

Design and evaluation of taste masked dextromethorphan hydrobromide oral disintegrating tablets

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The present study is aimed to develop dextromethorphan hydrobromide (DXM) oral disintegrating tablets (ODT) with acceptable palatability to help patients of all age groups. The bitter taste of the drug was masked by binding the drug to ion exchange resin. The effect of the particle size of resin on drug loading was studied. *In vitro* and *in vivo* disintegration time and *in vitro* drug release studies were performed. Drug loading increased significantly with a decrease in the particle size of the resin. DSC and XRPD studies reveal that the molecular state of the drug changed from crystalline to amorphous form. The dissolution efficiency calculated for optimized ODT and conventional directly compressed tablet were almost comparable, indicating free dissociation of the drug from the resinate. The bitter taste of DXM can be masked by binding with ion exchange resin and the resinate can be successfully formulated into oral disintegrating tablets.

Keywords: dextromethorphan hydrobromide, ion exchange resin, taste masking, superdisintegrants

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Oral disintegrating tablets (ODTs) have advantages of solid dosage forms such as good stability, accurate dosing, small packaging size, and easy handling, as well as those of liquid formulations such as easy administration and minimal risk of suffocation. Therefore, they are beneficial for children, elderly and schizophrenic patients who have difficulty in swallowing conventional solid dosage forms (1). The success of ODT depends on patient acceptance, palatability and the challenging aspect in the formulation of orally disintegrating tablets is to mask the bitterness of active pharmaceutical ingredients, since most drugs have bitter taste. The distasteful sensation of a drug can be masked either by the addition of flavors, sweeteners and effervescent agents or by reducing direct contact with the patient's taste buds through coating or granulation (2, 3). Flavor is often overpowered by the taste of the medicine and the use of effervescent agents is not always convenient. Moreover, coating and granulation of the active ingredient may

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often rupture during compression and chewing of the tablet, as well as contribute to a gritty feel.

Drug binding to ion exchange resin is a simple and efficient technique of masking drug bitterness. Active ingredients, if ionized, can be bound with fixed ions of ion-exchange resins (4–6). The advantages of utilizing ion-exchange resins include the simple preparation method and no uncontrolled burst effect in the drug resinate even in case of high drug loading. The only limiting factor for drug loading is the limited exchanging capacity of the resin. Particle size of the resin has been reported to have a pronounced effect on the rate and extent of drug loading (7). When active ingredient/resin complexes are administered orally, the active ingredient can be released by the ion-exchange reaction with ions present in the GI tract.

Dextromethorphan hydrobromide is an antitussive agent, used to relieve cough. The commercial formulations available for DXM are syrups, lozenges and spray forms but its availability as solid dosage forms is limited. Since liquid dosage forms are bulky and stability is a key issue, we decided to develop taste masked ODTs of DXM for immediate relief of cough with improved patient compliance. This could be achieved by selecting appropriate pharmaceutical excipients in correct proportion, in combination with optimal manufacturing techniques and compression parameters.

EXPERIMENTAL

Materials

Ion-exchange resin (Amberlite® IRP69, sodium polystyrene sulfonate (150–125, 106–75 and 63–45 μm) was donated by Rohm and Haas, USA. Dextromethorphan hydrobromide monohydrate (DXM) was obtained from Dr. Reddy's Laboratories Ltd, India. The diluents used were spray-dried mannitol (Pearlitol® SD 200, Roquette Frères, France) and microcrystalline cellulose (Avicel PH 101, FMC International, Ireland). The superdisintegrants used were Crospovidone (CP) (Polyplasdone XL-10, ISP Technologies, Inc, USA), sodium starch glycolate NF (SSG) (Primojel, DMV International, USA) and Amberlite IRP88 (potassium salt of methacrylic acid polymer with divinyl benzene, Rohm and Haas, USA). The glidants used were colloidal silicone dioxide NF (Aerosil®, Evonik Industries Degussa, Belgium) and sodium starch fumarate (JRS Pharma, Spain). The flavor used was tutti frutti flavor (Firmenich, India). All other chemicals and solvents used were of analytical grade.

Methods

Preparation of drug resinate. – Drug resinates were prepared by a single batch process. Purified resin (3.0 g) was placed in 200 mL of 1.5 % (*m/V*) of DXM aqueous solution. The mixture was stirred for 24 h on a magnetic stirrer at ambient temperature and intermittently the supernatant was removed to find out the amount of drug loaded in the resin spectrophotometrically at 278 nm (UV-2450/2550, Shimadzu, Japan). The resinate was retrieved by filtration and washed repeatedly with deionized water until the free drug was removed. The resinates were dried for 2 h at 60 °C and stored in a tightly

closed vial. The drug content in the final filtrate was analyzed at 278 nm. The amount of drug in the resinate was obtained by subtracting the amount of drug in final filtrate from the initial amount. Since the particle size of resin influences the extent of drug loading, we have tested different ranges of Amberlite® IRP69 particle size.

In vitro dissolution. – Dissolution study on resينات of different particle size (150–125, 106–75 and 63–45 μm) equivalent to 30 mg of DXM was carried out in 900 mL of simulated gastric fluid (SGF), without enzymes, using USP dissolution apparatus (8), type II (rotating paddle), maintained at 37 ± 0.5 °C and mixed at 50 rpm. Based on the dissolution data, we have selected Amberlite IRP69 of particle size 63–45 μm for further studies.

Differential scanning calorimetry (DSC). – 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 (DSC 6, Perkin Elmer, USA). Each sample was placed in an aluminum pan and then crimped with an aluminum cover. Heating and cooling rates were 10 and 250 °C min^{-1} , respectively. All measurements were performed over 40–250 °C under a nitrogen purge at 50 mL min^{-1} .

X-ray powder diffraction. – The XRPD patterns of pure drug, resin, physical mixture and resinate were obtained using an X-ray diffractometer (X'Pert PRO PANalytical, USA). The measuring conditions were as follows: $\text{CuK}\alpha$ radiation, nickel filtered, graphite monochromator, 45 kV voltage and 40 mA current with X'celerator detector. All samples were run at 1° (2θ) min^{-1} from 3 to 45° (2θ).

FTIR spectroscopy. – 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} .

Table I. Composition of DXM oral disintegrating tablets

Ingredient	Disintegrant concentration CP/SSG/ IRP88 (% , m/m)		
	3	5	10
Drug-resinate (32.5 %) (mg)	65	65	65
Pearlitol® SD 200 (mg)	85	81	71
Avicel pH 101 (20 %) (mg)	40	40	40
Superdisintegrants (mg)	6	10	20
Aspartame (0.5 %) (mg)	1	1	1
Aerosol® (1 %) (mg)	2	2	2
Sodium stearyl fumarate (0.5 %) (mg)	1	1	1
Total (mg)	200	200	200

CP, SSG and IRP88 indicate Crospovidone, sodium starch glycolate and ion exchange resin, respectively.

Formulation of DXM oral disintegrating tablets. – In our preliminary studies, ODTs were prepared using superdisintegrants like Crospovidone (CP), sodium starch glycolate (SSG) and amberlite IRP88 at various concentrations (3, 5 and 10 % *m/m*, respectively). The composition of ODTs prepared with different concentrations of superdisintegrants is shown in Table I. Based on the disintegration time, the type and concentration of superdisintegrant was selected and different batches of ODTs (A₁, A₂ and A₃) containing diluents like Avicel PH 101 and Pearlitol SD 200, either alone or in combination, were prepared as outlined in Table II. All formulation components were accurately weighed, passed through a 0.4-mm sieve (except lubricant) and mixed in a polyethylene bag for 15 min. The blend was lubricated with sodium stearyl fumarate and Aerosil® (each passed through 0.25-mm mesh) for another 5 min and directly compressed into tablets using an 8-station rotary tablet compression machine (Kambert, India). Round biconvex tablets of 200 mg in mass and 8 mm in diameter were prepared. Conventional tablets were also prepared with the same formula (A₁) using DXM instead of drug-resinate.

Evaluation of DXM oral disintegrating tablets

Mass variation, thickness and assay. – Mass variation was carried out using a digital balance (Shimadzu) and thickness was measured with a digital screw gauge micrometer (Digimatic micrometer Series 293, Mitutoyo, Japan). Accurately weighed amount of powder equivalent to a single dose of DXM was taken, in triplicate, and assayed for the drug content.

Hardness, friability and in vitro disintegration time. – Hardness, friability and *in vitro* disintegration time (DT) of ODTs was determined as per the procedure described for uncoated tablets in USP (8).

Wetting time and water absorption ratio. – The wetting time (WT) and water absorption ratio (R) were determined by using the procedures described in literature (9).

Taste evaluation and in vivo disintegration time. – The study was conducted after prior approval from the Institutional Ethical Committee, St Peter's Institute of Pharmaceutical Sciences, Warangal, India. After informed consent from six human volunteers, taste eva-

Table II. Composition of DXM oral disintegrating tablets containing different diluents

Ingredient	A ₁	A ₂	A ₃
Drug-resinate (32.5 %) (mg)	65	65	65
Pearlitol® SD 200 (mg)	–	111	77
Avicel pH 101 (mg)	111	–	34
Superdisintegrants (10 %) (mg)	20	20	20
Aspartame (0.5 %) (mg)	1	1	1
Aerosil® (1 %) (mg)	2	2	2
Sodium stearyl fumarate (0.5 %) (mg)	1	1	1
Total (mg)	200	200	200

luation was done by the time intensity method (10). Resinates equivalent to 30 mg of DXM and ODT formulations, with and without flavor, were held in the mouth of six volunteers for 30 seconds. Bitterness was recorded immediately according to the bitterness intensity scale from 0 to 3 where 0, 0.5, 1, 2, and 3 indicate no, threshold, slight, moderate and strong bitterness, respectively. The readings were taken immediately and at several intervals over a period of 10 min.

Oral DT of the optimized ODT formulation (determined based on its *in vitro* DT and drug release) was assessed on six healthy male human volunteers according to the procedure described by Abdelbary *et al.* (11). The subjects were informed of the purpose and protocol of the study. As per the protocol, all volunteers were asked to rinse their mouth with distilled water prior to the test. Tablets were placed on the tongue and a stopwatch was started immediately. Volunteers were allowed to move the tablet against the upper palate of the mouth with their tongue and cause a gentle tumbling action on the tablet without chewing it. Time taken for the volunteer to feel that the last noticeable granule had disintegrated in the oral cavity was considered the *in vivo* DT. Swallowing of saliva was prohibited during the test, and the mouth was rinsed after each measurement. This experiment was conducted on all six subjects and the mean \pm SD were calculated for each.

In vitro release. – Release studies of ODTs were performed according to the USP (8) type-II dissolution apparatus (Model-TDL 08L, Electrolab, India), equipped with an auto sampler and fraction collector. Paddle speed was maintained at 50 rpm and 900 mL of simulated gastric fluid without enzymes was used as the dissolution medium. Samples (5 mL) were collected at predetermined time intervals and replaced with an equal volume of fresh medium to maintain sink conditions. The samples were filtered through a 0.45- μ m membrane filter (Millipore, USA) and analyzed spectrophotometrically at 278 nm. Conventional tablets of DXM containing the same formula as A₁ batch (DXM instead of drug-resinate) were prepared by direct compression to compare the dissolution behavior of ODT.

Cumulative percent drug release was plotted as a function of time. Dissolution efficiency (DE) was calculated from the area under the dissolution curve at time *t* (measured using the trapezoidal rule) and expressed as a percentage of the area of the rectangle described by 100 % dissolution over the same time (12).

RESULTS AND DISCUSSION

Initially, ODTs containing superdisintegrants in concentrations of 3, 5, and 10 % (*m/m*) were tested for disintegration time. The tablets showed disintegration time of 8–10 s, 13–17 s and 13–20 s with Crospovidone, sodium starch glycolate and Amberlite IRP88, respectively (Table III). Among the superdisintegrants tested, CP at a concentration of 10 % *m/m* showed lower disintegration time. Since lower disintegration time is required for an ODT, we have selected CP at a concentration of 10 % *m/m*, for formulations of ODTs.

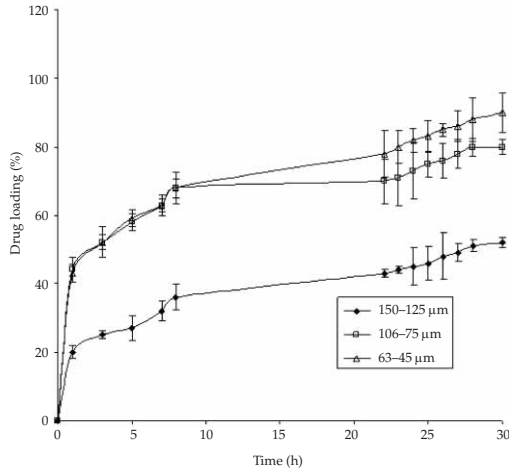


Fig. 1. Effect of particle size of ion-exchange resin on drug loading (mean \pm SD, $n = 3$).

Drug loading and in vitro dissolution from different particle size resins

Drug loading was 85 % with the resin particle size 63–45 μm and this was reduced to 75 and 50 % with an increase in the particle size of resin to 106–75 and 150–125 μm , respectively (Fig. 1). A linear relation of drug loading to resin particle size was established. As the particle size decreased, the drug loading increased significantly (7). Similar observations were made in our study as well. Fine particles have a larger surface area than coarse particles and less internal volume for ions to diffuse, so less time is required to establish equilibrium. Similarly, desorption of bound drug from the complex is faster in fine particles.

Particle size of resinate had an impact on the dissolution rate, as the sustained release was more evident from larger particles (13). From the dissolution profiles along with cross-linking, particle size was reported to be an important factor in controlling the

Table III. Effect of superdisintegrants on in vitro DT of DXM oral disintegrating tablets

	Superdisintegrant (% <i>m/m</i>)	<i>In vitro</i> DT (s)
Crospovidone	3	9.27
	5	10.41
	10	8.50
Sodium starch glycolate	3	13.54
	5	15.42
	10	17.51
Amberlite IRP 88	3	13.20
	5	20.03
	10	19.63

DT – dissolution time

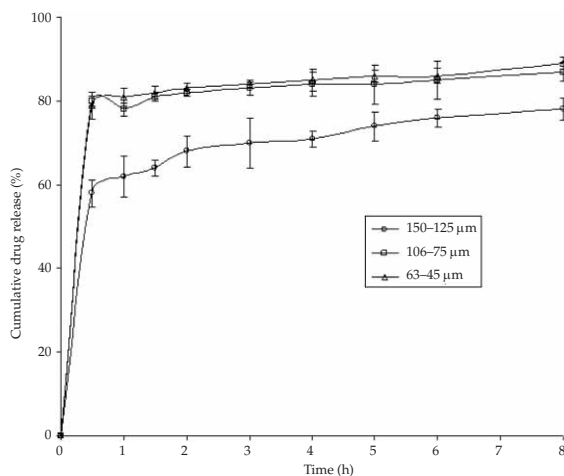


Fig. 2. Dissolution profiles of different particle size resins in simulated gastric fluid (pH 1.2) (mean \pm SD, $n = 3$).

release of the drug from ion exchange resin (14). The reduced dissolution behavior of DXM from resin with larger particle size might be due to the hurdles in drug movement through the polymeric network requiring more time for deeply penetrated drug molecules to elute. The dissolution of DXM was much higher from resin with particle sizes 63–45 and 106–75 μm compared to 150–125 μm particle size resin (Fig. 2). Since particle size is an important parameter for improved dissolution characteristics, we have selected the resin with smaller particle size of 63–45 μm .

Molecular interactions of drug and resin

Molecular interactions between drug and resin were studied using differential scanning calorimetry, X-ray powder diffraction and Fourier transform infrared spectroscopy.

Fig. 3 represents the DSC curves of DXM, Amberlite® IRP69, physical mixture and resin. A sharp endothermic peak was observed at 123.07 $^{\circ}\text{C}$ for pure drug, indicating the melting point of DXM. The endothermic peak of pure drug was also shown in case of the physical mixture at 120.1 $^{\circ}\text{C}$. On the other hand, no intense peak over the range of 40–250 $^{\circ}\text{C}$ was found in the DSC thermogram of resin, which clearly indicates that the drug was not in its native form in the resin. This finding could be considered indicative of drug amorphization as a consequence of interaction between the components (15), which was further confirmed by XRPD analysis.

The XRPD of the pure drug contained a number of sharp peaks, while the resin showed diffused peaks. The XRPD of the physical mixture exhibited simply the sum of characteristic peaks of the pure drug and diffused peaks of the resin, whereas the characteristic peaks of the pure drug were absent in the resin (Fig. 4). On the basis of diffractograms, it can be said that pure crystalline drug was found to convert into amorphous form with monomolecular dispersion in the resin (16). This was supported by the absence of sharp peaks of the drug in the resin. These results coincide with those obtained by Akkaramongkolporn and co-workers (17), who studied the change in molecular properties of propranolol upon binding with an ion exchanger.

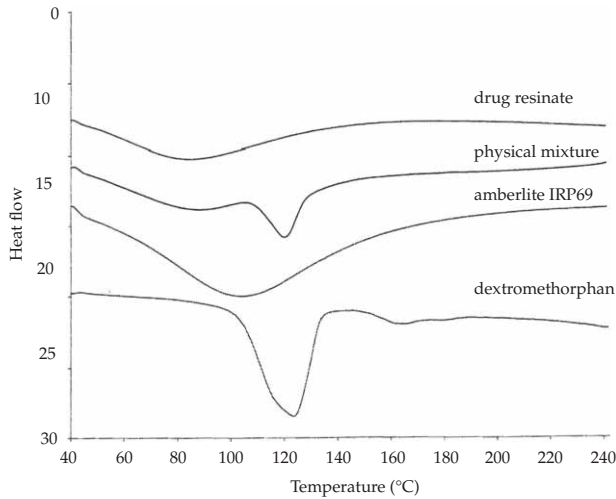


Fig. 3. DSC curves of dextromethorphan, Amberlite IRP69, physical mixture and drug resinate.

From Fig. 5, it is evident that the 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 and XRPD. The spectra of the resinate in the 2000–400 cm^{-1} region had a similar result, demonstrating the presence of the drug in the complex. However,

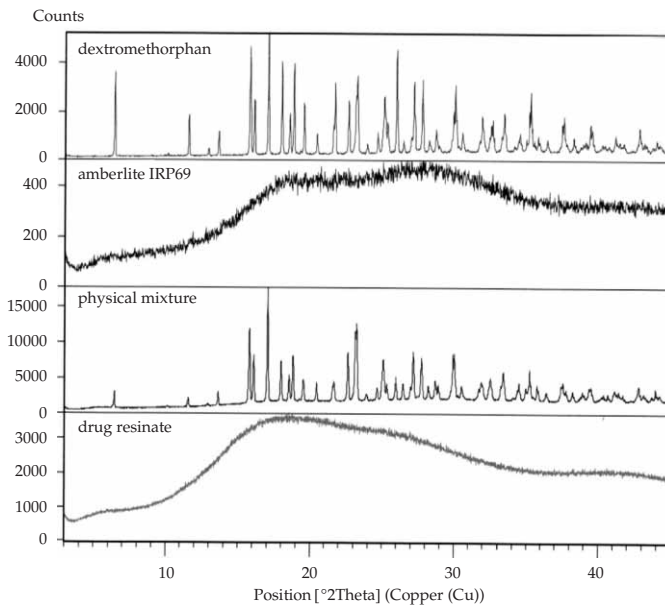


Fig. 4. XRPD patterns of dextromethorphan, Amberlite IRP69, physical mixture and drug resinate.

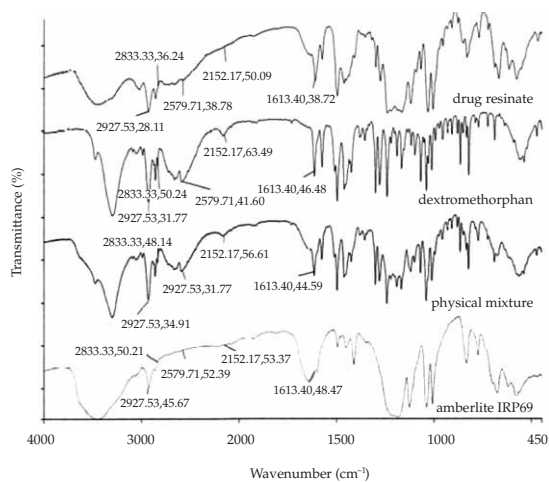


Fig. 5. FTIR spectra of dextromethorphan, Amberlite IRP69, physical mixture and drug resinate.

around 4000–2000 cm⁻¹ the spectrum was obviously different from the combination of each component. Drug spectrum shows that prominent absorption bands at 2167.03 and 2593.69 cm⁻¹, corresponding to the NH⁺ stretching vibration in the tertiary amine group of the drug, disappeared (or shifted) in the resinate. In addition, new absorption bands emerged around 3022.89 cm⁻¹ in the resinate spectra. In comparison with certain absorption bands around this wavelength position, the distinct increase in intensity of the new absorption bands in the resinate spectra indicates that they are not the usual absorption bands associated with either pure drug or resin. The formation of new chemical bonds would be expected to result in emergence of additional absorption bands or alterations in wavenumber position (18). 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 sulfonate group of the resin in the complex. This kind of ionic association is referred to as a »salt bridge«. Like the hydrogen-bonding effect, the degree of this ionic association, which closely relates to the H-donating and accepting ability of an ion pair, significantly affects the NH⁺ stretching. As the ionic association increases, the NH⁺ stretching decreases and subsequently shifts to a lower frequency, and *vice versa*. Therefore, the shifting of the NH⁺ stretching of the drug to a higher frequency in resinate suggests that the ionic association in resinate is weaker than in the drug (19).

Evaluation of tablets

Initially, tablets containing superdisintegrants in concentrations of 3, 5, and 10 % (*m/m*) were tested for disintegration time. The tablets containing CP showed fast disintegration (8–10 s) followed by SSG (13–17 s) and Amberlite IRP88 (13–20 s) (Table III). Based on the results, CP at a concentration of 10 % was selected for the formulations of ODTs.

Tablet thickness and hardness were maintained at 4.5 ± 0.1 mm and 3.5 ± 0.5 kg cm⁻², respectively, for all formulations. The mass variation (less than 7.5 %), friability (less than

Table IV. Evaluation parameters of DXM oral disintegrating tablets

Parameter	A ₁	A ₂	A ₃
WT (s)	19.2 ± 0.4	65.3 ± 0.7	35.6 ± 0.8
Water absorption ratio	82.69 ± 1.6	132.5 ± 1.8	116.7 ± 1.7
<i>In vitro</i> DT (s)	5.89 ± 1.2	19.2 ± 2.4	9.27 ± 1.9
Oral DT (s)	26.7 ± 1.6	45.39 ± 2.7	32.56 ± 1.7

WT and DT represent wetting time and disintegration time, respectively.

1 %) and content uniformity of tablets (95–100 %) of all batches (A₁, A₂ and A₃) were found to be within the limits. Wetting time of A₁ formulation of 19.2 ± 0.4 s was lower compared to A₂ and A₃ formulations (65.3 ± 0.6 and 35.6 ± 0.8 s, respectively) (Table IV). Faster wetting of A₁ tablets containing Avicel PH 101 might be due to its rapid water absorbing nature involving both capillary and swelling mechanisms (20). Water absorption ratio, *R*, of formulations containing Pearlitol® SD 200 (132.5 ± 1.8) was higher than that of Avicel PH 101 and combination of Pearlitol® SD 200 and Avicel PH 101 (82.7 ± 1.6 and 116.7 ± 1.3, respectively) (Table IV). Formulation containing a higher amount of Pearlitol® SD 200 showed increased wetting and disintegration time. Increase in wetting and disintegration time may be due to the increase in polyol quantity in the tablet formulation. As polyols are readily soluble in water, there is a competition between spray-dried mannitol and CP for water penetrating into the tablet, consequently leading to poor swelling of CP with subsequent delay in disintegration. These results are consistent with the reports of Shagufta *et al.* (21).

Taste evaluation and *in vivo* disintegration time

Taste evaluation was performed on six healthy human volunteers and the results are given in Table V. Pure drug was felt bitter immediately after it was kept on the ton-

Table V. Comparative taste evaluation

Form of DXM	Degree of bitterness after time			
	10 s	1 min	5 min	10 min
Pure drug	3	3	3	3
Drug resinate	0	0	0.5	0
Unflavoured tablet with drug resinate	0	0	0	0
Flavoured tablet with drug resinate	0+	0+	0+	0+

Results are the mean of 6 observations. + indicates palatability.

gue and the sense persisted up to 10 minutes. However, drug bitterness was masked af-

ter its binding to the resin. Among the formulations tested, unflavoured tablets exhibited no bitterness even after 10 min whereas flavoured tablets exhibited palatability. Since the drug is not in the native form and is bound to the resin, reduced availability of free drug in the saliva could have led to the masking of the bitter taste.

As regards wetting time, *R* value, *in vitro* DT, and cumulative drug released, formulations containing CP with Avicel pH 101 were considered to be better than those containing CP with Pearlitol® SD 200. A₁ formulations showed lower DT with 5.9 ± 1.2 s compared to A₂ and A₃ (19.2 ± 2.4 and 9.3 ± 1.9 , respectively). Complete *in vivo* disintegration was achieved within 26.7 ± 1.6 s for A₁ formulation whereas it increased to 45.4 ± 2.7 and 32.6 ± 1.7 for A₂ and A₃ formulations (Table IV). Based on *in vitro* and *in vivo* disintegration, A₁ was considered to be the optimal ODT formulation among all the formulations tested.

In vitro release

Based on the investigation, tablets of batch A₁ were considered to possess the best physical properties accompanied with fast disintegration time. Therefore, to understand the dissolution behavior, the *in vitro* release study was conducted for optimized DXM oral disintegrating tablets (A₁) and compared with the conventional, directly compressed DXM tablet that contains pure drug in place of drug-resin complex. Since ODT is meant to release the drug in stomach and the drug release from resinate is dependent on the exchange of hydrogen ions, the dissolution was conducted in simulated gastric fluid. The drug release from both formulations was almost 80 % within 60 min (Fig. 6). However, in case of A₁ formulation, the drug release was 55 % in 10 min, which is higher compared to the drug release from the conventional tablet (40 %). The dissolution efficiency calculated was 70.9 and 63.8 % for optimized and conventional directly com-

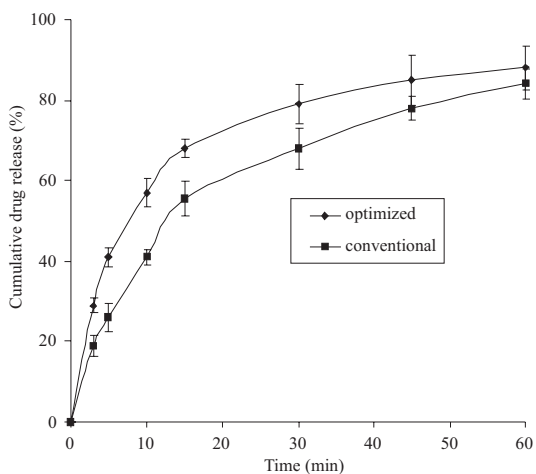


Fig. 6. *In vitro* release profiles of optimized formulation (A₁) and conventional tablet (mean \pm SD, $n = 6$).

pressed formulations, respectively. The optimized ODT dissolution behavior was almost comparable to the conventional tablet, which clearly demonstrates that drug is displaced from resinate without any delay in the dissolution process despite the fact that the drug is in complex with ion-exchange resin. Obviously, this could be due to free dissociation of the drug from resinate due to the exchange with hydrogen ions present in the dissolution medium. However, longer time was necessary for the drug to dissociate completely from the resinate.

CONCLUSIONS

The study has revealed the effect of particle size of resin on drug loading and release. The extent of drug loading and release were higher with small particle size resins compared to larger particle size resins. Characterization of the ODTs confirmed that adequate taste masking and faster disintegration could be achieved for the optimized (A₁) formulation. Based on the results, it can be concluded that the bitterness of DXM can be masked with the resin and can be incorporated in ODTs with good dissolution behavior.

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S A Ž E T A K

Dizajniranje i evaluacija oralnih raspadajućih tableta dekstrometorfan hidrobromida s maskiranim okusom

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Cilj rada bio je pripremiti raspadajuće tablete dekstrometorfan hidrobromida (DXM) za oralnu primjenu (ODT) prihvatljivog okusa s namjerom da se pomogne pacijentima svih dobnih skupina. Gorki okus ljekovite tvari maskiran je vezanjem lijeka na ionsko-izmjjenjivačku smolu. Proučavan je utjecaj veličine čestica smole na količinu ljekovite

tvori koja se može na nju vezati, vrijeme raspadanja *in vitro* i *in vivo*, te oslobađanje lijeka *in vitro*. Količina vezanog lijeka značajno se povećava sa smanjenjem veličine čestica smole. DSC i XRPD studije pokazuju da prilikom vezanja kristalinični oblik lijeka prelazi u amorfni. Oslobađanje ljekovite tvari izračunato za optimizirane ODT i izravno komprimirane tablete vrlo je slično, što ukazuje na slobodno oslobađanje lijeka iz smole. Gorki okus DXM može se maskirati vezanjem ljekovite tvari na ionsko-izmjenjivačku smolu iz koje se mogu pripremiti raspadajuće tablete za oralnu primjenu.

Ključne riječi: deksametorfan hidrobromid, ionsko-izmjenjivačka smola, maskiranje okusa, sredstvo za raspadanje

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