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# Formulation and Evaluation of taste masked oral suspension of Dextromethorphan Hydrobromide

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## Abstract

Taste is an important factor in the development of dosage form. The problem of bitter and obnoxious taste of drug in pediatric and geriatric formulations is a challenge to the pharmacist in the present scenario. In order to ensure patient compliance bitterness masking becomes essential. The purpose of this research was to mask the intensely bitter taste of Dextromethorphan Hydrobromide using ion exchange resin and to formulate oral suspension of the taste masked drug. When suspension is swallowed bitter taste may not be felt because ion exchange resin complex does not release drug at salivary pH. When it comes in contact with acidic environment of stomach, the complex will be broken down releasing the drug which may then absorbed. Batch method was used for formation of drug resin complex. Various ion exchange resins such as Ionex QM 1011, Ionex WC 23 and Kyron T- 114 were tried to obtained taste masked drug resin complex (DRC). Optimization of drug loading was carried out. With Ionex QM 1011, the drug-resin proportion of 1:6 achieved equilibrium in 6 hours. 96% w/w of drug loading was possible by this method. Complex formation was confirmed by DSC and IR studies. Oral taste masked suspension was prepared using xanthum gum and tween 80 and was evaluated with respect to parameters such as Colour, pH, Viscosity, Sedimentation volume, Redispersibility, Assay, drug release. Taste masking was evaluated with the help of panel of human volunteers and Rat Behavioral Avoidance Taste Model. Taste masked suspension showed easy redispersibility and more than 99.6 % of the drug release within 45 minutes at pH 1.2. Thus, results conclusively demonstrated successful taste masking and formulation of suspension with taste masked drug especially for pediatric, geriatric, bedridden, and non cooperative patients.

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***Key words:***

Resin, Dextromethorphan Hydrobromide, taste masking, pediatric, redispersibility, optimization.

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## 1. INTRODUCTION

A wide variety of active pharmaceutical agents exhibit the undesirable characteristic of bitter taste either during or immediately after oral administration. Among these are included such

diverse medicinal agents as acetaminophen, ampicillin, azithromycin, chlorpheniramine, cimetidine, dextromethorphan, diphenhydramine, erythromycin, ibuprofen, penicillin, phenylbutazone, psuedoephedrine, ranitidine, spironolactone and theophylline.[1]

Various techniques have been identified for taste masking which include polymer coating, inclusion complex formation with β-cyclodextrin, use of ion exchange resins, solubility limiting methods, etc[2]

Conventional taste masking techniques such as the use of sweeteners and flavoring agents alone are often inadequate in masking the taste of highly bitter drugs. Coating is more efficient technology for aggressively bitter drugs even though coating imperfections, if present, reduce the efficiency of the technique.[3]

With respect to OTC preparations, such as cough and cold syrups, the bitterness of the preparation leads to lack of patient compliance. There are numerous pharmaceutical and OTC preparations that contain Dextromethorphan Hydrobromide as active which is bitter in taste.[2]

Dextromethorphan Hydrobromide is an antitussive used in much over-the-counter cold medication. It has an opioid like structure but, being a d-isomer it does not possess the analgesic or addictive properties of opioids. It is active against dry cough and does not exhibit significant expectorant properties for productive cough.[4]

Dextromethorphan Hydrobromide has amine as a functional group, which is the cause of their obnoxious taste. If this functional group is blocked by complex formation the bitterness of the drug reduces drastically.[4]

Ion exchange resins have been increasingly used as taste masking agents.

Desired properties of pharmaceutical grade Ion Exchange Resins are: [5]

a) Fine, free flowing powders

b) Particle size of 25 - 150 microns

c) Contain functional group that capable of exchanging ions and/or ionic groups

d) Insoluble in all solvents & all pH conditions.

e) Not absorbed by body

Ion exchange resins are water insoluble, cross-linked polymers containing salt forming groups in repeating position on the polymer chain. Drug can be bound to the ion exchange resin by either repeated exposure of the resin to the drug in a chromatographic column (column method) or by prolonged contact of resin with the drug solution (batch method). Drugs are attached to the oppositively charged resin substrates or resinates through weak ionic bonding so that dissociation of the drug-resin complex does not occur under salivary pH conditions. This suitably masks the unpleasant taste and odour of drugs [5].

Thus the aim of present research work was to formulate & evaluate oral taste masked suspension of antitussive drug.

## 2. MATERIAL AND METHODS

### 2.1 Materials

Dextromethorphan Hydrobromide was procured from Divi's Laboratories Ltd., (Hyderabad, India). Ionex WC 23 and Ionex QM 1011 were obtained as gift sample from Phaex Polymers (Mumbai, India) whereas Kyron T-114 was obtained as gift sample from Corel Pharma Chem. (Ahmedabad, India). Sucrose, Sorbitol, Xanthum gum, Sucralose, Methyl paraben, Propyl paraben, Cherry and Pineapple flavour were purchased from S. D. Fine chemicals (Mumbai, India). All other chemicals/solvents of analytical grade were used.

### 2.2 Methodology

#### 2.2.1 Formation of Drug Complex Using Suitable Ion Exchange Resin

##### 2.2.1.1 Preparation of drug resin complex (DRC):

Drug and resin were accurately weighed in required ratio. Then slurry of resin was made in demineralised

water and stirred for half an hour at 900 rpm in order to allow polymer structure to swell uniformly. Drug was added slowly under stirred condition. The drug resin mixture was continuously stirred for 6 to 8 hours.

**2.2.1.2 Preparation of drug- resinate granules:**

After drug-resin mixtures were stirred for required time, the drug-resinates were thoroughly washed with demineralized water for several times then filtered by using 0.45µ filter paper and dried. The powdered drug-resinate particles were form into damp mass, then passed through sieve no-22 and dried at 50°C for 30 minutes. The dried granules were again passed through sieve no-22 over sieve no-44 to obtained uniform granules.

Quantities of drug and resin taken for different drug to resin ratios were as shown in Table 1.

**Table 1:** Quantities of drug and resin taken for different drug to resin ratios.

| Drug to resin ratio | Amount of Dextromethorphan Hydrobromide taken(grams) | Amount of resin taken (in grams) | Volume of water taken to disperse (in ml) |
|---|---|---|---|
| 1:1 | 1 | 1 | 100 |
| 1:2 | 1 | 2 | 100 |
| 1:3 | 1 | 3 | 100 |
| 1:4 | 1 | 4 | 100 |
| 1:5 | 1 | 5 | 100 |
| 1:6 | 1 | 6 | 100 |

**2.2.1.3 Selection of Optimum Resins and Drug to Resin Ratio**

Several trials were carried out for preparation of resinate using different resins in different drug to resin ratio as shown in table 2.

For the selection of the proper drug resin ratio, the concentration of resin was varied, keeping concentration of drug constant. The pH of the solution was maintained at 8. Solution of complex with pH below 8 was adjusted with 10 % KOH solution.

**2.2.1.4 Optimization of Process of Preparing Drug Resin Complex**

The process of preparing drug-resinate was optimized with respect to:

- Time of adsorption.
- Drug resin proportion

Loading was carried out by batch method with weak cation exchange resin Ionex QM 1011. The percentage of drug loading on the resin is shown in the table 3.3. Further batches (T18-1 to T18-5) were prepared by keeping 1:6 ratio constant and varying stirring time from 4 to 8 hrs. Then next batches (T18-6 to T18-8) were prepared by keeping stirring time constant as 6 hrs and varying ratio from 1:5 to 1:7.

**2.2.1.4.1 Evaluation of drug loading by UV analytical method:**

The mixtures of drug resin complex to be evaluated were kept aside to allow the particles to sediment and then filtered. From this filtrate 5 ml was diluted to 100 ml using distilled water and absorbances were noted at 278 nm, from which amount of uncomplexed drug was calculated. Results are shown in table 3.

**2.2.2 Characterization of Dextromethorphan Hydrobromide-Ionex QM 1011 Complex**

**a) pH of complex**

The pH of drug resin complex was checked using Metler Toledo pH meter. Result is shown in table 4.

**b) Differential scanning calorimetry (DSC)** [6]

The molecular state of the drug in the resinate was evaluated by performing DSC analyses of pure drug, resin, physical mixture and resinate. DSC curves of the samples were obtained with a differential scanning calorimeter (TA, Model Q200). Each sample was placed in an aluminum pan and then crimped with an aluminum cover. Heating rate was

10°C min−1. All measurements were performed over 0–500 °C under a nitrogen purge at 50 mL min−1. The onsets of the melting points and enthalpies of fusion were calculated by the thermal advantage software. The cell and sample were held isothermally at −79°C for 30 min to purge the headspace and sample with nitrogen before heating. Results are shown in Fig. 3.

**c) FTIR spectroscopy** [6, 7]

Chemical interaction between the drug and resin was studied by FTIR spectroscopy. The IR spectra of the samples were obtained using a Fourier transform infrared spectrometer (Perkin Elmer, USA). Measurements were carried out according to the KBr disk method, the scanning range was 4000 to 450 cm−1. Result is shown in Fig.4.

**d) Drug loading**

Percentage complexation was calculated using procedure given under *Evaluation of drug loading by UV analytical method*. Result is shown in table 4.

**e) Drug content** [8]

Resinate so prepared by the batch process, was evaluated for the drug content. Resinate equivalent to 300 mg of drug was magnetically stirred with about 70ml of buffer (pH 1.2 and 6.8) in 100 ml volumetric flask and then diluted to volume with buffer. Then the Suspension was filtered and further 5ml was diluted to 100 ml. The drug content was noted spectrometrically at 278nm using gastric simulated fluid (pH 1.2) or simulated salivary fluid (pH 6.8) as blank. The readings were taken in triplicate. Results are given in table 5.

**f) Taste Evaluation of Resinate** [9]

**i) Assessment of the bitter taste of the Dextromethorphan Hydrobromide (bitterness threshold)**

The bitter taste threshold value of Dextromethorphan Hydrobromide was determined based on the bitter taste recognized by six volunteers. A series of Dextromethorphan Hydrobromide aqueous solutions were prepared at different concentrations as standard solutions, i.e. 5, 10, 15, 20, 25, 30, 35, 40 and 45µg/ml, respectively. The test was performed as follows: 1 ml of each standard solution was placed on the center of the tongue, it was retained in the mouth for 30 s, and then the mouth was thoroughly rinsed with distilled water. The threshold value was correspondingly selected from the different Dextromethorphan Hydrobromide concentrations as the lowest concentration that had a bitter taste.

**ii) Evaluation of Taste of Resinate**

Taste of resinate was checked by time intensity method. For this purpose 6 human volunteers were selected. In this method a sample equivalent to a normal dose 15 mg was held in mouth for 60 seconds and volunteers were asked to evaluate the resinate for taste. Bitterness levels were recorded at 2, 10 and 60 sec. The bitterness level was recorded against pure drug (15 mg) using a numerical scale (3– Strong Bitter, 2 – Moderate Bitter, 1 –Slight Bitter, X – Threshold Bitter, 0 – No Bitter). These volunteers were instructed not to swallow the granules, which were placed on the tongue. They were instructed to thoroughly gargle their mouth with distilled water after the completion of test. Results are revealed in table 6 and fig. 5.

**2.2.3 Formulation of Oral Taste Masked Suspension**

A series of formulations were prepared as given in table 7 with various concentrations of suspending and wetting agents and were evaluated for sedimentation volume and redispersibility. DXM 4 was formulated using plain drug without resin, to provide clear distinction between actual taste of drug before masking and taste after masking by making complex with Ion Exchange Resin.

**Table 7:** Formula for Oral Taste Masked Suspension

| Drug/ excipients | Per 100 mL | | | |
|---|---|---|---|---|
| | DXM 1 (%) | DXM 2 (%) | DXM 3 (%) | DXM 4 (%) |
| Resinate equivalent to 300mg of Dextromethorphan HBr | 2.12 | 2.12 | 2.12 | - |
| Plain drug | - | - | - | 0.3 |
| Sucrose | 50 | 50 | 50 | 50 |
| Methyl paraben | 0.18 | 0.18 | 0.18 | 0.18 |
| Propyl paraben | 0.02 | 0.02 | 0.02 | 0.02 |
| **Xanthum gum** | **0.1** | **0.2** | **0.1** | 0.1 |
| Sorbitol 70 % | 10 | 10 | 10 | 10 |
| **Polysorbate 80** | **0.1** | **0.1** | **0.2** | 0.2 |
| Sucralose | 0.2 | 0.2 | 0.2 | 0.2 |
| Flavour cherry / Pineapple | 0.1 | 0.1* | 0.1 | 0.1 |
| Red dye/Quinolline yellow | 0.04 | 0.04* | 0.04 | 0.04 |
| Purified water q.s to | 100 | 100 | 100 | 100 |
| Sodium citrate | q.s to pH 7 | q.s to pH 7 | q.s to pH 7 | q.s to pH 7 |

* Pineapple and Quinolline yellow were used as flavouring and colouring agent respectively.

**2.2.3.1 Procedure:**

Syrup was prepared by heating between 60-80 ºC under constant stirring and the stability of prepared syrup was improved by addition of preservatives. Xanthum gum mucilage was prepared by boiling it with water and stirred well to allow it swell completely. DRC was added into syrup solution along with tween 80 and was stirred for 30 mins to allow proper dispersion of DRC. Further viscous xanthum gum mucilage was added to above bulk syrup solution and stirred for 30 mins. Colouring agent was dissolved in water and transferred to above mixture. At the end flavouring agent was added and stirred for 5 min. Finally volume was made upto 100ml with distilled water and pH was adjusted to 7 ± 0.05 with sodium citrate solution (1%). Developed batch was homogenized (Polytron PT 6100 Homogenizer) for 20 mins at 10 × 1000 rpm.

**2.2.4 Evaluation of Developed Oral Taste Masked Suspension of Dextromethorphan Hydrobrmide**

**a) Colour, odour and taste**

All the developed batches of suspension were evaluated for organoleptic properties such as colour, odour and taste.

**b) pH**

pH of the suspension was determined by the use of Metler Toledo pH meter.

**c) Viscosity**

The viscosity of suspension was determined at ambient condition using DV III+, Brookfield Programmable Rheometer. In adapter 15ml of suspension was taken and the adapter is set over the viscometer by a stand such a way that spindle is completely immersed in the suspension. Spindle no.So was used to measure the viscosity of suspension.

**d) Sedimentation Volume**

Fifty ml each of suspension was taken in 50 ml stoppered graduated measuring cylinder. The suspension was dispersed thoroughly by moving upside down for three times. Later, the suspension was allowed to settle for three minutes and the volume of sediment was noted. This is the original volume of sediment ($H_o$).The cylinder was kept undisturbed for 7 days. The volume of sediment read at 7 hr and every 24 hr for 7 days was considered as final volume of sediment (Hu).

Sedimentation Volume (F) = Hu/ Ho

The ultimate height of the solid phase after settling depends on the concentration of solid and the Particle size. To obtain an acceptable suspension, F should be at least 0.9 for 1 h but a longer period was preferred for our purpose.

**e) Redispersibility**

Fixed volume of each suspension (50 ml) was kept in stoppered cylinder which was stored at room temperature for 7 days. At regular interval, one stoppered cylinder was removed and moved upside down until there was no sediment at the bottom of the cylinder.

**f) Assay of Oral Taste Masked Suspension**

Suspension (5ml) was taken in 100 ml volumetric flask, 0.1 M HCl was added into it & sonicated it for 10 min. Volume was made up to 100 ml with 0.1 M HCl & filtered. Samples were prepared in duplicates. Area was measured using developed HPLC method & compared with standard and then % drug content was calculated as per the following formula.

$$\%\ Amount = \frac{Aspl}{Astd} \times \frac{Wmg}{100} \times \frac{15}{100} \times \frac{100}{5} \times \frac{P}{100} \times \frac{5}{15} \times 100$$

Aspl = Area of the Dextromethorphan Hydrobromide peak in the sample Chromatogram
Astd = Area of the Dextromethorphan Hydrobromide peak in the standard Chromatogram
P = Potency of the standard
W = Standard Weight

**g) *In-Vitro* Drug Release of Oral Taste Masked Suspension**

*In vitro* drug release of the suspension was carried out using USP – type II dissolution apparatus (paddle type). The dissolution medium, 500ml 0.1N HCL, was placed into the dissolution flask maintaining the temperature of 37°C ± 0.5°C and rpm of 50. Suspension (10ml) was placed in each flask of dissolution apparatus and 20 ml of marketed sample was poured in another dissolution apparatus. The apparatus was allowed to run for 45 minutes. Samples measuring 5 ml were withdrawn after every 5, 15, 30, & 45, min. manually. During sampling samples were filtered through 0.45 µm filter. The fresh dissolution medium was replaced every time with the same quantity of the sample. Collected samples were injected in HPLC system. This test was carried out only for final optimized batch DXM 3. Similar test was carried out for a commercial product (Triaminic, Novartis) for comparison. Similarly dissolution of DXM 3 was carried out in phosphate buffer pH 6.8 with time points 2, 4, 6, 8 and 10 mins.

**h) Taste Evaluation of Oral Taste Masked Suspension**

Taste evaluation was done by a panel of 6 volunteers using time intensity method. About 5 ml suspension of batch DXM 3 and DXM 4 and 10 ml of marketed product (Triaminic, Novartis) containing 15 mg of Dextromethorphan Hydrobromide was placed on tongue for 10 seconds bitterness levels were recorded instantly and then at the end of 10 seconds, 1 minute and 2 minutes, bitterness levels are again noted and recorded and compared with commercial product and DXM 4. Results are shown in table 8 and Fig.8.

**i) *In-vivo* study** [10]

The Rat Behavioral Avoidance Taste Model is based on the principle that presentation of a bitter solution to water-deprived rats reduces the drinking frequency (Boughter et al., 2002). Wistar rats (n=6) were used for the study. Results are given in table 9 and fig. 9.

**Procedure:**

Rats were deprived of water for a period of 24 hrs. Rats were then made to lick bottles containing water and the licking activity obtained in 5 minutes for water was taken as baseline. Rats were then allowed to lick bottles containing 3mg/ml, 6mg/ml and 9mg/ml concentrations of drug solution. The number of times the rat licks the bottle in 5 mins was counted and the concentration of drug solution causing 50% inhibition in licking frequency compared to water was calculated. The DXM 3, DXM 4 and Marketed formulations were then presented to the rats and the licking activity obtained was counted. All test trials were interspersed with 2 mins water rinse trials. The

average number of licks was then divided by average number of licks during the water presentation to generate the % of licking frequency as follows:

$$\%\ of\ licking\ frequency = \frac{mean\ number\ of\ licks\ to\ stimulus}{mean\ number\ of\ licks\ to\ water} \times 100$$

The other avoidance responses such as jaw smacking, withdrawal were also observed.

### 2.2.5 Accelerated stability study [11]

DXM 3 suspension was packed in 100 ml glass bottle. The packed bottles were placed in stability chamber maintained at 40 ± 2 °C and 75 ± 5% RH for 3 month. Samples were collected at days 0, 30, 60 and 90. The analyses comprised chemical testing of quantifiable parameters, which could possibly change during storage, such as viscosity, pH, drug contents, sedimentation volume, redispersibility, colour, taste, odour and drug release. Results are shown in table 10.

## 3. RESULTS AND DISCUSSIONS

### 3.1 Selection of Optimum Resins and Drug to Resin Ratio and Optimization of Process of Preparing Drug Resin Complex

**Table 2:** Selection of optimum resins and drug to resin ratio

| Resin | Batch no. | Ratio of drug to resin | Taste | pH |
|---|---|---|---|---|
| Ionex WC 23 | T1 | 1:1 | Bitter | 6.4 |
| | T2 | 1:2 | Bitter | 6.5 |
| | T3 | 1:3 | Bitter | 6.4 |
| | T4 | 1:4 | Bitter | 6.4 |
| | T5 | 1:5 | Less bitter | 8 |
| | T6 | 1:6 | Less bitter | 8.2 |
| Kyron T-114 | T7 | 1:1 | Bitter | 6.4 |
| | T8 | 1:2 | Bitter | 6.3 |
| | T9 | 1:3 | Bitter | 6.2 |
| | T10 | 1:4 | Bitter | 6.1 |
| | T11 | 1:5 | After taste bitter | 6.2 |
| | T12 | 1:6 | After taste bitter | 6.4 |
| Ionex QM 1011 | T13 | 1:1 | Bitter | 8.2 |
| | T14 | 1:2 | Bitter | 8.3 |
| | T15 | 1:3 | Bitter | 8.4 |
| | T16 | 1:4 | After taste bitter | 8.4 |
| | T17 | 1:5 | Tasteless (not bitter) | 8.3 |
| | **T18** | **1:6** | **Tasteless (not bitter)** | **8.3** |

**Table 3:** Amount of complexed drug for different times of mixing using resin IONEX QM 1011

| Drug to resin ratio | Batch no | Time in (hrs) | Absorbance* | Remaining drug in (mg) | Amount of complexed drug in (mg) | % complexed |
|---|---|---|---|---|---|---|
| 1:6 | T18-1 | 4 | 0.530 | 102 | 898 | 89.80 |
| 1:6 | T18-2 | 5 | 0.260 | 79.2 | 920.8 | 92.08 |
| **1:6** | **T18-3** | **6** | **0.103** | **41.6** | **958.4** | **95.84** |
| 1:6 | T18-4 | 7 | 0.102 | 41.2 | 958.8 | 95.88 |
| 1:6 | T18-5 | 8 | 0.101 | 40.8 | 959.2 | 95.92 |
| **Amount of complexed drug of different drug to resin ratios** | | | | | | |
| 1:5 | T18-6 | 6 | 0.300 | 116 | 884 | 88.40 |
| **1:6** | **T18-7** | **6** | **0.101** | **48.4** | **959.1** | **95.91** |
| 1:7 | T18-8 | 6 | 0.09 | 39 | 961 | 96.10 |

* Average of three readings

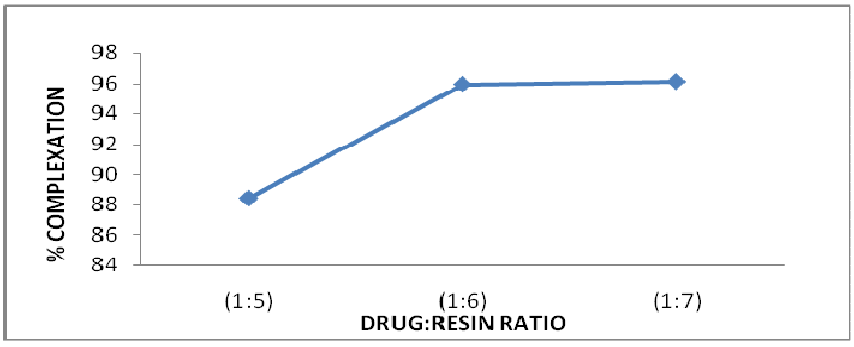


**Fig. 1** Optimization of Drug:Resin Ratio

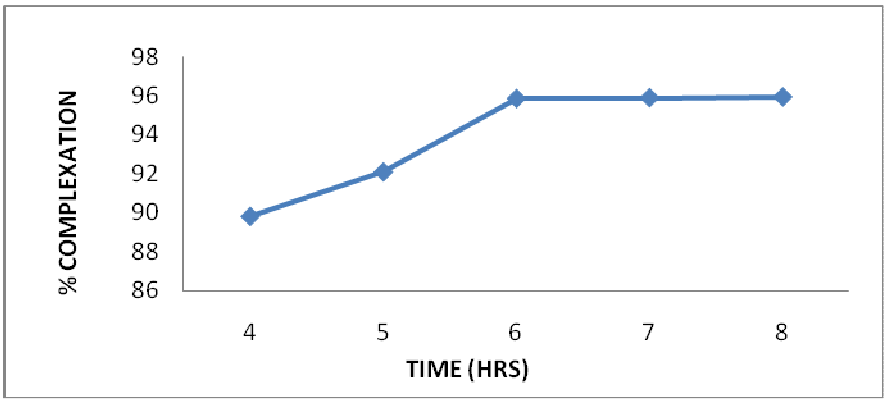


**Fig. 2** Optimization of Time of Sorption

**Discussion**

Taste masking was tried using three different ion exchange resins and no taste masking was obtained using Ionex WC 23 and Kyron T- 114 so were rejected. Batch T18 i.e; with Ionex QM 1011, tasteless complex was obtained with ratio 1:6 hence it was finalized for the study. When the pH is lower than 4, the resin exists in the free state. Therefore, drug/resin complex formation was carried out at pH 8 ± 0.5. With Ionex QM 1011, the drug-resin proportion of **1:6** achieved equilibrium in **6 hours, 96% w/w** of drug loading was achieved by this method. With 1:7 ratio, there was only negligible increase in the percentage complexed (Fig 1 and Fig. 2). Thus for final formulation 1:6 ratio was tested further and characterized.

**3.2 Characterization of Dextromethorphan Hydrobromide-Ionex QM 1011 Complex**

**3.2.1 Differential scanning calorimetry (DSC)**

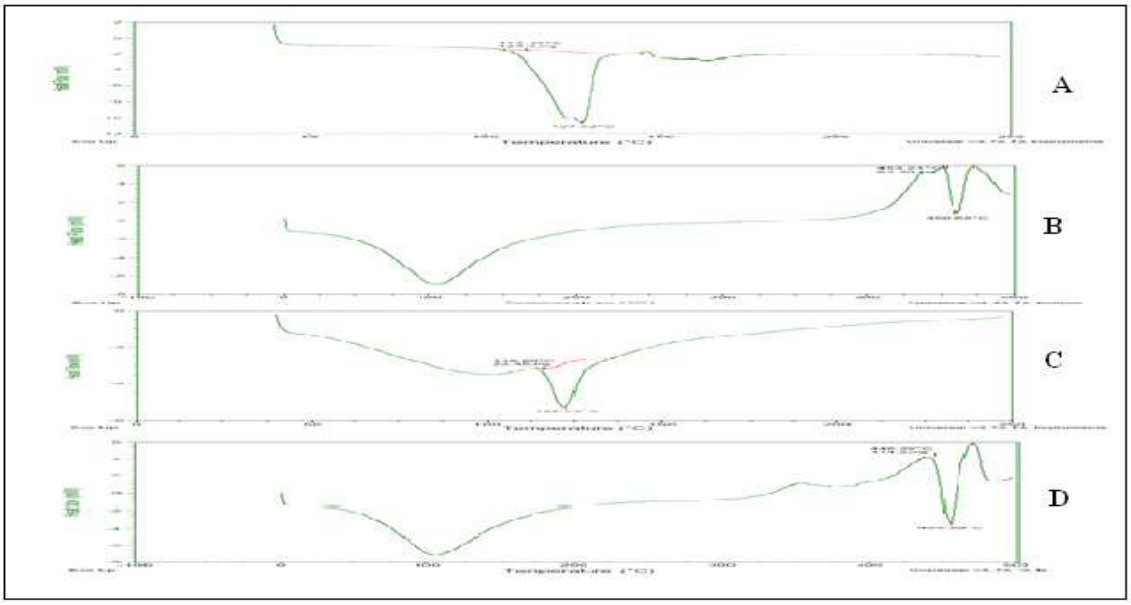


**Fig. 3** DSC Curves: A) Drug; B) Ion Exchange Resin; C) Physical Mixture; D) Resinate

In DSC a sharp endothermic peak was observed at **127.62 °C** for pure drug and at **460.68 °C** for pure resin, indicating the melting point of DXM and resin respectively. The endothermic peak of pure drug was also seen in case of the physical mixture at **122.59 °C.** On the other hand, **absence of peak at 127 °C** and at **455.89 °C** peak is observed with increase intensity in the DSC thermogram of resinate, which clearly indicates that the drug was complexed with resin.

### 3.2.2 FTIR spectroscopy

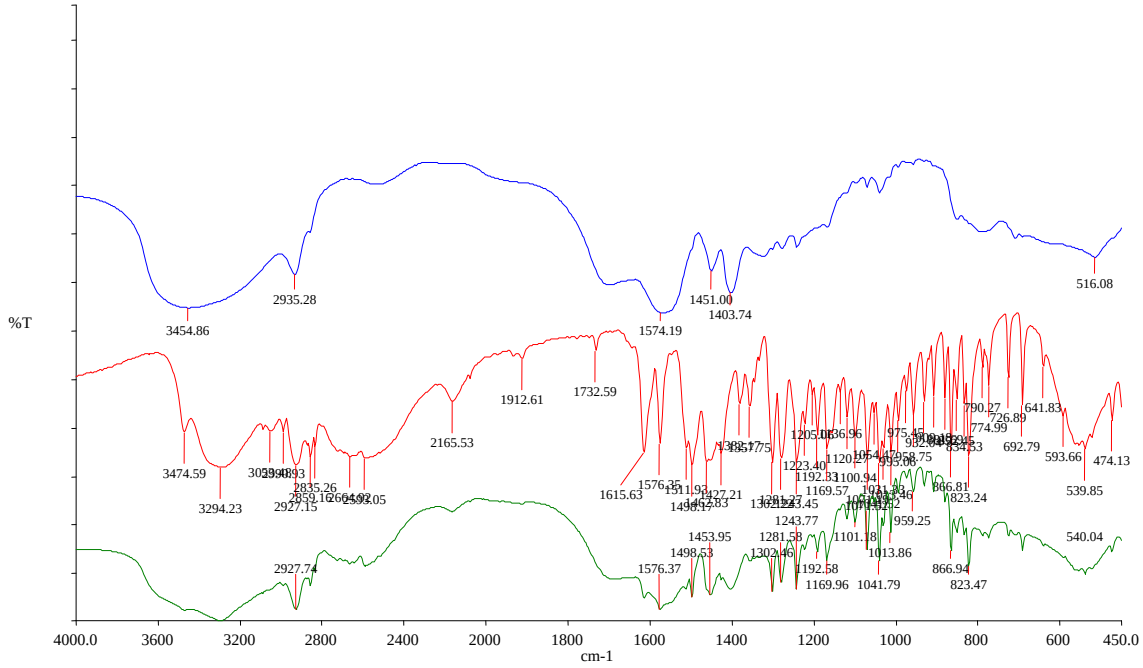


**Fig. 4** IR Spectra: A) Ion Exchange Resin; B) Resinate; C) Drug; D) Physical Mixture

FTIR spectra of the physical mixture exhibited superimposition of the drug and resin spectra. This indicates that there was no appreciable interaction between the drug and resin in the physical mixture, which is in accord with the results from DSC. Drug spectrum shows that prominent absorption bands at **2165.53** and **2593.05 cm−1**, corresponding to the NH+ stretching vibration in the tertiary amine group of the drug which is disappeared in the resinate. From this standpoint, the above finding can imply that dextromethorphan in resinate exists in the positively charged form (NH+ group of drug in resinate), which interacts with the carbonyl group of the resin in the complex.

### 3.2.3 pH and Drug Loading of DRC

**Table 4** Result showing pH and Drug Loading of DRC

| Drug to resin ratio | Time in (hrs) | Absorbance* | Remaining drug in (mg) | Amount of complexed drug in (mg) | % Complexed | pH* |
|---|---|---|---|---|---|---|
| 1:6 | 6 | 0.1 | 40.57 | 959.43 | 95.94 | 8.3 |

* Average of three readings

### 3.2.4 Drug Content

**Table 5:** Drug Content of DRC

| Buffer pH | Absorbance* | Amount | %Drug Content |
|---|---|---|---|
| 1.2 | 0.7819 | 299.5 | 99.85 |
| 6.8 | 0.117 | 35 | 11.67 |

* Average of three readings

### 3.2.5 Taste Evaluation of Resinate

**Table 6:** Results of Taste Evaluation Study of DRC

| Volunteers | Bitterness level after | | | | | |
|---|---|---|---|---|---|---|
| | Plain drug | | | Resinate | | |
| | 2 sec | 10 sec | 60 sec | 2 sec | 10 sec | 60 sec |
| 1 | 3 | 3 | 3 | 0 | 0 | X |
| 2 | 3 | 3 | 3 | 0 | 0 | 0 |
| 3 | 3 | 3 | 3 | 0 | 0 | 0 |
| 4 | 3 | 3 | 3 | 0 | 0 | 0 |
| 5 | 3 | 3 | 3 | 0 | 0 | 0 |
| 6 | 3 | 3 | 3 | 0 | 0 | 0 |
| **Mean Human Response** | 10 | 10 | 10 | 90 | 90 | 86.67 |

Score: 3=0-20%; 2=20-40%; 1=40-60%; X=60-80%; 0=80-100%

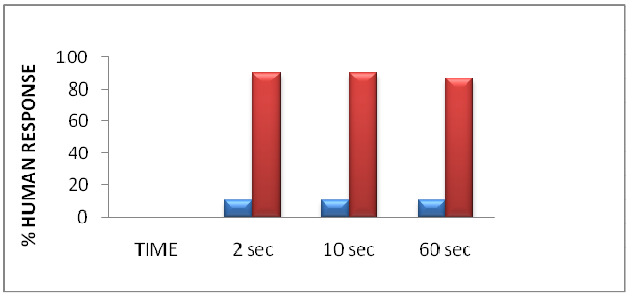


**Fig. 5** Graph of Taste Evaluation Study of DRC

**Discussion:**

Evaluation of Dextromethorphan HBr-Ionex QM 1011 Complex was carried out for various parameters like confirmation of formation of complex, pH, drug loading, drug content and taste evaluation. DSC and IR studies confirmed weak ionic bonding between drug and resin. Drug loading revealed 96% of drug was bound to ion exchange resin and 99.85% and 11.67% of the drug got released in buffer pH 1.2 and 6.8 respectively. Thus it confirms that bitter taste of Dextromethorphan Hydrobromide will not be felt because ion exchange resin complex releases negligible amount of drug at salivary pH. When it comes in contact with acidic pH, the complex is broken down releasing the drug. The bitter threshold of Dextromethorphan Hydrobromide recognized by the volunteers was between 35 and 45 µg/ml. From the majority of volunteers it was found that the threshold value of Dextromethorphan Hydrobromide was 40 µg/ml. Taste evaluation revealed that Ionex QM 1011 masks the bitter taste of the Dextromethorphan Hydrobromide completely.

### 3.3 Evaluation of Developed Oral Taste Masked Suspension of Dextromethorphan Hydrobromide

#### 3.3.1 Evaluation of Developed Dextromethorphan Hydrobromide Suspension

**Table 7:** Evaluation parameters of DXM Suspensions

| Parameters | DXM 1 | DXM 2 | DXM 3 | DXM 4 |
|---|---|---|---|---|
| Colour | Red | Yellow | Red | Red |
| Odour | Cherry | Pineapple | Cherry | Cherry |
| Taste | Sweet | Sweet | Sweet | Bitter |
| pH | 7.05 | 7.02 | 7.02 | 7.06 |
| Viscosity (cps) | 8471 | 8475 | 8470 | 8472 |
| Sedimentation volume (F) | 0.70 | 0.40 | 0.98 | 0.50 |
| Redispersibility | ++++ | caking | +++ | +++ |
| Assay | 96.0 | 93.7 | 99.0 | 98.9 |

"+" indicates number of times cylinder was moved upside down

#### 3.3.2 *In-Vitro* Drug Release

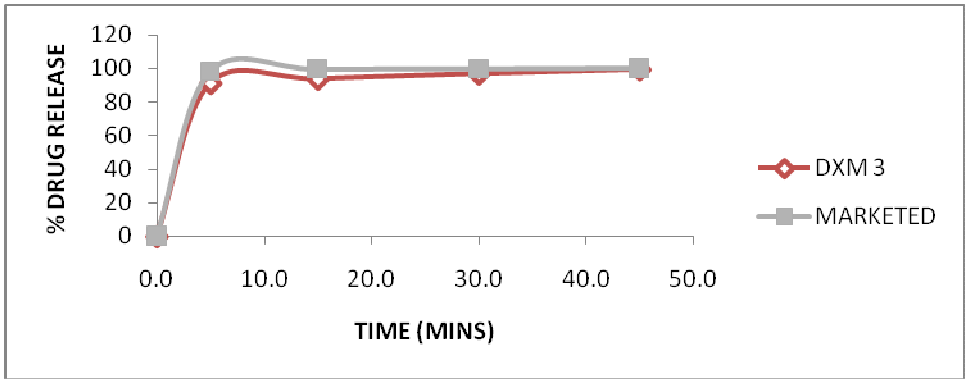


**Fig.6** Comparison of drug released profiles from DXM 3 and marketed product in 0.1 N HCl

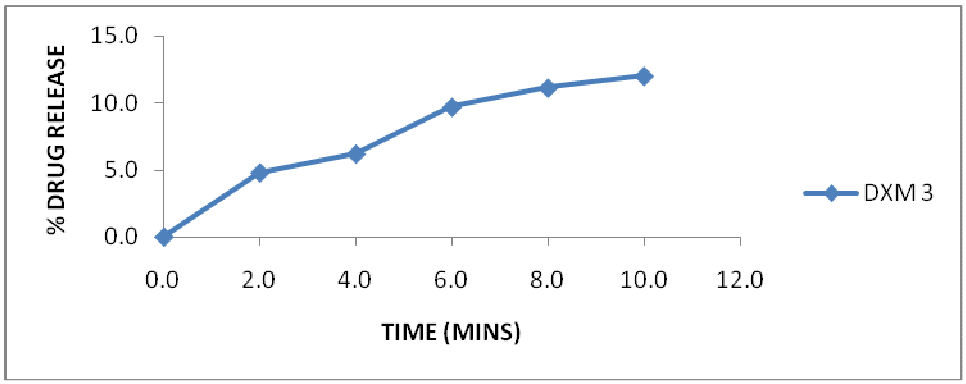


**Fig. 7** Drug release profile from DXM 3 in phosphate buffer

### 3.3.3 Taste Evaluation

**Table 3.8** Results of Taste Evaluation Study of Formulations

| Volunteers | Bitterness level after | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | DXM 3 | | | DXM 4 | | | Marketed | | |
| | 10sec | 1min | 2min | 10sec | 1min | 2min | 10sec | 1min | 2min |
| 1 | 0 | 0 | 0 | X | 2 | 3 | X | 3 | 3 |
| 2 | 0 | 0 | 0 | 1 | 2 | 3 | X | 3 | 3 |
| 3 | 0 | 0 | 0 | 1 | 3 | 3 | X | 3 | 3 |
| 4 | 0 | 0 | 0 | X | 2 | 3 | 0 | 3 | 3 |
| 5 | 0 | 0 | 0 | 1 | 3 | 3 | 1 | 2 | 3 |
| 6 | 0 | 0 | 0 | 1 | 3 | 3 | 1 | 3 | 3 |
| **Mean Human Response** | 90 | 90 | 90 | 56.67 | 20 | 10 | 66.67 | 13.33 | 10 |

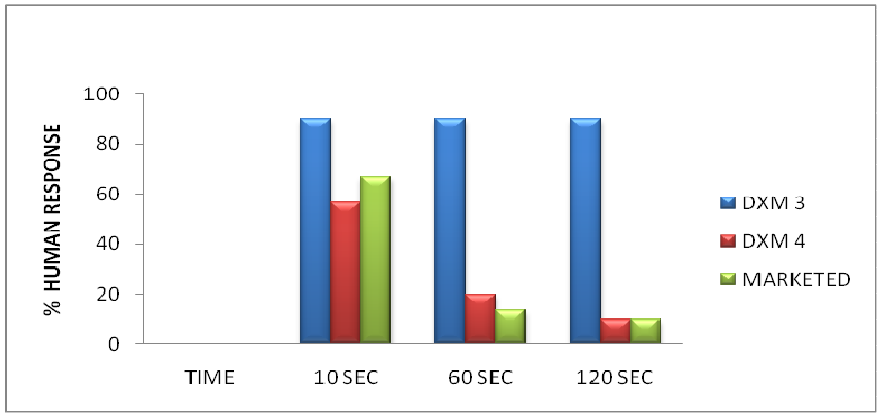


**Fig.8** Graph of Taste Evaluation Study of Formulations

### 3.3.4 *In-vivo* study

**Table 9**: Percentage licking response of rats

| | % of Licking Frequency | | | | | | |
|---|---|---|---|---|---|---|---|
| Rats | 1 | 2 | 3 | 4 | 5 | 6 | Mean |
| **3mg/ml** | 73.33 | 68.97 | 78.57 | 74.29 | 72.41 | 65.38 | 72.16 |
| **6mg/ml** | 55.00 | 51.72 | 46.43 | 51.43 | 48.28 | 46.15 | 49.84 |
| **9mg/ml** | 33.33 | 31.03 | 25.00 | 34.29 | 27.59 | 32.69 | 30.66 |
| **DXM 3** | 86.67 | 86.21 | 92.86 | 85.71 | 82.76 | 80.77 | 85.83 |
| **DXM 4** | 60.00 | 58.62 | 53.57 | 57.14 | 55.17 | 53.85 | 56.39 |
| **Marketed** | 56.67 | 62.06 | 57.14 | 54.29 | 58.62 | 57.69 | 57.75 |

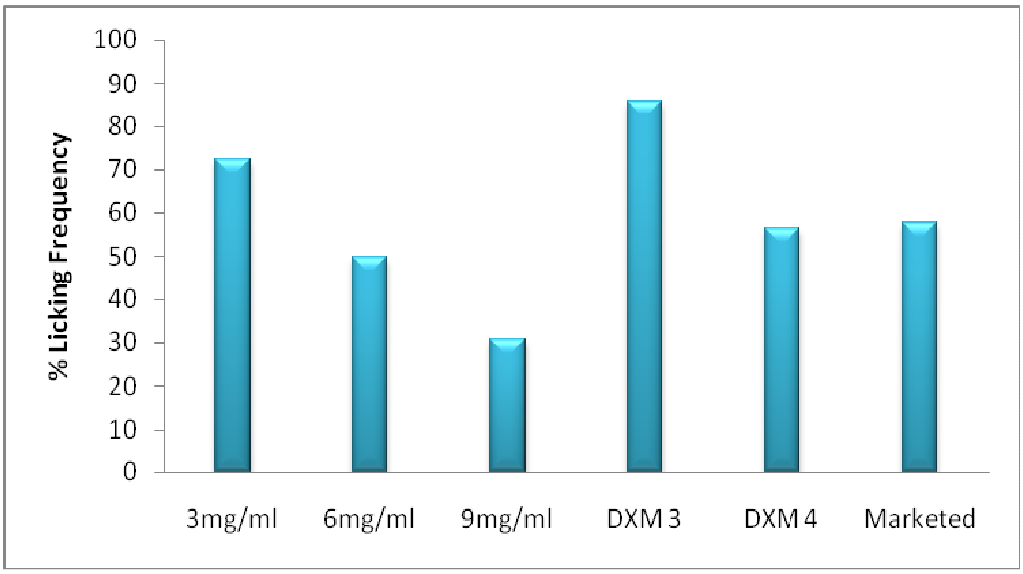


**Fig.9** Mean % licking frequency in rats

**Discussion:**

Formulation of oral taste masked suspension was found to be optimum with use of xanthum gum and tween 80 at 0.1% and 0.2% concentration respectively. DXM 1 and DXM 2 batches showed satisfactory assay result that is it fulfills the official requirements (To be comply with IP stated limits are between 90 to 110%). But physical properties of suspension were not satisfactory. DXM 1 was not easily redispersible and with DXM 2 caking was observed with sedimentation volume of 0.4, hence these batches were rejected. DXM 3 was found to be optimized batch as it showed complied assay result (99%) and was found to be easily redispersible even after 7 days with no cake formation and sedimentation volume of 0.98. *In vitro* dissolution studies showed a drug release up to 99.6% in 45 min, which was found to be equivalent to marketed product (100.4%). $T_{50}$ and $T_{90}$ were found to be 2.14 min. and 10.71 min. respectively. At salivary pH drug release is less (12.0%) hence no bitterness will be felt when suspension is administered orally. The taste evaluation study was performed using human volunteers.

DXM 3 formulation did not show any bitter taste when suspension is kept on the tongue by using time intensity method, which showed excellent taste masking effect of the resin. In case of marketed formulation and DXM 4, bitterness was felt by all the volunteers. According to the procedure of *In vivo* study, rats were allowed to drink water and various test substances and the inhibition in licking frequency was counted. A higher licking frequency of upto 72% was obtained for drug solution of concentration 3mg/ml indicating that the solution did not exhibit very bad taste. Almost 50% inhibition in licking frequency was obtained for drug solution concentration of 6 mg/ml whereas drug solution of 9mg/ml concentration induced less licking frequency only upto 31% indicating a higher inhibition due to the high concentration of bitter tasting Dextromethorphan Hydrobromide. DXM 3 formulation presented to the rats showed very high licking frequency of upto 86% and above whereas DXM 4 and marketed formulation induced less licking frequency of upto 55% indicating that the taste masking method was effective in masking the bitter taste of the Dextromethorphan Hydrobromide.

**3.3.5 Accelerated stability study**

**Table 10**: Accelerated stability study

| Parameters | Time Periods | | | |
|---|---|---|---|---|
| | Initial | 1 month | 2 month | 3 month |
| Colour | Red | No change | No change | Slight change |
| Odour | Cherry | Cherry | Cherry | No change |
| Taste | Sweet | Sweet | Sweet | Sweet |
| pH | 7.02 | 7.00 | 7.05 | 7.05 |
| Viscosity (cps) | 8471 | 8470 | 8458 | 8443 |
| Sedimentation volume (F) | 0.98 | 0.98 | 0.97 | 0.97 |
| Redispersibility | ++ | +++ | ++ | +++ |
| Assay | 98.5 % | 97.2 % | 96.8 % | 97.3 % |

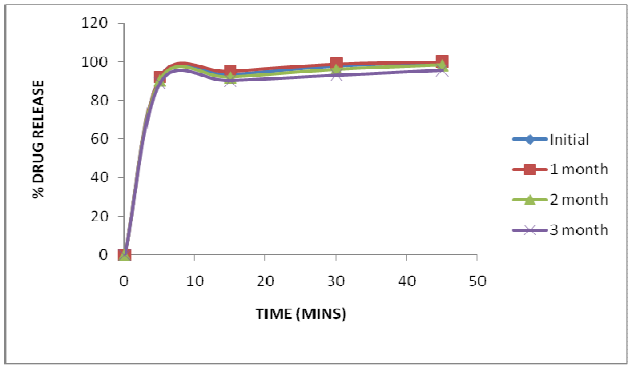


**Fig. 10** Dissolution profile of stability batch in simulated gastric fluid

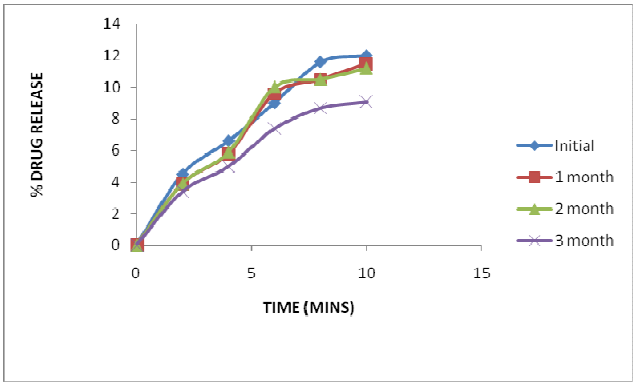


**Fig. 11** Dissolution profile of stability batch in simulated salivary fluid

### Discussion

Accelerated stability study of DXM 3 is shown in [Table 10]. Study revealed that prepared formulation can remain intact for a long period of time without major changes in assay, viscosity and sedimentation volume. It was found that formulation remained palatable without any appearance of degradation in assay result.

## 4. CONCLUSION

The efficient taste masking was obtained from drug–resin a complex that was formulated as oral suspension for better patient compliance. Use of weak cation exchange resin offers superior method for preparing taste-masked substrates of Dextromethorphan Hydrobromide. Results obtained in this work shows that drug-resin complexes effectively masked bitter taste of Dextromethorphan Hydrobromide while liquid formulation provides easier way to administer and getting the child to swallow. Also to overcome problem with non compliance with child especially around 8 years old for whom swallowing other dosage form can be challenging. Thus, the “patient friendly dosage form” of bitter drugs, especially for pediatric, geriatric, bedridden, and non cooperative patients, was successfully formulated using this technology.

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