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Research Article

TASTE MASKED CHEWABLE DISPERSIBLE TABLET OF ATOMOXETINE HYDROCHLORIDE

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ABSTRACT

In the present work, chewable dispersible tablets of Atomoxetine Hydrochloride were designed by preparing taste masked granulate of Atomoxetine Hydrochloride with Eudragit EPO. The taste masked granulate was prepared by the batch process in Rapid Mixer Granulator using Eudragit EPO with a drug: Avicel 101: Eudragit EPO ratios 1:1.5:0.5, 1:2.0:1.0, 1:2.6:1.33 and 1:3.0:1.5 (% w/w). Assay content and In-vitro decomplexation studies confirmed taste masking of granulate. It was found that maximum taste masking of drug with Eudragit EPO was noted at a ratio of 1:2.6:1.33. Drug release from Drug: Avicel 101: Eudragit EPO complex in salivary pH imparts slight after bitter taste which was overcome by addition of flavors for mouth feel and taste masking flavor to reduce after taste bitterness. A study on different flavor is studied to enhance mouth feel and taste in combination with taste masking flavor. The prepared batches of tablets were evaluated for hardness, friability, drug content uniformity and *in vitro* dispersion time. Based on acceptable physical characteristic, formulations were tested for *in vitro* drug release pattern (in 0.1N Hydrochloride).

Keywords: Dispersible Chewable Tablet; Atomoxetine Hydrochloride; Eudragit EPO; Rapid Mixer Granulator.

INTRODUCTION

The bitter taste of the drugs which are orally administered often contributes to patient non-compliance in taking medicines, especially for children and elderly (1). Unfortunately, majority of the drugs have a natural bitter taste that can create a burning feeling in the throat or in the mouth. In particular, a bitter taste can decrease the patient compliance and thus reducing an effective pharmacotherapy. In order to achieve an acceptable palatability, the addition of flavors or sweeteners is limited and may not be efficient enough to mask the taste buds of drugs and requires the use of technological processes (2). A number of taste masking approaches like the use of ion exchange resins (3), the use of inclusion complexes with cyclodextrins (4,17,18), viscosity modifications (5), granulation and melt granulation (6) have been described. More than 50 percent of pharmaceutical products are orally administered for several reasons and undesirable taste is one of the important formulation problem encountered with such oral products (7). The taste of a pharmaceutical product is an important parameter for governing compliance. Thus, taste masking of oral pharmaceuticals has become an important tool to improve patient compliance and the quality of treatment especially in pediatrics. Therefore, formulation of taste masked products is a challenge to the pharmacists (8-9).

In recent decades, a variety of research has been conducted to develop new dosage forms. Considering quality of life, most of these efforts have been focused on ease of medication (10). Among the dosage forms developed to facilitate ease of medication, the chewable dispersible tablet (CDT) is one of the most widely employed commercial products. The CDT has remarkable disintegration properties; it can disintegrate without water in the mouth. CDTs are useful in patients such as pediatric, geriatric, bedridden, or developmentally disabled who may face difficulty in swallowing conventional tablets or capsules leading to ineffective therapy, persistent nausea, sudden episodes of allergic attacks, or coughing. CDTs are also applicable when local action in the mouth is desirable such as local anesthetic 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. Chewable tablets are formulated and manufactured so that they may be chewed, producing a pleasant tasting residue in the oral cavity that is easily swallowed and does not leave a bitter or unpleasant aftertaste. Chewable tablets are prepared by compression, usually utilizing sorbitol, mannitol, or sucrose as binders and fillers, and containing colors and flavors to enhance their appearance and taste. Chewable dispersible tablets have the advantages like better bioavailability through bypassing disintegration (and perhaps enhancing dissolution), patient convenience through the elimination of the need for water for swallowing, possible use as a substitute for liquid dosage forms where rapid onset of action is needed, improved patient acceptance through pleasant taste, and product distinctiveness from marketing perspective. Chewable dispersible tablets represent the largest market segment of chewable dosage forms.

Granulation is process of size enlargement where small particles are gathered into larger aggregates intended for compression into tablets. Following are some reasons for performing granulations (11)

- Increase flow property which required producing consistent weight and uniform strength
- Increase Compressibility which is essential to form stable, intact and compact mass when pressure is applied
- Improve Appearance, mixing properties, to avoid dustiness.
- Moreover, granulations prepared by spray granulation are devoid of the unpleasant taste of drug probably due to coating of polymer on drug. Taste of API masked using strong polymer (binders) forming a film on API

Thus the first part of our study consisted of the preparation of taste masked granulate of Atomoxetine Hydrochloride. Thereafter, the second part of the study encompassed the preparation of tablets to evaluate the potential of compressing prepared taste masked granulate using different excepient. The potential of flavoring agent and taste masking flavor was also evaluated. Finally, the technological characteristics of the prepared tablets were evaluated in order to find the formula with the least time of disintegration and friability and eventually the best hardness.

Atomoxetine hydrochloride is a selective nor-epinephrine reuptake inhibitor indicated for the treatment of Attention-Deficit/Hyperactivity Disorder (12). In general, emesis is preceded with nausea and in such condition it is difficult to administer drug with a glass of water; hence it is beneficial to administer such drugs as chewable dispersible tablet. Atomoxetine Hydrochloride is an intensely bitter drug; hence, if it is incorporated directly into a CDT the main objective behind formulation of such a dosage form will definitely get futile.

Eudragit EPO is known for its taste masking effect (13). Thus in the present study an attempt has been made to mask the taste of Atomoxetine Hydrochloride and to formulate chewable dispersible tablet with good mouth feel so as to prepare a "patient-friendly dosage form."

MATERIALS AND METHOD

Materials

Atomoxetine Hydrochloride was a gift from Sun pharmaceuticals (Mumbai). Eudragit EPO was a gift from Evonik Degussa Mumbai. Mannitol, Avicel 101 (microcrystalline cellulose), Avicel 112 (low moisture content microcrystalline cellulose) and Prosolv SMCC 90 (silicified microcrystalline cellulose) were provided as gift samples by Signet chemicals. Flavors and taste masking flavor of Firmenich were provided by Manish global. All other chemicals used in the study were of analytical grade.

Method

Preparation of Atomoxetine taste masked granulate

Atomoxetine Hydrochloride taste masked granulate was prepared using granulation process. Trials with Superpolyestate, Precirol ATO and β-cyclodextrins were not helpful in taste masking, so Eudragit EPO was selected for the same. Complexatation trials with atomoxetine were with a ration of 1:1 to 1:4 were not helpful in taste masking, so diluting the API with diluents and then granulating the blend was a good option. For preliminary study, we optimized the ratio of Drug:Avicel 101:EPO at 1:1.5:0.5, 1:2.0:1.0, 1:2.6:1.33 and 1:3.0:1.5. Based on the preliminary sensory evaluation of taste masked granulate the following concentration was finalized 1:2.6:1.33 so as to have a reduced tablet weight. Drug (68.57 g) microcrystalline cellulose (180.0 g) and Povidone K-30 was dry mix for 5 min in Rapid Mixer Granulator (RMG) and were granulated in RMG using water to form granules. The granules were sifted through 60# after drying in a retsch dryer. The dried granules were again spray granulated with solution of Eudragit EPO and talc (25 % w/w in 60:40 IPA : Acetone). The 25 % w/w in 60:40 IPA : Acetone was selected to reduce the drying time after granulation as the spraying of the solution was done in 2 step. The granulate was stirred in the 6.8 phosphate buffer at 37°C. The supernatant was collected and assayed spectrophotometrically at a wavelength of 269 nm (Lambada 35 UV/VIS Spectrometer, Perkin Elmer) to determine the taste masking.

Characteristics of Atomoxetine taste masked granulate

Atomoxetine content

Atomoxetine Hydrochloride taste masked granulate (equivalent to 60 mg of Atomoxetine) was placed in a beaker to which 0.1 N Hydrochloride (50 ml) was added for eluting Atomoxetine from the taste masked granulate. The eluate was decanted and replaced with the same volume of fresh eluent. The volume of eluate was measured and assayed for the content of Atomoxetine by spectrophotometry at wavelength of 269 nm. The elution process was stopped when the absorbance of the last eluate was lower than 0.01. The sum of the content of Atomoxetine in each eluate was equal to the total content of Atomoxetine in taste masked granulate. (Table 1)

Table 1: Drug content and In vitro taste evaluation taste masked granulate in simulated salivary fluid

Ratio of drug: Avicel 101 :Eudragit EPO	1:1.5:0.5	1:2.0:1	1:2.6:1.33	1:3.0:1.5
Assay of Atomoxetine taste masked granulate	98.9	98.7	99.1	99.0
% Drug dissolved in SSF after Time 2min*	7. 270±0.314	3.110±0.212	1.764±0.17	1.423±0.20
Assay of pure drug	99.9			

In vitro taste Evaluation

In vitro taste was evaluated by determining drug release in simulated salivary fluid (SSF) (pH 6.8) to predict release in the human saliva. Atomoxetine Hydrochloride taste masked granulate equivalent to 60 mg of drug was subjected to release rate study. Weighed quantity added to 10 ml pH 6.8 Aliquot was withdrawn after 5 min. The sample was filtered through whattman filter paper. The absorbance was measured at 269 nm (Table 1).

Molecular Properties

Molecular properties on taste masked granulate were studied by x-ray powder diffraction (XRPD). The X-ray powder diffractograms of the Drug: Avicel 101: Eudragit EPO (1:2.6:1.33), were recorded. using a Philips PW 1729 X-ray diffractometer (Legroupe Interconnection, Saint Jurie, Clubac, Canada) with monocrotized Cu Kα radiation (1.314 A^0), at a speed of 2θ min−1 from 10- to 60-(2θ) under the voltage and current of 40 Kv and 30 Kv respectively (Figure 1 and 2).

Selection of Flavor

Different Flavor like strawberry, banana and mint alone or in combination were tested for taste masking effect and mouth feel. Effect of taste masking flavor was also studied along with other flavor to reduce the after taste bitterness. Table 2 shows the concentration of flavor used alone or in combination with other flavor along with taste masking flavor in formulation. Table 3 represents the rating index used by evaluator for sensory evaluation. Table 4 shows sensory evaluation for flavor combination to be used in final formulation.

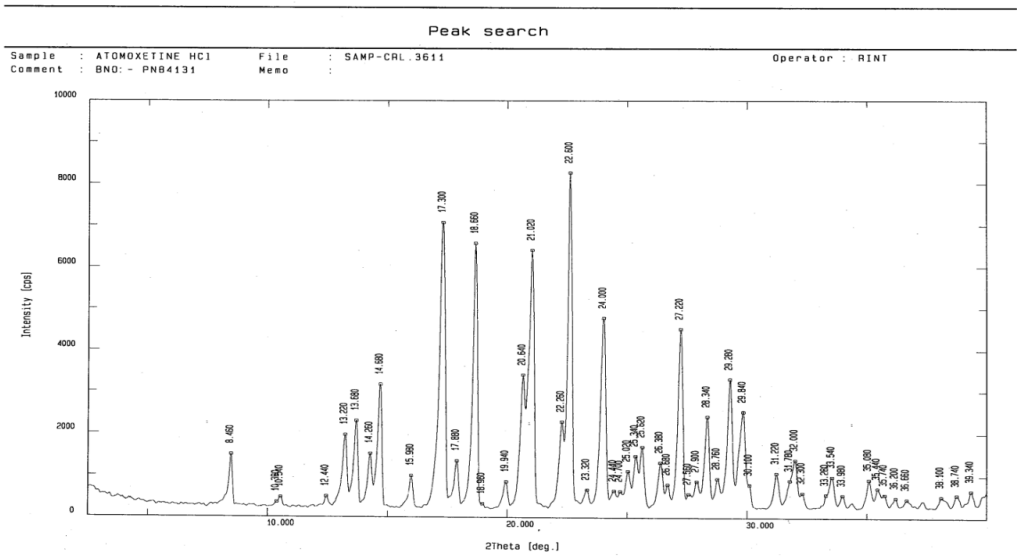

Fig. 1: X-ray diffraction pattern of Atomoxetine hydrochloride

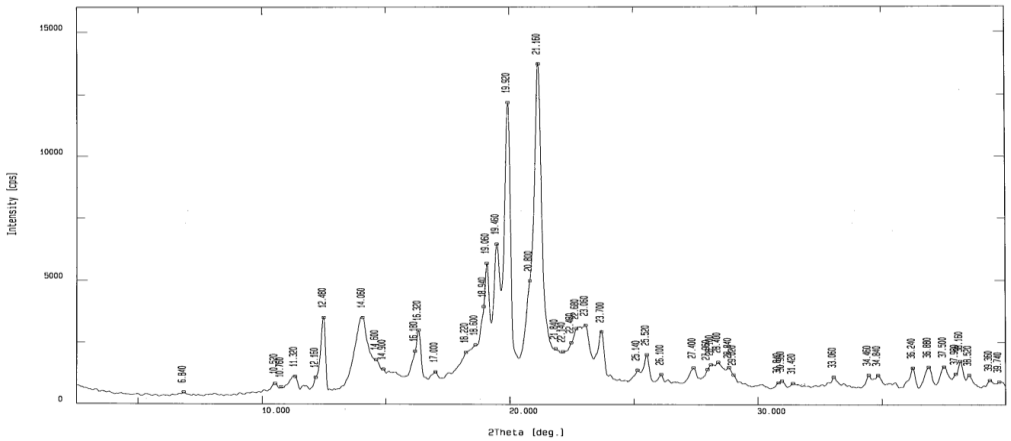

Fig. 2: X-ray diffraction pattern of Atomoxetine hydrochloride taste masked granulate

Table 2: Selection of Flavor

S. No.	Batch	Strawberry	Banana	Mint	Taste masking flavor
1	D1	1	-	1	-
2	D2	-	1	1	-
3	D3		1	1	1
4	D4	2	-	2	-
5	D5	-	2	2	-
6	D6		2	2	2
7	D7	3	-	3	-
8	D8	-	3	3	-
9	D9	-	3	3	3

*D6 was finalized based on the sensory evaluation result

Table 3: Sensory Evaluation Rating Index

Comments	Score
Liked extremely	9
Liked very much	8
Liked moderately	7
Liked slightly	6
Neither liked nor disliked	5
Disliked slightly	4
Disliked moderately	3
Disliked very much	2
Disliked extremely	1

Table 4: Sensory Evaluation for combination of flavor

Attribute		Sample D3	Sample D6	Sample D9	Sample D3	Sample D6	Sample D9
	Score	Volunteers			Comments		
Flavour	1	--	--	--	--	--	--
	2	1	--	--	Increase flavor	--	--
	3	3	1	--	--	--	--
	4	2		1	Ok	--	--
	5	14			Ok	--	--
	6	1	2	5	Good	Ok	Ok
	7	1	10	9	Good	Good / Increase slightly	Good / Decrease slightly
	8	--	8	6	--	Good / Appropriate / Should be less	Good / Should be less
	9	--	1	1	--	Very good	Very good
Total volunteers		22					
Mouth feel (Grittiness)	1	2			need to improve	--	--
	2	3			--	--	--
	3	5	1	1	Bitter	--	--
	4	12	1	2	slightly Bitter	Ok	Ok
	5	1	2	4	Ok	Good / Increase slightly	Good
	6	1	6	7	--	Good	Ok
	7		9	7	--	Ok	Ok
	8	--	2	1	--	Good / Appropriate / Should be less	Good / Appropriate
	9	--	1	--	--	Very good	--
Total volunteers		22					

Table 5: Formulation composition for an CDT

S. No.	Ingredient per tablet	Formulation							
	Taste masked Granulate	F1	F2	F3	F4	F5	F6	F7	F8
1	Atomoxetine Hydrochloride	11.428	11.428	11.428	11.428	11.428	11.428	11.428	11.428
2	Avicel 101	30.00	30.00	30.00	30.00	30.00	30.00	30.00	30.00
3	Povidone K 30	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00
4	Eudragit EPO	15.2	15.2	15.2	15.2	15.2	15.2	15.2	15.2
5	Talc	3.6	3.6	3.6	3.6	3.6	3.6	3.6	3.6
Extragranular									
6	Prosolv 90	40.272	-	-	24	-	24	20	18
7	MCC 112	-	-	40.272	-	24	16.272	10.272	12.272
8	Mannitol SD 200	-	40.272	-	16.272	16.272	0	10	10
9	Aspartame	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00
10	Banana flavor	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00
11	Mint flavor	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00
12	Taste masking flavor	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00
13	Aerosil SD 200	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00
14	Talc	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
	Total weight	115.0	115.0	115.0	115.0	115.0	115.0	115.0	115.0

Selection of Diluents and Formulation of CDT

Before formulation of tablets, the best diluent was screened out. The best diluent which would give the required physical parameter was used for the final formulation of tablets. Tablets were prepared in various batches containing a blend of mannitol, microcrystalline cellulose and prosolve SMCC 90 (Table 5). Tablets were prepared by direct compression using 7.0 mm round for 10 mg and 12.5 mm for 60 mg, standard concave beveled edge punch.

Physical Properties of the Tablet Blend (14)

Physical properties such as bulk density, tapped density, the angle of repose and compressibility index of blend were determined (Table 6). Bulk density was determined by the USP method I; tapped density was determined by USP method II. Percent compressibility was calculated using Equations 1.

Percent compressibility = {(Dt − Db / Dt } × 100 ……(1)

Where, Dt and Db are tapped and bulk densities.

Evaluation of Tablet

The prepared tablets were evaluated for hardness, weight variation, thickness, friability and drug content (Table 7) (15-16). Hardness of the tablets was tested using a Strong- Cobb hardness tester (Tabmachine, Mumbai, India). Friability of the tablets was determined in a Roche friabilator (Campbell Electronics, Mumbai, India). The thickness of the tablets was measured by vernier caliper. Weight variation test was performed according to the official method as per USP.

In Vitro Disintegration Time

In vitro disintegration time for CDTs was determined using USP and disintegration of tablet in a beaker containing 50 ml of SSF. The volume of the media will give a discriminatory nature to the disintegration time.

In-vitro Dissolution studies

The In-vitro dissolution studies were carried out using USP apparatus type II (paddle) at 50 rpm.

The dissolution medium used was 0.1 N Hydrochloride (900 ml) maintained at 37 ± 0.5°C. Aliquots of dissolution media were withdrawn at different intervals and content of Atomoxetine Hydrochloride was measured by determining absorbance at 269 nm.

The dissolution experiments were conducted in triplicate. In vitro Dissolution studies for Marketed Capsule were also carried out. Results were shown in table 8 along with % RSD and figure 3 and 4 representing the graph.

Table 6: Physical properties of tablet blend

Batch No	Bulk density (g/mL)	Tapped density (g/mL)	Angle of Repose* (°)±SD	% Compressibility	Hausner ratio
F1	0.55	0.65	26.56±0.70	15.38	1.18
F2	0.56	0.66	25.45±0.60	15.15	1.18
F3	0.50	0.64	27.13±0.78	21.88	1.28
F4	0.56	0.65	26.5±0.67	13.85	1.16
F5	0.51	0.65	26.45±0.85	21.54	1.27
F6	0.54	0.65	25.25±0.54	16.92	1.20
F7	0.56	0.66	27.61±0.63	15.15	1.18
F8	0.56	0.65	26.21±0.43	13.85	1.16

Table 7: Physical properties of tablet

Batch No.	Friability	Hardness (Kg/cm2) ±SD	Thickness ±SD	% Weight variation ±SD	Disintegration time (Sec) ±SD	Sticking or Smearing on tablet
F1	0.25 ± 0.09	6.13±0.24	2.40 ± 0.05	115.20± 1.70	152.0± 2.2	Observed
F2	0.30 ± 0.15	6.00±0.24	2.40 ± 0.02	115.50± 1.80	160.0± 3.0	Observed
F3	0.26 ± 0.13	6.50±0.24	2.39 ± 0.04	115.00± 1.20	154.0± 4.0	Observed
F4	0.25 ± 0.12	6.25±0.20	2.48 ± 0.06	115.70± 1.35	140.0± 4.0	Slightly Observed
F5	0.25 ± 0.11	5.50±0.30	2.40 ± 0.03	115.70± 1.40	138.0± 1.0	Slightly Observed
F6	0.23 ± 0.08	6.40±0.32	2.39 ± 0.07	115.20± 1.80	139.0± 4.0	Slightly Observed
F7	0.20 ± 0.10	6.70±0.25	2.39 ± 0.03	115.15± 1.50	140.0± 4.0	Not Observed
F8	0.20 ± 0.09	7.00±0.40	2.38 ± 0.02	115.10± 1.50	140.0± 2.0	Not Observed

Table 8: Comparative dissolution for trials

Time in min	Reference	% RSD	F4	% RSD	F5	% RSD	F6	% RSD	F7	% RSD	F8	% RSD
0	0	0	0	0	0	0	0	0	0	0	0	*0*
5	60	1.6	64	2.85	54	3.81	65	4.38	70	3.71	76	2.12
10	82	1.52	80	1.61	65	2.68	78	3.45	95	2.01	97	1.78
15	97	1.24	91	1.04	86	2.21	92	2.89	96	1.01	98	1.03
20	101	0.2	99	0.58	95	1.72	100	2.64	100	0.8	100	1.02
30	101	0.2	99	0.57	100	1.12	100	0.53	100	0.8	100	0.0
45	101	0.2	100	0.46	100	1.00	100	0.0	100	0.0	100	0.0

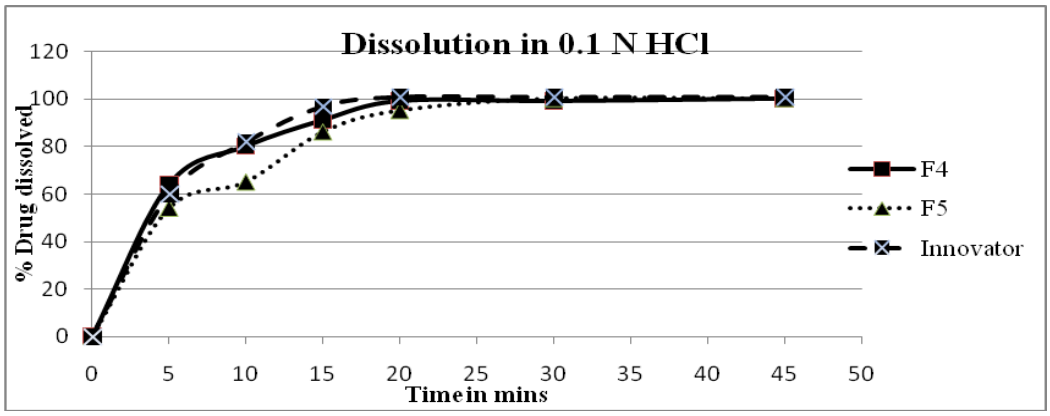

Fig. 3: In-vitro release profile of capsule of marketed product and batches F4 & F5

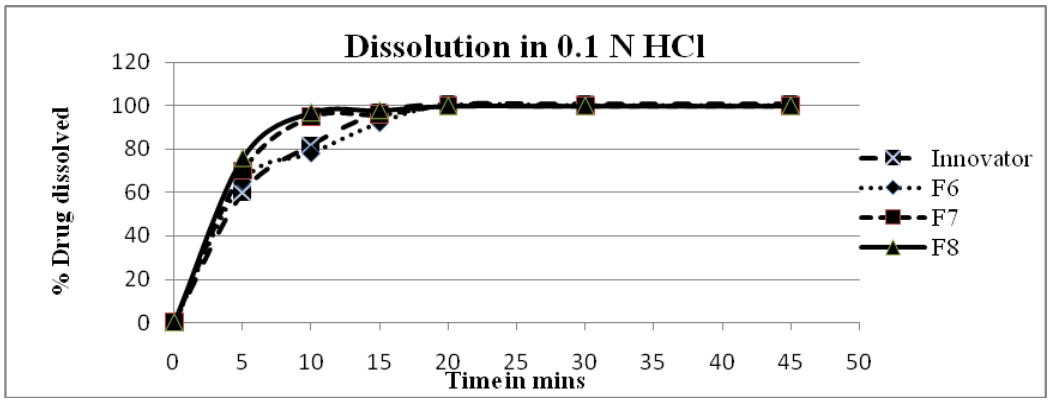

Fig. 4: In-vitro release profile of capsule of marketed product and batches F6 to F8

RESULTS AND DISCUSSION

Characterization of Taste masked Granulate

Percentage drug loading in taste masked granulate was found from 98.7 to 99.1. No drug release was observed in SSF from taste masked granulate with the drug:Avicel 101:Eudragit EPO ratio of 1:2.6:1.33 and 1:3.0:1.5, therefore, the ratio 1:2.6:1.33 was considered the optimal taste masked granulate with complete masking of bitter taste for further studies. The x-ray diffractogram of Atomoxetine Hydrochloride confirms its crystalline nature, as evidenced from the number of sharp and intense peaks (Figure 1). However, the diffraction patterns of taste masked granulate represents crystalline peaks (Figure 2). These finding suggest that there is no formation of new solid phase with a change in degree of crystallinity due to granulation; it's a surface phenomenon only and no chemical bond formation.

Selection of Flavor

The initial screening of Atomoxetine Hydrochloride taste masked granulate suggest that the taste has been masked but there is slight after taste bitterness which need to be masked using flavor. Formulation of CDT was made by using Atomoxetine Hydrochloride taste masked granulate. Batches using combination flavor with taste masking flavor D1 to D9 were prepared by direct compression and were tested for sensory evaluation, from the results the flavor concentration as per D6 were finalized in Table 2, it can be concluded that the taste masking cannot be achieved using single flavor for which combination flavor is required. Mint has a strong flavor which helps in taste masking so combination with mint help to overcome the initial bitter taste. From the study surprisingly it was found that the after taste bitterness was also reduced due to taste masking flavor in combination with other flavor with acceptable mouth feel.

Physical Properties of the Tablet Blend

The tablet blend of all the batches was evaluated for different derived properties like angle of repose (between 25 to 27), bulk density (between 0.50 to 0.56 gm/cm3), Compressibility index (between 13 to 21). The results angle of repose and compressibility indicated that the flowability of blend is significantly good. All the tablets passed weight variation test as the percent weight variation was within the pharmacopoeial limits. Hardness was shown in the range of 5.50±0.30 to 7.00±0.40 Kg/cm2 in all the formulations. The hardness of all tablets was kept within the above mentioned range

to compare the disintegration time between the formulations prepared using different diluents and their varying concentrations. No disintegrant's were used as Avicel 112 and Prosolv SMCC 90 have in bound disintegration properties. The friability of all formulations was determined. The friability values of none of the formulations exceeded 1%. The results of friability indicate that the tablets were mechanically stable and can withstand rigors of transportation and handling. Thickness of all tablets was between 2.38±0.02 to 2.48 ± 0.06 mm showing fairly uniform tabletting. The results of disintegration of all the tablets were found to be within prescribed limits and satisfactory. The values were found to be in the range of 138.0± 1.0 to 160.00 ± 3.0 sec. The time intensity study for taste in human volunteers of both the taste masked granulate and CDT revealed considerable masking of the bitter taste of Atomoxetine Hydrochloride with degree of bitterness below the threshold value (1.0) ultimately reaching to 0 within 15 minutes. Sensory evaluation of the optimized tablet proved good palatability.

Drug Release from CDT

The tablets from batch number F4 to F8 prepared were subjected for release profile based on the physical characteristic. Among five batches, batch F8 which contain Prosolve 90, Mannitol and Avicel 112 of its acceptable physical characteristic shows lowest disintegration time and highest drug release. The drug release of the marketed product and F8 formulation was found to be 97 (RSD 1.24) and 98 (RSD 1.03) at the end of 15 minutes. From the above observations, it may be concluded that optimized formulation is better or as good as a marketed conventional capsule in release rate of drug with taste masked characteristic.

CONCLUSION

The study conclusively demonstrated complete taste masking of Atomoxetine Hydrochloride, CDT and dissolution of CDT. The process is feasible scalable and shows effective taste masking. Taste masking and complete disintegration of tablets formulated in this investigation may possibly help in administration of Atomoxetine Hydrochloride in a more palatable form without water during emesis. Thus, the "patient-friendly dosage form" of bitter drugs, especially for pediatric, geriatric, bedridden, and non co-operative patients, can be successfully formulated using this technology.

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