Design and evaluation of taste masked Drotaverine HCl orodispersible tablets using polymethacrylate polymers

Srikanth MV[*1], Uhumwangho MU[2], Sunil SA[1], Sreenivasa Rao N[1], Ravi Kiran CH[1] and Ramana Murthy KV[1]

[1]University College of Pharmaceutical Sciences, Andhra University, Visakhapatnam, India
[2]Department of Pharmaceutics and Pharmaceutical Technology, Faculty of Pharmacy, University of Benin, Nigeria

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ABSTRACT

The objective of this present study was to mask the intensely bitter taste of drotaverine hydrochloride and to formulate orodispersible tablet. Taste masking was done by complexing drotaverine HCl with polymethacrylate polymers (Eudragit E100 and Eudragit RD100) by solvent evaporation technique. The drug: polymer ratio was (1:10) with drug content 40mg. The granules of two optimized drug-polymer complexes (DPCs) were tested for packing and flow properties. These granules were compressed into tablets and evaluated for hardness, friability, drug content, wetting, in vitro disintegration time and in vitro taste in simulated salivary fluid (SSF) of pH 6.2. Their dissolution profiles (i.e. F_1 and F_2) were compared with commercial formulation (MKT). The optimized formulations were further characterized with Fourier-Transform Infrared Spectroscopy (FTIR) to investigate any interactions between the drug and the added excipients. The granules of the optimized DPCs were free flowing with angle of repose $<28^0$. The DPCs tablets (i.e. F1 and F2) had hardness and friability values of $\geq 4kg/cm^2$ and $<0.9\%$ respectively. These tablets disintegrated rapidly ($<75sec$) with a wetting time of $\leq 22sec$. It also showed rapid drug release in stimulated gastric fluid (SGF) compared with marketed formulation. For instance, the maximum release of drotaverine hydrochloride in F_1, F_2 and MKT were achieved in 30, 15 and 90mins respectively. Taste evaluation of the DPCs tablets (F_1 and F_2) in human volunteers revealed considerable taste masking with the degree of bitterness below threshold value. There were also no drug/excipient interactions. This study shows the suitability of polymethacrylate polymers (Eudragit E100 and Eudragit RD100) in masking the bitter taste of orodispersible tablets of drotaverine HCl.

Keywords: Taste masking, drotaverine hydrochloride, Eudragit E100 and Eudragit RD100.

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INTRODUCTION

The oral route is the most convenient, appropriate and acceptable way to administer medications. Orodispersible tablets are known as quick dissolve, fast melt, rapid disintegrating or orally dissolving tablets [1]. They are suitable for mentally ill, bedridden and patients who do not have

quick access to water. Several oral active pharmaceuticals ingredients and bulking agents have unpleasant bitter taste; hence this often times results to non compliance to medications by patients. Taste masking is a means of masking the bitter taste of drug in order to improve the palatability of the drug, which in turn improves patience compliance.

Several efforts have been used by researchers to develop an orodispersible masking tablets with different techniques. Some of such efforts include the use of ion exchange resin complexation to mask the taste of orodispersible tablet of ambroxol hydrochloride and roxithromycin [1,2]. In these studies, Indion 204 and Amberlite IRP64 were found to be good taste masking agents. Other bitter medications have also been masked by some other researchers with the application of other ion exchange resins such as Tulsion 335 [3], Indion 234 resin [4]. However, other techniques used for taste masking of bitter drugs include microencapsulation [5], solvent evaporation technique [6], mass extrusion technique [7], coacervation method [8], melt granulation technique [9] and solid dispersion [10].

Drotaverine hydrochloride is an antispasmodic agent used for smooth muscle spasm and pain associated with gastrointestinal colics, biliary colics, postsurgical spasm, renal colics, dysmenorrhoea and uterine neck spasm. Its Chemical name is 1- [(3,4-diethoxy phenyl) methylene]-6,7-diethoxy-1, $\underline{2}$, $\underline{3}$, 4-tetrahydroisoquinoline with a molecular formula of C_{24} H_{31} NO_4. HCl [11]. Its oral bioavailability is about 100% with a biologic half- life of about 7 to 12 h [12]. It adult dose is about 40 to 80mg one to three times a day. Drotaverine hydrochloride has a very bitter taste and compliance to the medication is always very poor. Hence, due to its bitter taste it was selected as a model drug for taste masking by solvent evaporation technique.

MATERIALS AND METHODS

Drotaverine HCl and Aspartame were generous gift samples from M/s. Anglo French drugs and Industries Ltd, Banglore, India. Eudragit E 100 and Eudragit RD 100 were obtained as gift samples from Degussa Pharm, Germany. Microcrystalline Cellulose, crospovidone and magnesium sterarate were purchased from Gujarat microwax Pvt, Ltd, India. Other materials used were of analytical grade.

Preparation of drug-polymer complex granules*:*
From preliminary studies in our laboratory, an optimized drug-polymer complex (DPC) was formed by solvent evaporation technique. The Eudragit E100 or Eudragit RD100 (50g) was dissolved in 400ml of acetone and 5g of drotaverine HCl was added and kept under stirring on a hot plate maintained at 40°C, so as to allow the solvent to evaporate. The obtained complex was scrapped and triturated in a mortar to get maximum complexation of polymer and drug. The drug- polymer complexes were passed through sieve #30 and dried for 15 minutes. These dried granules were again passed through sieve #40 to obtain uniform granules.

Characterization of granules
Packing property of the granules:
The packing properties were determined by measuring the difference between bulk density (BD) and the tapped density (TD) using standard procedure. In the procedure, a 20g quantity of granule sample was placed into 250ml clean, dry measuring cylinder and the volume, V_0 occupied by the sample without tapping was determined. An automated tap density tester (model C-TDA2, Campbell Electronics, Mumbai, India) was used for tapping the granules according to USP Chapter 616 Method I [13]. After 500 taps the occupied volume, V_{100} was also noted. The

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bulk and tap densities were calculated from these volumes (V_0 and V_{100}) using the formula. Density = Weight/Volume occupied by sample. The Hausner ratio was determined by dividing the tapped density (TD) by the bulk density (BD), and Carr's compressibility index (CI) [14] was determined using Equation 1:

$$CI = \left\{ \left(\frac{TD - BD}{TD} \right) x\,100 \; \% \right\} \; – \; – \; – \; – \; – \; – \; – \; – \; (1)$$

Flow property of granules:
The flowability of the granules was determined by measuring the angle of repose formed when a sample of the granules (40g) was allowed to fall freely from the stem of a funnel to a horizontal bench surface [15]. The radius (r) and the height (H) of the powder heap was then determined. The angle of repose (θ) was calculated using the expression:

$\theta = \tan^{-1}(h/r)$ -------------------------------- (2)

Preparation of tablets:
All excipients used to formulate tablets as per Table-1 were passed through sieve # 40 and mixed in geometric dilution. Drug-polymer complexes equivalent to 40 mg of drug were compressed on Cadmach rotary 16 station to form flat faced tablets of diameter 12mm and weight 530mg.

Table 1: Formulae for tablets formulated with Eudragit E100 (F_1) and Eudragit RD100 (F_2) polymers.

Ingredients	F_1	F_2
Drug-polymer complex	Equivalent to 40 mg of drug 440	Equivalent to 40 mg of drug 440
Micro Crystalline Cellulose (MCC)	33	37
Aspartame (4%)	21	21
Cross Povidone (CP) (3%)	15	11
PVP K 30 (3%)	16	5
Magnesium stearate (1%)	5	16
Total tablet weight	**530mg**	**530mg**

Evaluation of tablets:
The formulated tablets were evaluated for physical parameters. These include hardness, friability, disintegration time, drug content and *in vitro* dissolution studies.

Determination of tablet hardness and friability:
The fracture loads (Kg) of ten tablets were determined individually with the Monsanto hardness tester [16]. The mean values of the fracture loads were recorded. The friability test is to evaluate the ability of the tablet to withstand abrasion in packaging, handling and shipping. 10 tablets were weighed initially (w_1), placed in friabilitator (Roche) and were allowed to rotate at the speed of 25 rpm for 4 mins. After four minutes of this treatment or 100 revolutions, the tablets are weighed and the weight (w_2) compared with the initial weight. The loss due to abrasion is a measure of the tablet friability. The % friability was calculated by using equation 3 below.

% Friability = $(w_1 - w_2)$ x $100/ w_1$ --------------------------(3)

Disintegration test:
The method described in the British Pharmacopoeia BP [17] was followed using water maintained at $37^{\circ}C$ as the disintegration fluid. Six tablets were used in each determination, which was carried out in triplicate and the mean results are reported.

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Drug content:

Five tablets were placed in 100 ml volumetric flask, dissolved and makeup to volume with acetonitrile. 3 ml of the stock solution was further diluted up to 100 ml with 1% sodium lauryl sulphate solution. The sample was filtered with whatman No. 3 filter paper and was analyzed for the drug content by using UV-spectrophotometer (Elico SL 210) at 272 nm.

***In vitro* studies:**

One tablet of F_1 or F_2 or MKT formulation were placed in a cylindrical basket (aperture size 425µm: diameter 20mm; height 25mm), and immersed in 900ml of leaching fluid (Stimulated gastric fluid maintained at $37 \pm 2^{o}C$). The fluid was stirred at 100rpm (Model Disso 2000, Lab India). Samples of the leaching fluid (5ml) were withdrawn at selected time intervals with a syringe fitted with a cotton wool plug and replaced with an equal volume of drug-free dissolution fluid. The samples were suitably diluted with blank dissolution fluid and were analysed for content of drotaverine hydrochloride spectrophotometrically at λ_{max}, 302.8 nm by using an Elico SL 210 UV-Visible double beam spectrophotometer (Elico, India). The amounts released were expressed as a percentage of the drug content in each dissolution medium. The dissolution test was carried out in quadruplicate and the mean results reported.

***In vitro* dispersion and *In vivo* disintegration time:**

This test was performed by method described previously by Purnima et al [18]. *In vitro* dispersion time was measured by dropping a tablet in a measuring cylinder containing 6ml of simulated salivary fluid of pH 6.2. Three tablets from each formulation were randomly selected and *in vitro* dispersion time was reported. Six healthy human volunteers were used for *in vivo* disintegration time. Written consent was obtained from all volunteers. Each volunteer randomly took one tablet and kept on the tongue. The time taken for complete disintegration of the tablet on the tongue was noted. After the test, mouth was washed with distilled water. The same procedure was repeated for 3 trials and was carried out after 2 days interval**.**

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 6.2, and the time for complete wetting was measured. Five tablets from each batch were used.

Taste evaluation:

Taste evaluation was done on 6 volunteers by using time intensity method. One tablet was held in mouth for 10 seconds bitterness levels were recorded instantly and after 10 seconds, 30seconds, 1 minute and 2 minutes, bitterness levels were recorded.

Fourier Transform Infrared Spectroscopy (FTIR):

The FTIR spectrum of the different samples were recorded in an Infra Red spectrometer (Nicolet Magna 4R 560, MN, USA) using potassium bromide discs prepared from powdered samples. The spectrum was recorded in the region of 4000 to 400 cm^{-1}.

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RESULTS AND DISCUSSION

Packing and flow properties

 The results (Table 2) showed the packing and flow properties of the drug–polymer complex granules. All the granules exhibited satisfactory flow properties as indicated by the low angles of repose (<27°) [19]. This consideration is important when the granules are to be compressed into tablets. The results also showed that the granules were fairly compressible during tapping. CI values were 20.4% and 25% and Hausner's ratio values were 1.26 and 1.33 for F_I and F_2 respectively.

Table 2. Physical properties of the optimized complex granules

Parameters evaluated	F_1	F_2
Angle of repose θ	27.54°	24.94°
Bulk density	0.573g/cm^3	0.386 g/cm^3
Tap density	0.72 g/cm^3	0.515 g/cm^3
Compressibility index	20.4%	25.0 %
Hausner's ratio	1.26	1.33

Table 3: Physicochemical properties of F1, F2 and MKT

Physico chemical parameters	F_1	F_2
Hardness (kg/cm^2)	4.2±0.2	4.1±0.5
Friability (%)	0.79±0.3	0.68±0.5
Drug content (%)	99.25±1.58	99.67± 1.64
In vitro disintegration time* with water (sec)	72±1.5	60±1.0
In vitro dispersion time* with simulated salivary fluid (sec)	64±1.0	66±2.0
In vivo disintegration time*(sec)	54±1.5	48±1.5
Wetting time*(sec)	22±1.0	18±1.5

* (Mean ± SD (n=3) seconds)

Physical parameters of the tablets.

The physicochemical parameters of the tablets formulations are presented in table 3. The tablets had hardness values between 4.1 to 4.2 kg/cm^2 while their friability percentage were <0.8%.The content uniformity of the tablets were <99%. All of these values were within acceptable limits. The *in vitro* disintegration and dispersion as well as the *in vivo* disintegration time were <70 secs for the tablets formulation prepared with both polymers. The decrease in these values might be attributable to the presence of a superdisintegrant (Crospovidone) as well as microcrystalline cellulose (hydrophilic diluents) which were incorporated as excipients in the formulation of the polymer complex. Hence, these excipients enhanced the influx of fluid into the tablets and improved the disintegration time of the tablets formulations.

Table 4: Taste evaluation (bitterness) of F_1 and F_2

Volunteers	Bitterness level after									
	30 sec		60 sec		90 sec		120 sec		Mouth feel	
	F1	F2	F1	F2	F1	F2	F1	F2	F1	F2
1	0	0	0	0	0	0	×	0	-	+
2	0	0	0	0	0	×	0	×	+	-
3	0	0	0	0	0	0	×	×	-	-
4	0	0	0	0	0	0	0	×	+	-
5	0	0	0	0	0	0	0	0	+	+

0 = No bitterness; + = Smooth and pleasant feeling; X = Threshold bitterness; -= Gritty and pleasant feeling; Xx = Slight bitterness; -- = Gritty and unpleasant feeling; Xxx = Strong bitterness.

Taste evaluation of F_1 and F_2 formulations:
The time intensity study for taste in human volunteers of the formulated drotaverine hydrochloride with the polymer complex (F_1 and F_2) revealed considerable masking of the bitter taste of drotaverine HCl with degree of bitterness below the threshold value within 120seconds (See Table 4). Sensory evaluation of the two optimized tablets with both polymethacrylate polymers proved good palatability.

Drug Release from formulation F_1 and F_2:
The dissolution profiles of the optimized formulations (i.e F_1 and F_2) were compared with those of the MKT. Their dissolution profiles are presented in Fig 1. It was observed that the dissolution profiles of these optimized tablets prepared with these polymethylacrylate polymers revealed faster release when compared with MKT. For instance, the time for maximum release of F_1, F_2 and MKT formulations were 30, 15 and 90mins respectively.

Fourier-Transform Infrared Spectroscopy (FTIR) studies:
In order to investigate if there is any chemical interaction between added excipients and drotaverine HCl in the formulated products (F_1 and F_2), the FTIR of pure drotaverine HCl (Fig 2a), the polymers Eudragit E 100 (2b) and Eudragit RD 100 (2c), tablets of drotaverine HCl {ie F_1 (2d) and F_2 (2e)}, were recorded. The IR spectrum of drotaverine HCl showed characteristic peaks at peaks 3500-3300 cm^{-1} (N-H secondary amine), 1600-1475cm^{-1} for (aromatic C=C stretching), 3000-2840cm^{-1}(sp^{3}C-H stretching), 1260-1000 cm^{-1}(C-O stretching) and 1650-1580 cm^{-1} (N-H bending). It was observed however, that all the characteristic peaks observed for both pure drug and excipients (ie Eudragit E 100 and Eudragit RD 100) remained unchanged and the spectra data was superimposed (See Figs 2d and e). This observation ruled out the possibility of chemical interaction between the drug and added excipient (ie the polymethylacrylate polymers) during solvent evaporation technique to form the granules and also during tableting of the complex granules.
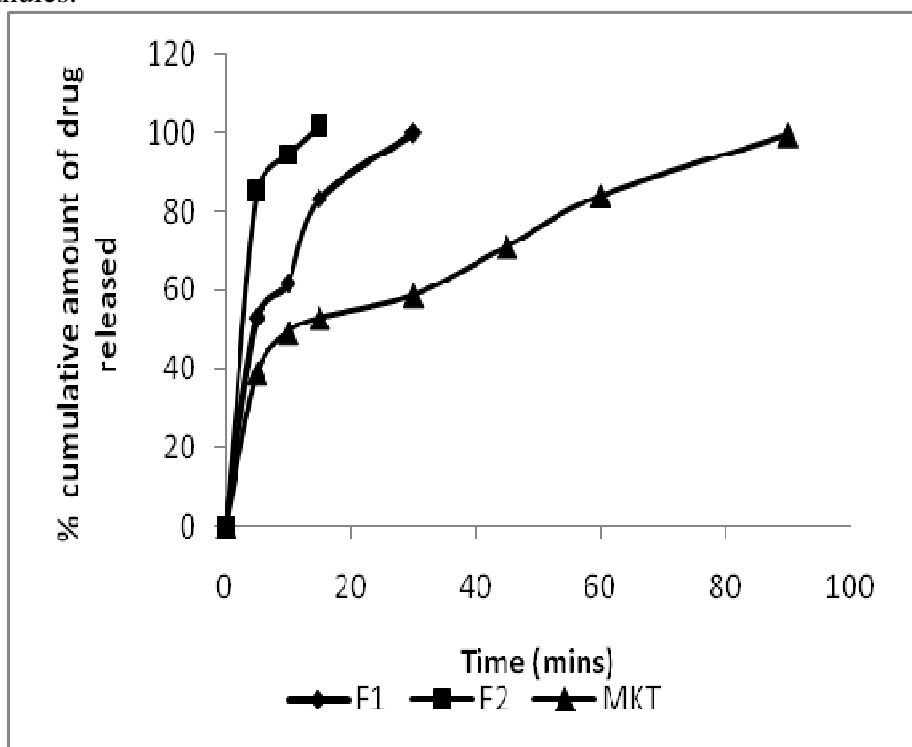

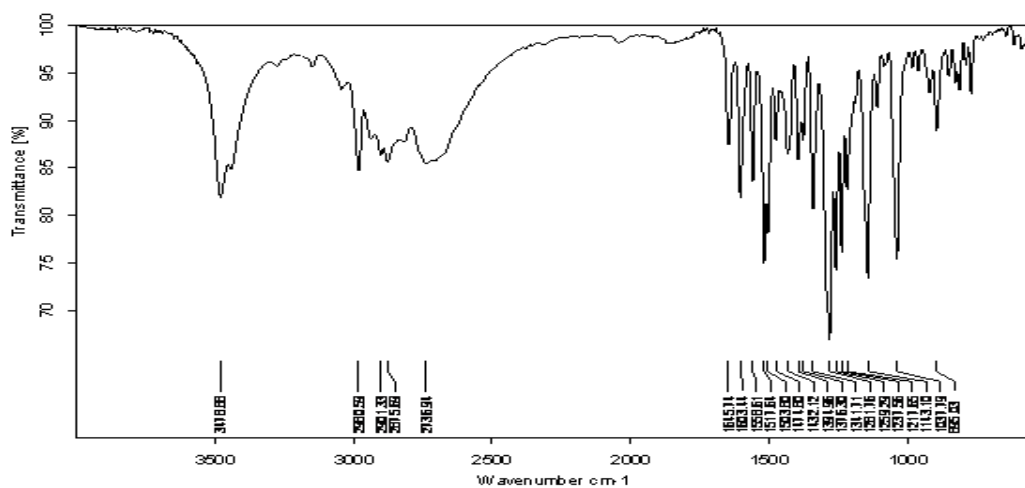**Fig 1: Dissolution profile of F_1, F_2 and MKT formulations**

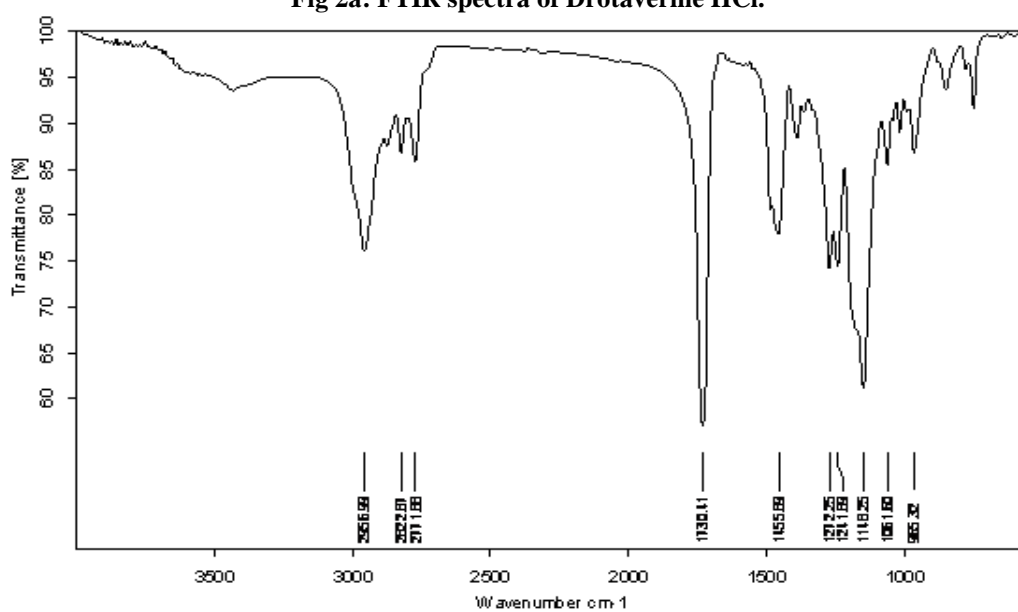**Fig 2a: FTIR spectra of Drotaverine HCl.**

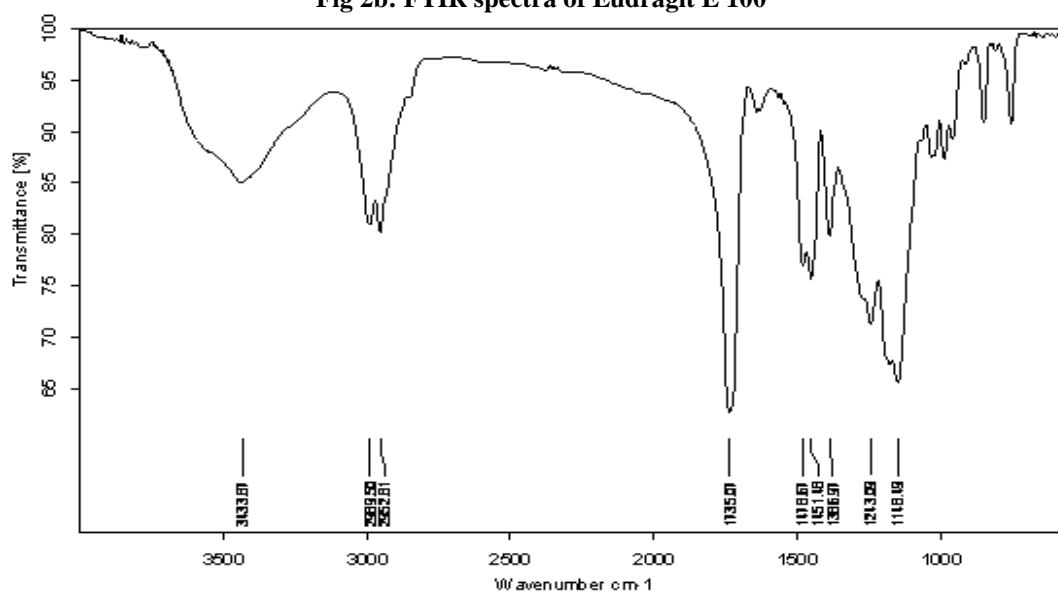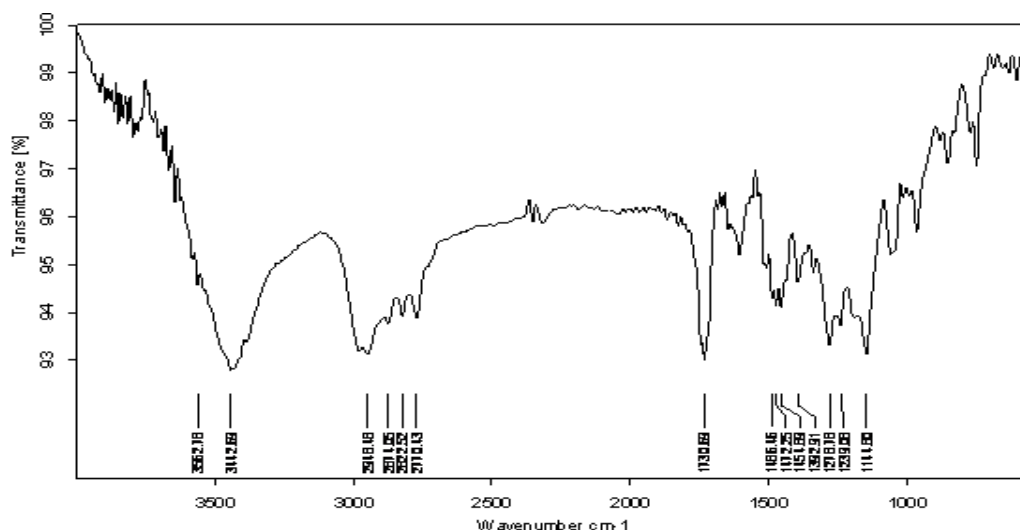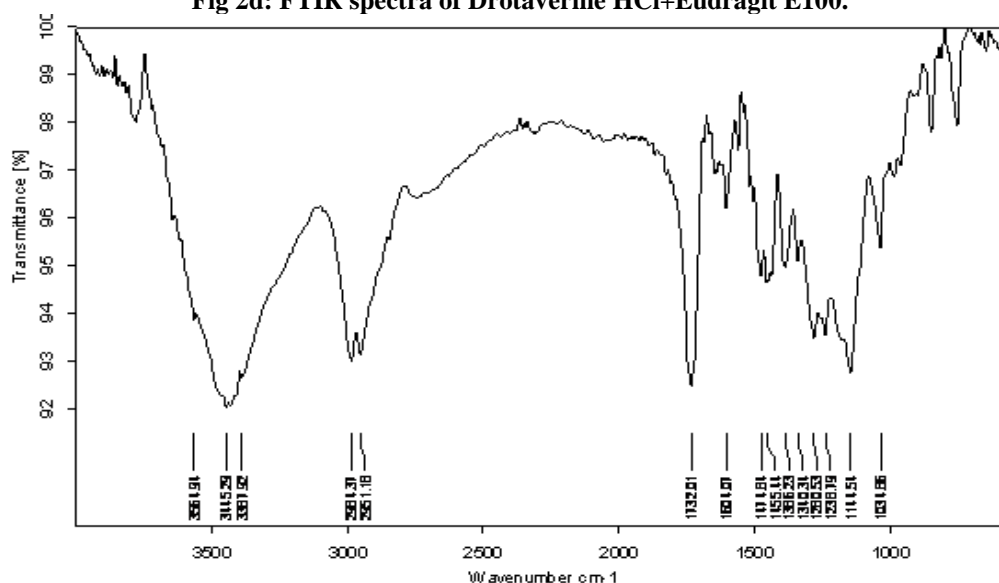**Fig 2b: FTIR spectra of Eudragit E 100**

Fig 2c: FTIR spectra of Eudragit RD 100

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Fig 2d: FTIR spectra of Drotaverine HCl+Eudragit E100.

Fig 2e: FTIR spectra of Drotaverine HCl+Eudragit RD 100

CONCLUSION

This study has established effective taste masking of drotaverine HCl with the used of these two polymethylacrylates polymers. Taste masking and rapid disintegration of drotaverine HCl tablets formulated in this investigation may possibly help in the administration of drotaverine HCl in a more palatable form in the absence of water and more importantly since drotaverine HCl orodispersible formulations are not presently in the market. Hence, "patient-friendly dosage form" of bitter drugs, especially for pediatric and geriatric patients, can be deveolped using this technique and these polymers.

Acknowledgments

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