.

Table V: Trial batch with Amberlite® IRP64 ion exchange resin at different pH values

Batch	Drug & resin ratio	Swelling time (min.)	Stirring time (min.)	pH	% Drug loading
B1	1:1	30	360	1.2	96.93±0.02
B2	1:2	30	360	1.2	97.26±0.01
B3	1:3	30	360	1.2	97.53±0.03
B4	1:4	30	360	1.2	98.11±0.01
B5	1:1	30	360	4	97.11±0.01
B6	1:2	30	360	4	97.52±0.01
B7	1:3	30	360	4	98.17±0.02
B8	1:4	30	360	4	98.92±0.01
B9	1:1	30	360	6.8	97.85±0.005
B10	1:2	30	360	6.8	98.03±0.02
B11	1:3	30	360	6.8	98.52±0.45
B12	1:4	30	360	6.8	99.76±0.23
B13	1:1	30	360	7	98.94±0.03
B14	1:2	30	360	7	99.31±0.01
B15	1:3	30	360	7	99.34±0.03
B16	1:4	30	360	7	99.41±0.01

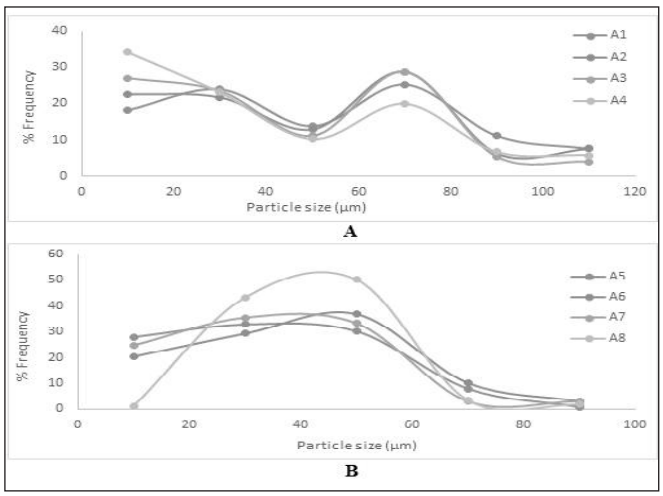

Fig. 4: Particle size distribution of ambroxol hydrochloride resinates A) batch A1-A4 and B) batch A5-A8

Particle size distribution

Optical microscopy was used to analyse the particle size distribution of ambroxol hydrochloride. The particle sizes of resinates from different batches were between 39.03 and 54.55 µm as shown in Fig. 4. The drug-to-resin ratio is more significant than the stirring speed. The findings suggested that ion exchange between the drug and resin required the drug solution to gradually penetrate the resin particles for more interaction[36].

In vitro drug release study

Using USP II equipment (Electrolab Dissolution Tester USP TDT-08L INDIA), the drug release from ambroxol hydrochloride resinate was examined for 1 h in pH 1.2 acidic buffer. The findings are displayed in Table VI. In 1 h, the maximum amount of drug discharge was seen.

Table VI: Drug release from different batches of ambroxol hydrochloride in pH 1.2 acidic buffer

Drug release (%), Mean±S.D.	Time (min.)					
	5	10	15	30	45	60
A1	56.54±0.02	60.25±0.01	63.58±0.04	65.63±0.04	69.12±0.05	72.62±0.07
A2	50.09±0.215	52.04±0.218	53.78±1.03	59.49±0.11	64.84±0.01	71.41±0.02
A3	52.76±1.2	58.92±2.06	62.05±0.01	65.2±0.75	68.43±0.01	73.41±0.01
A4	51.56±0.01	56.38±0.009	59.95±0.08	62.49±0.09	65.97±0.11	70.7±0.03
A5	26.08±02.03	35.36±0.04	40.77±0.07	51.43±0.04	77.8±0.03	82.97±0.05
A6	28.96±0.014	37.07±0.54	44.4±0.04	69.48±0.06	77.82±0.44	82.29±0.01
A7	32.61±0.42	48.44±0.003	57.97±0.07	67.55±0.24	86.18±0.43	91.74±0.75
A8	28.56±1.48	49.07±0.05	59.98±0.09	70.54±0.75	85.27±0.51	90.05±0.01

Pre-compression evaluation of ambroxol hydrochloride orodispersible tablets

The angle of repose was observed to range from 33.02 ± 0.18 to 39.69 ± 0.25 for all formulations, including sodium starch glycolate and additional excipients. The bulk density of the mixture powder containing super disintegrated sodium starch glycolate with ambroxol hydrochloride and other excipients was found in the range of 0.41 ± 0.04 to 0.46 ± 0.08 g cm^{-3}. All the formulations of this combination showed good bulk density. The tapped density of the mixture of powders in the formulations F1 to F9 containing super disintegrated sodium starch glycolate with ambroxol hydrochloride and other excipients varied from 0.50 ±0.02 to 0.55 ± 0.02 g cm^{-3}. For all the formulations from F1 to F9, Carr's index was in the series of 10.02 ±0.05 to 19.73 ± 0.08, demonstrating excellent flow. Among the formulations, F3 & F10 showed the best result. The Hausner for all formulations from F1 to F9 was established to be in the range of 1.20±0.01 to 1.29±0.07 (Table VII).

Post-compression evaluation of ambroxol hydrochloride orodispersible tablets

Ambroxol hydrochloride orodispersible tablets were fabricated through direct compression. All the formulations of the tablet were selected for evaluation of mass variation, thickness, friability, hardness, and disintegration time (Table VIII). The tablets formulated were sunset yellow in colour and round in shape. It was found that the weight variance ranged from 250.2 ±0.18 to 250.7 ±0.22g. The formulated batches of tablets had a uniform weight. It was found that the tablets' thickness ranged from 2.48 to 2.68

Table VII: Result of pre-compression evaluation of batches F1 to F9

Formulation code (F)	Angle of repose (°) (n=3)	Bulk density (g cm^{-3}) (n=3)	Tapped density (g cm^{-3}) (n=3)	Carr's index (%) (n=3)	Hausner ratio (n=3)
F1	34.99 ±0.34	0.42 ±0.01	0.51±0.02	17.18±0.02	1.20±0.01
F2	37.23±0.42	0.42 ±0.02	0.52 ±0.01	10.02 ±0.10	1.23±0.06
F3	33.42 ±0.52	0.41 ±0.04	0.50 ±0.04	18.21±0.05	1.22±0.01
F4	37.95 ±0.35	0.43 ±0.03	0.52 ±0.05	17.11±0.06	1.20±0.02
F5	36.12 ±0.54	0.42 ±0.06	0.51 ±0.02	17.61±0.05	1.21±0.04
F6	39.69 ±0.32	0.41 ±0.06	0.52 ±0.02	19.73±0.08	1.24±0.03
F7	33.82 ±0.28	0.46 ±0.08	0.51 ±0.02	18.75±0.01	1.23±0.02
F8	33.02 ±0.44	0.43 ±0.07	0.53 ±0.03	16.52±0.09	1.29±0.07
F9	38.65 ±0.62	0.42 ±0.02	0.52 ±0.02	17.12±0.05	1.25±0.01

Table VIII: Result of post-compression evaluation of F1 to F9 batches

Formulation code (F)	Weight variation	Thickness (mm)	Friability (%)	Hardness (kg cm^{-2})	Disintegration time (sec.)
F1	250.8 ±0.18	2.22 ±0.01	0.78 ±0.30	3.20 ±0.82	49.66±1.52
F2	250.4 ±0.23	2.21 ±0.02	0.70 ±0.91	3.25 ±0.65	45.66±0.57
F3	250.7 ±0.20	2.26 ±0.01	0.37 ±0.14	3.63 ±0.20	55.66±2.30
F4	252.6 ±0.25	2.24 ±0.01	0.32 ±0.60	3.15 ±0.60	48.33±1.15
F5	250.4 ±0.38	2.22 ±0.02	0.53 ±0.82	3.26 ±0.14	49.33±1.15
F6	25.5 ±0.24	2.25 ±0.01	0.36 ±0.70	3.32 ±0.70	52.33±1.15
F7	249.9 ±0.20	2.28 ±0.01	0.43 ±0.92	3.18 ±0.30	59.00±3.46
F8	250.9 ±0.18	2.19 ±0.02	0.67 ±0.60	3.25 ±0.50	56.66±2.30
F9	251.4 ±0.22	2.26 ±0.01	1.50 ±0.50	3.60 ±0.82	60.33±2.88

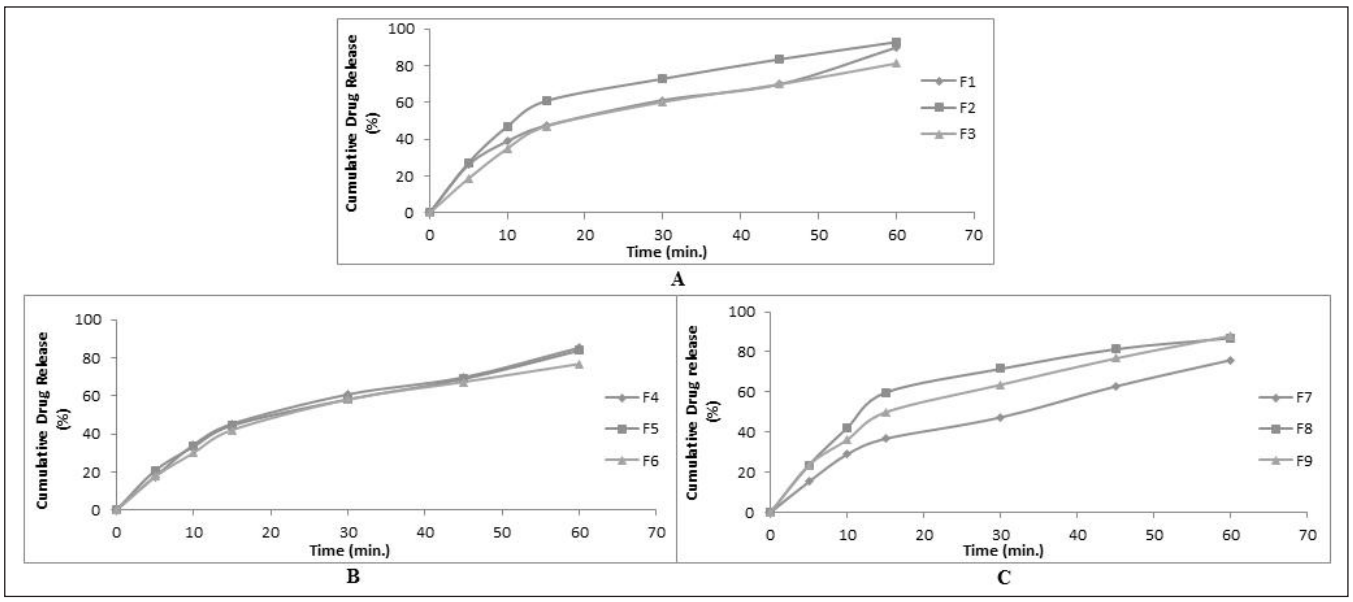

Fig. 5: Cumulative drug release profile A) batch F1, F2 and F3 B) batch F4, F5 and F6 C) batch F7, F8 and F9

mm. It was found that for every combination of formulations, the tablet's hardness increased with thickness. The friability was found to be between 0.32 ± 0.06 % and 1.5 ± 0.05%, which represents less than 1%, demonstrating a good resistance to abrasion during handling, packing, and transport. There is adequate mechanical strength in the formulation. The range of hardness was resolved to be 2.85 ±0.2 to 4.31 ±0.7 kg cm^{-2}. For all formulations, the time was found to be less than 60 seconds, fulfilling the official requirement. It was shown that greater wetting times led to greater disintegration times. F7 and F9 had the greatest disintegration times, whereas F2 showed the shortest.

USP equipment type II (Dissolution tester USP TDT-08L INDIA) was used for the *in vitro* dissolution investigations, which were conducted for 60 minutes at 50 rpm. Phosphate buffer with a pH of 6.8 was the dissolving medium. We plotted the percent cumulative drug release against time for formulations F1-F9, as shown in Fig. 5. The highest score in 60 minutes was 92.86 % for F2.

Drug release kinetics analysis

To understand the release mechanism of ambroxol hydrochloride from the orodispersible tablet (ODT) formulations, the *in vitro* drug release profiles of F1-F9 were analysed using four kinetic models: zero-order, first-order, Higuchi, and Korsmeyer Peppas equations. The coefficient of determination (R^2) was initially used to assess model fitness (Table IX).

While many formulations showed high R^2 values for both Higuchi (diffusion-controlled) and zero-order models, a deeper analysis revealed that the Higuchi model consistently produced higher R^2 values across the majority of formulations ($R^2 > 0.99$ in F5, F6, F8, and F9). This suggests that diffusion through a porous matrix or swollen polymer layer is the primary mechanism governing drug release.

To further strengthen the model selection, Akaike Information Criterion (AIC) and adjusted R^2 were also evaluated (data not shown but computed using GraphPad Prism). These indicated better goodness-of-fit for the Higuchi model in most cases, compared to zero-order or Korsmeyer-Peppas models.

Additionally, the Korsmeyer-Peppas model's n 'values (release exponent) were found to be in the range of 0.45-0.89, suggesting that the drug release follows a non-Fickian (anomalous) diffusion mechanism, involving a combination of diffusion and erosion processes.

Therefore, while zero-order release was initially assumed based on R^2 values, the updated model comparison supports the conclusion that drug release from these ODTs is predominantly diffusion-controlled, consistent with the Higuchi kinetic model, potentially coupled with minor matrix erosion.

The findings from model fitting confirm that diffusion is the dominant release mechanism from ambroxol-loaded resinates in the ODT matrix. This aligns with the physicochemical nature of the ion-exchange resinate

complex and the hydrophilic excipients used. The Higuchi model's superior fit (based on R^2 and AIC values) supports a matrix-controlled drug release. The non- Fickian behaviour observed from the Korsmeyer- Peppas model suggests that additional polymer swelling or erosion may be contributing to the sustained release[36,37].

Table IX: Release kinetics of ambroxol hydrochloride from resinate formulations

Formulation code	R^2				Best Fit
	Zero order	First order	Higuchi model	Korsmeyer-Peppas model	
F1	0.891	0.935	0.988	0.853	Higuchi
F2	0.818	0.980	0.971	0.844	Higuchi
F3	0.879	0.979	0.986	0.887	Higuchi
F4	0.898	0.976	0.988	0.884	Higuchi
F5	0.910	0.978	0.994	0.889	Higuchi
F6	0.898	0.983	0.990	0.901	Higuchi
F7	0.938	0.981	0.988	0.913	Higuchi
F8	0.808	0.964	0.994	0.860	Higuchi
F9	0.938	0.987	0.994	0.873	Higuchi

In vivo animal taste assessment

Rats were allowed to consume standard ambroxol hydrochloride tablet solution, selected formulation solution, pure drug solution, and simple distilled water at the designated time point by the experimental protocol. The frequency of licking water was determined. The frequency of licking water was thought to be 100%, whereas 50% suppression of licking frequency suggests that the medication tastes terrible. The rat demonstrated that a commercial formulation had 88 licks, whereas pastilles had 81 licks (Fig. 6). These findings imply that there is no discernible difference between the marketed and pastilles treatments' licking behaviors. The commercial formulation had an excellent taste. If the frequency of licking is greater than 80, taste masking is working and the bitter taste is totally covered up. Here, the observed data was compared using Post hoc Tukey's test and one-way ANOVA. The p-value of the pastille and commercialized formulations, however, was determined to be > 0.05, indicating that the result is statistically insignificant. It follows that the marketed formulation and the taste of pastilles have similar licking frequencies, which human volunteers find acceptable. Using Prism software, a comparison of pure ambroxol, formulated ODTs, marketed tablets, and simple distilled water was conducted.

The novelty of this research lies in the comparative assessment of two ion exchange resins (Amberlite® IRP64 and IRP69) for taste masking in ambroxol hydrochloride formulations, an area minimally explored in the existing literature. Unlike previous works that examined individual formulation aspects, our study systematically investigated multiple drug-resin ratios, pH environments, and disintegration agents. Importantly, the use of *in vivo* taste assessment in rats provided practical insights into palatability, which is rarely incorporated in similar studies. This positions our study as a comprehensive and innovative contribution to paediatric oral drug delivery systems.

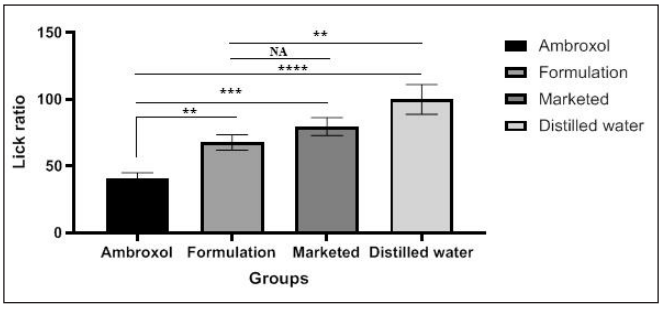

Fig. 6: Lick ratio

CONCLUSION

In this study, orodispersible tablets of ambroxol hydrochloride were successfully developed using Amberlite® IRP69 and Amberlite® IRP64 polymeric scaffolds. The tablets showed rapid oral disintegration and potential for quick onset of pharmacological action. The 1:4 drug-resin ratio was most effective in masking the taste of ambroxol hydrochloride. The prepared tablets exhibited satisfactory physical and chemical properties, including weight variation, thickness, friability, and hardness. The tablets achieved a disintegration time of <60 seconds and released 92.86% of the drug within 60 minutes, indicating their potential for fast-acting formulations. The use of Amberlite® IRP64 ion exchange resin complexes successfully masked the taste without compromising drug release, suggesting a promising approach for improving patient compliance and therapeutic efficacy of ambroxol hydrochloride formulations.

ETHICAL APPROVAL

This work was recommended by the institutional animal ethical committee at IFTM University (license number: 837/PO/Re/S/04/CPCSEA).

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