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Preparation and evaluation of drotaverine hydrochloride orally disintegrating tablets using melt granulation

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ABSTRACT

The objective of the present study is to formulate and evaluate orally disintegrating taste masked drotaverine hydrochloride (HCl) tablets prepared by the melt granulation technique. Taste-masked drug—polymer melt granules of drotaverine HCl were prepared by using either compritol 888 ATO (compritol) or precirol ATO 5 (precirol) using varying drug-polymer ratios of 1:1, 1:2, 1:5, and 1:7. Prepared drug-polymer blends were evaluated for taste masking and the ratio of drug-polymer is optimized. The drug-polymer ratios 1:7 with compritol and 1:5 with precirol were optimized based on taste evaluation. The granules and tablets prepared with optimized drug-polymer ratio were evaluated for pre- and post-compression parameters. From all the prepared taste masked drotaverine HCl tablets, formulations CP9 and PF5 were optimized based on taste, mouthfeel, dissolution, and other oral disintegrating tablet (ODT) parameters. Formulations CP9 and PF5 showed the release of >50% drug in 5 minutes and 100% of the drug in 45 and 30 minutes, respectively. The optimized formulations were characterized by Fourier transformed infrared spectroscopy, differential scanning calorimetry, and XRD studies and found no incompatibility. The results demonstrated that the prepared drotaverine HCl ODT showed better taste masking meeting the parameters of ODT formulations PF5 > CP9. The present melt granulation technique can be effectively used for taste masking.

INTRODUCTION

Drotaverine HCl is a benzyl isoquinoline 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 an oral disintegrating tablet (ODT) 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; hence, taste masking is necessary for ODT. In the case of drotaverine HCl, simple technology of ODT is not suitable and technologies that are suitable for improving both taste and disintegration rate are necessary. Earlier workers reported on taste masking of drotaverine HCl by using approaches like solid dispersion, drug coating, complexation with polymers, and coprocessing with superdisintegrants (Anusha *et al*., 2013; Pandey *et al*., 2012; Srikanth *et al*., 2010; Ujwala *et al*., 2014). Though these techniques could effectively mask the bitter taste of the drug, its solubility and bioavailability are not improved significantly. There are no reports cited earlier for the applicability of ODT technology for drotaverine HCl. The applicability of techniques like sublimation and solid mixtures was tried for drugs like fisinopril, fenofibrate, levocetirizine dihydrochlorie, and itraconzole in the design of ODT (Ashwini *et al*., 2008; Raghavendra *et al*., 2012;

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Ravi Kumar *et al*., 2009; Uddhav *et al*., 2010). Melt granulation technique was applied in the preparation of lamotrigine using precirol ATO 5 (Pankaj *et al*., 2010). Earlier workers used polymers like Eudragit E100 and hydroxypropyl cellulose for the preparation of taste masked granules. Hence, in the present investigation, it is proposed to prepare taste-masked ODT of drotaverine HCl using the melt granulation technique using compritol and precirol as melt granulating polymers with a disintegration time of less than 1 minute with complete drug release in 30–60 minutes.

MATERIALS AND METHODS

Materials

Drotaverine HCl was gifted by Biocon Ltd, compritol and precirol were gifted by Gattefosse. Croscarmellose sodium, crospovidone, mannitol, aspartame, microcrystalline cellulose, sodium starch glycolate, and magnesium stearate all are of analytical grade.

Preparation of taste masked drug-polymer melt granules

Taste masked melt granulations of drotaverine HCl were prepared by using either compritol or precirol using varying drug-polymer ratios of 1:1, 1:2, 1:5, and 1:7. Drug and polymer were passed through sieve #40. Compritol was melted at about 65°C and precirol at about 52°C in a porcelain dish on a hot water bath with continuous stirring. The drug was added to the molten polymer and mixed uniformly. The molten mass was allowed to cool slowly with continuous mixing. After solidification, the drug-polymer agglomerates were triturated and passed through sieve #30 to obtain the granules. As there is no reported work on drotaverine HCl ODT, we adopted our own methodology in the design of ODT from the literature survey and not used any statistical method.

Evaluation of the drug-polymer blend for taste masking

The drug-polymer granules prepared by hot melt method were subjected to evaluation of masking of bitterness. The study protocol was approved from Andhra University Institutional Ethics Committee vide approval No. 53 dated July 5, 2012. 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 seconds, 30 seconds, and 1 minute and the bitterness levels, grittiness, and numbness levels are noted and recorded (Uchida *et al*., 2002).

For *in vivo* disintegration test for tablets, five healthy human volunteers were selected. Prior to the test, all the volunteers were asked to rinse their mouth with distilled water. Each of the five subjects was given a tablet. The tablets were placed on the tongue and immediately the time was recorded. It was expressed in seconds. They were allowed to move the tablet against the upper palate of the mouth with their tongue and to cause a gentle tumbling action on the tablet without biting on it or tumbling it from side to side. Immediately after the last noticeable mass had disintegrated, the time was recorded. 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-day interval between trials. The test results were presented as the mean value.

Preparation of drotaverine HCl ODT

Drotaverine HCl ODT was prepared from the optimized drug-polymer melt granules. Each time 150 tablets were prepared using melt granules equivalent to a dose of 40 mg of drotaverine HCl. The formulae are shown in Tables 1 and 2. The other ingredients were passed through sieve #40. The ingredients were mixed in geometric progression. The blend was compressed on Karnavati 12 station rotary tablet compression machine using 10 mm concave punches.

Evaluation of granules

The prepared granules were evaluated for flow properties like the angle of repose, compressibility index, and Hausner's ratio (Craick, 1958; Tran, 1957; USP, 2007). The relationship between the flow behavior and these parameters are shown in Table 3.

Evaluation of the tablets

All tablets were evaluated for general appearance, hardness, thickness, uniformity of weight, uniformity of content, friability, fineness of dispersion, *in vitro* disintegration test, *in vitro* dispersion, wetting time, *in vitro* dissolution, *in vivo* disintegration, taste evaluation, and drug excipients compatibility studies (Abdelbary *et al*., 2005; Bi *et al*., 1999; Craick, 1958; IP, 2010; Sivaprasad *et al*., 2011; Subrahmanian *et al*., 2010).

Table 1. Formulae of drotaverine HCl ODT prepared with melt granules of drotaverine HCl-compritol (1:7) melt granules.

Ingredients (mg)	CP1	CP2	CP3	CP4	CP5	CP6	CP7	CP8	CP9	CP10	CP11
Melt granules equivalent to drotaverine HCl 40 mg	320	320	320	320	320	320	320	320	320	320	320
Mannitol	-	-	-	-	-	16	32	32	32	32	32
Microcrystalline cellulose	-	-	-	16	32	-	-	-	-	-	-
Crospovidone	-	16	32	32	32	32	32	-	-	-	-
Croscarmellose sodium	-	-	-	-	-	-	-	16	32	-	-
Sodium starch glycolate	-	-	-	-	-	-	-	-	-	16	32
Aspartame	13	13	13	13	13	13	13	13	13	13	13
Magnesium stearate	3	3	3	4	4	4	4	4	4	4	4
Total weight (mg)	336	352	368	385	401	385	401	385	401	385	401

Table 2. Formulae of drotaverine HCl ODT prepared with melt granules of drotaverine HCl-precirol (1:5) melt granules.

Ingredients (mg)	PF1	PF2	PF3	PF4	PF5	PF6
Melt granules equivalent to Drotaverine HCl 40 mg	240	240	240	240	240	240
Croscarmellose sodium	12	18	24	18	18	18
Mannitol	-	-	-	12	24	36
Aspartame	10	10	10	10	10	10
Magnesium stearate	3	3	3	3	3	3
Total weight (mg)	265	271	277	283	295	307

Drug-excipient compatibility studies

The optimized formulations were evaluated for drug excipient interaction studies via differential scanning calorimetry (DSC), X-ray diffractometry (XRD), and Fourier transformed infrared spectroscopy (FTIR).

Differential scanning calorimetry

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

X-ray diffractometry

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

Fourier transformed infrared spectroscopy

FTIR spectra 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

Preparation of drotaverine HCl ODT was attempted first with taste masking of the drug and then formulating it for disintegrating tablets. Taste masking of drotaverine HCl was carried out either with compritol or precirol by melt granulation.

In the present investigation, drug-polymer mixture was evaluated for taste masking and the optimized ratio was used for the preparation of ODT by direct compression.

Optimization of the drug-polymer ratio for taste masking

The ratio of drug-polymer was optimized by the taste evaluation by human volunteers for the bitterness of the prepared granules. The results are shown in Table 3.

Bitterness of the drug was effectively masked as per the bitterness scale by the melt granules prepared with 1:7 ratio of compritol and 1:5 ratio of precirol. Hence, they were considered as best among the prepared melt granules. These ratios were selected for the preparation of ODT of drotaverine HCl by using different superdisintegrants and diluents.

Table 3. Bitterness evaluation of melt granules of drotaverine HCl.

Volunteers	Drug-Compritol ratio				Drug-Precirol ratio			
	1:1	1:2	1:5	1:7	1:1	1:2	1:5	1:7
I	1	2	0	0	2	2	0	1
II	2	1	1	1	1	2	1	0
III	3	1	0	0	3	2	0	1
IV	1	3	1	0	1	1	0	0
V	2	2	1	0	1	2	0	2
VI	1	1	0	1	2	3	0	1

0 = no bitterness; 1 = threshold bitterness; 2 = very slight bitterness; 3 = slight bitterness.

Evaluation of flow properties

The flow properties of the prepared agglomerates were evaluated using the parameters like angle of repose, compressibility index, and Hausner's ratio for their suitability for direct compression. The angle of repose observed was found to be 20.56° lowest for CP1 and 24.5° highest for CP7 and PF6. The observed values for the angle of repose are lower than 25° indicating good flow characteristics. The values of compressibility index for all varied between 10.44% and 15.09%. The observed values are either lower or very near to 15% indicate good flow characteristics of the granules. As per standard, values of Hausner's ratio observed were between 1.0 and 1.12 and are below 1.14 indicating good flow properties.

Evaluation of the prepared tablets

The prepared tablets were evaluated for general appearance, hardness, thickness, uniformity of weight, friability, *in vitro* disintegration time, uniformity of content, fineness of dispersion, *in vitro* dispersion time, wetting time, *in vitro* dissolution and *in vivo* disintegration time, and taste evaluation and results are tabulated in Tables 4 and 5. The tablets were pale yellow in color.

The average hardness of the all the tablets prepared by using compritol and precirol were in the range of 3–4 kg/cm^2. This ensures good handling characteristics of the formulations. The tablet thickness was found to be in the range of 4.12–4.34 mm. All the prepared tablets passed weight variation test, as percent weight variation was within the pharmacopoeia limits i.e., ±5%.

In line with the IP limits for the disintegration of dispersible tablets, orodispersible tablets must disintegrate within 3 minutes, i.e., 180 seconds. The prepared tablets with melt granules of compritol showed the disintegration time in the range of 49–345 seconds and melt granules precirol in the range of 32–78 seconds. Tablets CP1, CP2, and CP3 failed to pass the test. The remaining tablets confirmed to the norms of ODT, i.e., disintegrated in less than 3 minutes.

All the tablets showed values less than 0.5%. The percentage friability was less than 1% in all the formulations, ensuring that the tablets were mechanically stable. The percentage drug content present in all the batches prepared was found to be in the range of 99%–100%. The percentage deviation observed between the individual tablets was found to be less than 2% indicating the uniform mixing of the drug with polymer during the preparation of melt granules.

The formulations CP1, CP2, and CP3 were not subjected to this test as they failed to confirm the *in vitro* disintegration time

Table 4. Tabletting parameters of ODT prepared with drotaverine HCl-compritol melt granulation.

Formulation	Hardness (kg/cm²)	Thickness (mm)	Friability (%)	Uniformity of weight[a] (mg)	Uniformity of content[b] (%)	*In vitro* disintegration time* second	*In vitro* dispersion time* second	*In vivo* disintegration time* second	Wetting time* second	Fineness of dispersion
CP1	3–4	4.24 ± 1.48	0.2	336 ± 1.05	99.25 ± 1.39	345 ± 1.04	337 ± 1.22	325 ± 1.32	391 ± 1.22	Not done
CP2	3–4	4.34 ± 1.05	0.15	352 ± 1.52	99.67 ± 0.66	235 ± 1.55	227 ± 1.09	217 ± 1.4	211 ± 1.0	Not done
CP3	3–4	4.12 ± 1.22	0.18	368 ± 1.45	99.58 ± 1.45	198 ± 1.50	188 ± 1.3	179 ± 1.06	173 ± 1.4	Not done
CP4	3–4	4.14 ± 1.24	0.21	385 ± 1.09	98.9 ± 1.89	145 ± 1.22	137 ± 1.3	125 ± 1.4	112 ± 1.2	Pass
CP5	3–4	4.24 ± 1.16	0.39	401 ± 1.01	99.62 ± 1.22	80 ± 1.0	73 ± 1.44	65 ± 1.37	57 ± 1.03	Pass
CP6	3–4	4.32 ± 0.98	0.22	385 ± 1.22	99.24 ± 1.02	102 ± 1.34	95 ± 1.2	87 ± 0.8	79 ± 0.84	Pass
CP7	3–4	4.26 ± 1.02	0.31	401 ± 1.54	99.51 ± 1.54	84 ± 1.44	78 ± 1.22	72 ± 1.33	65 ± 0.6	Pass
CP8	3–4	4.18 ± 1.97	0.27	385 ± 1.34	99.67 ± 1.78	71 ± 1.25	62 ± 1.6	56 ± 0.57	44 ± 0.88	Pass
CP9	3–4	4.26 ± 1.26	0.35	401 ± 1.45	99.78 ± 1.33	49 ± 1.0	40 ± 0.7	32 ± 1.22	24 ± 1.34	Pass
CP10	3–4	4.24 ± 1.84	0.24	385 ± 1.65	99.58 ± 1.45	78 ± 1.76	68 ± 1.24	61 ± 1.05	51 ± 0.78	Pass
CP11	3–4	4.28 ± 1.28	0.32	401 ± 1.22	99.25 ± 1.83	64 ± 0.9	58 ± 0.56	51 ± 1.44	43 ± 1.03	Pass

a = mean ± % deviation (n = 20); b = mean ± SD (n = 10); *mean ± SD (n = 6).

Table 5. Tabletting parameters of ODT prepared with drotaverine HCl-precirol melt granulation.

Formulation	Hardness (kg/cm²)	Thickness (mm)	Friability (%)	Uniformity of weight[a] (mg)	Uniformity of content[b] (%)	*In vitro* disintegration time* second	*In vitro* dispersion time* second	*In vivo* disintegration time* second	Wetting time* second	Fineness of dispersion
PF1	3–4	4.24 ± 1.24	0.37	265 ± 1.05	99.78 ± 1.65	78 ± 1.61	70 ± 0.89	63 ± 1.23	57 ± 1.22	Pass
PF2	3–4	4.32 ± 2.09	0.18	271 ± 1.45	99.67 ± 1.23	54 ± 1.22	49 ± 1.09	42 ± 1.35	36 ± 1.45	Pass
PF3	3–4	4.28 ± 1.86	0.25	277 ± 1.78	99.74 ± 1.35	38 ± 1.05	32 ± 1.34	27 ± 0.85	20 ± 1.22	Pass
PF4	3–4	4.30 ± 1.98	0.24	283 ± 0.57	99.67 ± 1.45	41 ± 1.21	35 ± 1.0	27 ± 0.45	18 ± 0.87	Pass
PF5	3–4	4.28 ± 0.98	0.21	295 ± 1.02	99.87 ± 1.04	34 ± 1.03	26 ± 1.55	20 ± 1.43	14 ± 0.5	Pass
PF6	3–4	4.32 ± 1.24	0.34	307 ± 1.37	99.85 ± 1.09	32 ± 1.33	27 ± 1.09	19 ± 0.87	13 ± 1.03	Pass

a = mean ± % deviation (n = 20); b = mean ± SD (n = 10); *mean ± SD (n = 6).

for ODT. All the remaining formulations passed this test as they formed fine dispersion within 3 minutes and passed through sieve #22 without any residue left on the sieve.

The tablets showed less *in vitro* dispersion time. The lowest dispersion time of 40 ± 0.7 seconds for CP9 and 26 ± 1.55 seconds for PF5 were observed. The wetting times were found to be 18 ± 0.46 seconds to 211 ± 1.0 seconds. The formulations showed a wetting time of 24 ± 1.34 seconds for CP9 and 14 ± 0.5 seconds for PF5. Lower wetting times indicate the likelihood of passing disintegration test for ODT.

Cumulative percent drug released vs. time data for compritol melt granules are shown in Tables 6 and 7 and the respective dissolution profiles are shown in Figures 1 and 2. The drug release was less than 60% in 60 minutes for formulation CP1 prepared without superdisintegrant and diluent. To improve the dissolution, 5% and 10% of the weight of melt granules of crospovidone were included in the formulation as superdisintegrant CP2 and CP3, respectively. Though there was an improvement in dissolution, only 90% of the drug was released in 90 minutes. Maximum drug release of 99% was observed after 90 minutes with CP4 and 75 minute with CP5 with microcrystalline cellulose at 5% and 10% weight of melt granules CP4 and CP5, respectively. To improve the release further, mannitol was included in formulation CP7 at the concentration of 10% of the weight of melt granules. The formulation CP7 released more than 50% of the drug in 10 minutes and 100% of the active drug at the end of 60 minutes. Influence of various other superdisintegrants such as croscarmellose sodium and sodium starch glycolate was studied further keeping mannitol at 10% level. From the results, it was observed that maximum dissolution enhancement was reached with croscarmellose sodium CP9. The formulation CP9 released more than 50% of the drug in 5 minutes and 100% of the drug in 45 minutes. Hence, it was selected as an optimized formulation. The dissolution data of drotaverine HCl ODT prepared with precirol melt granules is shown in Table 8 and the respective profiles in Figure 3. The formulations PF1, PF2, and PF3 with croscarmellose sodium at 5%, 7.5%, and 10% weight of melt granules showed the drug release of 81.46%, 89.23%, and 90.46%, respectively at the end of 45 minutes. The superdisintegrant at the concentration of 7.5% and 10% weight of melt granules exhibited similar results. To improve dissolution further, mannitol was included in the formulation at a concentration of 5% PF4, 10% PF5, and 15% PF6 weight of melt granules to enhance the end stage release. The formulation PF5 showed more than 50% of the drug release in 5 minutes and 100% of the drug in 30 minutes and this has been selected as optimized formulation. The marketed formulation released about 50% of the drug in 5 minutes and 99.9% of the drug in 90 minutes. The comparative dissolution profiles of optimized formulations and marketed formulation are shown in Table 9 and Figure 4.

In vivo *disintegration and taste evaluation*

The optimized formulations were tested on human volunteers. The optimized formulations were given to a panel of healthy human volunteers for taste masking evaluation using the time intensity method. The results showed satisfactory masking of taste associated with a pleasant feeling as shown in Table 10.

Table 6. Cumulative percent drug released vs. time from ODT prepared with drotaverine HCl-compritol melt granules (mean ± SD, *n* = 3).

Time (minute)	CP1	CP2	CP3	CP4	CP5	CP6	CP7
5	2.1 ± 0.23	8.3 ± 0.98	12.11 ± 0.56	16.68 ± 0.76	23.5 ± 0.28	18.65 ± 0.56	22.23 ± 0.78
10	8.65 ± 0.67	20.12 ± 0.88	26.85 ± 0.89	35.41 ± 0.98	50.0 ± 0.12	43.76 ± 0.98	53.26 ± 0.88
15	15.21 ± 0.18	27.12 ± 0.77	39.87 ± 0.11	47.50 ± 0.35	55.2 ± 0.68	60.21 ± 0.56	69.06 ± 0.99
20	24.12 ± 1.09	39.99 ± 1.05	47.12 ± 1.60	53.62 ± 1.23	65.8 ± 1.66	66.12 ± 1.55	76.02 ± 1.34
30	30.05 ± 1.44	50.11 ± 1.36	58.38 ± 1.45	64.56 ± 1.58	80.7 ± 1.78	77.43 ± 1.22	82.12 ± 1.14
45	46.12 ± 1.08	60.12 ± 1.66	64.11 ± 1.04	73.51 ± 1.22	87.8 ± 1.03	84.23 ± 1.12	91.12 ± 1.23
60	57.98 ± 1.34	66.84 ± 1.77	70.12 ± 1.05	79.91 ± 1.05	94.5 ± 1.45	92.12 ± 1.56	100.01 ± 1.02
75	67.94 ± 1.03	78.92 ± 1.34	82.8 ± 1.45	88.12 ± 1.77	99.9 ± 1.33	100.12 ± 1.02	
90	72.11 ± 1.34	89.11 ± 1.06	94.33 ± 1.34	99.09 ± 1.59			

Table 7. Cumulative percent drug released *vs*. time from ODT prepared with drotaverine HCl-compritol melt granules (mean ± SD, *n* = 3).

Time (minute)	CP7	CP8	CP9	CP10	CP11
5	22.23 ± 0.78	35.00 ± 0.55	52.47 ± 0.56	29.12 ± 0.34	40.91 ± 0.34
10	53.26 ± 0.88	54.43 ± 0.28	69.53 ± 0.23	47.54 ± 0.23	60.21 ± 0.55
15	69.06 ± 0.99	70.12 ± 0.76	75.91 ± 0.78	63.12 ± 0.86	72.93 ± 0.78
20	76.02 ± 1.34	79.12 ± 1.45	82.11 ± 1.23	72.23 ± 1.56	79.11 ± 1.55
30	82.12 ± 1.14	83.23 ± 1.77	88.12 ± 1.46	81.54 ± 1.49	85.59 ± 1.67
45	91.12 ± 1.23	89.99 ± 1.35	99.43 ± 1.66	88.32 ± 1.60	91.11 ± 1.77
60	100.01 ± 1.02	98.12 ± 1.29	99.99 ± 1.79	94.12 ± 1.87	99.98 ± 1.56
75		100.11 ± 1.02		100.09 ± 1.33	

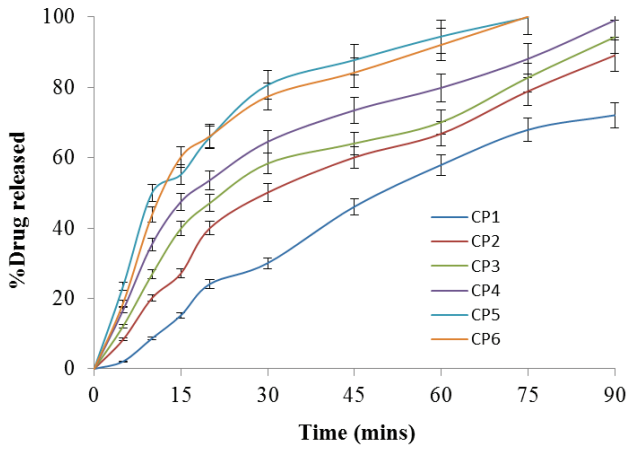

Figure 1. Dissolution profiles of drotaverine HCl ODT prepared with compritol melt granules (CP1–CP6).

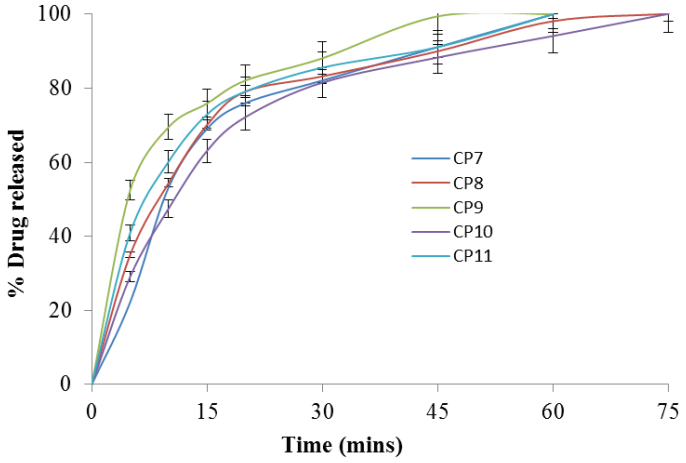

Figure 2. Dissolution profiles of drotaverine HCl ODT prepared with compritol melt granules (CP7–CP11).

This could be because of the presence of mannitol which acts as a sweetener and causes cooling effect during the disintegration of the tablet without grittiness (Eri *et al*., 2013; Tomohiro *et al*., 2002).

Drug-excipient compatibility studies

The characterization of drotaverine HCl in ODT was carried out by using DSC, XRD, and FTIR techniques for any changes in its physical state or chemical interactions if any between the drug and melting agent.

DSC analysis

The DSC thermograms of pure drug, excipients used in the study, and optimized formulations are shown in Figure 5. 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. Precirol ATO5 showed an endothermic melting peak at 58°C. The formulation indicated no endothermic peak compared to the pure drug at 215.12°C which indicated the complete conversion of the drug into amorphous form in precirol ATO5.

XRD analysis

The X-ray diffractograms of pure drug drotaverine HCl and optimized formulation are shown in Figure 6. 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

Table 8. Cumulative percent drug released *vs*. time from ODT prepared with drotaverine HCl-precirol melt granules (mean ± SD, *n* = 3).

Time (minute)	PF1	PF2	PF3	PF4	PF5	PF6
5	31.90 ± 0.29	48.12 ± 0.19	54.32 ± 0.23	52.12 ± 0.28	58.43 ± 0.39	59.54 ± 0.45
10	54.32 ± 0.36	65.43 ± 0.28	64.32 ± 0.29	70.32 ± 0.35	76.33 ± 0.55	77.93 ± 0.66
15	64.43 ± 0.55	68.43 ± 0.45	67.12 ± 0.45	73.12 ± 0.50	84.32 ± 0.67	84.43 ± 0.78
20	69.32 ± 0.78	74.23 ± 0.75	70.23 ± 0.77	81.22 ± 0.79	92.32 ± 1.02	92.05 ± 1.32
30	73.92 ± 1.20	81.33 ± 1.56	81.21 ± 1.45	87.43 ± 1.39	99.95 ± 1.22	100.32 ± 1.41
45	81.46 ± 1.34	89.23 ± 1.67	90.94 ± 1.55	96.43 ± 1.58		
60	89.12 ± 1.50	99.99 ± 1.56	99.83 ± 1.66	99.92 ± 1.55		
75	99.09 ± 1.05					

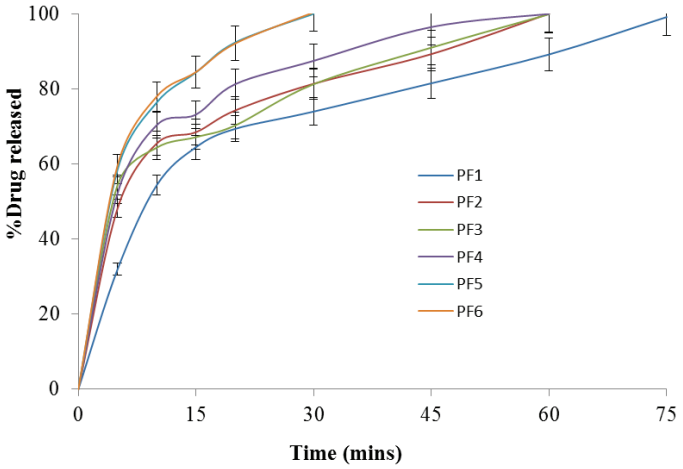

Figure 3. Dissolution profiles of drotaverine HCl ODT prepared with precirol melt granules (PF1 –PF6).

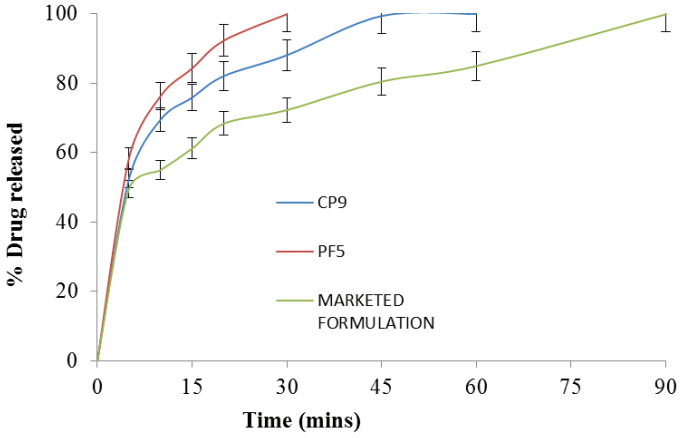

Figure 4. Dissolution profiles of drotaverine HCl ODT optimized formulations (CP9 and PF5) and marketed formulation.

Table 9. Cumulative percent drug released vs. time of drotaverine HCl ODT and marketed formulation (mean ± SD, *n* = 3).

Time (minute)	CP9	PF5	Marketed formulation
5	52.47 ± 0.56	58.43 ± 0.39	49.6 ± 1.13
10	69.53 ± 0.23	76.33 ± 0.55	55.0 ± 1.21
15	75.91 ± 0.78	84.32 ± 0.67	61.2 ± 0.58
20	82.11 ± 1.23	92.32 ± 1.02	68.4 ± 1.04
30	88.12 ± 1.46	99.95 ± 1.22	72.3 ± 0.99
45	99.43 ± 1.66		80.5 ± 1.08
60	99.99 ± 1.79		85.0 ± 1.40
90			99.9 ± 0.86

optimized formulation PF5 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.

FTIR studies

FTIR analysis for pure drug, compritol, formulation CP9, precirol ATO5 and formulation PF5, compritol and formulation CP9 were carried out. The FTIR spectra of pure drug and its combinations are presented in Figures 7 and 8. Drotaverine HCl pure drug showed N–H secondary amine peak at 3,478.19 cm^{-1}, C–H stretching at 2,874.45 cm^{-1}, N–H bending at 1,647.39 cm^{-1}, aromatic C=C stretching at 1,517.94 cm^{-1} and for C–O stretching at 1,237.10 cm^{-1}. Compritol showed C–H stretching at 2,840 cm^{-1}, strong C–O stretching at 1,743.39 cm^{-1}. The formulation CP9 showed C–H stretching at 2,886.43 cm^{-1}, N–H bending at 1,647.39 cm^{-1}, aromatic C=C stretching at 1,517.94 cm^{-1} and for C–O stretching at 1,237.10 cm^{-1}. Precirol ATO5 showed C–H stretching at 2,915 cm^{-1}, strong C–O stretching at 1,738.15 cm^{-1}, aromatic C=C stretching at 1,510.19 cm^{-1} and C–O stretching at 1,200 cm^{-1}. The formulation PF5 showed C–H stretching at 2,886.43 cm^{-1}, N–H bending at 1,721.93 cm^{-1}, aromatic C=C stretching at 1,575.19 cm^{-1} and for C–O stretching at 1,267.15 cm^{-1}. The optimized formulations CP9 and PF5 did not showed major shift in principal peaks of drotaverine HCl, indicating no interaction due to the presence of excipients. Hence, all the optimized formulations are compatible.

Table 10. Taste evaluation and mouth feel of the formulations.

Volunteers		I	II	III	IV	V	VI
Formulation CP9	Bitterness	1	0	0	2	1	0
	Mouth feel	+	+	−	−	+	−
Formulation PF5	Bitterness	0	0	1	0	0	1
	Mouth feel	+	−	+	+	+	−

0 = no bitterness; 1 = threshold bitterness; 2 = very slightly bitterness; + = smooth and pleasant; − = gritty and pleasant feel.

CONCLUSION

In the present work, an attempt was made to prepare taste masked ODT using compritol and precirol as taste masking agents. As there are no reports on the development of taste masked

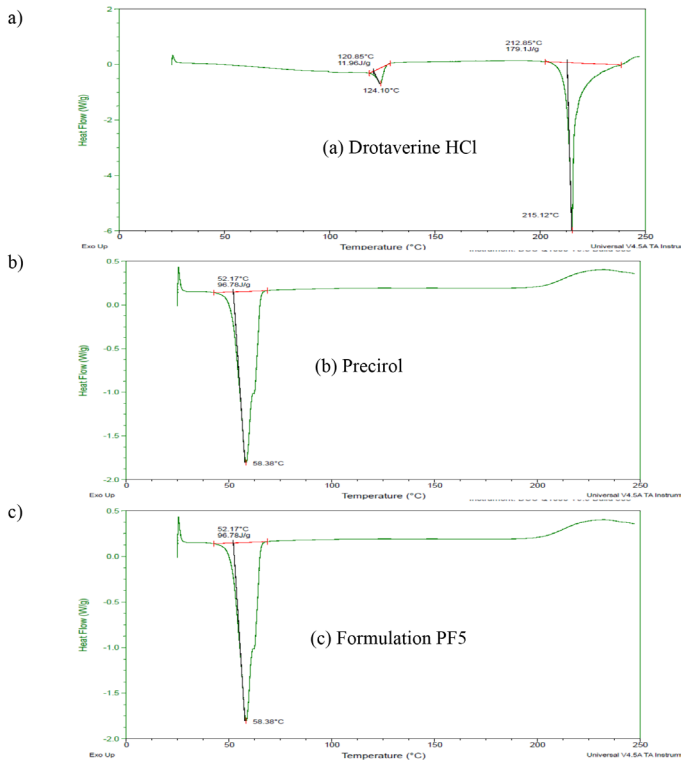

Figure 5. DSC thermograms of (a) Drotaverine HCl (b) Precirol ATO5 and (c) formulation PF5.

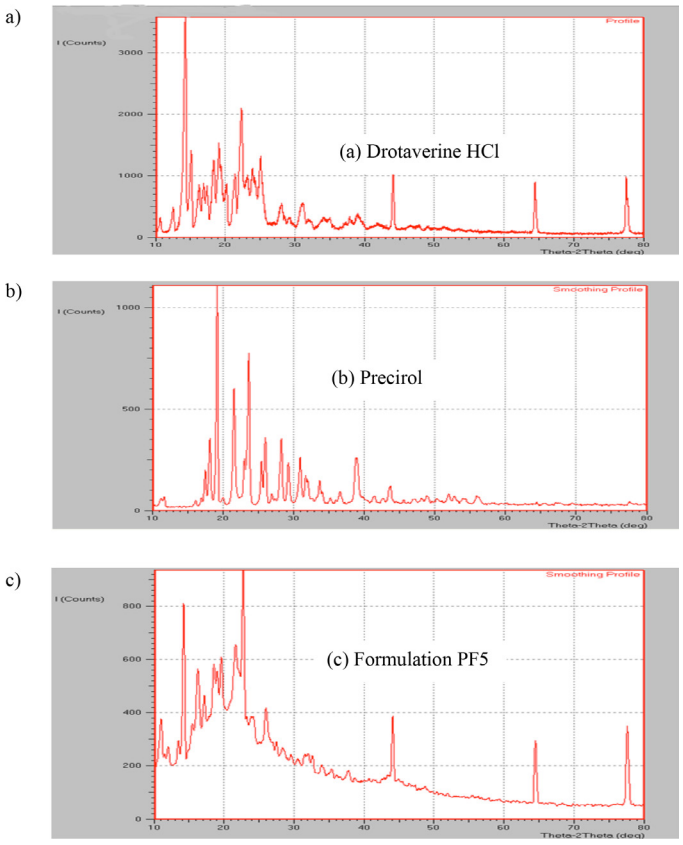

Figure 6. X-ray diffractograms of (a) Drotaverine HCl (b) Precirol ATO5 and (c) Formulation PF5.

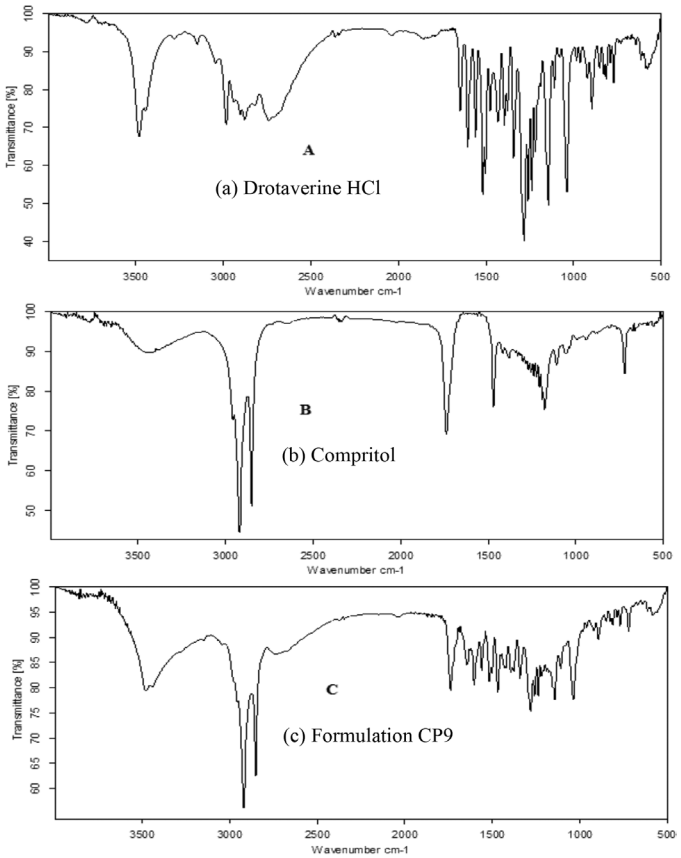

Figure 7. FTIR spectra of (a) DrotaverineHCl (b) Compritol and (c) Formulation CP9.

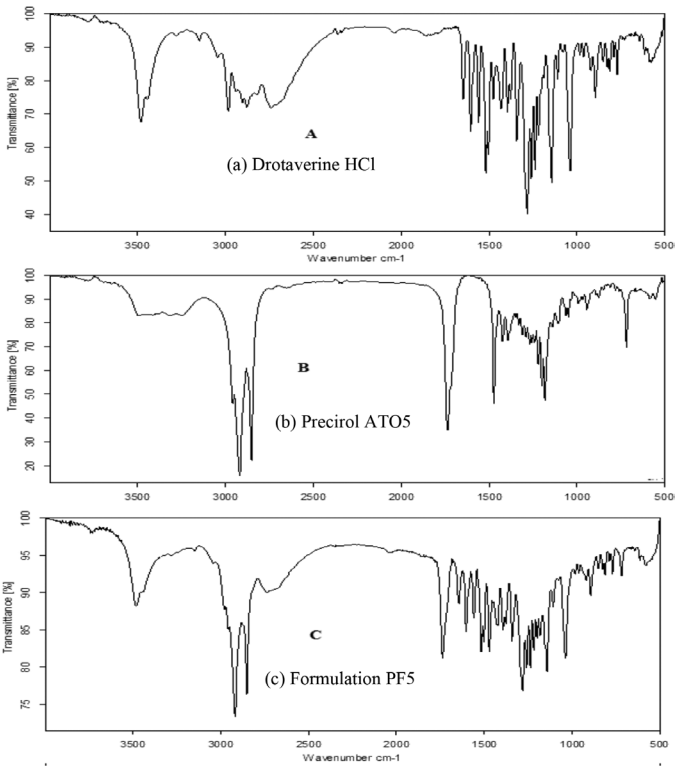

Figure 8. FTIR spectra of (a) Drotaverine HCl (b) Precirol ATO5 and (c) Formulation PF5.

dosage forms for drotaverine HCl by using compritol and precirol, an attempt was made for the development of taste masked tablets of drotaverine HCl using the melt granulation technique. In the present investigation, the drug-polymer mixture was prepared by the melt granulation technique. The order of taste masking ability of the carriers was found to be precirol > compritol and found that 1:7 ratio of drug-compritol and 1:5 drug-precirol were optimized with respect to masking of bitterness and considered as optimized. The optimized melt granules were compressed into ODT using different superdisintegrants like crospovidone, crosscarmellose sodium, and sodium starch glycolate. Diluents like microcrystalline cellulose and mannitol were also used for enhancing the drug release along with aspartame as a sweetening agent. Among these trials, ODT prepared with croscarmellose sodium with mannitol as diluent (both at 10% weight of melt granules) gave complete drug release in 60 minutes with acceptable taste and mouthfeel. Hence, these two formulations CP9 and PF5 were considered as optimized formulations.

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CONFLICT OF INTERESTS

We have no conflict of interests.

REFERENCES

Abdelbary G, Eouani C, Prinderre P, Joachim J, Reynier J, Piccerelle P. Determination of the *in vitro* disintegration profile of rapidly disintegrating tablets and correlation with oral disintegration. Int J Pharm, 2005; 292:29–41.

Anusha P, Nirajana A, Mohammed S, Jilani S, Murali C, Harish G. Development and evaluation of drotaverine taste masked tablets with improved dissolution efficiency using sold dispersion technique. IJRPB, 2013; 1:275–80.

Ashwini M, Shivajirao K, Varsha P. Studies on formulation development of mucoadhesive sustained release itraconazole tablet using response surface methodology. AAPS Pharm Sci Tech, 2008; 9:998–1005.

Bi YX, Sunada H, Yonezawe Y, Danzo K. Evaluation of rapidly disintegrating tablets. Drug Dev Ind Pharm, 1999; 25:571–81.

Craick DJ. The flow properties of starch powders and mixtures. J Pharm Pharmacol 1958; 10:10.

Indian Pharmacopoeia. Govt of India, Ministry of Health and Family Welfare, the Indian Pharmacopeia Commission, Ghaziabad, India, pp 187–93, 2010.

Katsuno E, Tahara K, Takeuchi Y, Takeuchi H. Orally disintegrating tablets prepared by a co-processed mixture of micronized crospovidone and mannitol using a ball mill to improve compatibility and tablet stability. Powder Technol, 2013; 241:60–6.

Kumar R, Patil S, Patil MB, Patil SR, Paschapur MS. Formulation evaluation of mouth dissolving tablets of fenofibrate using sublimation technique. Int J Chem Tech Res, 2009; 1:840–50.

Pandey B, Mallik S, Ahmad S. Coprocessing of super disintegrants for drug release of taste masked Drotaverine HCl. Novel Sci IJPS, 2012; 1:758–63.

Pankaj A, Sanjay P, Abhijeet T, Manoj W, Parag K, Rajendra S. Design and evaluation of taste masked chewable dispersible tablet of lamotrigine by melt granulation. Int J Drug Delivery, 2010; 2:183–91.

Raghavendra N, Mahesh K, Srikanth M, Kistayya C, Mahipal B. Development and evaluation of fast dissolving tablets of fosinopril by sublimation method. Int J Pharm Sci Drug Res, 2012; 4:230–35.

Sivaprasad S, Hindustan A, Sreenivasulu R, Kishore R, Krishna CH, Kranthi G, et al. Novel approach in designing of mouth dissolving tablets for bitter drugs taking clozapine as model drug. Der Pharmacia Lett, 2011; 3:113–20.

Srikanth M, Uhumwangho M, Sunil S, Sreenivasa N, Ravi C, Ramana Murthy K. Design and evaluation of taste masked Drotaverine HCl orodispersible tablets using polymethacrylate polymers. Der Pharmacia Lett, 2010; 2:223–31.

Subrahmanian S, Sankar V, Asha A. Formulation and evaluation of cetirizine dihydrochloride orodispersible tablet. Pak J Pharm Sci, 2010; 23:232–35.

Tran D. Some aspects of the property of angle of repose of powders. J Pharm Pharmacol, 1957; 1:127–35.

Uchida T, Nakamura T, Tanigake A. The effect of various substances on the suppression of the bitterness of quinine-human gustatory sensation, binding and taste sensor studies. Chem Pharm Bull (Tokyo), 2002; 50:1589–93.

Uddhav B, Kishore G, Nancy P, Sanjeevani A, Shalaka D. Formulation and evaluation of sublimed fast melt tablets of levocetirizine dihydrochloride. IJPSR, 2010; 2:76–80.

Ujwala B, Dinesh S, Sarika Z, Varsha K, Nanda R. Development and evaluation of drotaverine taste masked tablets with improved dissolution efficiency using sold dispersion technique. Res J Pharm Tech, 2014; 7:301–6.

USP30-NF25. The official compendia of standards. The United States Pharmacopoeial Convention. Powder flow (e book), 2007; 643.

USP30-NF25. The official compendia of standards. The United States Pharmacopoeial Convention. Bulk Dens Tapped Dens (e book), 2007; 242.

Yoshinari T, Forbes RT, York P, Kawashima Y. Moisture induced polymorphic transition of mannitol and its morphological transformation. Int J Pharm, 2002; 247:69–77.

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