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Original Article

PREPARATION AND EVALUATION OF ORALLY DISINTEGRATING TABLETS OF DROTAVERINE HYDROCHLORIDE USING SUBLIMATION TECHNIQUE

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ABSTRACT

Objective: To formulate orally disintegrating taste masked tablets of drotaverine hydrochloride (HCl) by sublimation technique.

Methods: Initially superdisintegrant was selected and its concentration was optimized by pre-compression and post-compression parametric evaluation. Camphor and menthol were used as sublimating agents alone and in combination to mask the taste of drotaverine hydrochloride. Prepared tablets were evaluated for physicochemical evaluation, *in vitro* dissolution studies and fourier transformation-infrared spectroscopy, differential scanning calorimetry and X-ray diffractometry studies.

Results: The optimised formulation DCM2 prepared with a mixture of camphor and menthol was characterised by fourier transformation-infrared spectroscopy, differential scanning calorimetry and X-ray diffractometry studies and found no incompatibility and no major shifts were noticed.

Conclusion: The results demonstrated that the prepared drotaverine HCl orally disintegrating tablets showed better taste masking. The present sublimation technique can be effectively used for taste masking and also for orally disintegrating tablets.

Keywords: Drotaverine hydrochloride, Camphor, Menthol, Croscarmellose sodium, sublimation, Taste masking and orally disintegrating tablets

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INTRODUCTION

Drotaverine hydrochloride (HCl) is a benzylisoquinoline derivative, which causes relaxation of smooth muscle that suppresses pain associated with spasm caused by smooth muscle contraction. Drotaverine HCl is sparingly soluble drug having a very bitter taste and patients are reluctant to its taste when the ordinary tablet is kept on the tongue during swallowing. Hence, there is a poor patient compliance of using drotaverine HCl which necessitates the masking of its bitter taste during administration and improvement in its solubility and dissolution rate for patient compliance and improved bioavailability.

In this technology, the disintegration step will be completed in the oral cavity such that dissolution can be initiated in the stomach thereby improving the efficacy of the drug. However, the taste of the drug plays a vital role in the success of this technique as the disintegration occurs in the mouth. In case of drotaverine, HCl simple technology of oral disintegrating tablet (ODT) is not suitable and technologies that are suitable for improving both taste and disintegration rate are necessary [1-4]. Earlier workers reported on taste masking of drotaverine HCl by using approaches like solid dispersion, a drug coating, complexation with polymers and coprocessing with superdisintegrants [5-8].

There are no reports cited earlier for the applicability of ODT technology for drotaverine HCl. The applicability of techniques like sublimation and solid mixtures were tried for drugs like fisinopril, fenofibrate, levocetirizine dihydrochloride and itraconazole in the design of ODT [9-12]. Hence, in the present investigation, it is proposed to prepare taste masked ODT of drotaverine HCl using camphor and menthol as subliming agents with a disintegration time of less than 1 min with complete drug release in 30-60 min.

MATERIALS AND METHODS

Materials

Drotaverine HCl was gifted by Biocon Ltd, Avicel PH 101, sodium starch glycolate were gifted by Dr. Reddy's Labs. Camphor, Menthol, Croscarmellose sodium, PVP K-30, Mannitol, Talc and Magnesium stearate all are of analytical grade.

Selection and optimizing super disintegrant concentration

Drotaverine HCl tablets were prepared by wet granulation method using different superdisintegrants namely Avicel PH101, sodium starch glycolate and croscarmellose sodium and were evaluated for the selection and optimization of super disintegrant.

Preparation of granules with superdisintegrant

The required quantities of materials were weighed according to the formulae given in table 1. The materials are passed through sieve #40 (aperture 425 µm ASTM). Drug was geometrically mixed with other excipients except lubricants until a homogeneous blend was obtained. Granules were prepared by using 5% w/v solution of pvp k-30 in isopropyl alcohol as binder solution and the wet mass was passed through sieve #18 (aperture 1000 µm ASTM) and dried at 40 °C. The dried granules were sifted through sieve #30 (aperture 600 µm ASTM). The dried granules were blended with talc and magnesium stearate.

Preparation of granules with a sublimating agent

The granules with sublimating agents as per formulae shown in table 2 were prepared using the procedure described in the above section.

Evaluation of granules

The prepared granules were evaluated for flow properties like the angle of repose, compressibility index and Hausner's ratio.

Angle of repose

It was determined by the fixed funnel and free-standing cone method. A powder funnel in which the end of the stem is perpendicular to its axis of symmetry was fixed at a given height (h) above the graph paper placed on a flat horizontal surface. The material was carefully poured through the funnel until the apex of the conical pile just touched the tip of the funnel [13, 14]. The radius (r) of the base of the pile was determined and the tangent angle of repose (θ) was calculated using the Eq. 1.

$$Tan\theta = \frac{h}{r} \quad \text{..... Eq. 1}$$

Table 1: Formulae of drotaverine hydrochloride orally disintegrating tablets prepared using superdisintegrants

Formula	Drotaverine HCl	Avicel +PH 101	Sodium starch glycolate	Croscarmellose sodium	PVPk-30	Magnesium stearate	Talc	Mannitol	Total weight (mg)
DX1	40	2	-	-	5	1	1	51	100
DX2	40	3	-	-	5	1	1	50	100
DX3	40	4	-	-	5	1	1	49	100
DY1	40	-	2	-	5	1	1	51	100
DY2	40	-	3	-	5	1	1	50	100
DY3	40	-	4	-	5	1	1	49	100
DZ1	40	-	-	2	5	1	1	51	100
DZ2	40	-	-	3	5	1	1	50	100
DZ3	40	-	-	4	5	1	1	49	100

Table 2: Formulae of drotaverine HCl ODT prepared using sublimating agents

Formula	Drotaverine HCl	Croscarmellose sodium	Camphor	Menthol	PVP K-30	Magnesium stearate	Talc	Mannitol	Total weight (mg)
DC1	40	2	1	-	5	1	1	50	100
DC2	40	3	1	-	5	1	1	49	100
DC3	40	4	1	-	5	1	1	48	100
DC4	40	4	3	-	5	1	1	46	100
DC5	40	4	5	-	5	1	1	44	100
DM1	40	4	-	1	5	1	1	48	100
DM2	40	4	-	2	5	1	1	47	100
DM3	40	4	-	3	5	1	1	46	100
DM4	40	4	-	4	5	1	1	45	100
DM5	40	4	-	5	5	1	1	44	100
DM6	40	4	-	6	5	1	1	43	100
DCM1	40	4	5	3	5	1	1	41	100
DCM2	40	4	5	4	5	1	1	40	100
DCM3	40	4	5	5	5	1	1	39	100
DCM4	40	4	5	6	5	1	1	38	100

Carr's index

Powder/granules were accurately weighed, transferred into a 100 ml measuring cylinder and placed on to the tapped density tester and subjected to USP II method i.e., 250 drops per minute with a drop height of 3±0.3 mm for 250 tappings. Volume (V_t) of the powder was measured after 500 tapings. The tapping was repeated for additional 750 times and volume was noted as (V_b). If the difference between the two volumes is less than 2 % then V_t is the final tapped density else it is repeated for another 1250 taps [15, 16]. It is calculated by the Eq. 2.

$$\%\ CI = \frac{Tapped\ density - bulk\ density}{Tapped\ density} X100$$ ..... Eq. 2

Hausner ratio

Hausner ratio is related to inter particulate friction and as such, could be used to predict powder flow properties. The powder with low interparticle friction such as coarse spheres has ratios of approximately 1.2, whereas more cohesive, less free-flowing powders such as flakes have Hausner ratio greater than 1.6 [15, 16]. It is calculated by using the following formula Eq. 3.

$$Hausner\ ratio = \frac{\text{Tapped density}}{\text{Untapped density}}$$ ..... Eq. 3

Preparation of drotaverine HCl tablets

The dried granules were subjected to lubrication and the blend was compressed into tablets on Karnavati 12 station rotary tablet compression machine using 8 mm concave punches. Compressed tablets prepared with sublimating agents were subjected to sublimation at 40 °C for different time points i.e. 1 h, 3 h and 5 h in a hot air oven.

Evaluation of the tablets

The compressed tablets were evaluated for general appearance, hardness, thickness, uniformity of weight, friability, uniformity of content, *in vitro* disintegration test, fineness of dispersion, *in vitro* dispersion, wetting time, *in vitro* dissolution, *in vivo* disintegration, taste evaluation and drug excipients compatibility studies.

General appearance

Five tablets were selected randomly and evaluated for color and shape.

Hardness

The hardness of tablets is determined by using Monsanto hardness tester. It is expressed in $Kgcm^{-2}$(n = 5).

Thickness: Thickness is measured in mm using Vernier calipers and recorded (n=5).

Uniformity of weight

Twenty tablets were selected at random, weighed individually and average weight was calculated as per IP [12]. The mean and the standard deviation were determined.

Friability test

Friability test was carried out in Roche friabilator according to IP [13]. The percent loss in weight (F) was calculated by the Eq. 4. The limit for friability is less than 1%.

$$F = \left[1 - \frac{W}{W_o}\right] X\ 100$$ ..... Eq. 4

Uniformity of content

Ten tablets were taken randomly. All the tablets were crushed separately to a fine powder and each tablet analysed individually for drug content. Powder of each tablet was taken into a 100 ml volumetric flask. 50 ml of 0.1N HCl was added, shaken for 30 min and was made to volume with 0.1N HCl and filtered. 1 ml of the filtrate was taken into 10 ml volumetric flask and volume were made up to mark with 0.1N HCl. The absorbance was measured at 303 nm using UV spectrophotometer. Each tablet should contain not less than 85 % and not more than 115 % of the labelled claim [17].

***In vitro* disintegration test**

Simulated salivary fluid is prepared by dissolving 13.872 gm of potassium dihydrogen phosphate, 35.084 gm of disodium hydrogen phosphate in sufficient water and was made up to 1000 ml. Finally, the pH was adjusted to 6.8 with NaOH solution. The test was performed to ensure disintegration of tablets as per IP in the simulated salivary fluid at 37 °C. To be in compliance with the IP standards, dispersible tablets must disintegrate within 3 min [18].

***In vitro* dispersion time (with simulated salivary fluid)**

This test was performed to ensure disintegration of tablets in the salivary fluid, if it is to be used as an orodispersible tablet. *In vitro* dispersion time was measured by dropping a tablet in a measuring cylinder containing 6 ml of simulated salivary fluid of pH 6.8. Three tablets from each formulation were randomly selected and *in vitro* dispersion time was performed [19].

Wetting time

Wetting time corresponds to the time taken for the tablet to disintegrate when kept motionless on the tissue paper in a petri dish. This method will duplicate the *in vivo* disintegration, as the tablet is motionless on the tongue. Wetting time was measured by placing a tablet on a piece of tissue paper folded twice and was placed in a small petri dish containing 6 ml of simulated saliva pH 6.8, and the time for complete wetting was measured [20]. Five tablets from each batch were used.

***In vitro* dissolution studies**

The release of drotaverine HCl from prepared tablets was studied in 0.1N HCl by using USP Type II apparatus. 900 ml of 0.1N HCl solution was used as the dissolution medium for drug release studies. The paddle rotation was adjusted to 50 rpm and the bath temperature at 37±0.5 °C was maintained throughout the dissolution test. Aliquots of 5 ml of the dissolution medium were withdrawn at appropriate time intervals (5, 10, 15, 30, 45, 60, 90 and 120 min). The volume withdrawn at each time interval was replaced by the same quantity of the fresh dissolution medium maintained at 37±0.5 °C. The samples were suitably diluted with 0.1N HCl solution and analyzed at 303 nm using UV-visible spectrophotometer against the blank.

***In vivo* disintegration time and taste evaluation**

The study protocol was approved from Andhra University Institutional Ethics Committee vide approval No.53 dated 05.07.2012. For *in vivo* disintegration test, five healthy human volunteers were selected. Prior to the test, all the volunteers were asked to rinse their mouth with distilled water [21]. Each of the five subjects was given a tablet. The tablets were placed on the tongue immediately the time was recorded. It was expressed in seconds. The subjects were asked to spit out the content of the oral cavity after tablet disintegration and rinse their mouth with distilled water. The swallowing of the saliva was prohibited during the test and also saliva was rinsed from the mouth after each measurement. Three trials were performed with 2 d intervals between trials [22]. The test results were presented as the mean value.

Taste evaluation was done on five volunteers by using the time-intensity method. One tablet was held in mouth and bitterness levels were recorded instantly at 10 secs, 30 secs and 1 min the bitterness levels, grittiness and numbness levels are noted and recorded.

Drug-excipient compatibility studies

The optimized formulations were evaluated for drug excipient interaction studies via differential scanning calorimetry, X-Ray diffractometry and Fourier transformed infrared spectroscopy.

Differential scanning calorimetry

DSC was performed utilizing DSC Q20 Universal V4.5A TA Instruments. Samples were allowed to equilibrate for 1 min and then heated in an atmosphere of nitrogen over a temperature range from 0 to 300 °C. Thermograms were obtained by using TA Instruments universal analysis software 2000.

X-Ray diffractometry

The samples were recorded on X-Ray diffractometer (PW 1729, Philips, Amsterdam, Netherlands). XRD patterns were recorded using monochromatic CuKα radiation with Ni filter at a voltage of 40 kV and a current of 30 m A between 10 ° to 80 ° 2θ values. The data were processed with the software Diffrac Plus V1.01.

Fourier transformed infrared spectroscopy

FTIR spectra can be used to detect drug-excipient interactions by following the shift in vibrational or stretching bands of key functional groups. KBr pressed pellet technique was used in the preparation of pellet. The resultant pellet was kept in the IR chamber and the IR spectra of the mixtures were recorded on a Bruker FTIR spectrophotometer equipped with Opus software.

RESULTS AND DISCUSSION

The drotaverine HCl ODT was prepared and evaluated by using the different superdisintegrants namely Avicel PH101, sodium starch glycolate and croscarmellose sodium.

Evaluation of the granules

The prepared granules were evaluated for their flow characteristics using the angle of repose, Carr's Index and Hausner's ratio. Though the values obtained are close and all are well below the desirable limits indicate good granule characteristics for tablet compression. The formulation DZ3 with 4 % croscarmellose sodium with values of angle of repose 20.28 and Carr's index 7.6 has shown the lowest values among all the formulations. The values of angle of repose, Carr's index and Hausner's ratio of granules with sublimating agents are low indicating good flow characteristics. The results were mentioned in table 3 and 4.

Selection and optimization of the superdisintegrant

The superdisintegrants, viz., croscarmellose sodium, sodium starch glycolate and Avicel PH 101 were evaluated and concentration required in the formulations was optimized by trial and error method in which superdisintegrant concentration was varied from 2 to 4 % w/w of the total weight of the tablet. Tablets prepared with croscarmellose sodium at 4 % w/w shown least disintegration time. Hence 4 % w/w of croscarmellose sodium as the superdisintegrant was selected to further develop the formulations for taste masking. Further studies with superdisintegrant concentration above 4 % w/w were not considered necessary as the required lower disintegration time is attained. Further disintegration times may reduce with sublimating agents which form pores facilitating faster disintegration times. Increasing croscarmellose beyond 4 % may prolong disintegration times due to swelling nature of the polymer. The disintegration time values for different super-disintegrant concentrations are expressed in the table 5.

Table 3: Flow parameters for drotaverine HCl granules prepared using superdisintegrants

Formulation	Angle of repose (°)	Carr's index (%)	Hausner's ratio
DX1	22.35	9.99	1.09
DX2	20.36	8.33	1.10
DX3	22.96	7.60	1.13
DY1	21.57	14.2	1.08
DY2	24.14	11.5	1.10
DY3	22.58	10.7	1.11
DZ1	21.52	13.7	1.15
DZ2	21.43	11.5	1.12
DZ3	20.28	7.6	1.08

Table 4: Flow parameters for drotaverine HCl granules prepared using subliming agents

Formulation	Angle of repose (°)	Carr's index (%)	Hausner's ratio
DC1	21.52	8.33	1.08
DC2	20.35	7.4	1.12
DC3	22.96	9.09	1.09
DC4	21.57	14.2	1.08
DC5	23.15	11.5	1.10
DM1	23.15	10.7	1.12
DM2	20.28	13.7	1.15
DM3	21.43	11.5	1.13
DM4	22.35	7.6	1.08
DM5	20.46	9.09	1.10
DM6	23.33	8.33	1.09
DCM1	22.61	14.2	1.16
DCM2	23.45	11.5	1.13
DCM3	21.73	7.6	1.08
DCM4	20.76	10.7	1.12

Table 5: Effect of superdisintegrant concentration on the disintegration of the tablet

Superdisintegrant*	Disintegration time (secs)		
	Croscarmellose sodium	Sodium starch glycolate	Avicel PH 101
2	65	80	90
3	39	62	76
4	19	45	30

*Percent weight based on total tablet weight

Evaluation of the tablets

The tablets prepared with different superdisintegrants were evaluated for hardness, frialbility, weight variation, thickness and *in vitro* disintegration time only. However all the prepared tablets with sublimating agents were evaluated for the general properties like appearance, thickness, hardness, friability, uniformity of weight, uniformity of content, *in vitro* disintegration, *in vitro* dispersion, uniformity of dispersion, wetting time, *in vitro* dissolution and *in vivo* disintegration and taste evaluation. The results were tabulated in table 6, 7 and 9.

The average hardness of all the tablets prepared was in the range of 2-3 Kg/cm^2. The thickness of the tablets was in the range of 3.10 to 3.14 mm. All the prepared tablets passed the weight variation test, as the % weight variation was within the pharmacopoeial limits i.e.±7.5 %. The percentage friability of the tablets prepared using superdisintegrant are shown in table 6 and that of sublimating agents are shown table 7. All the tablets showed values around 0.5 %. The values are less than 1 % in all the tablets ensuring that the tablets were mechanically stable.

***In vitro* disintegration time**

All the tablets prepared for evaluation of superdisintegrant disintegrated within 90 secs. The lowest disintegration time of 19 secs is noticed with formulation DZ3 having 4 % croscarmellose sodium. The results are shown in table 6. The results of *in vitro* disintegration test for tablets with sublimating agents varied between 4 and 10 secs indicate the tablets passing the compendial limit of 3 min for dispersible tablets and the results indicated in table 7. The disintegration time of the tablets from batch DC5 (camphor formulation) is 6 secs. DM6 (menthol formulations) showed the disintegration time of 4 secs. DCM2 (camphor+menthol) showed the disintegration time of 4 secs. The formula with camphor and menthol combined as sublimating agents showed the least disintegration time indicating that they were suitable as orodispersible tablets.

Uniformity of content

The results of drug content uniformity are given in table 7. The percentage drug content present in all the batches were about 98–99 %. The result indicated very less deviation in drug content indicating the uniform mixing of the drug in the granulation during tablet preparation.

Fineness of dispersion

All the tablets prepared formed a uniform dispersion and passed through sieve #22 thereby meeting the compendial requirement.

***In vitro* dispersion time**

The dispersion time of all the tablets prepared were 5 to 9 secs with camphor, 4 to 9 secs with menthol and 3 to 9 secs with camphor and menthol combination. Tablets prepared with a combination of menthol and camphor has shown faster dispersion and the values of *in vitro* dispersion time are given in table 7.

Wetting time

The wetting time values are in close range and however, the values varied from lowest of 3.7 secs with a DCM4 formulation to the highest 9.6 secs for DM1. The values of the wetting time were given in table 7.

Table 6: Tabletting properties of drotaverine HCl ODT (superdisintegrant evaluation)

Formulation code	Hardness (Kg/cm^2)	Friability (%)	Weight variation[a] (mg)	Tablet thickness[b] mm	*In vitro* disintegration time[c]
DX1	2-3	0.52	101±1.45	3.10±1.02	90±0.90
DX2	2-3	0.50	100.5±1.20	3.12±1.22	76±1.00
DX3	2-3	0.48	97.5±1.35	3.14±1.10	30±1.32
DY1	2-3	0.47	104±1.60	3.12±1.14	80±0.80
DY2	2-3	0.46	101.5±1.20	3.10±1.12	62±0.10
DY3	2-3	0.36	101±1.45	3.14±1.24	45±1.26
DZ1	2-3	0.21	98.6±1.55	3.12±1.24	65±1.29
DZ2	2-3	0.25	100.4±1.64	3.10±1.16	39±1.43
DZ3	2-3	0.33	101±1.53	3.10±1.18	19±1.36

a =mean±percent deviation (n=20); b=mean±SD (n=5); c= mean±SD (n=6)

Optimization of the sublimation time of exposure

After finalizing the superdisintegrant, further tablets were made with sublimating agents, viz., camphor, menthol and combination of both camphor and menthol. The prepared granules were evaluated for their flow characteristics and values are given in table 4. Further, the tablets prepared with sublimating agents were evaluated for all the tabletting parameters and for taste and *in vivo* disintegration studies were given in table 7.

The time of exposure at which the tablets subjected to sublimation was optimized by exposing the tablets to 40 °C for 1 h, 3 h and 5 h. The tablets were further subjected to *in vitro* disintegration test. The tablets that were subjected to 5 h of sublimation showed least disintegration time. The details are shown in table 8.

***In vitro* dissolution studies**

The drug dissolution data of the tablets prepared by using camphor, menthol and combination of camphor and menthol are given in the table 9 to 11. The corresponding dissolution profiles of all the prepared tablets are shown in the fig. 1 to 3. The dissolution profile of the batch DC5 (camphor formulations) showed 102 % drug release in 10 min. DM6 of the menthol formulation showed 102.7 % release of the drug in 5 min. DCM2 of the combination formulations (camphor+menthol) showed drug release of 100.16% in 5 min.

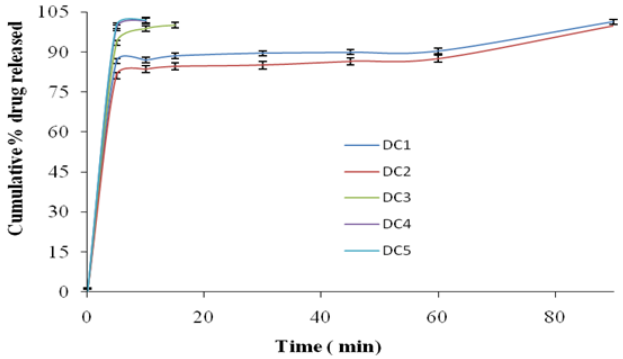


Fig. 1: Dissolution profile of the formulations DC1 to DC5 prepared using camphor

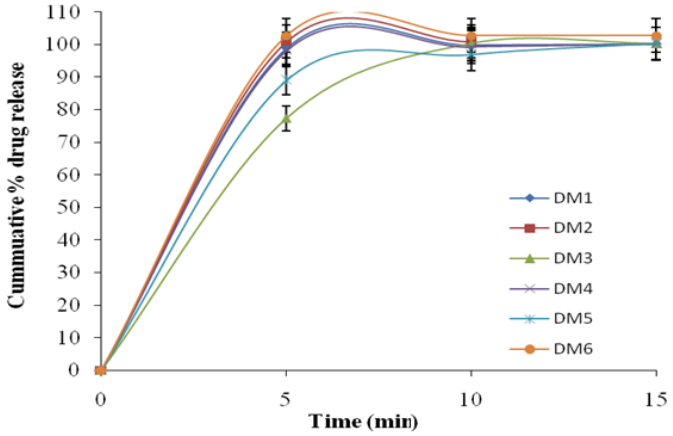


Fig. 2: Dissolution profile of the formulations DM1 to DM6 prepared using menthol

Table 7: Tabletting properties of drotaverine HCl ODT

Formulation code	Hardness (Kg/cm²)	Thickness (mm)	Friability (%)	Uniformity of weight[a] (mg)	Uniformity of content[b] (%)	*In vitro* disintegration time[c] (Sec)	*In vitro* dispersion time (Sec)	*In vivo* disintegration time (Sec)	Wetting time (Sec)	Uniformity of dispersion
DC1	2.3	3.08±1.02	0.52	101±1.45	99.25±1.22	8.61±0.90	9±1.20	9.00±1.23	8.75±0.67	Pass
DC2	2.3	3.10±1.22	0.50	100.5±1.20	99.78±1.34	8.66±1.00	10±0.90	10.12±1.05	9.23±1.34	Pass
DC3	2.6	3.12±1.10	0.48	97.5±1.35	99.23±1.45	6.84±1.32	7±1.23	7.20±0.61	6.42±0.86	Pass
DC4	2.6	3.10±1.14	0.47	104±1.60	99.65±1.23	6.3±0.80	6±1.35	6.50±1.35	6.24±0.88	Pass
DC5	2.6	3.12±1.12	0.46	101.5±1.20	99.84±1.04	5.6±0.10	5±1.15	4.90±0.92	4.75±1.44	Pass
DM1	2.2	3.12±1.24	0.36	101±1.45	99.45±1.20	9.6±1.26	9±1.32	10.3±1.28	9.6±1.23	Pass
DM2	2.2	3.12±1.24	0.21	98.6±1.55	99.24±1.43	8.6±1.29	8±1.06	9.5±1.27	8.7±1.41	Pass
DM3	2.5	3.10±1.16	0.25	100.4±1.64	99.31±1.35	6.7±1.43	7±1.03	7.7±1.32	6.9±0.94	Pass
DM4	2.4	3.10±1.18	0.33	101±1.53	99.14±1.13	5.2±1.36	7±1.22	6.7±1.41	6.8±0.64	Pass
DM5	2.6	3.12±1.24	0.28	99.85±1.44	99.48±1.24	4.5±1.55	6±1.29	5.9±1.08	5.6±1.29	Pass
DM6	2.8	3.10±1.16	0.46	99.45±1.23	99.43±1.32	4.2±1.56	4±1.35	4.0±1.21	4.6±1.31	Pass
DCM1	2.5	3.14±1.18	0.36	99.5±1.43	99.59±0.96	8.7±1.52	8±1.03	7.7±1.32	8.2±1.23	Pass
DCM2	2.3	3.12±1.24	0.21	100.2±1.47	99.66±0.76	3.5±1.49	6±1.22	6.7±1.41	7.0±1.41	Pass
DCM3	2.4	3.10±1.16	0.25	98.8±1.38	99.74±0.65	4.2±1.32	5±1.29	4.9±1.08	5.3±0.94	Pass
DCM4	2.6	3.10±1.18	0.33	101±1.40	99.83±0.88	4±1.26	4±1.35	4.4±1.21	3.7±0.64	Pass

a =mean±percent deviation (n=20); b=mean±s. d (n=10); c= means±s. d (n=6)

Table 8: Effect of sublimation time of exposure on disintegration time of the tablet

Superdisintegrant*	Disintegration time (secs)			
	Before sublimation	Sublimation time		
		1 h	3 h	5 h
2	65	62	53	35
3	39	35	27	18.5
4	19	17	12	6.3

*Percent weight based on total tablet weight

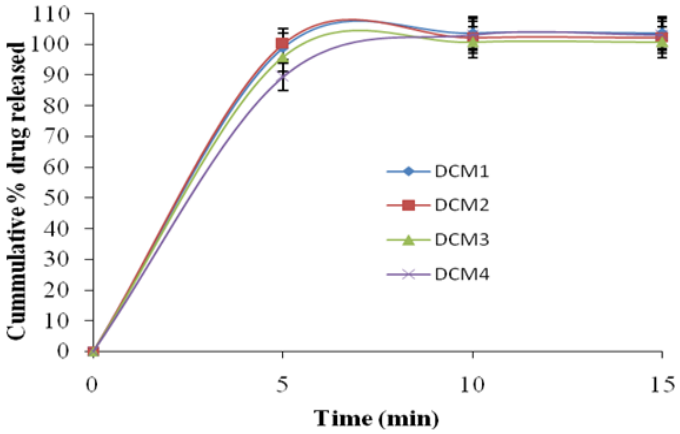


Fig. 3: Dissolution profile of the formulations DCM1 to DCM4 tablet prepared using camphor and menthol

***In vivo* disintegration and taste evaluation**

The values of the *in vivo* disintegration times are given in table 12. Though the differences are not much all the tablets have shown faster disintegration time. The human volunteers were asked to evaluate the taste and mouthfeel on a scale of 0–4 and the results are shown in table 12.

It was observed that 3/5 volunteers reported threshold bitterness and 2/5 reported very slight bitterness with DC5 of the camphor formulation. And 4/5 volunteers reported smooth and pleasant mouthfeel and 1/5 reported gritty and pleasant feel with DC5 over other formulations. Hence, it showed better taste masking in formulations made with camphor. But, numbness of the tongue and bitterness was still persisted.

Among the formulations made with menthol, 2/5 volunteers reported no bitterness and 3/5 reported threshold bitterness and 4/5 reported smooth and pleasant mouthfeel and 1/5 reported gritty and pleasant feel with DM6. Hence, DM6 has better taste masking among formulations made with menthol. Bitterness was not felt but numbness still existed.

Out of the combination formulations, with DCM2, 4/5 volunteers reported no bitterness and 1/5 reported threshold bitterness. 3/5 reported smooth and pleasant mouthfeel and 2/5 reported gritty and pleasant mouthfeel. DCM2 showed the best taste masking with no bitterness or numbness observed until 1 minute. of all the optimized formulations, i.e., DC5, DM6 and DCM2, the formulation DCM2 prepared using a combination of camphor and menthol as sublimating agents showed the best taste masking.

By considering all the parameters like hardness, *in vitro* disintegration time, *in vivo* disintegration time, wetting time, dispersion time, and dissolution profile of all the tablets prepared, the batch DCM2 prepared using a combination of the sublimating agents i.e. camphor and menthol can be considered for optimization.

Table 9: Cumulative percent drug released vs. time form drotaverine HCl ODT using camphor (mean±SD, n=3)

Time (min)	Cumulative % drug released				
	DC1	DC2	DC3	DC4	DC5
5	86.58±1.56	81.2±1.22	93.42±0.63	99.00±0.53	99.78±1.14
10	87.07±1.19	83.64±1.15	98.80±1.51	101.7±1.51	102.0±1.23
15	88.53±1.37	84.62±1.44	100.1±1.22		
30	89.51±1.24	85.11±1.18			
45	90.00±1.42	86.58±1.22			
60	90.49±1.32	87.55±1.09			
90	101.3±1.41	99.83±1.53			

Table 10: Cumulative percent drug released vs. time form drotaverine HCl ODT using menthol (mean±SD, n=3)

Time (min)	Cumulative % drug released					
	DM1	DM2	DM3	DM4	DM5	DM6
5	98.9±1.24	98. 8±1.53	77.28±0.98	98.1±1.11	89.02±1.36	102.7±1.54
10	99.8±1.31	100.8±1.66	100.2±1.14	99.2±1.21	96.85±1.11	102.7±1.44
15	100.1±1.23	100.8±1.58	100.2±1.27	100.12±1.05	100.3±1.21	102.7±1.06

Table 11: Cumulative percent drug released vs. time form drotaverine HCl ODT using a combination of camphor and menthol (mean±SD, n=3)

Time (min)	Cumulative % drug released			
	DCM1	DCM2	DCM3	DCM4
5	98.8±0.21	100.2±1.15	95.87±1.02	89.51±1.32
10	103.7±1.14	102.3±0.92	100.7±1.24	103.2±1.25
15	103.7±0.94	102.3±0.94	100.7±1.16	103.2±1.38

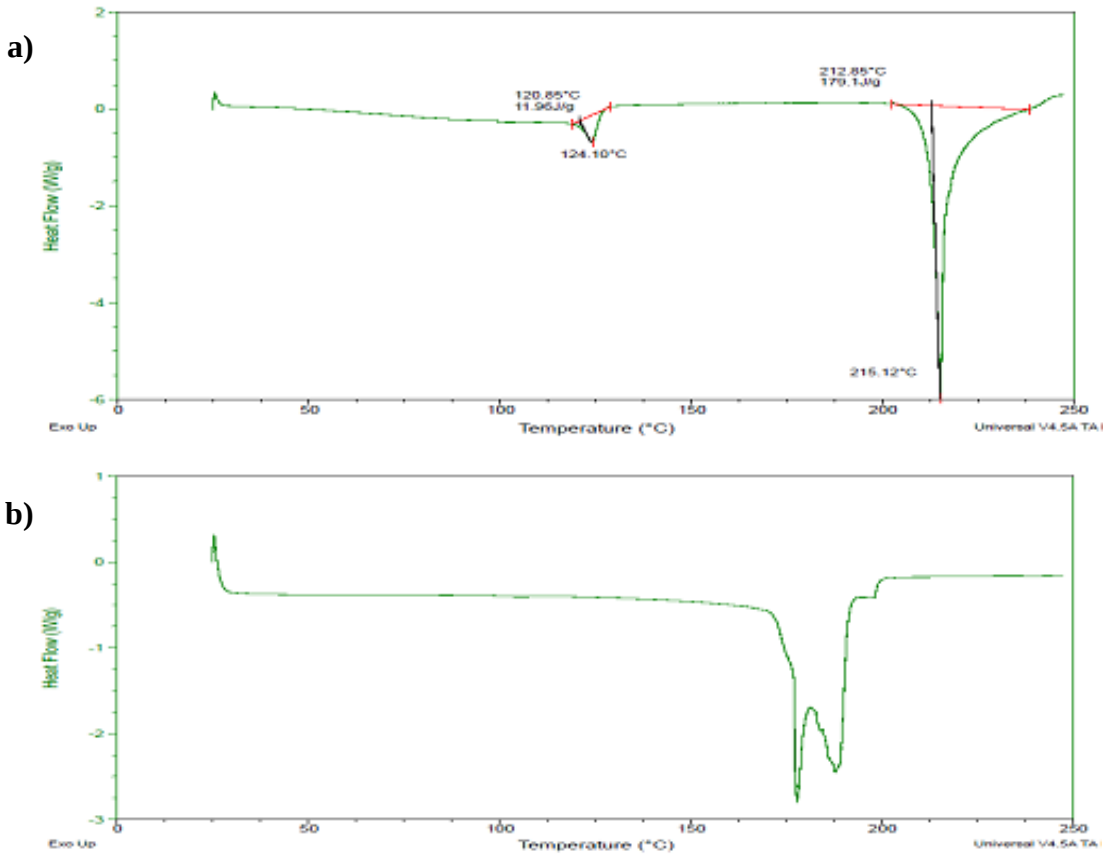
Table 12: Taste evaluation and mouthfeel of Drotaverine HCl ODT in human volunteers

Camphor as sublimating agent										
Volunteers	**DC1**		**DC2**		**DC3**		**DC4**		**DC5**	
	T	**M**	**T**	**M**	**T**	**M**	**T**	**M**	**T**	**M**
I	3	-	3	+	2	+	2	+	1	+
II	2	-	3	+	3	-	2	+	2	+
III	3	+	2	-	3	-	3	-	2	+
IV	3	+	3	-	3	+	2	-	1	-
V	2	-	2	-	2	+	3	+	1	+

Menthol as sublimating agent												
Volunteers	**DM1**		**DM2**		**DM3**		**DM4**		**DM5**		**DM6**	
	T	**M**	**T**	**M**	**T**	**M**	**T**	**M**	**T**	**M**	**T**	**M**
I	3	-	3	-	3	+	3	+	2	+	1	+
II	2	-	3	+	2	+	2	+	2	+	0	+
III	3	+	3	+	2	+	2	-	3	+	1	+
IV	3	-	2	-	3	-	3	+	1	+	1	-
V	2	+	2	-	2	-	1	-	1	-	0	+

Camphor+menthol as sublimating agents								
Volunteers	**DCM1**		**DCM2**		**DCM3**		**DCM4**	
	T	**M**	**T**	**M**	**T**	**M**	**T**	**M**
I	2	+	1	+	1	+	1	+
II	2	-	0	+	1	+	2	+
III	1	-	0	-	2	-	2	+
IV	2	+	0	+	2	+	2	-
V	2	+	0	+	0	-	0	+

0 = No bitterness
1 = Threshold bitterness
2 = Very slight bitterness
3 = Slight bitterness
4 = strong bitterness
+= Smooth and pleasant feel
-= Gritty and pleasant feel
--= Gritty and unpleasant feel



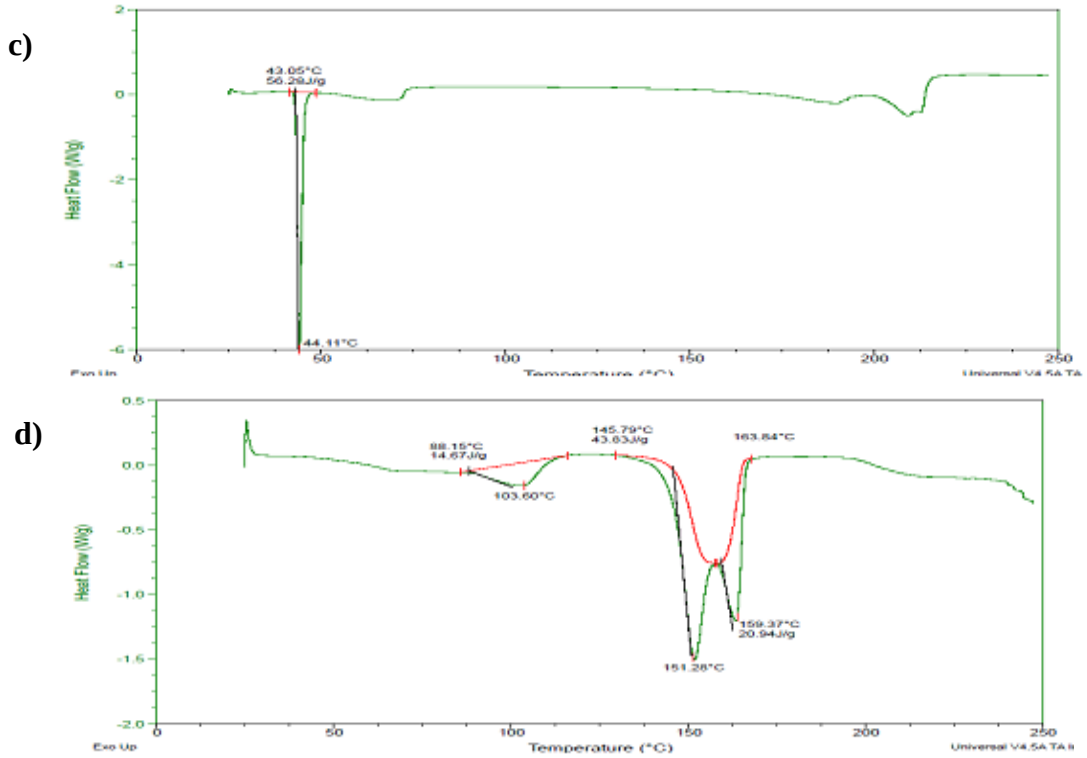


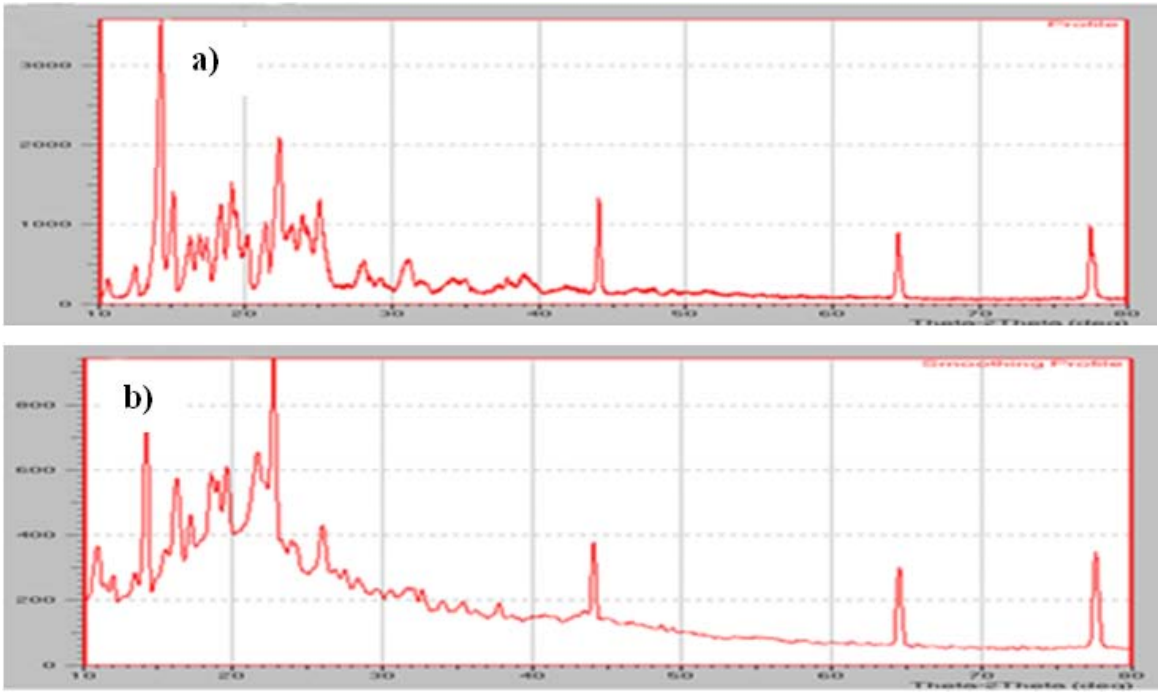
Fig. 4: DSC thermograms a) Drotaverine HCl, b) Camphor, c) Menthol and d) optimized formulation of a combination of camphor and menthol DCM2

Drug-excipient compatibility studies

DSC analysis: The DSC thermograms of pure drug, sublimating agents camphor and menthol used in the study and DCM2 optimized formulation are shown in fig. 4. The DSC thermogram of pure drotaverine HCl exhibited a sharp endothermic peak at 215.12 °C corresponding to its melting point, indicating its crystalline nature. Camphor showed an endothermic melting peak at 177 °C and Menthol at 44.1 °C.

XRD analysis

The X-ray diffractograms of pure drug Drotaverine HCl, camphor, menthol and DCM2 formulation are shown in fig. 5. The diffractogram of Drotaverine HCl showed characteristic sharp intensity diffraction peaks at 2θ values of 14.5°, 22°, 44°, 65° and 77°, which reflected the crystalline nature of the drug. The optimized formulation (DCM2), showed diffraction peaks at respective 2θ values of pure drotaverine HCl although their relative intensities were reduced, suggesting a reduced degree of crystallinity of drug in these formulations.



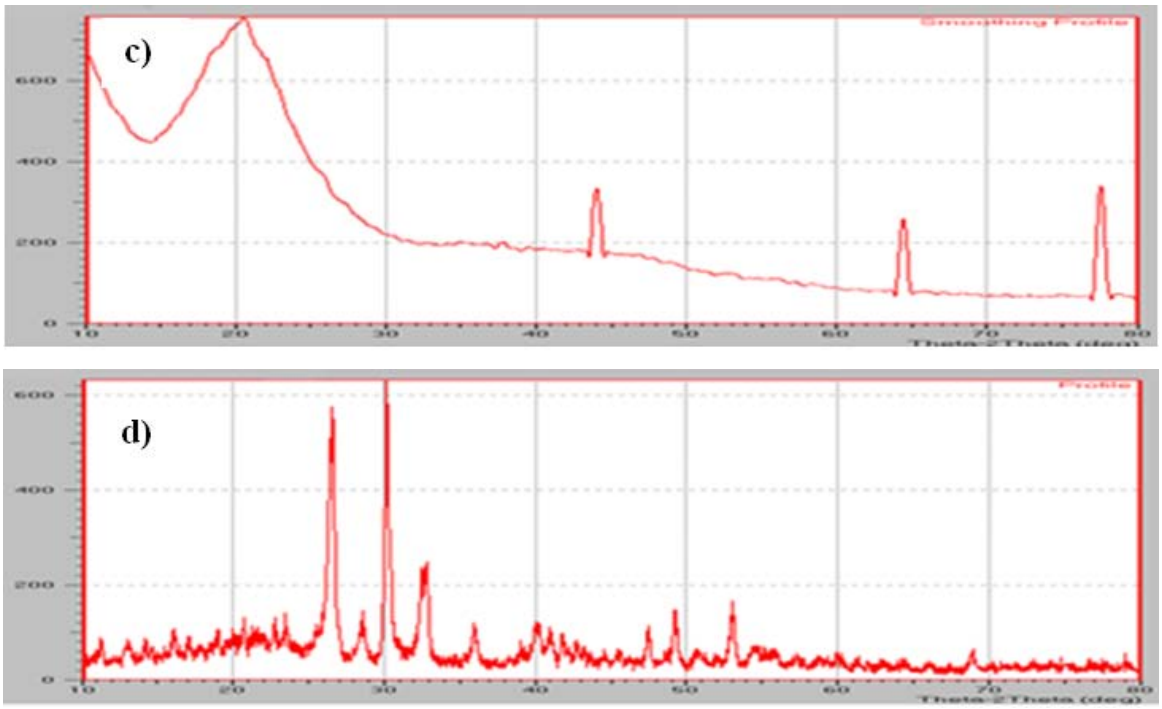
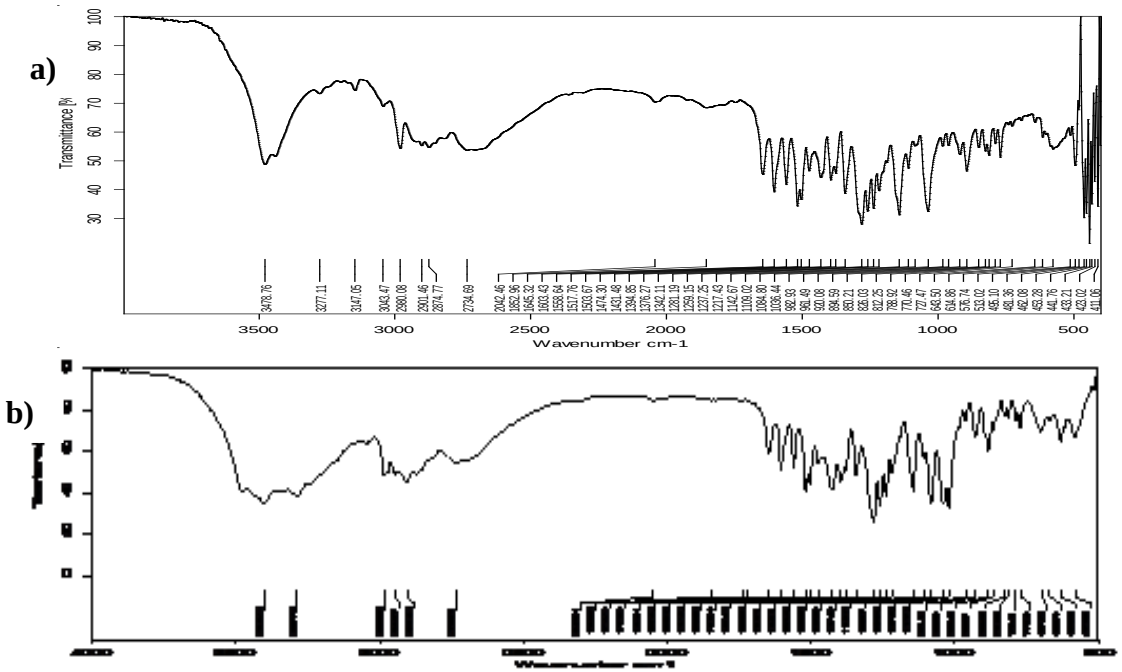


Fig. 5: X-ray diffractograms a) Drotaverine HCl, b) Camphor, c) Menthol and d) optimized formulation of a combination of camphor and menthol DCM2

Fourier transform infrared spectroscopy

FTIR analysis for the pure drug, sublimating agents and formulation DCM2 were performed and FTIR spectra are shown in fig. 3.6 and the tab optimized formulations viz., with camphor DC5, with menthol DM6 and with camphor and menthol DCM2 were subjected to FTIR studies for drug excipient incompatibility studies. Theoretically drotaverine HCl will give principal peaks for N-H secondary amine (3500-3300 cm-¹), for aromatic C=C stretching (1600-1475 cm-¹), for C-H stretching (3000-2840 cm-¹), for C-O stretching (1260-1000 cm-¹) and N-H bending (1650-1580 cm-¹). The major peaks for pure drug were 3478.19, 2979.95, 2874.45, 2670.34, 1902.93, 1666.00, 1647.39, 1603.29, 1560.22, 1517.94, 1503.87, 1476.76, 1432.20, 1401.87, 1395.04 and 1237.10 cm-¹which are well in support to the theoretical prediction.

The drug solid dispersion combination did not produce a major shift in principal peaks of drotaverine HCl, indicating no interaction due to the presence of excipients. Hence, all the optimized formulations are compatible. Thus, FTIR spectral analysis proved the compatibility between drug and excipients. The FTIR spectra of pure drug and its combinations are presented in fig. 3.6.



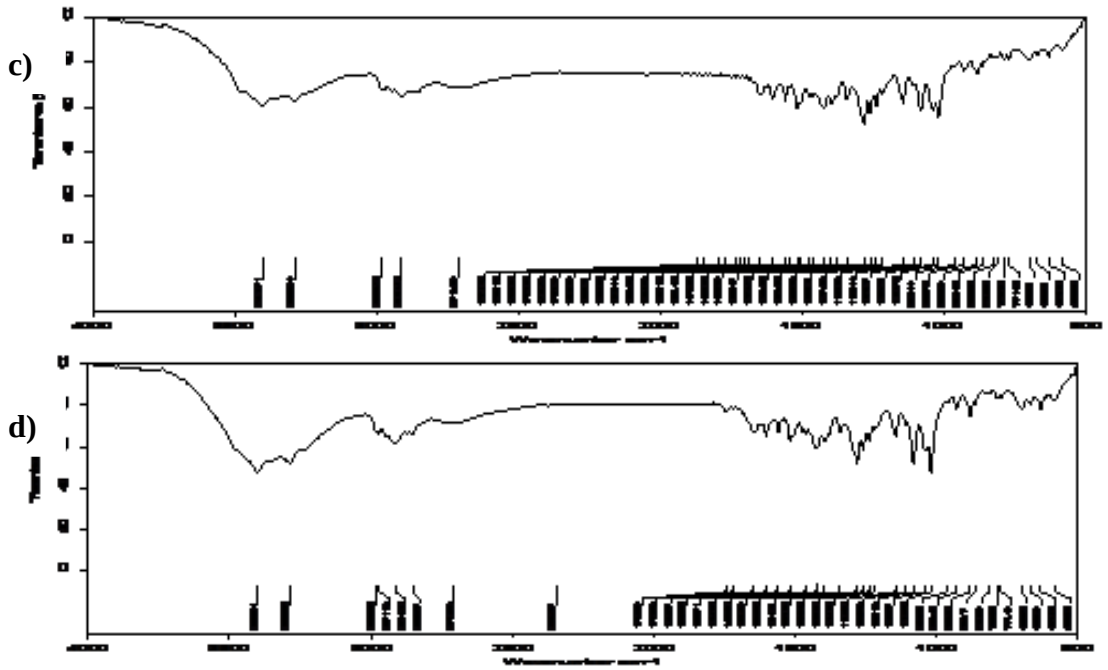


Fig. 6: FTIR spectra a) Drotaverine HCl, optimized formulations of b) Camphor (DC5), c) Menthol (DM6) and d) Combination of camphor and menthol (DCM2)

CONCLUSION

Drotaverine HCl tablets were prepared using the optimized superdisintegrant concentration with different ratios of drug-subliming agent i.e. camphor or menthol or combination of both. The prepared tablets were exposed for different sublimation times keeping the exposure temperature constant at 40 °C. The sublimation evaluated at different temperatures, but at a higher temperature, the integrity of the tablet is lost due to friability. The sublimed tablets were evaluated for taste masking in healthy human volunteers and only those tablets which complied with the taste were further evaluated for the remaining tabletting parameters. All the evaluated tablets complied with the tabletting parameters and the majority of the formulations released the drug within 15 min. Among all the formulations, formulation DCM2 prepared with a mixture of camphor and menthol was optimized for better taste masking and complete drug release with good oral disintegration.

AUTHORS CONTRIBUTIONS

Dr. K. Hari, performed experiments, interpreted data, wrote the manuscript and acted as the corresponding author. Dr. S. Rajeswari has helped in the development of work and manuscript preparation. And Prof. K. V. Ramana Murthy had supervised the study and helped to evaluate and edit the manuscript.

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CONFLICT OF INTERESTS

We declare that we have no conflict of interest.

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