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Research Article

Preparation and Characterization of Orodispersible tablets of Antispasmodic drug manufactured with Co-Processed mixtures

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Abstract

In the present investigation drug–polymer complex was prepared kneading method for the sucrose fatty acid ester .The drug and polymer in different ratios were prepared and found that taste of drug was masked 1:10 for sucrose fatty acid ester. The drug-polymer complexes were compressed into tablets with different superdisintegrants like croscarmellose sodium diluents like mannitol and microcrystalline cellulose. The tablets were subjected to evaluation studies for the parameters like general appearance, hardness, weight variation, friability, *in vitro* and *in vivo* disintegration tests. The disintegration tests conducted on these products showed that, there is rapid disintegration of the tablets, which is much less than the official limit for dispersible tablets (3minutes). After disintegration, the dispersion produced was smooth with pleasant mouth feel, the bitter taste being totally masked. The *in vitro* dissolution studies for all the formulations and optimized results were obtained with sucrose fatty acid ester based formulations. The formulations F5 were selected as optimized formulations made with sucrose fatty acid ester respectively. The formulations F5 showed more than 60% of the drug in 5 min and 100% of the drug at the end of 30 min. The drug and polymer complexes were subjected to FTIR studies. It was observed that no chemical interaction was found in between the drug and polymer.

Keywords: Drug, polymer, drug: polymer complex, taste masking and tablets.

INTRODUCTION

The bitter taste of drugs is one of the most serious problems where masking of the bitter taste is very important from the marketing point of view as well as for the improvement of the treatment by patient compliance[1]. "Taste masking is defined as a perceived reduction of an undesirable taste that would otherwise exist"[2]. Taste masking is one of the most important areas in the preparation of the ODTs. Because ODTs disperse or disintegrate in the patient's mouth, the drug will be partially dissolved in close proximity to the taste buds. After swallowing, there should be minimal or no residue in the mouth. A pleasant taste is critical for patient acceptance. When the drug is tasteless or does not have a desirable taste, taste masking techniques should be used. An ideal taste masking technology should not impart grittiness and should produce good mouth feel. The amount of taste masking materials

used in the dosage forms should be minimized to avoid excessive tablet size. The taste masking technology should also be compatible with other components and properties of the formulation[3]. Solid dispersion has been defined as dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by melting (fusion) solvent or melting solvent method. Solid dispersion of the drug with the help of polymers, sugar, or other suitable agents is very useful for taste masking. Carriers used in solid dispersion system include povidone, polyethylene glycol of various molecular weights, hydroxy propyl methyl cellulose, urea, mannitol and ethyl cellulose[4]. Various approaches for preparation of solid dispersion are described below:

1. Melting method: In this method, the drug or drug mixture and carrier are melted together by heating. The melted mixture is cooled and solidified rapidly in an ice bath with vigorous stirring. The final solid mass is crushed and pulverized. 2. Solvent evaporation method: In this method, the active drug and carrier are dissolved in a common solvent, followed by solvent evaporation and recovery of the solid dispersion.

3. Melting solvent method: In this method, drug in solution is incorporated into molten mass of polyethylene glycol at a temperature 700C without removing the solvent[5].

Advances in novel drug delivery system aims to enhance safety and efficacy of drug molecule by formulating a convenient dosage form for administration and to achieve better patient compliance. One such approach is Oro Dispersible Tablets(ODTs)[6]. Recent market studies indicate that more than half of the patient population prefers ODTs to other dosage forms and most consumers would ask their doctors for ODTs (70%), purchase ODTs (70%), or prefer ODTs to regular tablets or liquids (>80%)[10]**.** Difficulty in swallowing or dysphagia is seen to afflict nearly 35% of the general population[7] . In order to assist these patients, several fast-dissolving drug delivery systems have been developed[8]. Oro dispersible are also applicable when local action in the mouth is desirable such as local anaesthetic for toothaches, oral ulcers, cold sores, or teething and to deliver sustained release multiparticulate system to those who cannot swallow intact sustained action tablets/capsules[9]. The mechanism of the oral disintegration of an ODT involved a three-step disintegration processafter an ODT is placed in the oral cavity, [1] saliva permeates the surface of the ODT, [2] this permeated region is softened and, [3] the softened portion is destroyed and removed by tongue pressure and friction between the tongue and the upper jaw. Next, saliva again permeates the non-disintegrated region of the ODT. After following these steps several times, the ODT disintegrates completely.

Drotaverine Hydrochloride has a miotropic spasmolytic vasodilating hypotensive action. It dilates the unstriped muscles and blood vessels strongly and prolonged, reduces their motion activity, lowers the arterial blood pressure. Action mechanism is determined by the reduction of the supply of active ionized calcium to unstriped muscle cells by way of phosphodiesterase inhibition and intracellular uptake of cyclic adenosine monophosphate. peak concentrations occur approximately 1 to 3 hours after an oral dose. Oral bioavailability is about 100%. Drug and its metabolites are 80% to 95% protein bound and it has a volume of distribution of 193 to 195 liters. It is extensively metabolized in the liver and it is excreted in the urine and feces. The half- life of this drug ranges from 7 to 12 hours.

Methods

Preparation of standard stock solution:

50 mg of drotaverine HCl was weighed and transferred into 50ml volumetric flask. 25ml of 0.1N HCl solution was added and sonicated for 10 minutes. Final volume was made up to 50 ml with 0.1N HCl solution to get 1mg/ml stock solution. From this solution 5 ml was transferred into 100ml volumetric flask and volume was made up to 100ml with 0.1 N HCl to get sub stock solution of 50µg/ml. The method obeyed beers law in the concentration range of 10-40µg/ml. The degree of linear relationship correlation coefficient(r) was calculated and found to be 0.9994. The regression line describing the relation between concentration and absorbance was as follows:

$$y=0.0196x+0.0044$$

Where, y is the absorbance at 303 nm and

x is the concentration of drotaverine HCl in µg/ml.

Preparation of taste masked oro dispersible tablets ODT (Table 1)

All the excipients used to formulate into tablets were passed through sieve # 40 and mixed in geometric dilution. Drug-polymer complex equivalent to 40 mg of drug were compressed on rotary 16 station tablet press machine.

Angle of repose[11]:

The flow properties are important in the manufacture of tablets and are measured by angle of repose. Angle of repose is defined as the maximum angle possible between the surface of a pile of powder and the horizontal plane. Lower the angle of repose, better

the flow property. Rough and irregular surface of particles gives higher angle of repose. Non-uniform flow results in weight variation, which affects the dose of the drug per tablet. It also creates a problem of hardness during compression of tablets. It is measured by fixed funnel method.

$\theta = \tan^{-1}(h/r)$, where θ is the angle of repose,

Carr's/compressibility index[12]:

Compressibility index can be a measure of the potential strength that a powder could build up in its arch in a hopper and also the ease with which such an arch could be broken.

$$I = [1- v/v_0]* 100$$

Hausner's ratio[13]:

The ratio of D_t/D_b was related to interparticulate friction and as such, could be used to predict powder flow properties. The powder with low interparticle friction such as coarse spheres had ratios of approximately 1.2, whereas more cohesive, less free-flowing powders such as flacks have hausner's ratio greater than 1.6. This value was calculated by making use of bulk and tapped densities of powders samples.

Hausner's ratio= D_t/D_b where, D_t is tapped density of the powder.

D_b is the bulk density of the powder.

Evaluation of prepared tablets:

The prepared tablets were evaluated for the general properties like general appearance, thickness, hardness, weight variation, friability, *In vitro* disintegration time, *In vitro* dispersion time(with simulated salivary fluid), *In vivo* disintegration time, wetting time, uniformity of dispersion, taste evaluation, mouth feel, *In vitro* dissolution studies.

Hardness[14]:

Tablets require a certain amount of strength of hardness and resistance to withstand mechanical shocks of handling in manufacture, packing and shipping. The hardness of tablets is determined by using Monsanto hardness tester. It is expressed in $Kgcm^{-2}$.

Friability test[15]:

Friability test was carried out in Roche friabilator. Ten tablets were initially weighed (W_0). They were placed in the apparatus which were subjected to 100 rotations at 25 rpm for 4 min at height of 6 inches. After completion of rotations, tablets were dedusted by using camel hair brush and weighed (W). The percent loss in weight (F) was calculated by the formula $F = [1-W/W_0]*100$

Drug content uniformity[16]:

Ten tablets were taken randomly. All the tablets were crushed and the quantity equivalent to 40 mg of the drug was taken into a 100 ml volumetric flask. 50 ml of 0.1N HCl was added and shaken for 30 min and was made to volume and filtered. 1ml of the filtrate was taken into 10ml volumetric flask and volume is made up to mark with 0.1n HCl. The absorbance was measured at 303nm using U.V spectrophotometer. Each tablet should not contain less than 90% and not more than 110% of the labeled claim

***In vitro* disintegration test:**

The test was performed to ensure disintegration of tablets in water at 37^0 C. One tablet is introduced in to each tube of disintegration apparatus and a disc is added into the tube. The assembly is suspended in the beaker containing distilled water and the apparatus is operated until the tablet disintegrated.

To be in compliance with the IP standards, dispersible tablets must disintegrate within 3 minutes when examined by the disintegration test for tablets.

***In vitro* dispersion time (with simulated salivary fluid) [17]:**

This test was performed to ensure disintegration of tablets in the salivary fluid, if it is to be used as an oro dispersible tablet.

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 performed

Fineness of dispersion[18]:

This test is applicable to dispersible tablets only. It is an assessment of the grittiness which arises due to disintegration of the tablet into coarse particles. The test is performed by placing two tablets in 100 ml water and stirring it gently until the tablets get completely disintegrated. The formulation is considered to form a smooth dispersion, if the complete dispersion passes through a sieve screen with a nominal mesh aperture of 710µm (sieve#22) without leaving any residue on the mesh.

***In vivo* disintegration time[19]:**

Six healthy human volunteers were selected and their written consent was obtained. 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. It is expressed in seconds. After the test, mouth was washed with distilled water. The same procedure was repeated for 3 trials and was carried out with 2 days interval.

Wetting time[20]**:**
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[21]**:**
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 are noted and recorded.

Mouth feel or Sensory Evaluation of Roughness[22]**:**
This test was also done on the same human volunteers participated in taste evaluation test. They were asked for their opinion about the feeling of smoothness or grittiness of the dispersion soon after the tablet was disintegrated.

***In vitro* dissolution studies:**
The release of drotaverine HCl from prepared tablets and commercial tablets was studied in 0.1N HCl by using USP Type II apparatus and the data obtained was tabulated.

Procedure:
900 ml of 0.1N HCl solution was used as the dissolution media for drug release studies. The tablets equivalent to 40 mg of drotaverine HCl were selected. The paddle rotation was adjusted to 50 rpm and the temperature of 37±0.5^{o} C was maintained throughout the dissolution test. An aliquot of 5 ml of the dissolution medium was withdrawn at appropriate time intervals (5, 10, 15, 20, 30, 40, 50, 60, 75 and 90).The volume withdrawn at each time interval was replaced by the same quantity of the fresh dissolution medium. The samples were suitably diluted with respective buffer solution and the dilutions were analyzed at 303 nm using Thermo spectrophotometer using respective buffer solution as blank.
Dissolution test was performed for both commercial tablet and prepared tablets. The percentage of drotaverine HCl released at each time interval was calculated and the results were tabulated.

Drug-excipient compatibility studies using Fourier Transform Infrared Spectroscopy:
Infrared spectroscopy was conducted using a Shimadzu FTIR 8300 Spectrophotometer and the spectrum was recorded in the region of 4000 to 400 cm^{-1}. The procedure consisted of dispersing a sample (drug and drug complex mixture) in KBr (200-400 mg) and compressing into discs by applying a pressure of 5 tons for 5 min in a hydraulic press. The pellet was placed in the light path and the spectrum was obtained. Spectra were recorded in duplicate for each of the samples.

RESULTS AND DISCUSSION
Drotaverine HCl is the drug of choice in treatment of spasms of various organs, regardless of their function and innervations. But it is a very bitter drug and slightly soluble in water. So the objective of the present work is to formulate dispersible or orodispersible tablets of this highly bitter drug, where in which its bitter taste is masked. In the present study, the taste masking is done by using kneading methods. It was preferred over other taste masking methods, because the drug will be coated and the taste buds may not feel the taste, where by the bitterness of the drug gets taste masked.

Optimization of the ratio drug-polymer complex:
The ratio of drug: polymer was optimized by the taste evaluation of the prepared granules. The drug: polymer ratios optimized for taste masking were 1:10 for sucrose fatty acid ester.

Pre compression parameters (Table 2)
Angle of repose:
The angle of repose observed was found to be good (≤ 25°) for all granules and therefore comply with the standards (stated limits are 25-30 for good flow).

Compressibility Index (I):
As per standard, the value of I below 15% usually gives rise to good flow characteristics. All the granules prepared showed the values ≤ 15indicating good flow properties.

Hausner's ratio:
As per standard, the value between1.0-1.12 usually gives rise to good flow characteristics.The granules prepared were having values 1.00-1.14 indicating good flow properties.

Evaluation of tablets (in process parameters):
The prepared tablets were evaluated for the general properties like general appearance, hardness, weight variation, friability, *In vitro* disintegration time, *In vitro* dispersion time(with simulated salivary fluid), *In vivo* disintegration time, wetting time, uniformity

of dispersion, taste evaluation, mouth feel, *In vitro* dissolution studies and results were tabulated.

Tabletting parameters (Table 3)
General appearance:
All the formulations prepared shown pale yellow colour.

Hardness:
The average hardness of the all the tablets prepared by using sucrose fatty acid ester, were in range of 4-6Kg/cm^2. This ensures good handling characteristics of the formulations.

Drug content:
The percentage drug content present in all the tablets was about 99% and therefore comply with the standard stated limits i.e., between 90 to 110%.

Weight variation:
All the prepared tablets passed weight variation test, as % weight variation was with in the Pharmacopoeia limits i.e., ±5%.

Friability:
The percentage friability was less than 1% in all the formulations, ensuring that the tablets were mechanically stable. All the tablets showed values less than 0.5%.

***In vitro* disintegration time:**
To be compliant with the IP standards, orodispersible tablets must disintegrate within 3 minutes. The prepared tablets with sucrose fatty acid ester in range of 33-198 sec. The optimized formulation exhibited very less disintegrating time of 45 sec for sucrose fatty acid ester indicating that they were suitable as orodispersible tablets.

Uniformity of dispersion:
In the test for uniformity of dispersion all tablets prepared fulfilled the official (I.P) requirement. The dispersion produced in water passed through the sieve # 22.

***Invitro* dispersion time:**
The tablets showed less *in vitro* dispersion time. The dispersion time of 39±1.34 sec for F5 were observed.

Wetting time:
The wetting time were found to be 18±0.46 to 211±1.0. The formulations showed wetting time of 26±0.8 for F5.The results of invitro wetting time were found to satisfy the criteria of orodispersible tablets.

Taste and mouth feel evaluation of the prepared tablets:
The optimized formulations were tested on human volunteers. The optimized formulations were given to panel of healthy human volunteers for taste masking evaluation using time intensity method which shows satisfactory masking of taste and also the tablet gave a pleasant feeling Table 4.

***In vitro* dissolution studies:**
The data regarding percent drug dissolved versus time obtained from the dissolution tests and the corresponding dissolution profiles of all the prepared tablets and commercial tablet are shown in the Table 6. The dissolution profile of ODT of drotaverine HCl with sucrose fatty acid ester was shown in Table 5 From the results it was observed that the maximum dissolution rate was achieved with the formulation F5 (5% and 15% w/w to drug polymer complex of croscarmellose sodium and mannitol respectively). The formulation F5 showed more than 60% of the drug in 5 min and 100% of the drug achieved at the end of 30 min.
The marketed formulation (Drotin) released more than 60% of the drug in 5 min and 100% of the drug in 60 min. the comparative dissolution profiles of optimized formulations and marketed formulation was shown in the Table From the results the formulation made with sucrose fatty acid ester showed comparable results with marketed formulation . Hence, F5 was considered to be the best experimental formulation among all the prepared drotaverine HCl formulations.

Drug interaction studies using Fourier Transform Infrared Spectroscopy:
FTIR analysis for pure drug and its complexes were carried out. Theoretically drotaverine HCl will give principal peaks for N-H secondary amine (3500-3300 cm-^{1}), for aromatic C=C stretching (1600-1475cm-^{1}), for C-H stretching (3000-2840cm-^{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 1237.10cm-^{1} which are well in support to theoretical prediction. The drug complex combination did not produce major shift in principal peaks of drotaverine HCl, indicating no interaction due to presence of excipients. Thus,FTIR spectral analysis proved the compatibility between drug and polymers.

CONCLUSION

In conclusion, this study showed that sucrose fatty acid esters can be suitably used for taste masking of bitter drugs. Thus, we are able to achieve our objective of preparing taste masked orodispersible tablets of drotaverine HCl by direct compression method which is a simple method of manufacture. All the optimized formulations masked the bitter taste of the drug, the formulation F5 using sucrose fatty acid ester showed faster and better drug release than others.

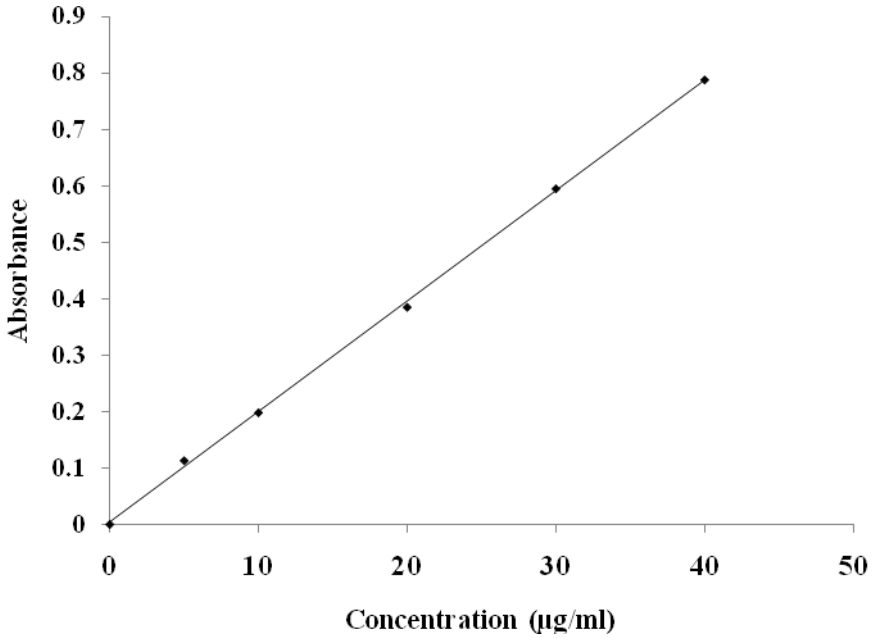

Fig. 1
Standard graph of drotaverine HCl in 0.1N HCl

Table 1
Formula of ODT of drotaverine HCl by using sucrose fatty acid ester

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7
Drotaverine	40	40	40	40	40	40	40
Sucrose fatty acid ester	410	410	410	410	410	410	410
Croacarmellose sodium	11	22	22	22	22	11	33
Mannitol	-	-	22	44	66	66	66
Aspartame	18	18	18	18	18	18	18
Magnesium sterate	4.5	4.5	5	5	5	5	5
Total weight	**483.5**	**494.5**	**517**	**539**	**561**	**550**	**572**

Table 2
Pre compression parameters for formulations using sucrose fatty acid ester

Formulation	Angle of repose (°)	Compressibility index (%)	Hausners ratio
F1	23.00	11.23	1.11
F2	21.60	14.55	1.04
F3	22.20	15.09	1.09
F4	20.88	11.11	1.13
F5	22.12	15.08	1.07
F6	21.09	12.33	1.06

Table 3
Tabletting parameters of ODT of drotaverine tablets using sucrose fatty acid ester

Formulation	Hardness (Kg/cm^2)	Friability(%)	Weight variation[a] (mg)	Drug Content[b] (%)	*In vitro* disintegration time*(with water)	*In vitro* dispersion time*(with simulated salivary fluid)	*In vivo* disintegration time*	Wetting time*
F1	4-6	0.27	473.5±1.23	99.54±1.33	198±1.34	190±1.34	183±0.89	175±1.8
F2	4-6	0.39	484.5±1.56	99.34±1.56	143±1.22	136±1.25	128±1.29	120±1.3
F3	4-6	0.41	507±1.39	99.78±1.45	89±1.45	81±0.9	74±1.35	68±1.22
F4	4-6	0.38	529±0.47	99.65±1.32	61±1.5	54±1.5	48±1.37	40±1.04
F5	4-6	0.19	551±1.76	99.84±1.45	45±1.09	39±1.34	32±1.35	26±0.87
F6	4-6	0.27	540±1.78	99.75±1.23	58±1.3	50±1.33	43±0.5	35±0.69

a :mean±s.d.(n=20); b: mean±s.d.(n=10); *(Mean±s.d. (n=3) seconds)

Table 4
Taste evaluation of formulation F5

Volunteers	Bitterness level after				Mouth feel
	5 sec	20sec	1 min	3 min	
1	0	0	0	0	+
2	0	0	×	×	-
3	0	0	0	×	-
4	0	0	0	×	-
5	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			

Table 5
Dissolution profiles of TM ODT of drotaverine HCl by using sucrose fatty acid ester

Time	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
5	8.12±0.23	16.12±0.22	32.12±0.24	41.12±0.12	62.12±0.23	46.12±0.33
10	16.22±0.34	24.12±0.36	47.43±0.23	62.12±0.34	75.99±0.38	69.98±0.45
15	32.95±0.66	41.73±0.44	59.12±0.55	76.23±0.56	82.12±0.58	79.09±0.56
20	44.98±0.78	54.98±0.67	71.98±0.68	87.89±0.78	90.36±0.78	87.98±0.77
30	61.09±0.98	71.33±0.87	89.99±0.78	95.98±1.20	100.87±0.99	96.22±0.98
45	71.87±1.22	84.98±1.22	96.1±1.33	100.04±1.25		100.04±1.05
60	86.99±1.45	95.98±1.34	101.98±1.43			
90	94.29±1.04	102.12±1.44				
120	101.03±1.44					

*each value is (Mean±s.d. (n=3)

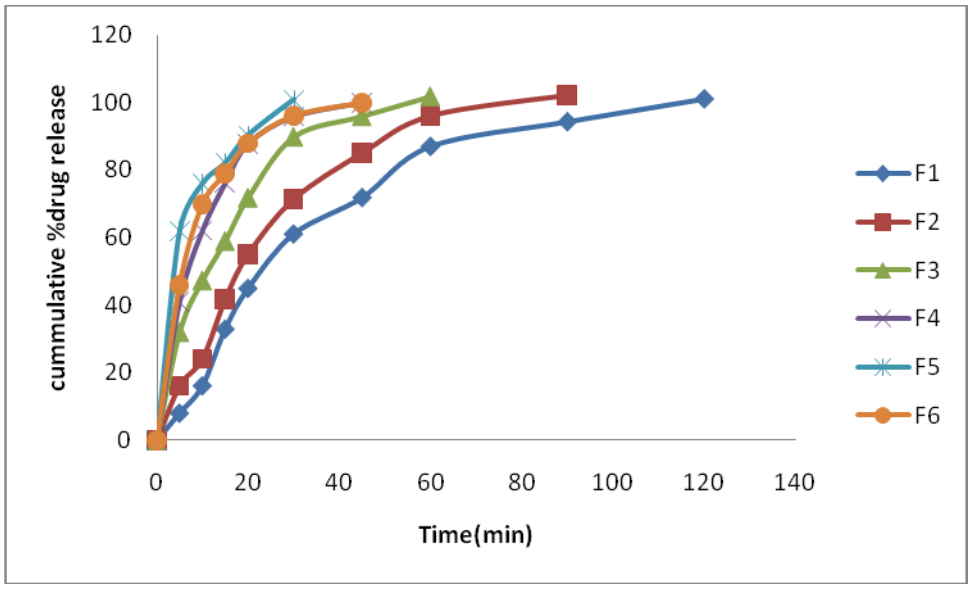

Fig.2 (A)
Dissolution profiles of ODT of drotaverine HCl using
A)sucrose fatty acid ester

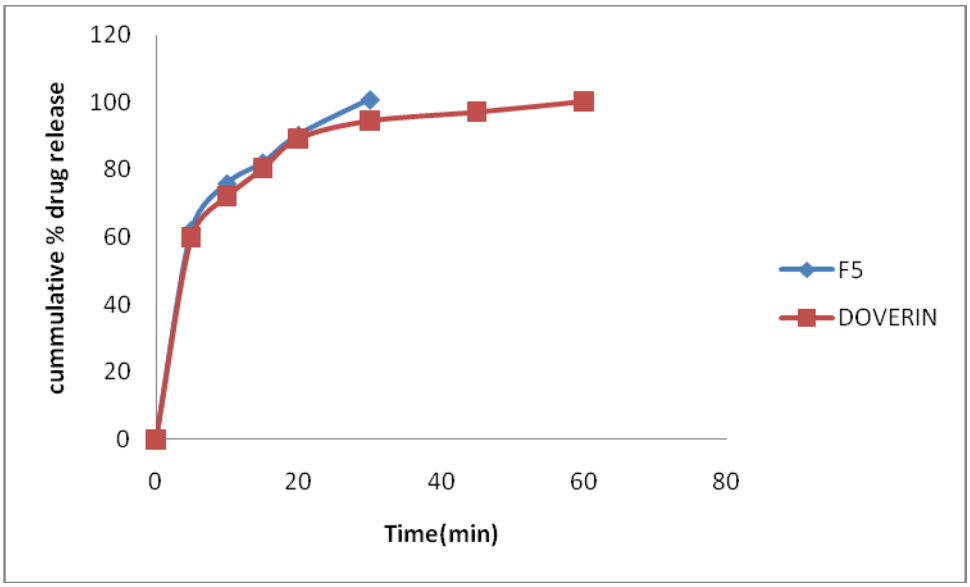

Fig.2 (B)
Dissolution profiles of ODT of drotaverine HCl using
A)sucrose fatty acid ester
(B)optimized formulations and marketed formulation

Table 6
Dissolution profiles of TM ODT of drotaverine HCl by using croscarmellose sodium as disintegrant and marketed formulation

Time	F5	DORTIN
0	0	0
5	62.12±0.23	60.12±0.10
10	75.99±0.38	72.15±0.45
15	82.12±0.58	80.52±0.58
20	90.36±0.78	89.42±0.89
30	100.87±0.99	94.65±0.99
45		97.27±1.24
60		100.41±1.40
90		

*each value is (Mean±s.d. (n=3)

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